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Diseases of the Nervous System

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Introduction

This chapter focuses on the diagnosis, treatment, and control of large animal diseases primarily affecting the nervous system. In general, the principles of clinical neurology and their application to large animal neurology has not kept pace with the study of neurology in humans and small animals, although remarkable progress has been made in equine neurology over the last 30 years. To a large extent this shortfall is caused by the failure of large-animal clinicians to relate observed clinical signs to a **neuroanatomical location** of the lesion. In many cases this failure has been because of adverse environmental circumstances, or the large size or nature of the animal, all of which adversely impact the quality of the neurologic examination. It may be very difficult to do an adequate neurologic examination on an ataxic belligerent beef cow that is still able to walk and attack the examiner. An aggressive, paretic bull in broad sunlight can be a daunting subject if one wants to examine the pupillary light reflex; ophthalmoscopic examination of the fundus of the eye in a convulsing steer in a feedlot pen can be an exasperating task. Thus at one end of the spectrum is the clinical examination of pigs affected with nervous system disease, which is limited to an elementary clinical examination and necropsy examination. At the other end, neurologic examination of the horse with nervous system disease is very advanced. The global occurrence of bovine spongiform encephalopathy (BSE) has highlighted the importance of accurate clinical diagnosis in adult cattle with neurologic abnormalities.

Discrete lesions of the central nervous system (CNS) resulting in well-defined neurologic signs are not common in agricultural animals. Many diseases are characterized by diffuse neurologic lesions associated with bacteria, viruses, toxins, nutritional disorders, and embryologic defects, and the clinical findings of each disease are similar. Rather than attempting to localize lesions in the nervous system, large-animal practitioners more commonly devote much of their time to attempting to identify whether an animal has diffuse brain edema or increased intracranial pressure, as in polioencephalomalacia (PEM); whether it has clinical signs of asymmetric brainstem dysfunction and depression of the reticular activating system, as in listeriosis; or whether the dysfunction is at the neuromuscular level, as in hypomagnesemic tetany.

Radiographic examination, including myelography, is not used routinely as a diagnostic aid in large-animal practice. The

collection of cerebrospinal fluid (CSF) from the different species and ages of large animal without causing damage to the animal or contaminating the sample with blood is a technique that few large-animal veterinarians have mastered. However, the collection of CSF from the lumbosacral cistern is not difficult if the animals are adequately restrained, and the information obtained from analysis of CSF can be very useful in the differential diagnosis of diseases of the brain and spinal cord. Referral veterinary centers are now providing detailed neurologic examinations of horses with nervous system disease, and the clinical and pathologic experience has expanded the knowledge base of large-animal clinical neurology.

In spite of the difficulties, the large-animal practitioner has an obligation to make the best diagnosis possible using the diagnostic aids available. The principles of large-animal neurology are presented in this chapter, and the major objective is to recognize the common diseases of the nervous system by correlating the clinical findings with the location and nature of the lesion. **Accurate neuroanatomical localization of the lesion**(s) remains the fundamental requirement for creating a differential diagnosis list and diagnostic and treatment plan.

A disease such as rabies has major public health implications, and it is important for the veterinarian to be able to recognize the disease as early as possible and to minimize human contact. It is also important to be able to recognize treatable diseases of the nervous system, such as polioencephalomalacia (PEM), listeriosis, and nervous ketosis, and to differentiate these diseases from untreatable and globally important diseases such as Bovine Spongiform Encephalopathy (BSE).

The nontreatable diseases must also be recognized as such, and slaughter for salvage or euthanasia recommended if necessary. There must be a major emphasis on prognosis because it is inhumane and uneconomic to hospitalize or continue to treat an adult cow or horse with incurable neurologic disease for an indefinite period. If they are recumbent, the animals commonly develop secondary complications such as decubitus ulcers and other self-inflicted injuries because of repeated attempts to rise. Very few diseases of the nervous system of farm animals are treatable successfully over an extended period of time. This has become particularly important in recent years with the introduction of legislation prohibiting the slaughter of animals that have been treated with antibiotics until after a certain withdrawal period, which may vary from 5 to 30 days. This creates even greater pressure on the clinician to make a rapid, inexpensive, and accurate diagnosis and prognosis.

Because of limitations in the neurologic examination of large animals, there must be much more emphasis on the history and epidemiologic findings. Many of the diseases have epidemiologic characteristics that give the clinician a clue to the possible causes, thus helping to narrow the number of possibilities. For example, viral encephalomyelitis of horses occurs with a peak incidence during the insect season, lead poisoning is most common in calves after they have been turned out on to pasture, and PEM occurs in grain-fed feedlot cattle and sheep.

The functions of the nervous system are directed at the maintenance of the body's spatial relationship with its environment. These functions are performed by the several divisions of the nervous system including the following:

- Sensorimotor system, responsible for the maintenance of normal posture and gait
- Autonomic nervous system, controlling the activity of smooth muscle and endocrine glands, and thus the internal environment of the body
- Largely sensory system of special senses
- Psychic system, which controls the animal's mental state

The nervous system is essentially a reactive one geared to the reception of internal and external stimuli and their translation into activity and consciousness; it is dependent on the integrity of both the afferent and efferent pathways. This integrative function makes it often difficult to determine in a sick animal whether abnormalities are present in the nervous system; the musculoskeletal system; or acid-base, electrolyte, and energy status. Accordingly, the first step when examining an animal with apparent abnormalities in the nervous system is to determine whether other relevant systems are functioning normally. A decision to implicate the nervous system is often made on the exclusion of other systems.

The nervous system itself is not independent of other organs, and its functional capacity is regulated to a large extent by the function of other systems, particularly the cardiovascular system. Inadequate oxygen delivery caused by cardiovascular disease commonly leads to altered cerebral function because of the dependence of the brain on an adequate oxygen supply.

It is important to distinguish between primary and secondary diseases of the nervous system because both the prognosis and the treatment will differ with the cause.

In primary disease of the nervous system, the lesion is usually an anatomic one with serious, long-range consequences. **In secondary disease,** the lesion, at least in its early stages, is more likely to be functional and therefore more responsive to treatment, provided the defect in the primary organ can be corrected. The clinical findings that should arouse suspicion of neurologic disturbance include abnormalities in the three main functions of the system.

Posture and Gait

An animal's ability to maintain a normal posture and to proceed with a normal gait depends largely on the tone of the skeletal muscle but also on the efficiency of the postural reflexes. Abnormalities of posture and gait are among the best indications of nervous system disease because these functions are governed largely by the coordination of nervous activity. Along with contributing to posture and gait, skeletal muscle tone is characteristic in its own right. However, its assessment in animals is subject to great inaccuracy because of our inability to request complete voluntary relaxation by the patient. In humans it is a very valuable index of nervous system efficiency, but in animals it has serious limitations. The most difficult step whenever there is a defect of gait or posture is to decide whether the defect originates in the skeleton, the muscles, or the nervous system.

Sensory Perceptivity

Tests of sensory perception in animals can only be objective and never subjective, as they can be in humans, and any test used in animals is based heavily on the integrity of the motor system.

Mental State

Depression or enhancement of the psychic state is not difficult to judge, particularly if the animal's owner is observant and accurate. A helpful method for evaluating mental state is to answer the question: Is the animal responding appropriately for its environment? The difficulty usually lies in deciding whether the abnormality is caused by primary or secondary changes in the brain.

Principles of Nervous Dysfunction

Nervous tissue is limited in the ways in which it can respond to noxious influences. Because of its essentially coordinating function, the transmission of impulses along nerve fibers can be enhanced or depressed in varying degrees, with the extreme degree being complete failure of transmission. Because of the structure of the system, in which nerve impulses are passed from neuron to neuron by relays at the nerve cells, there may also be excessive or decreased intrinsic activity of individual cells giving rise to an increase or decrease in nerve impulses discharged by the cells. The end result is the same whether the disturbance is one of conduction or discharge, and these are the only two ways in which disease of the nervous system is manifested. Nervous dysfunction can thus be broadly divided into two forms, **depressed activity** and **exaggerated activity**. These can be further subdivided into four common modes of nervous dysfunction; **excitation (irritation) signs**,

release of inhibition signs, **paresis or paralysis caused by tissue damage**, and **nervous shock**.

MODES OF NERVOUS DYSFUNCTION

Excitation (Irritation) Signs

Increased activity of the reactor organ occurs when there is an increase in the number of nerve impulses received either because of excitation of neurons or because of facilitation of passage of stimuli.

The excitability of nerve cells can be increased by many factors, including stimulant drugs, inflammation, and mild degrees of those influences that in a more severe form may cause depression of excitability. Thus early or mild hypoxia may result in increased excitability, whereas sustained or severe hypoxia will cause depression of function or even death of the nerve cell.

Irritation phenomena may result from many causes, including inflammation of nervous tissue associated with bacteria or viruses, certain nerve poisons, hypoxia, and edema. In those diseases that cause an increase in intracranial pressure, irritation phenomena result from interference with circulation and the development of local anemic hypoxia. The major manifestations of irritation of nervous tissue are tetany, local muscle tremor, and whole-body convulsions in the motor system and hyperesthesia and paresthesia in the sensory system. For the most part the signs produced fluctuate in intensity and may occur periodically as nervous energy is discharged and reaccumulated in the nerve cells.

The area of increased excitability may be local or sufficiently generalized to affect the entire body. Thus a local lesion in the brain may cause signs of excitatory nervous dysfunction in one limb, and a more extensive lesion may cause a complete convulsion.

Release of Inhibition Signs

Exaggeration of normal nervous system activity occurs when lower nervous centers are released from the inhibitory effects of higher centers. The classic example of a release mechanism is experimental decerebrate rigidity caused by transection of the brainstem between the colliculi of the midbrain. This results in an uninhibited extensor tonus of all the antigravity muscles. The head and neck are extended markedly in a posture of opisthotonus, and all four limbs in the quadruped are extended rigidly. The tonic mechanism or myotactic reflex involving the lower motor neuron has been released from the effects of the descending inhibitory upper motor neuron pathways.

Cerebellar ataxia is another example of inhibitory release. In the absence of cerebellar control, combined limb movements are exaggerated in all modes of action including rate, range, force, and direction. In general, release phenomena are present constantly while the causative lesion operates, whereas excitatory phenomena fluctuate with the building up and exhaustion of energy in the nerve cells.

Paresis or Paralysis Caused by Tissue Damage

Depression of activity can result from depression of metabolic activity of nerve cells, and the terminal stage is complete paralysis when nervous tissue is destroyed. Such depression of activity may result from failure of supply of oxygen and other essential nutrients, either directly from their general absence or indirectly because of failure of the local circulation. Infection of the nerve cell itself may cause initial excitation, then depression of function, and finally complete paralysis when the nerve cell dies.

Signs of paralysis are constant and are manifested by muscular paresis or paralysis when the motor system is affected and by hypoesthesia or anesthesia when the sensory system is involved. Deprivation of metabolites and impairment of function by actual invasion of nerve cells or by toxic depression of their activity produce temporary, partial depression of function that is completely lost when the neurons are destroyed.

Nervous Shock

An acute lesion of the nervous system causes damage to nerve cells in the immediate vicinity of the lesion but there may be, in addition, a temporary cessation of function in parts of the nervous system not directly affected. The loss of function in these areas is temporary and usually persists for only a few hours. Stunning is an obvious example. Recovery from the flaccid unconsciousness of nervous shock may reveal the presence of permanent residual signs caused by the destruction of nervous tissue.

Determining the type of lesion is difficult because of the limited range of modes of reaction to injury in the nervous system. Irritation signs may be caused by bacterial or virus infection, by pressure, by vascular disturbance or general hypoxia, by poisons, and by hypoglycemia. It is often impossible to determine whether the disturbance is structural or functional. Degenerative lesions produce mainly signs of paresis or paralysis but unless there are signs of local nervous tissue injury, such as facial nerve paralysis, paraplegia, or local tremor, the disturbance may only be definable as a general disturbance of a part of the nervous system. Encephalopathy is an all-embracing diagnosis, but it is often impossible to go beyond it unless other clinical data, including signalment of the animal, epidemiology, and systemic signs, are assessed or special tests, including radiographic examination and examination of the CSF, are undertaken.

Some information can be derived from a study of the **sign-time relationship** in the development of nervous disease. A lesion that develops suddenly tends to produce maximum disturbance of function, sometimes accompanied by nervous shock. Slowly developing lesions permit a form of compensation in that undamaged pathways and centers may assume some of the functions of the damaged areas. Even in rapidly developing lesions partial recovery may occur in time, but the emphasis is on maximum depression of function at the beginning of the disease. Thus a slowly developing tumor of the spinal cord will have a different pattern of clinical development from that resulting from an acute traumatic lesion of the vertebrae. Another aspect of the rapidity of onset of the lesion is that irritation phenomena are more likely to occur when the onset is rapid and less common when the onset is slow.

Clinical Manifestations of Diseases of the Nervous System

The major clinical signs of nervous system dysfunction include the following:

- **Altered mentation**
- **Involuntary movements**
- **Abnormal posture and gait**
- **Paresis or paralysis**
- **Altered sensation**
- **Blindness**
- **Abnormalities of the autonomic nervous system**

ALTERED MENTATION

Excitation States

Excitation states include **mania**, **frenzy**, and **aggressive behavior**, which are manifestations of general excitation of the cerebral cortex. The areas of the cortex that govern behavior, intellect, and personality traits in humans are the frontal lobes and temporal cortex. The clinical importance of these areas, which are poorly developed in animals, is not great. The frontal lobes, temporal cortex, and limbic system are highly susceptible to influences such as hypoxia and increased intracranial pressure.

Mania

In mania the animal acts in a bizarre way and appears to be unaware of its surroundings. Maniacal actions include licking, chewing of foreign material and sometimes themselves, abnormal voice, constant bellowing, apparent blindness, walking into strange surroundings, drunken gait, and aggressiveness in normally docile animals. A state of delirium cannot be diagnosed in animals, but mental disorientation is an obvious component of mania.

Diseases characterized by mania include the following:

- Encephalitis, e.g., the furious form of rabies, Aujeszky's disease in cattle (pseudorabies, mad itch)

- Degenerative diseases of the brain, e.g., mannosidosis, early PEM, poisoning by *Astragalus* sp.
- Toxic and metabolic diseases of brain, e.g., nervous ketosis, pregnancy toxemia, acute lead poisoning, poisoning with carbon tetrachloride, and severe hepatic insufficiency, especially in horses

Frenzy

Frenzy is characterized by violent activity and with little regard for surroundings. The animal's movements are uncontrolled and dangerous to other animals in the group and to human attendants, and are often accompanied by aggressive physical attacks.

Examples of frenzy in diseases of the nervous system include the following:

- Encephalomyelitides, e.g., Aujeszky's disease.
- Toxic and metabolic brain disease, e.g., hypomagnesemic tetany of cattle and sheep, poisoning with ammoniated roughage in cattle.

Examples of frenzy in diseases of other body systems include the following:

- Acute pain of colic in horses.
- Extreme cutaneous irritation, e.g., photosensitization in cattle. Apparently reasonless panic, especially in individual horses or groups of cattle, is difficult to differentiate from real mania. A horse taking fright at a botfly or a swarm of bees and a herd of cattle stampeding at night are examples.

Aggressive Behavior

Aggression and a willingness to attack other animals, humans, and inert objects is characteristic of the early stages of rabies and Aujeszky's disease in cattle, in sows during postparturient hysteria, in the later stages of chronic hypoxia in any species, and in some mares and cows with granulosa-cell tumors of the ovary. The latter are accompanied by signs of masculinization and erratic or continuous estrus. It is often difficult to differentiate between an animal with a genuine change in personality and one that is in pain or is physically handicapped, e.g., pigs and cattle with atlantoaxial arthroses.

Depressive States

Depressive mental states include somnolence, lassitude, narcolepsy/catalepsy, syncope, and coma. They are all manifestations of depression of cerebral cortical function in various degrees and occur as a result of those influences that depress nervous system function generally, as well as those that specifically affect behavior, probably via the limbic system. It is not possible to classify accurately the types of depressive abnormality and relate them to specific causes, but the common occurrences in farm animals are listed next.

Depression Leading to Coma

In all species this may result from the following:

- Encephalomyelitis and encephalomalacia
- Toxic and metabolic diseases of the brain such as uremia, hypoglycemia, hepatic insufficiency, toxemia, septicemia, and most toxins that damage tissues generally
- Hypoxia of the brain, as in peripheral circulatory failure of periparturient hypocalcemia in dairy cows
- Heat stroke
- Specific poisons that cause somnolence, including bromides, amitraz in horses, methyl alcohol, *Filix mas* (male fern), and kikuyu grass

Syncope

The sudden onset of fainting (syncope) may occur as a result of the following:

- Acute circulatory and heart failure leading to acute cerebral hypoxia
- Spontaneous cerebral hemorrhage, a most unlikely event in adult animals
- Traumatic concussion and contusion
- Lightning strike, electrocution

Narcolepsy (Catalepsy)

Affected animals experience episodes of uncontrollable sleep and literally "fall" asleep. The disease is recorded in Shetland ponies and is thought to be inherited in them, in other horses, and in cattle.

Compulsive Walking or Head Pressing

Head-pressing is a syndrome characterized by the animal pushing its head against fixed objects and into a corner of a pen as well as leaning into a stanchion or between fence posts. Head-pressing should be differentiated from compulsive walking, in which affected animals put their heads down and walk slowly while appearing blind. If they walk into an object, they lean forward and indulge in head-pressing; if confined to a stall they will often walk around the pen continuously or head-press into a corner. The syndrome represents a change in behavior pattern caused by an unsatisfied compulsive drive characteristic of a disorder of the limbic system. Causes include the following:

- Toxic and metabolic brain disease, especially PEM and hepatic encephalopathy
- Diseases manifested by increased intracranial pressure
- Encephalomyelitides

Aimless Wandering

A similar but less severe syndrome to compulsive walking is aimless walking, severe mental depression, and apparent blindness with tongue protrusion and continuous chewing movements, although the animal is unable to ingest feed or drink water. Causes include the following:

- Toxic and metabolic diseases of brain, including poisoning by *Helichrysum* sp. and tansy mustard
- Degenerative brain diseases, e.g., nigropallidal encephalomalacia in horses, ceroid lipofuscinosis in sheep, hydrocephalus in the newborn

INVOLUNTARY MOVEMENTS

Involuntary movements are caused by involuntary muscle contractions, which include gradations from fasciculations, shivering and tremor, to tetany, seizures, or convulsions. Opisthotonus or "backward tone" is a sustained spasm of the neck and limb muscles resulting in dorsal and caudal extension of the head and neck with rigid extension of the limbs.

Tremor

This is a continuous, repetitive twitching of skeletal muscles that is usually visible and palpable. The muscle units involved may be small and cause only local skin movement, in which case the tremor is described as fasciculations; or the muscle units may be extensive and the movement much coarser and sufficient to move the extremities, eyes, or parts of the trunk. The tremor may become intensified when the animal undertakes some positive action. This is usually indicative of cerebellar involvement and is the counterpart of intention tremor in humans. True tremor is often sufficiently severe to cause incoordination and severe disability in gait. Examples of causes of tremor include the following:

- Diffuse diseases of the cerebrum, cerebellum, and spinal cord
- Degenerative nervous system disease, e.g., hypomyelinogenesis of the newborn as in congenital tremor of pigs and calves, poisoning by *Swainsona* sp.
- Toxic nervous system disease caused by a large number of poisons, especially poisonous plants and fungi, *Clostridium botulinum* toxin in shaker foal syndrome; metabolic disease such as hyperkalemic periodic paralysis in the horse; early stages of hypocalcemia in the cow (fasciculations of the eyelids and ears).

Tics

Tics are spasmodic twitching movements made at much longer intervals than in tremor. The intervals are usually at least several seconds in duration and often much longer. The movements are sufficiently widespread to be easily visible and are caused by muscles that are ordinarily under voluntary control. They are rare in large animals but may occur after traumatic injury to a spinal nerve.

Tetany

Tetanus is a sustained contraction of muscles without tremor. The most common cause is *C. tetani* intoxication following localized infection with the organism. The degree of muscular contraction can be exaggerated by

stimulation of the affected animal, and the limbs are rigid and cannot be passively flexed easily ("lead pipe" rigidity).

Myoclonus is a brief, intermittent tetanic contraction of the skeletal muscles that results in the entire body being rigid for several seconds, followed by relaxation. Inherited congenital myoclonus (hereditary neuraxial edema) of polled, horned, and crossbred Hereford calves is a typical example. Affected calves are bright and alert and can suck normally, but if they undertake a voluntary movement or are handled their entire body becomes rigid for 10 to 15 seconds.

Convulsions

Convulsions, seizures, fits, or ictus are violent muscular contractions affecting part or all of the body and occurring for relatively short periods as a rule, although in the late stages of encephalitis they may recur with such rapidity they give the impression of being continuous.

Convulsions are the result of abnormal electrical discharges in forebrain neurons that reach the somatic and visceral motor areas and initiate spontaneous, paroxysmal, involuntary movements. These cerebral dysrhythmias tend to begin and end abruptly, and they have a finite duration. A typical convulsion may have a prodromal phase or aura that lasts for minutes to hours, during which the animal is oblivious to its environment and seems restless. The beginning of the convulsion may be manifested as a localized partial convulsion of one part of the body that soon spreads to involve the whole body, when the animal usually falls to the ground thrashing rhythmically. Following the convulsion there may be depression and temporary blindness, which may last for several minutes up to a few hours.

The convulsion may be clonic with typical "paddling" (involuntary movement in which repeated muscle spasms alternate with periods of relaxation). Tetanic or tonic convulsions are less common and are manifested by prolonged muscular spasm without intervening periods of relaxation. True tetanic convulsions occur only rarely, chiefly in strychnine poisoning and in tetanus, and in most cases they are a brief introduction to a clonic convulsion.

Convulsions can originate from disturbances anywhere in the prosencephalon, including cerebrum, thalamus, or even the hypothalamus alone. However, the initiating cause may be in the nervous system outside the cranium or in some other system altogether; convulsions are therefore often subdivided into intracranial and extracranial types. Causes are many and include the following.

Intracranial convulsions are caused by

- Encephalomyelitis, meningitis
- Encephalomalacia
- Acute brain edema
- Brain ischemia, including increased intracranial pressure
- Local lesions caused by trauma (concussion, contusion), abscess, tumor, parasitic injury, hemorrhage
- Inherited idiopathic epilepsy

Extracranial convulsions are caused by brain hypoxia, as in acute circulatory or cardiac failure, and toxic and metabolic diseases of the nervous system, including the following:

- Hepatic encephalopathy
- Hypoglycemia (as in newborn piglets and in hyperinsulinism caused by islet cell adenoma of the pancreas as described in a pony)
- Hypomagnesemia (as in lactation tetany in cows and mares)
- Inorganic poisons, poisonous plants, and fungi; there are too many to give a complete list, but well-known examples are the chlorinated hydrocarbons, pluronics used in bloat control in cattle, *Clostridium* spp.; intoxications, e.g., *C. perfringens* type D and *C. sordellii,* and subacute fluoroacetate poisoning
- Congenital and inherited defects without lesions, e.g., familial convulsions and ataxia in Angus cattle

Involuntary Spastic Paresis

Involuntary, intermittent contractions of large muscle masses may result in spasmodic movements of individual limbs or parts of the body. In most, contractions occur when voluntary movement is attempted. Diseases in this category include the following:

- Stringhalt and Australian stringhalt of horses
- Inherited spastic paresis (Elso heel) of cattle
- Inherited periodic spasticity (stall cramp) of cattle
- Inherited congenital myotonia of cattle
- Inherited myotonia of goats

ABNORMAL POSTURE AND GAIT

Posture

Posture is evaluated with the animal at rest. Abnormal postures may be adopted intermittently by animals in pain, but in diseases of the nervous system the abnormality is usually continuous and repeatable. Deviation of the head and neck from the axial plane or rotation of the head and neck from the horizontal plane (head tilt); drooping of the lips, eyelids, cheeks, and ears; and opisthotonus and orthotonos are examples, although the latter two are often intermittent because they occur as part of a convulsive seizure. Head pressing and assumption of a dog-sitting posture are further examples. Abnormalities of posture and gait are the result of lesions of the brainstem, cerebellum, all levels of the spinal cord, spinal nerve roots, peripheral nerves, neuromuscular junctions, and muscles. The clinical emphasis is on vestibular disease, cerebellar disease, and spinal cord disease. It is important to emphasize that cerebral lesions do not cause abnormalities in posture and gait.

Vestibular Disease

The vestibular system is a special proprioceptive system that assists the animal in maintaining orientation in its environment with respect to gravity. It helps to maintain the position of the eyes, trunk, and limbs in relationship to movements and positioning of the head.

From the vestibular nuclei, the vestibulospinal tracts descend ipsilaterally through the length of the spinal cord. These neurons are facilitatory to ipsilateral motor neurons going to extensor muscles of the limbs, are inhibitory to ipsilateral motor flexor muscles, and are inhibitory to contralateral extensor muscles. The principal effect of unilateral stimulation of this system on the limbs is a relative ipsilateral extensor tonus and contralateral flexor tonus, which promote ipsilateral support of the trunk against gravity. Conversely, a unilateral vestibular lesion usually results in ipsilateral flexor and contralateral extensor tonus, forcing the animal toward the side of the lesion.

The nuclei of cranial nerves (CNs) III, IV, and VI, which control eye movement, are connected with the vestibular system by way of a brainstem tract called the medial longitudinal fasciculus. Through this tract, coordinated eye movements occur with changes in positioning of the head. Through these various pathways, the vestibular system coordinates movements of the eye, trunk, and limbs with head movements and maintains equilibrium of the entire body during motion and rest.

Signs of vestibular disease vary depending on whether there is unilateral or bilateral involvement and whether the disease involves peripheral or central components of the system.

The vestibular influence on balance can be affected

- At the inner ear
- Along the vestibular nerve or
- At the vestibular nucleus in the medulla.

Unilateral excitation or loss of function can be caused by lesions at any of these points.

General signs of vestibular system dysfunction are staggering, leaning, rolling, circling, drifting sideways when walking and a head tilt, and various changes in eye position such as strabismus and nystagmus. The walking in a circle toward the affected side is accompanied by increased tone in the contralateral limbs, which is most easily observed in the contralateral forelimb. Rotation or tilt of the head occurs, and severely affected animals fall to the affected side.

When the lesion affects the inner ear, as in some cases of otitis media, the affected side is turned down, the animal falls to that side, and there may be facial paralysis on the same side if the lesion is extensive and affects CN VII. In

the recumbent position, the affected side is held to the ground, and if these animals are rolled over to the opposite side they quickly roll back to the affected side. When the vestibular nuclei are affected, as in listeriosis, the animal falls to the affected side.

Nystagmus and forced circling are common when there is irritation of the vestibular nucleus or the medial longitudinal fasciculus.

Causes of vestibular disease include the following:

- Otitis media interna with involvement of the inner ear
- Focal lesion at the vestibular nucleus, e.g., listeriosis
- Traumatic injury to the vestibular apparatus in the horse caused by fracture of the basisphenoid, basioccipital, and temporal bones; the clinical signs include lack of control of balance, rotation of the head, circling to the affected side, nystagmus, and facial paralysis

In paradoxical vestibular syndrome there is also head tilting, but circling in a direction away from the side of the lesion. Deviation of the head and neck must be distinguished from a head tilt. Asymmetric lesions of the forebrain such as a brain abscess, some cases of PEM, verminous larval migration, or head trauma may cause an animal to hold its head and neck turned to one side, but there is no head tilt and the circle is large in diameter. In fact, the presence of a head tilt (deviation of eyes away from a horizontal plane) accompanied by a tight circle provide clinically useful methods of differentiating a cerebral lesion from a vestibular lesion.

Gait

Gait is assessed when the animal is moving. Neurologic gait abnormalities have two components, **weakness** and **ataxia**. Weakness (paresis) is evident when an animal drags its limbs, has worn hooves, or has a low arc to the swing phase of the stride. When an animal bears weight on a weak limb, the limb often trembles and the animal may even collapse on that limb because of lack of support. While circling, walking on a slope, and walking with the head elevated, an animal frequently will stumble on a weak limb and knuckle over at the fetlock. During manipulation of the limb, the clinician will usually make the subjective observation that the muscle tone is reduced.

Ataxia

Ataxia is an unconscious, general proprioceptive deficit causing incoordination when the animal moves. It is manifested as a swaying from side to side of the pelvis, trunk, and sometimes the whole body (truncal sway). Ataxia may also appear as a weaving of the affected limb during the swing phase of the stride. This often results in abducted or adducted foot placement, crossing of the limbs, or stepping on the opposite foot.

Hypermetria is an increased range of movement and is seen as an overreaching of the limbs with excessive joint movement. Hypermetria without paresis is characteristic of spinocerebellar and cerebellar disease. It is a decreased range of movement that is characterized by a stiff or spastic movement of the limbs with little flexion of the joints, particularly the carpal and tarsal joints.

Dysmetria is a term that includes both hypermetria and hypometria, with goose-stepping being the most common sign. It usually is caused by a lesion in the cerebellum or cerebellar pathway.

In equine degenerative myeloencephalopathy (EDM), there is dysmetria of the hindlimbs and tetraparesis caused by neuraxonal dystrophy originating in the accessory cuneate nuclei. Severely affected horses lift their feet excessively high and stamp them to the ground.

Cerebellar Disease

When cerebellar function is abnormal there is ataxia, which is an incoordination when the animal moves. In general terms, there are defects in the rate, range, and direction of movement. In typical cerebellar diseases, ataxia of the limbs is common and no weakness is evident. In true cerebellar ataxia (e.g., cerebellar hypoplasia), the affected animal stands with the legs wide apart, sways, and has a tendency to fall. Ataxia of the head and neck are characterized by wide, swinging, head excursions; jerky head bobbing; and an intention tremor (nodding) of the head.

The head tremor may be the most obvious sign in mild cases of cerebellar hypoplasia in young foals. The limbs do not move in unison, the movements are grossly exaggerated, muscular strength is usually preserved, and there is a lack of proper placement of the feet (hypermetria and hypometria); falling is common. The fault in placement is the result of poor motor coordination and not related in any way to muscle weakness or proprioceptive deficit. Attempts to proceed to a particular point are usually unsuccessful, and the animal cannot accurately reach its feed or drinking bowl. Examples of cerebellar disease include the following:

- Inherited defects of cerebellar structure or abiotrophy in most breeds of cattle and in Arabian horses[1]
- Congenital cerebellar defects resulting from maternal viral infections such as bovine virus diarrhea (BVD) infection in cattle
- Dysplastic disease of the cerebellum of the horse
- Traumatic injury, e.g., by parasite larvae such as *Hypoderma bovis,* which have caused unilateral cerebellar ataxia in adult cattle
- Tremorgenic mycotoxicoses and ryegrasses
- Cerebellar degeneration in cattle in Uruguay caused by grazing the perennial shrub *Solanum bonariense* ("Naranjillo")[2]
- Encephalomyelitis in which other localizing signs also occur

Spinal Cord Disease

Ataxia caused by cerebellar dysfunction can be difficult to differentiate from the proprioceptive defects and partial motor paralysis (weakness) that occur in animals with spinal cord lesions, and it is most important that this differentiation is made. Spinal cord disease, causing varying degrees of weakness, and ataxia are common in large animals. The weakness is caused by damage to the upper or lower motor neurons and the proprioceptive deficit by damage to the ascending sensory neurons. With a mild or even moderate cervical spinal cord lesion in an adult cow or horse, signs of ataxia and weakness may be evident in the pelvic limbs only, and it can be difficult to determine whether the thoracic limbs are involved.

Close examination of the gait, posture, and postural reactions in the limbs, together with a search for localizing abnormalities, will often be productive in localizing the lesion. Signs of weakness or ataxia may be elicited by gently pushing the hindquarters to one side or pulling the tail to one side as the animal is walked (the sway response). The normal animal resists these movements or steps briskly to the side as it is pushed or pulled. The weak animal can be easily pulled to one side and may stumble or fall and may also tend to buckle or collapse when strong pressure is applied with the hand over the withers and loin regions. The ataxic animal may sway to one side, be slow to protract a limb, cross its hindlegs, or step on its opposite limb.

It is often difficult to distinguish paresis from ataxia, but in most instances it is unimportant because of the close anatomic relationship of the ascending general proprioceptive and descending upper motor neuron tracts in the white matter of the spinal cord. These same abnormal sway responses can be elicited in the standing animal.

The ataxic animal may abduct the outside pelvic limb too far as it is pushed to one side or moved in a small circle. This may appear as a hypermetric movement similar to a stringhalt action and is assumed to be a sign of a general proprioceptive tract lesion. The pushed or circled animal may keep a clinically affected pelvic limb planted in one position on the ground and pivot around it without moving it. The same failure to protract the limb may be seen on backing. It may even force the animal into a "dog-sitting" posture.

Examples of ataxia caused by spinal cord disease include the following:

- Limited trauma to the spinal cord
- The early stages of a developing compression lesion in the vertebral canal

- Degenerative and inflammatory diseases of the nervous system, especially those causing enzootic incoordination in horses and staggers in sheep (both of them dealt with under their respective headings)
- Functional diseases in toxic and metabolic diseases of the nervous system in which lesions have not yet been identified and that are caused mainly by poisons, especially plant materials; typical examples are poisoning by the fungi *Claviceps paspali, Diplodia* spp., *Acremonium lolii,* the grass *Phalaris aquatic,* the ferns *Zamia* and *Xanthorrhea* spp., and herbaceous plants such as *Kallstroemia, Vicia, Baccharis, Solanum, Aesculus,* and *Ficus* spp.
- Heat stress in lambs[3]
- Nutritional deficiency especially of thiamine, occurring naturally in horses poisoned by bracken and horsetail, and experimentally in pigs
- Developmental defects including congenital abnormalities and abiotrophic abnormalities that develop sometime after birth; examples are Brown Swiss weavers and Pietrain creeper pigs.

In many of these diseases, incoordination and paresis are a stage in the development of tetraplegia or paraplegia.

PARESIS AND PARALYSIS

The motor system comprises the following:

- Pyramidal tracts, which originate in the motor cortex
- Extrapyramidal system, which originates in the corpus striatum, red nucleus, vestibular nucleus, and roof of the midbrain
- Peripheral nerves, which originate in the ventral horn cells

The pyramidal tracts are of minor importance in hoofed animals (ungulates), reaching only to the fourth cervical segment. Accordingly, lesions of the motor cortex in farm animals do not produce any deficit of gait. There is also no paresis, although in an acute lesion weakness may be evident for the first day or two. If the lesion is unilateral, the paresis will be on the contralateral side. This is in marked contradistinction to the severe abnormalities of posture and gait that occur with lesions of the pons, medulla, and spinal cord.

The main motor nuclei in these animals are subcortical and comprise the extrapyramidal system, and most combined movements are controlled by nerve stimuli originating in the tectal nuclei, reticular nuclei, vestibular nuclei, and possibly red nuclei. The pyramidal and extrapyramidal tracts comprise the upper motor neurons, which reach to the ventral horn cells of the spinal cord, whose cells, together with their peripheral axons, form the lower motor neurons. Paralysis is a physiologic result in all cases of motor nerve injury, which if severe enough is expressed clinically. The type of paralysis is often indicative of the site of the lesion.

A lesion of the upper motor neuron causes the following:

- **Spasticity with loss of voluntary movement**
- **Increased tone of limb muscles**
- **Increased spinal reflexes**

The spasticity of an upper motor neuron lesion usually occurs with the affected limb in extension. These are all release phenomena resulting from liberation of spinal reflex arcs from higher control.

A lesion of the lower motor neuron causes:

- **Paresis or paralysis with loss of voluntary movement**
- **Decreased tone of the limb muscles**
- **Absence of spinal reflexes**
- **Wasting of the affected muscle (neurogenic atrophy)**

Because injuries to specific peripheral nerves are treated surgically, these are dealt with in surgical textbooks and are not repeated here.

A special form of paralysis is the **Schiff–Sherrington syndrome**, which is common in dogs but recorded rarely in large animals. It is caused by acute, severe compressive injury of the thoracolumbar spinal cord and manifested by extensor rigidity or hypertonia of the forelimbs and hypotonic paralysis of the hindlimbs. Neurons located in the lumbar spinal cord are responsible for the tonic inhibition of extensor muscle alpha motor neurons in the cervical intumescence. The cell bodies of these neurons are located in the ventral gray column from L1-L7, with a maximum population from L2-L4. Their axons ascend to the cervical intumescence. Acute severe lesions cranial to these neurons and caudal to the cervical intumescence will suddenly deprive the cervical intumescence neurons of this source of tonic inhibition, resulting in a release of these latter neurons. This results in extensor hypertonia observed in the thoracic limbs, which can function normally in the gait and postural reactions, except for the hypertonia.

The degree of paresis or paralysis needs to be defined. Paralysis is identified as an inability to make purposeful movements. Thus convulsive, uncontrolled movements as they occur in PEM may still fit a description of paralysis. Paresis, or weakness short of paralysis, can be classified into four categories:

- Animals that cannot rise or support themselves if helped up but can make purposeful movements in attempting to rise
- Animals that cannot rise but can support themselves if helped up
- Animals that can rise but are paretic and can move the limbs well and stumble only slightly on walking
- Animals that move with difficulty and have severe incoordination and stumbling.

Probably the most difficult decision in farm animal neurology is whether a patient's inability to move is because of a nervous or muscular deficit. For example, the horse recumbent because of exertional rhabdomyolysis often resembles a horse with an injured spinal cord. Examples of paresis and paralysis include the following:

- Focal inflammatory, neoplastic, traumatic lesions in the motor pathway. These lesions usually produce an asymmetric nervous deficit.
- Toxic and metabolic diseases of the nervous system in their most severe form, e.g., flaccid paralysis associated with tick bite (*Ixodes holocyclus, Ornithodoros* sp.), poisoning, botulism, and snakebite. Comparable tetanic paralyses include tetanus, lactation tetany of mares, and hypomagnesemic tetany of cows and calves. In contrast to inflammatory, neoplastic, and traumatic lesions in the motor pathway, toxic and metabolic lesions usually produce a symmetric nervous deficit.

Neurogenic Muscular Atrophy

Destruction of the lower motor neurons either within the vertebral canal or peripheral to it causes neurogenic atrophy. Whether or not the atrophy is visible depends on how many neurons and therefore how many muscle fibers are affected.

ALTERED SENSATION

Lesions of the sensory system are rarely diagnosed in animals, except for those affecting sight and the vestibular apparatus, because of the impossibility of measuring subjective responses.

Although animals must experience paresthesia, as in Aujeszky's disease (pseudorabies) in cattle and sheep, the animal's response of licking or scratching does not make it possible to decide whether the diagnosis should be paresthesia or pruritus. Lesions of the peripheral sensory neurons cause hypersensitivity or decreased sensitivity of the area supplied by the nerve. Lesions of the spinal cord may affect only motor or only sensory fiber tracts or both, or may be unilateral.

Although it is often difficult to decide whether failure to respond to a normally painful stimulus is caused by failure to perceive or inability to respond, certain tests may give valuable information. The test usually used is pricking the skin with a needle, or pinching the skin with a pair of forceps, and observing the reaction. In exceptional circumstances, light stroking may elicit an exaggerated response. The **"nibbling"** reaction stimulated by stroking the lumbar back of sheep affected with scrapie is a striking example of hypersensitivity.

In every test of sensitivity, it must be remembered that there is considerable variation between animals and in an individual animal from time to time, and much discretion must be exercised when assessing the response. In any animal, there are also cutaneous areas that are more sensitive than others. The face and the cranial cervical region are highly sensitive, the caudal cervical and shoulder regions less so, with sensitivity increasing over the caudal thorax and lumbar region and to a high degree on the perineum. The proximal parts of the limbs are much less sensitive than the distal parts and sensitivity is highest over the digits, particularly on the medial aspect.

Absence of a response to the application of a painful stimulus to the limbs (**absence of the withdrawal reflex**) indicates interruption of the reflex arc; absence of the reflex with persistence of central perception, as demonstrated by groaning or body movement such as looking at the site of stimulus application, indicates interruption of motor pathways and that central perception of pain persists. In the horse, the response can be much more subtle than in other species, and movements of the ears and eyelids are the best indicators of pain perception. Increased sensitivity is described as **hyperesthesia**, decreased as **hypoesthesia**, and complete absence of sensitivity is described as **anesthesia**. Special cutaneous reflexes include the anal reflex, in which spasmodic contraction of the anus occurs when it is touched, and the corneal reflex, in which there is closure of the eyelids on touching the cornea. The (cutaneous trunci) panniculus reflex is valuable in that the sensory pathways, detected by the prick of a pin, enter the cord at spinal cord segments T1-L3, but the motor pathways leave the cord only at spinal cord segments C8, T1, and T2. The quick twitch of the superficial cutaneous muscle along the whole back, which is the positive response (**panniculus reflex**), is quite unmistakable. Examination of the eye reflexes and hearing are discussed under the section Cranial Nerves (see later).

BLINDNESS

Blindness is manifested as a clinical abnormality by the animal walking into objects that it should avoid. Vision is a cerebral cortical function and is evaluated using the pupillary light reflex, the menace response, and the ability to navigate around a novel obstacle course.

The **pupillary light reflex** is present at birth in large animals but does not need an intact cerebral cortex. This is the reason why ruminants with thiamine-responsive polioencephalomalacia appear blind but have an intact pupillary light reflex; in contrast, ruminants with lead poisoning and a greater extent of cerebral dysfunction appear blind but have a depressed or absent pupillary light reflex. The pupillary light reflex measures the integrity of the retina, optic nerves and chiasm, and oculomotor and pretectal nuclei in the midbrain, and then to a descending motor pathway that includes the oculomotor nerve, ciliary ganglion, and constrictor pupillae muscle.

The **menace or blink response** is used to test the integrity of the entire visual pathway (retina, optic nerves, optic chiasm, optic tract, lateral geniculate nucleus, and internal capsule to the visual area in the cerebrum [occipital lobe]). The visual cortex processes the information and relays signals to the motor cortex. The descending motor pathway receives some input from the cerebellum and proceeds from the ipsilateral pons to the contralateral facial nerve nucleus in the medulla oblongata, and then to the facial nerve, and finally the orbicularis oculi muscle. A threatening gesture of the hand (or even better by the index finger in a pointing manner) toward the eye elicits immediate closure of the eyelids. The finger must come close enough to the eye without touching the tactile hairs of the eyelids or creating a wind that can be felt by the animal. Some stoic, depressed, or even excited animals may not respond to a menace reflex with closure of the eyelids; others may keep the eyelids partially or almost closed. It may be necessary to alert the patient to the risk of injury by touching the eyelids first. The menace response is a learned response that is absent in neonates. Most foals have a menace response by 9 days after birth and most calves by 5 to 7 days after birth. Group housing of neonatal calves appeared to facilitate faster learning of the menace response as a result of more visual threats.[4]

The most definitive test is to make the animal walk an **obstacle course** and place objects in front of it so that it must step over the objects easily. A similar procedure is the only way to test for **night blindness (nyctalopia)**. The area should be dimly lit, but the observer should be able to see the obstructions clearly. A decision that the animal is blind creates a need for examination of the visual pathways.

Central or Peripheral Blindness

Blindness may be central or peripheral. Animals with forebrain lesions are centrally blind, with depressed menace response in one or both eyes, whereas the pupillary light reflexes are usually intact. In peripheral blindness, such as hypovitaminosis A, the menace reflex is absent, and the pupillary light reflexes are also absent.

Blindness can be caused by lesions along the visual pathway, from the eye to the cerebral cortex:

- **Diseases of the orbit** include keratoconjunctivitis, hypopyon, cataract, panophthalmia, mixed ocular defects inherited in white Shorthorn and Jersey cattle, night blindness in Appaloosa horses, and sporadic cases of blindness caused by idiopathic retinal degenerative disease in cattle.
- **Diseases of the retina** include retinal dysplasia of goats, lenticular cataracts caused by poisoning with hygromycin in pigs, and congenital ocular malformations in calves after intrauterine infection with BVD virus (usually accompanied by cerebellar defects).
- **Diseases of the optic nerve and chiasma,** e.g., abscess of pituitary rete mirabile, constriction of optic nerve by diet deficient in vitamin A, tumor of pituitary gland, and injury to the optic nerve, especially in horses after rearing and falling backward. There is a sudden onset of unilateral or bilateral blindness with no ophthalmologic change until 3 to 4 weeks after the injury, when the optic disc becomes paler and less vascular.
- **Metabolic or ischemic lesions of the cerebral cortex** as in PEM, cerebral edema, and hydrocephalus.
- **Localized infectious or parasitic lesions** caused by abscesses or migrating larvae.
- **Functional blindness** in which there is complete, often temporary, apparent blindness in the absence of any physical lesions is seen. Causes are acetonemia, pregnancy toxemia, and acute carbohydrate indigestion (hyper D-lactatemia) of ruminants.
- **Specific poisonings** causing blindness include *F. mas* (male fern), *Cheilanthes* spp. (rock fern), and rape. *Stypandra* spp. cause a specific degeneration of the optic nerves. Lead poisoning in cattle can also cause blindness.

ABNORMALITIES OF THE AUTONOMIC NERVOUS SYSTEM

Lesions affecting the cranial parasympathetic outflow do so by involvement of the oculomotor, facial, vagus, and glossopharyngeal nerves or their nuclei. The effects produced are discussed in the Cranial Nerves section of Special examination of the Nervous System.

In general, the lesions cause abnormality of pupillary constriction, salivation, and involuntary muscular activity in the upper part of the alimentary and respiratory tracts. Lesions of the spinal sympathetic system interfere with normal function of the heart and alimentary tract. For the most part, affections of the autonomic nervous system are of minor importance in farm animals. Central lesions of the hypothalamus can cause abnormalities of heat exchange, manifested as neurogenic hyperthermia or hypothermia and obesity, but they are also of minor importance.

Some manifestations of autonomic disease are important. Autonomic imbalance

is usually described as the physiologic basis for spasmodic colic of horses; grass sickness of horses is characterized by degenerative lesions in the sympathetic ganglia; and involvement of the vagus nerve in traumatic reticuloperitonitis of cattle can lead to impaired forestomach and abomasal motility as well as the development of vagus indigestion.

Defects of sphincter control and motility of the bladder and rectum may also be of importance in the diagnosis of defects of sacral parasympathetic outflow and the spinal sympathetic system. The sacral segments of the spinal cord are the critical ones, and loss of their function will cause incontinence of urine and loss of rectal tone. The parasympathetic nerve supply to the bladder stimulates the detrusor muscle and relaxes the sphincter; the sympathetic nerve supply has the reverse function. A spinal cord lesion may cause loss of the parasympathetic control and result in urinary retention. Incontinence, if it occurs, does so from overflow. When the sympathetic control is removed, incontinence occurs but the bladder should empty. Similar disturbances of defecation occur. Both micturition and defecation are controlled by medullary and spinal centers, but some measure of control is regained even when the extrinsic nerve supply to the bladder and rectum is completely removed.

Special Examination of the Nervous System

Veterinarians commonly include several components of a neurologic examination in a complete clinical examination. Most often a diagnosis and differential diagnosis can be made from consideration of the history and the clinical findings. However, if the diagnosis is uncertain it may be necessary to conduct a complete neurologic examination, which may uncover additional clinical findings necessary to make a diagnosis and give a prognosis.

The accuracy of a clinical diagnosis of neurologic diseases in the horse is high. In a study of 210 horses in which a definitive pathologic diagnosis was confirmed, the overall accuracy of clinical diagnosis for all diseases was 0.95; the accuracy ranged from 0.79 to 1.00, the sensitivity varied from 0.73 to 0.95, and the specificity varied from 0.88 to 1.00 for individual disease categories. Some neurologic diseases are therefore underdiagnosed, whereas others are overdiagnosed. The use of careful and thorough clinical examinations and diagnostic techniques, combined with confirmed pathologic diagnoses, will result in more accurate diagnosis and therapy. Retrospective studies of series of ataxic horses, for example, will add to the body of knowledge and improve diagnosis.

NEUROLOGIC EXAMINATION

The primary aim of the neurologic examination is to confirm whether or not a neurologic abnormality exists and to determine the neuroanatomical location of the lesion. A clinicoanatomic diagnosis is necessary before one can develop a list of differential diagnoses and decide whether or not treatment is possible. The format for a precise practical examination procedure that is logical in sequence, easy to remember with practice, and emphasizes the need for an anatomic diagnosis is outlined later. The rationale for the sequence is that the examination starts from a distance to assess posture and mentation and then proceeds to a closer examination that may require placing the animal in stocks or a chute. The examination sequence is therefore suitable for minimally handled beef cattle, dairy cattle, horses, sheep, goats, and New World camelids. The results of the neurologic examination should be documented and not left to memory. There are many standard examination forms available that outline each step in the examination and provide for documentation of the results.

SIGNALMENT AND EPIDEMIOLOGY

The age, breed, sex, use, and value of the animal are all important considerations in the diagnosis and prognosis of neurologic disease. Some diseases occur more frequently under certain conditions, for example, lead poisoning in nursing beef calves turned out to pasture in the spring of the year. *Histophilus somni* meningoencephalitis is most common in feedlot cattle from 6 to 10 months of age, and hypovitaminosis A is most common in beef calves 6 to 8 months of age after grazing dry summer pastures. In the horse, there are several clearly defined diseases that affect the spinal cord including cervical stenotic myelopathy, degenerative myeloencephalopathy, protozoal myelitis, equine rhinopneumonitis myelopathy, rabies polioencephalomyelitis, and equine motor neuron disease. Some of these diseases have distinguishing epidemiologic characteristics that are useful in diagnosis and differential diagnosis. The neurologic examination of the newborn foal is fraught with hazards because of the different responses elicited from those in adults. The differences relate mostly to the temporary dysmetria of gait and exaggerated responses of reflexes.

HISTORY

Special attention should be given to the recording of an accurate history. The questioning of the owner should focus on the primary complaint and when it occurred and how it has changed over time (**the sign-time relationship**). The duration of signs; the mode of onset, particularly whether acute with later subsidence, or chronic with gradual onset; the progression of involvement; and the description of signs that occur only intermittently should be ascertained. When the disease is a herd problem, the morbidity and mortality rates and the method of spread may indicate an intoxication when all affected animals show signs within a very short period. Diseases associated with infectious agents may have an acute or chronic onset. Neoplastic diseases of the nervous system may begin abruptly but are often slowly progressive. For some diseases, such as epilepsy, consideration of the history may be the only way to make a diagnosis. Traumatic injuries have a sudden onset and then often stabilize or improve.

When obtaining a history of convulsive episodes, an estimate should be made of their duration and frequency. The pattern is also important and may be diagnostic, e.g., in salt poisoning in swine. The occurrence of pallor or cyanosis during the convulsion is particularly important in the differentiation of cardiac syncope and a convulsion originating in the nervous system.

HEAD

Behavior

The owner should be questioned about the animal's abnormal behavior, which can include bellowing, yawning, licking, mania, convulsions, aggressiveness, head-pressing, wandering, compulsive walking, and head-shaking. Head-shaking may be photic in origin and can be tested by the application of blindfolds, covering the eyes with a face mask, and observing the horse in total darkness outdoors. In one horse, head-shaking ceased with blindfolding or night darkness outdoors, and became less with the use of gray lenses. Outdoor behavior suggested efforts to avoid light.

Mental Status

Assessment of mental status is based on the animal's level of awareness or consciousness. Coma is a state of complete unresponsiveness to noxious stimuli. Other abnormal mental states include stupor, somnolence, deliriousness, lethargy, and depression. Animals may exhibit opisthotonus, either spontaneously or in response to stimulation (Fig. 14-1). Large animals that are recumbent because of spinal cord disease are usually bright and alert unless affected with complications, which may cause fever and anorexia. Mature beef cattle that are recumbent with a spinal cord lesion and not used to being handled may be quite aggressive and apprehensive.

Head Position and Coordination

Lesions of the vestibular system often result in a head tilt. Lesions of the cerebrum often result in deviation of the head and neck. In

cerebellar disease, there may be jerky movements of the head, which are exaggerated by increasing voluntary effort. These fine jerky movements of the head are called intention tremors. Animals with severe neck pain will hold their neck in a fixed position and be reluctant to move the head and neck. Head-shaking in horses has been associated with ear mite infestation, otitis externa, CN dysfunction, cervical injury, ocular disease, guttural pouch mycosis, dental periapical osteitis, and vasomotor rhinitis. However, idiopathic head-shaking in the horse is often associated with evidence of nasal irritation, sneezing and snorting, nasal discharge, coughing, and excessive lacrimation.

Cranial Nerves

Abnormalities of CN function assist in localizing a lesion near or within the brainstem.

Fig. 14-1 Abnormal mentation in Simmental calf with bacterial meningitis. The calf is exhibiting opisthotonus and is acting inappropriately for its surroundings.

Some of the information on CN dysfunction is presented in tabular form (Tables 14-1 through 14-6) in addition to the more detailed examination described here.

Olfactory Nerve (Cranial Nerve I)

Tests of smell are unsatisfactory in large animals because of their response to food by sight and sound.

Optic Nerve (Cranial Nerve II)

The only tests of visual acuity applicable in animals are testing the eye preservation (menace) reflex (provoking closure of the eyelids and withdrawal of the head by stabbing the finger at the eye) and by making the animal run a contrived obstacle course. Both tests are often difficult to interpret and must be performed in such a way that other senses are not used to determine the presence of the obstacles or threatened injury. In more intelligent species, a good test is to drop some light object, such as a handkerchief or feather, in front of the animal. It should gaze at the object while it is falling and continue to watch it on the ground. The same method can be applied to young ruminants, which demonstrate normal vision by following the examiner's moving hand at an age so early that they have not yet developed a menace reflex. Ophthalmoscopic examination is an integral part of an examination of the optic nerve.

Oculomotor Nerve (Cranial Nerve III)

This nerve supplies the pupilloconstrictor muscles of the iris and all the extrinsic

Table 14-1 Correlation between clinical findings and location of lesions in the nervous system of farm animals: abnormalities of mental state (behavior)

Principal sign	Secondary signs	Location of lesion	Example
Mania hysteria/ hyperexcitability	Continuous, leading to paralysis; aggression, convulsions	Cerebrum-limbic system	Peracute lead poisoning, rabies, encephalitis
	Intermittent, acetonuria, signs of hepatic insufficiency	Cerebrum-limbic system	Hypoglycemia, hypoxia
Coma (recumbency with no response to stimuli; dilated pupils)	Gradual development Hypothermia, peripheral vascular collapse. Clinicopathologic tests	Cerebral-brainstem reticular formation (ascending reticular activating system)	Hepatic insufficiency, uremia, toxemia, septicemia
	Sudden onset Normal temperature, pulse/heart rate slow to normal, nosebleed, skin laceration, bruising middle of forehead or poll	Cerebral-brainstem reticular formation (ascending reticular activating system)	Accidental, severe blunt trauma with edema, concussion, contusion of brain
Narcolepsy/catalepsy Uncontrollable sleep	With or without sudden loss of consciousness, intermittent falling caused by loss of voluntary motor function	Brainstem control of cerebral cortex	Inherited in Shetland ponies, American Miniature horses, and Suffolk horses
Compulsive walking and head-pressing, aggressive behavior, grinding of teeth.	Apparent blindness, nystagmus	Cerebral-visual cortex and limbic system	Increased intracranial pressure in polioencephalomalacia
No ataxia	Apparent blindness, no nystagmus, hepatic insufficiency shown on clinical pathology tests	Cerebral-visual cortex and limbic system	Hepatic insufficiency (i.e., ammonia intoxication; in pyrrolizidine poisoning)
Imbecility in neonate; lack of response to normal stimuli; can walk, stand	Blindness	Cerebral cortex absent; hydranencephaly	Intrauterine infection with Akabane or bovine virus diarrhea virus in calves

Table 14-2 Correlation between clinical findings and location of lesion in the nervous system of farm animals: involuntary movements

Principal sign	Secondary signs	Location of lesion	Example
Tremor (continuous repetitive movements of skeletal muscles)	Moderate tetany	No specific focal lesion Generalized disease, e.g., hypomyelinogenesis	Congenital tremor of Herefords Hypomyelinogenesis, shaker pigs, lambs with border disease
	Intention tremor, sensory ataxia	Cerebellum	Cerebellar hypoplasia
	With head rotation	Vestibular apparatus	Otitis media and interna Fracture of petrous temporal bone
Nystagmus	Usually with tetraparesis, impaired consciousness, abnormal pupils, opisthotonus, facial palsy, dysphagia	Cerebellopontine and midbrain areas	Injury, increased intracranial pressure, polioencephalomalacia, listeriosis
	Pendular nystagmus	No lesion	Benign sporadic occurrence in dairy cattle, inherited in Finnish Ayrshire bulls
	Independent episodes	Focus of irritation in cerebral cortex or thalamus, with spread of excitation	Idiopathic or traumatic epilepsy
Convulsions	Continuous, leading to paralysis	Cerebral cortex	Increased intracranial pressure, encephalitis
	Intermittent, related to periods of metabolic stress	Cerebral cortex	Hypomagnesemia (lactation tetany); hypoglycemia (e.g., of baby pigs)
Tenesmus (straining)	Later paralysis of anus, sometimes tail head	Caudal cord segments and cauda equina, stimulation of nerve cells, later paralysis	Rabies, subacute local meningitis
	Sexual precocity in male		
Compulsive rolling	Disturbance of balance, cannot stand, must lie on one side	Vestibular apparatus	Brain abscess, otitis media
	Nystagmus		

Table 14-3 Correlation between clinical findings and location of lesion in the nervous system of farm animals: abnormalities of posture

Principal sign	Secondary signs	Location of lesion	Example
Paresis (difficulty in rising, staggering gait, easily falling)	Persistent recumbency, muscle tone and reflexes variable depending on site of lesion	Loss of function in nervous tissue, e.g., spinal cord, may be upper or motor neuron lesion	Lymphosarcoma affecting spinal cord
	General loss of muscle tone including vascular, alimentary systems	Depression of synaptic or neuromuscular transmission for metabolic reasons or toxic reasons	Periparturient hypocalcemia, botulism, peracute coliform mastitis, tick paralysis
Flaccid paralysis			
(1) Pelvic limbs only	Thoracic normal	Tissue destruction, myelomalacia at lumbosacral cord segments L4 to end osteomyelitis, fracture	Paralytic rabies
	Pelvic limbs flaccid, no tone, or reflexes, no anal reflex, urinary incontinence straining initially		Spinal cord local meningitis, vertebral body
	Thoracic limbs normal	Cord damage at thoracolumbar cord segments T3-L3	Spinal cord local meningitis as previously mentioned, damage by vertebral fracture, lymphosarcoma
	Pelvic limbs normal tone and reflexes, anal reflex normal		
	No withdrawal reflex caudally		
(2) Thoracic and pelvic limbs	Flaccid paralysis, normal tone and reflexes hindlimbs	Cord damage at cervicothoracic segments C6-T2	Fracture of vertebra lymphosarcoma, abscess
	Absent tone and reflexes in front limbs	Cord damage at upper cervical segments C1-C5	Injury while running or falling, abscess or lymphosarcoma
	Atrophy only in front		
	No withdrawal reflex caudally		
	Intact perineal reflex		
	Flaccid paralysis all four legs and neck		
	Unable to lift head off ground		
	Normal tone and reflexes all legs		
	Pain perception persists		
	No withdrawal reflex caudally		
Spastic paralysis (permanent, no variation, all four limbs in extension, increased tone, exaggerated reflexes, opisthotonus)	Cranial nerve deficits trigeminal to hypoglossal	Medulla, pons and midbrain	Abscess, listeriosis
	Loss of central perception of pain		
	Depression		

Table 14-3 Correlation between clinical findings and location of lesion in the nervous system of farm animals: abnormalities of posture–cont'd

Principal sign	Secondary signs	Location of lesion	Example
Tremor	Tremor (fine or coarse; no convulsions)	Red nucleus and reticular apparatus and midbrain/basal ganglia area tracts	Congenital disease of calves, e.g., hypomyelinogenesis, neuraxial edema
Tetany (all four limbs extended, opisthotonus)	Intense hyperesthesia, prolapse third eyelid	Decreased synaptic resistance generally	Tetanus
Tetanu (variable intensity modifiable by treatment)	Exaggerated response to all external stimuli, i.e., hyperesthesia	Increased neuromuscular transmission	Hypomagnesemia
Paralysis of anus	No anal or perineal reflex May be straining	Damage to spinal cord at segments S1-S3	Injury or local meningitis, early rabies
Paralysis of tail	Flaccid tail with anesthesia	Injury to caudal segments	Injury or local meningitis, early rabies
Opisthotonus	With spastic paralysis, tremor, nystagmus, blindness Part of generalized tetanic state or convulsion	Cerebrum, cerebellum and midbrain Neuromuscular transmission defect, tetanus, hypomagnesemia	Polioencephalomalacia, trauma Tetanus
Falling to one side	Mostly with circling Also with deviation of tail	No detectable lesion in spinal cord	*Xanthorrhea hastile* poisoning

Table 14-4 Correlation between clinical findings and location of lesion in the nervous system of farm animals: abnormalities of gait

Principal sign	Secondary signs	Location of lesion	Example
Circling			
(1) Rotation of the head	Nystagmus, circles, muscle weakness, falls easily, may roll, other cranial nerves affected	Vestibular nucleus	Brain abscess, listeriosis
	Nystagmus, walks in circles, falls occasionally, animal strong Falls easily if blindfolded, sometimes facial paralysis	Inner ear (vestibular canals), cranial nerve VII, facial nerve	Otitis media, otitis interna, fracture petrous temporal bone (horse)
(2) Deviation of the head	Deviation of head and gaze, compulsive walking, depression Can walk straight Balance may be normal	Cerebrum	Brain abscess in calf (infection from dehorning or umbilicus)
	Unable to walk straight Facial paralysis, other cranial nerve deficits, head may be rotated	Medulla	Listeriosis
Cerebellar ataxia	Exaggerated strength and distance of movement, direction wrong Hypermetria Incoordination because of exaggerated movement No paresis	Cerebellum	Inherited cerebellar hypoplasia in all species, especially Arabian horses; *Claviceps paspali* poisoning; Gomen disease a probable plant poisoning; destruction by a virus, especially BVD in cattle; hematoma in the fourth ventricle causes cerebellar displacement Idiopathic cerebellar degeneration in adult cattle
Sensory ataxia	No loss of movement or strength but timing movement wrong, legs get crossed, feet badly placed when pivoting	Damage to sensory tracts in spinal cord	Cervical cord lesion, thoracolumbar if just pelvic limb
Sensorimotor ataxia	Weakness of movement, e.g., scuffing toes, knuckling, incomplete flexion, extension causes wobbly, wandering gait, falls down easily, difficulty in rising	Moderate lesion to spinal cord tracts	Plant poisonings, e.g., sorghum Cervical vertebral compression of spinal cord Degenerative myelopathy

BVD, bovine viral diarrhea.

Table 14-5 Correlation between clinical findings and location of lesion in the nervous system of farm animals: abnormalities of the visual system

Principal sign	Secondary signs	Location of lesion	Example
Blindness (bumps into objects)	Pupillary dilatation No pupillary light reflex No menace reflex	Optic nerve (examine fundus of eye)	Vitamin A deficiency Pituitary rete mirabile abscess Congenital retinal dysplasia of goats
Peripheral blindness or night blindness		Retina	Nutritional deficiency of vitamin A Inherited defect of Appaloosa foals
Central blindness	Pupil normal size Pupillary light reflexes normal	Cerebral cortex	Polioencephalomalacia, lead poisoning
Abnormal dilatation of pupils (mydriasis)	Absence of pupillary light reflex Can see and does not bump into objects	Motor path of oculomotor nerve	Snakebite, atropine poisoning, milk fever
	Absent pupillary light reflex No vision Retinal damage on ophthalmoscopic examination	Retinal lesion	Toxoplasmosis, trauma, ophthalmitis
	Absent pupillary light reflex No vision Retina normal	Optic nerve atrophy and fibrosis	Avitaminosis A in cattle
Abnormal constriction of pupil (miosis)	Diarrhea, dyspnea	Failure to activate acetylcholine	Organophosphate poisoning
	Blindness, coma, semicoma, spastic paralysis	Diffuse lesion	Polioencephalomalacia, acute lead poisoning
Horner's syndrome Drooping upper eyelid, miosis, enophthalmos	Hemilateral sweating and temperature rise side of face and upper neck Unilateral exophthalmus; nasal obstruction	Damage to cranial thoracic and cervical sympathetic trunk	Mediastinal tumor Guttural pouch mycosis Neoplastic space-occupying lesions of the cranium involving the periorbit; perivascular injection around jugular vein or normal intravenous injection of xylazine hydrochloride in normal horses, melanoma at the thoracic inlet in a horse
Nystagmus	See Table 14-2		
Abnormal position of eyeball and eyelids	Dorsomedial deviation of eyeball and eyelid	Trochlear (cranial nerve IV) Facial (cranial nerve VII)	Polioencephalomalacia Listeriosis
	Ventrolateral fixation	Oculomotor (cranial nerve III)	
	Protrusion and medial deviation	Abducent (cranial nerve VI)	Abscess/tumor, e.g., bovine viral leukosis
No palpebral reflex		Deficit sensory branch of cranial nerve V	Trauma
Absence of menace response		Facial nerve (provided vision is present)	Listeriosis
Absence of pupillary light reflex		Oculomotor (provided vision is present)	

Table 14-6 Correlation between clinical findings and location of lesion in the nervous system of farm animals: disturbances of prehension, chewing, or swallowing

Principal sign	Secondary signs	Location of lesion	Example
Inability to prehend or inability to chew	Facial (nasal septal) hypalgesia	Sensory branch of trigeminal (cranial nerve V) dysfunction	Poisoning by *Phalaris aquatica* in cattle Local medullary lesion
	Inappropriate movements of tongue	Hypoglossal (cranial nerve XII) nerve dysfunction	Poisoning by *P. aquatica* in cattle Listeriosis, local medullary lesion
	Inappropriate movements of lips	Facial (cranial nerve VII) nerve dysfunction	Traumatic injury to petrous temporal bone, otitis media and interna, listeriosis, guttural pouch mycosis
	Inadequate chewing movements of jaw	Motor branch of the trigeminal (cranial nerve V) nerve dysfunction	Poisoning by *P. aquatica* in cattle, listeriosis
Inability to swallow (in absence of physical foreign body; in pharyngeal paresis or paralysis)	Regurgitation through nose and mouth, inhalation into lungs causing aspiration pneumonia Inappropriate swallowing movements	Glossopharyngeal (cranial nerve IX) nerve dysfunction. Also vagus (cranial nerve X) Nuclei in medulla globus pallidus and substantia nigra	Abscess or tumor adjacent to nerve Listeriosis, abscess in medulla Poisoning by *Centaurea* sp.

muscles of the eyeball except the dorsal oblique, the lateral rectus, and the retractor muscles. Loss of function of the nerve results in pupillary dilatation and defective pupillary constriction when the light intensity is increased, abnormal position (ventrolateral deviation) or defective movement of the eyeballs, and palpebral ptosis.

The pupillary light reflex is best tested by shining a bright point source of light into the eye, which causes constriction of the iris of that eye (direct pupillary reflex). Constriction of the opposite eye (consensual pupillary light reflex) will also occur. The consensual light reflex may be used to localize lesions of the optic pathways.

Examination of the menace reflex (eye preservation reflex to a menace) and the results of the pupillary light reflex can be used to distinguish between blindness caused by a lesion in the cerebral cortex (central blindness) and that caused by lesions in the optic nerve or other peripheral parts of the optic pathways (peripheral blindness).

As examples, in PEM (central blindness) the menace reflex is absent, but the pupillary light reflex is present. In the ocular form of hypovitaminosis A (peripheral blindness) in cattle, the menace reflex is also absent, the pupils are widely dilated, and the pupillary light reflex is absent. In PEM, the optic nerve, oculomotor nucleus, and oculomotor nerve are usually intact but the visual cortex is not; in hypovitaminosis A, the optic nerve is usually degenerate, which interferes with both the menace and pupillary light reflexes.

Testing of ocular movements can be performed by moving the hand about in front of the face. In paralysis of the oculomotor nerve, there may also be deviation from the normal ocular axes and rotation of the eyeball. There will be an absence of the normal horizontal nystagmus reaction with a medial jerk of the eyeball in response to quick passive movement of the head. Failure to jerk laterally indicates a defect of the abducens nerve.

Trochlear Nerve (Cranial Nerve IV)

This nerve supplies only the dorsal oblique muscle of the eye so that external movements and position of the eyeball are abnormal (dorsolateral fixation) when the nerve is injured. This is common in PEM in cattle, resulting in a dorsomedial fixation of the eyeball. In other words, the medial angle of the pupil is displaced dorsally when the head is held in normal extension.

Trigeminal Nerve (Cranial Nerve V)

The sensory part of the trigeminal nerve supplies sensory fibers to the face and can be examined by testing the palpebral reflex and the sensitivity of the face. The motor part of the nerve supplies the muscles of mastication and observation of the act of chewing may reveal abnormal jaw movements and asymmetry of muscle contractions. There may also be atrophy of the muscles, which is best observed when the lesion is unilateral.

Abducent Nerve (Cranial Nerve VI)

Because the abducent nerve supplies motor fibers to the retractor and lateral rectus muscles of the eyeball, injury to the nerve may result in protrusion and medial deviation of the globe. This is not readily observable clinically. An inherited exophthalmos and strabismus occurs in Jersey cattle.

Facial Nerve (Cranial Nerve VII)

The facial nerve supplies motor fibers for movement of the ears, eyelids, lips, and nostrils, in addition to the motor pathways of the menace, palpebral, and corneal reflexes. The symmetry and posture of the ears, eyelids, and lips are the best criteria for assessing the function of this nerve. Ability to move the muscles in question can be determined by creating a noise or stabbing a finger at the eye. Absence of the eye preservation reflex may be caused by facial nerve paralysis or blindness. Facial paralysis is evidenced by ipsilateral drooping of the ear, ptosis of the upper eyelid, drooping of the lips, and pulling of the philtrum to the unaffected side. There may also be drooling of saliva from the commissures of the lips, and in some cases a small amount of feed may remain in the cheeks of the affected side.

The common causes of damage to the nerve are fracture of the petrous temporal bone, guttural pouch mycosis, and damage to the peripheral nerve at the mandible. A common accompaniment is injury to the vestibular nerve or center. A diagnosis of central, compared with peripheral, nerve involvement can be made by identifying involvement of adjacent structures in the medulla oblongata. Signs such as depression, weakness, and a head tilt would result, and are frequently present in ruminants and New World camelids with listeriosis.

Vestibulocochlear Nerve (Cranial Nerve VIII)

The cochlear part of the vestibulocochlear nerve is not easily tested by simple clinical examination, but failure to respond to sudden sharp sounds, created out of sight and without creating air currents, suggests deafness. The cochlear portion can be tested electronically (the brainstem auditory evoked response, or BAER, test) to diagnose a lesion of the auditory nerve, eliminating the possibility of a central brain lesion. Abnormalities of balance and carriage of the head (rotation around the long axis and not deviation laterally) accompany lesions of the vestibular part of the vestibulocochlear nerve, and nystagmus is usually present.

In severe cases, rotation of the head is extreme, the animal is unable to stand and lies in lateral recumbency; moving to achieve this posture is compulsive and forceful. There is no loss of strength. In some species there is a relatively common occurrence of paralysis of the facial and the vestibular nerves as a result of otitis interna and otitis media. This does occur in the horse but is less common than traumatic injury to the skull as a result of falling.

Pendular nystagmus should not be mistaken as a sign of serious neurologic disease. It is characterized by oscillations of the eyeball that are always the same speed and amplitude and appear in response to a visual stimulus, e.g., a flashing light. Pendular nystagmus is observed most frequently in Holstein Friesian cattle (prevalence of 0.51% in 2932 Holstein Friesian and Jersey cows), is not accompanied by other signs, and there is no detectable histologic lesion. A familial relationship was observed in Ayrshire bulls in Finland.

Glossopharyngeal Nerve (Cranial Nerve IX) and Vagus Nerve (Cranial Nerve X)

The glossopharyngeal nerve is sensory from the pharynx and larynx, and the vagus nerve is motor to these structures. Dysfunction of these nerves is usually accompanied by paralysis of these organs with signs of dysphagia or inability to swallow, regurgitation through the nostrils, abnormality of the voice, and interference with respiration.

Because of the additional role of the vagus nerve in supplying nerve fibers to the upper alimentary tract, loss of vagal nerve function will lead to paralysis of the pharynx and esophagus. Parasympathetic nerve fibers to the stomach are also carried in the vagus, and damage to them could cause hypomotility of that organ. The principal clinical finding in vagus nerve injury is laryngeal and pharyngeal paralysis.

Spinal Accessory Nerve (Cranial Nerve Xi)

Damage to this nerve is extremely rare and the effects are not documented. Based on its anatomic distribution, loss of function of this nerve could be expected to lead to paralysis of the trapezius, brachiocephalic, and sternocephalic muscles and lack of resistance to lifting the head.

Hypoglossal Nerve (Cranial Nerve XII)

As the motor supply to the tongue, the function of this nerve can be best examined by observing the motor activity of the tongue. There may be protrusion and deviation or fibrillation of the organ, which all result in difficulty in prehending food and drinking water. The most obvious abnormality is the ease with which the tongue can be pulled out. The animal also has difficulty in getting it back into its normal position in the mouth, although diffuse cerebral disease can also produce this clinical sign. In lesions of some duration, there may be obvious unilateral atrophy.

POSTURE AND GAIT

The examiner evaluates posture and gait to give a general assessment of brainstem, spinal cord, and peripheral nerve and muscle function. Evaluation of posture and gait consists of determining which limbs are abnormal and looking for evidence of lameness suggesting a musculoskeletal gait abnormality. Weakness and ataxia are the essential components of gait abnormality. Each limb is examined for evidence of these abnormalities. This is done while the animal is standing still, walking, trotting, turning tightly (pivoting), and backing up. To detect subtle asymmetry in the length of the stride, the observer should walk parallel to or behind the animal, step for step. If possible, the gait should also be evaluated while the animal is walking up and down a slope or walking with the head and neck held extended, while blindfolded and while running free in an enclosure.

The best observations are made when the animal is running free, preferably at a fast gait, to avoid abnormalities resulting from being led. Also, slight abnormalities such as a high-stepping gait, slight incoordination of movement, errors of placement of feet, stumbling, and failure to flex joints properly are all better observed in a free animal.

Weakness or paresis is evident when an animal drags its limbs, has worn hooves, or has a low arc to the swing phase of the stride. When an animal bears weight on a weak limb, the limb often trembles and the animal may even collapse on that limb because of lack of support. While circling, walking on a slope, and walking with the head held elevated, an animal frequently will stumble on a weak limb and knuckle over on the fetlock.

The presence of weakness in the limbs of horses or cattle can be determined by pulling the tail while the animal is walking forward. A weak animal is easily pulled to the side and put off stride. While the animal is circling, the examiner can pull on the lead rope and tail simultaneously to assess strength. Ease in pulling the animal to the side occurs because of weakness caused by lesions of the descending upper motor neuron pathway, the ventral horn gray matter level with the limb, or peripheral nerves or muscle. With lower motor neuron lesions, the weakness is often so marked that it is easy to pull an animal to the side while it is standing or walking. In contrast, a weak animal with a lesion of the upper motor neuron pathways will often fix the limb in extension, reflexly, when pulled to one side. It resists the pull and appears strong.

Severe weakness in all four limbs, but with no ataxia and spasticity, suggests neuromuscular disease. Obvious weakness in only one limb is suggestive of a peripheral nerve or muscle lesion in that limb.

Ataxia is an unconscious, general proprioceptive deficit causing poor coordination when moving the limbs and the body. It results in swaying from side to side of the pelvis, trunk, and sometimes the entire body. It may also appear as a weaving of the affected limb during the swing phase. This often results in abducted or abducted foot placement, crossing of the limbs, or stepping on the opposite foot, especially when the animal is circling or turning tightly. Circumduction of the outside limbs when turning and circling is also considered a proprioceptive deficiency. Walking an animal on a slope, with the head held elevated, often exaggerates ataxia, particularly in the pelvic limbs. When a weak and ataxic animal is turned sharply in circles, it leaves the affected limb in one place while pivoting around it. An ataxic gait may be most pronounced when an animal is moving freely, at a trot or canter, especially when attempting to stop. This is when the limbs may be wildly abducted or adducted. Proprioceptive deficits are caused by lesions affecting the general proprioceptive sensory pathways, which relay information on limb and body position to the cerebellum (unconscious proprioception) and to the thalamus and cerebral cortex (conscious proprioception).

Knuckling the flexed foot while the animal stands on the dorsum to determine how long the animal leaves the foot in this state before returning it to a normal position is a test for conscious proprioception in dogs and cats. The test has not been useful in horses and adult cattle but is useful in sheep, goats, New World camelids, and calves. Depressed animals will often allow the foot to rest on the dorsum for prolonged periods. Crossing the limbs and observing how long the animal maintains a cross-legged stance has been used to test conscious proprioception.

Hypermetria is used to describe a lack of direction and increased range of movement, and is seen as an overreaching of the limbs with excessive joint movement. Hypermetria without paresis is characteristic of spinocerebellar and cerebellar disease.

Hypometria is seen as stiff or spastic movement of the limbs with little flexion of the joints, particularly the carpal and tarsal joints. This generally is indicative of increased extensor tone and of a lesion affecting the descending motor or ascending spinocerebellar pathways to that limb. A hypometric gait, particularly in the thoracic limbs, is best seen when the animal is backed up or when it is maneuvered on a slope with the head held elevated. The thoracic limbs may move almost without flexing.

Dysmetria is a term that incorporates both hypermetria and hypometria. Animals with severe cerebellar lesions may have a high-stepping gait but have limited movement of the distal limb joints, especially in thoracic limbs.

The degree of weakness, ataxia, hypometria, and hypermetria should be graded for each limb. The types of gait abnormalities and the degree of weakness reflect various nervous and musculoskeletal lesions. Generally, with focal, particularly compressive, lesions in the cervical spinal cord or brainstem, neurologic signs are one grade more severe in the pelvic limbs than in the thoracic limbs. Thus with a mild, focal, cervical spinal cord lesion, there may be more abnormality in the pelvic limbs with no signs in the thoracic limbs. The anatomic diagnosis in such cases may be a thoracolumbar, cervical, or diffuse spinal cord lesion.

A moderate or severe abnormality in the pelvic limbs, and none in the thoracic limbs, is consistent with a thoracolumbar spinal cord lesion. With a mild and a severe change in the thoracic and the pelvic limb gaits, respectively, one must consider a severe thoracolumbar lesion plus a mild cervical lesion, or a diffuse spinal cord disease.

Lesions involving the brachial intumescence (spinal cord segments C6-T2) with involvement of the gray matter supplying the thoracic limbs, and diffuse spinal cord lesions may both result in severe gait abnormality in the thoracic limbs and the pelvic limbs.

A severely abnormal gait in the thoracic limbs, with normal pelvic limbs, indicates lower motor neuron involvement of the thoracic limbs; a lesion is most likely to be present in the ventral gray columns at spinal cord segments C6-T2 or thoracic limb peripheral nerves of muscle.

Gait abnormalities can occur in all four limbs, with lesions affecting the white matter in the caudal brainstem, when head signs, such as CN deficits, are used to define the site of the lesion. Lesions affecting the cerebrum cause no change in gait or posture.

It is important for clinicians to recognize that a poor level of agreement exists between skilled and experienced observers of gait abnormalities in horses.[5] There is also poor agreement between pathology and clinical signs. The level of agreement is particularly poor when gait abnormalities are subtle. Consequently, there is an important need to develop a set of objective parameters that quantify the severity of ataxia in horses, with appropriate repeatability.

NECK AND FORELIMBS

If a gait abnormality was evident in the thoracic limbs and there was no evidence of brain involvement, then examination of the neck and forelimbs can confirm involvement of the spinal cord, peripheral nerves (spinal cord segments C1-T2), or thoracic limb muscles. The neck and forelimbs are examined for evidence of gross skeletal defects, asymmetry of the neck, and muscle atrophy. The neck should be manipulated from side to side and up and down to detect any evidence of resistance or pain. Localized unilateral sweating of the neck and cranial shoulder is evidence of **Horner's syndrome**, in which

there are varying degrees of ptosis; prolapse of the third eyelid; miosis; enophthalmos; and increased temperature of the face, neck, and shoulder. The syndrome is associated with lesions affecting the descending sympathetic fibers in the white matter of the spinal cord or gray matter in the cranial thoracic segments, thoracocervical sympathetic trunk, cervical vagosympathetic trunk, or cranial cervical ganglion and its preganglionic and postganglionic fibers.

Sensory perception from the neck and forelimbs is assessed using a painful stimulus such as a blunt needle or forceps. The local responses as well as the cerebral responses are noted when the skin over the shoulders and down the limbs is pricked.

Gait deficits are evaluated by making the horse or halter-broken ruminant perform a series of movements. Such exercises should include walking and trotting in a straight line, in large circles, in tight circles, backing on a level ground and on a slight slope, walking and trotting over curbs or low obstacles, walking in straight lines and circles, and walking on a slope with the head held elevated. The sway reaction for the thoracic limb is assessed by pushing against the shoulders and forcing the animal first to resist and then to take a step laterally. This can be done while the animal is standing still and walking forward. Pulling the tail and lead rope laterally at the same time will assess the strength on each side of the body. Making the animal turn in a tight circle by pulling the lead rope and tail at the same time will indicate strength; an adult horse should be able to pull the examiner around and should not pivot on a limb or be pulled to the side. Pressing down with the fingers on the withers of a normal animal causes some arching, followed by resistance to the downward pressure. An animal with weakness in the thoracic limbs may not be able to resist this pressure by fixing its vertebral column but will arch its back more than normal and often buckle in the thoracic limbs.

In smaller farm animal species, other postural reactions can be performed. These include wheelbarrowing and the hopping response test. The spinal reflexes are assumed to be intact in animals that are ambulating normally.

If a large mature horse, cow, or pig has a gait abnormality, it is very rare to cast the animal to assess the spinal reflexes. However, spinal reflexes are usually examined in calves, sheep, and goats.

A recumbent animal that can use its thoracic limbs to sit up in the dog-sitting position may have a lesion caudal to spinal cord segment T2. If a recumbent animal cannot attain a dog-sitting position, the lesion may be in the cervical spinal cord. In lambs aged between 4 and 10 weeks with thoracic vertebral body abscesses extending into the epidural space causing spinal cord compression, the thoracic limbs are normal and the lambs frequently adopt a dog-sitting position and move themselves around using the thoracic limbs only. Lambs with a cervical spinal cord lesion are unable to maintain sternal recumbency and have paresis of all four limbs.

However, mature cattle with the downer cow syndrome secondary to hypocalcemia may be unable to use both the thoracic and pelvic limbs. If only the head, but not the neck, can be raised off the ground, there may be a severe cranial cervical lesion. With a severe caudal cervical lesion, the head and neck can usually be raised off the ground but thoracic limb function is decreased and the animal is unable to maintain sternal recumbency.

Assessment of limb function is done by manipulating each limb separately, in its free state, for muscle tone and sensory and motor activity. A limb that has been lain on for some time cannot be properly evaluated because there will be poor tone from the compression. A flaccid limb, with no motor activity, indicates a lower motor lesion to that limb. A severe upper motor neuron lesion to the thoracic limbs causes decreased, or absent, voluntary effort, but there is commonly normal or increased muscle tone in the limbs. This is caused by release of the lower motor neuron, which reflexly maintains normal muscle tone from the calming influence of the descending upper motor neuron pathways.

The tone of skeletal muscle may be examined by passively flexing and extending the limbs and moving the neck from side to side and up and down. Increased muscle tone, spasticity, or tetany may be so great that the limb cannot be flexed without considerable effort. If the spastic-extended limb does begin to flex but the resistance remains, this is known as lead-pipe rigidity, which is seen in tetanus. If after beginning to flex an extended spastic limb the resistance suddenly disappears ("clasp-knife release"), then this suggests an upper motor neuron lesion, which occurs in spastic paresis in cattle.

Flaccidity, or decreased muscle tone, indicates the presence of a lower motor neuron lesion with interruption of the spinal reflex arc.

Localized atrophy of muscles may be myogenic or neurogenic and the difference can be determined only by electromyography (EMG), a technique not well suited to large-animal practice. If the atrophic muscle corresponds to the distribution of a peripheral nerve, then it is usually assumed that the atrophy is neurogenic. In addition, neurogenic atrophy is usually rapid (will be clinically obvious in a few days) and much more marked than either disuse or myogenic atrophy.

Spinal Reflexes of the Thoracic Limbs

Spinal reflexes of the thoracic limbs include the flexor reflex, the biceps reflex, and the triceps reflex. The flexor reflex is tested by stimulation of the skin of the distal limb and observing for flexion of the fetlock, knee, elbow, and shoulder. The reflex arc involves sensory fibers in the median and ulnar nerves, spinal cord segments C6-T2, and motor fibers in the axillary, musculocutaneous, median, and ulnar nerves. Lesions cranial to spinal cord segment C6 may release this reflex from the calming effect of the upper motor neuron pathways and cause an exaggerated reflex with rapid flexion of the limb, and the limb may remain flexed for some time. A spinal reflex may be intact without cerebral perception. Cerebral responses to the flexor reflex include changes in the facial expression, head movement toward the examiner, and vocalization. Conscious perception of the stimulus will be intact only as long as the afferent fibers in the median and ulnar nerves, the dorsal gray columns at spinal cord segments C6-T2, and the ascending sensory pathways in the cervical spinal cord and brainstem are intact.

The laryngeal adductory reflex is of special interest in the examination of ataxic horses. In normal horses, a slap on the saddle region just caudal to the withers causes a flickering adductory movement of the contralateral arytenoid cartilage that is visible by an endoscope. Reflex muscle contraction can be palpated on the dorsolateral surfaces of the larynx. The reflex is absent when there is damage to afferent tracts up the spinal cord, when there is damage to the recurrent laryngeal nerves, and in tense or frightened horses. Elicitation of the reflex is called the **slap test**.

TRUNK AND HINDLIMBS

If examination of the posture, gait, head, neck, or thoracic limbs reveals evidence of a lesion, then an attempt should be made to explain any further signs found during examination of the trunk and hindlimbs that could have been caused by the lesion. If there are only signs in the trunk and hindlimbs, then the lesion(s) must be either between spinal cord segments T2 and S2 or in the trunk and pelvic limb nerves or muscles. It must be remembered that a subtle neurologic gait in the pelvic limbs may be anywhere between the midsacral spinal cord and the rostral brainstem.

The trunk and hindlimbs are observed and palpated for malformations and asymmetry. Diffuse or localized sweating, the result of epinephrine release and sympathetic denervation, is often present in horses affected with a severe spinal cord injury.

Gentle pricking of the skin over the trunk and over the lateral aspects of the body wall on both sides, including on either side of the thoracolumbar vertebral column, will test-stimulate the cutaneous trunci reflex. The sensory stimulus travels to the spinal cord in thoracolumbar spinal nerves at the level of the site of stimulation. These impulses

are transmitted up the spinal cord to spinal cord segments C8-T1, where the lateral thoracic nerve is stimulated, causing contraction of the cutaneous trunci muscle, which is seen as a flicking of the skin over the trunk. Lesions anywhere along this pathway will result in suppression or absence of this reflex caudal to the site of the lesion. Degrees of hypalgesia and analgesia have been detected caudal to the sites of thoracolumbar spinal cord lesions, especially if they are severe. In mature cattle with fractured thoracolumbar vertebrae associated with traumatic injury or vertebral body abscesses in calves, the site of the lesion may be able to be localized with this reflex. Sensory perception of pinpricking the trunk and hindlimbs may also be absent caudal to the lesion.

The sway reaction for the pelvic limbs involves pushing against the pelvis and pulling on the tail with the animal standing still and walking forward. An animal that is weak in the pelvic limbs will be easily pulled and pushed laterally, especially while walking. Proprioceptive deficits can be observed as overabduction and crossing of the limbs when a step is taken to the side.

Pinching and pressing down on the thoracolumbar or sacral paravertebral muscles with the fingers causes a normal animal to extend slightly, then fix, the thoracolumbar vertebral column. It also resists the ventral motion and usually does not flex the thoracic or pelvic limbs. A weak animal usually is not able to resist the pressure by fixing the vertebral column; thus it overextends the back and begins to buckle in the pelvic limbs.

In the recumbent animal, examination of the pelvic limbs includes the pelvic limb spinal reflexes, the degree of voluntary effort, and the muscle tone present. Observing the animal attempting to rise on its own or following some coaxing will help to assess the pelvic limbs. The **flexor spinal reflex** is performed by pricking the skin and observing the flexion of the limb; central perception of the painful stimulus is also noted. The afferent and efferent pathways for this reflex are in the sciatic nerve and involve spinal cord segments L5-S3.

The **patellar reflex** is evaluated by placing the animal in lateral recumbency and supporting the limb in a partly flexed position. The intermediate patellar ligament (horses) or patellar ligament (ruminants, pigs, and New World camelids) is then tapped with a heavy metal plexor. This results in extension of the stifle joint. The sensory and motor fibers for this reflex are in the femoral nerve, and the spinal cord segments are L4 and L5. The patellar reflex is hyperactive in newborn farm animals. The gastrocnemius reflex and the cranial tibial reflex are not evaluated because they cannot be reliably induced.

The spinal cord of the calf has more control of basic physical functions than in humans, dogs, and horses. For example, calves are able to retain control of the pelvic limb in spite of experimentally induced lesions that cause hemiplegia in dogs and humans. Also, transection of the spinothalamic tract in the calf cord does not produce an area of hypalgesia or analgesia on the contralateral side as such a lesion would do in a human.

Skin sensation of the pelvic limbs should be assessed independently from reflex activity. The femoral nerve is sensory to the skin of the medial thigh region, the peroneal nerve to the dorsal tarsus and metatarsus, and the tibial nerve to the plantar surface of the metatarsus.

TAIL AND ANUS

Tail tone is evaluated by lifting the tail and noting the resistance to movement. A flaccid tail, with no voluntary movement, is indicative of a lesion of the sacrococcygeal spinal cord segments, nerves, or muscles. Decreased tone in the tail can be detected with severe spinal cord lesions cranial to the coccygeal segment.

The perineal reflex is elicited by lightly pricking the skin of the perineum and observing reflex contraction of the anal sphincter and clamping down of the tail. The sensory fibers are contained within the perineal branches of the pudendal nerve (spinal cord segments S1-S3). Contraction of the anal sphincter is mediated by the caudal rectal branch of the pudendal nerve, and tail flexion is mediated by the sacral and coccygeal segments and nerves (spinal cord segments S1-coccyx). An animal with a flaccid tail and anus, caused by a lower motor neuron lesion, will not have an anal or tail reflex. However, it may still have normal sensation from the anus and tail provided that the sensory nerves and spinal cord and brainstem white matter nociceptive pathways are intact.

Observation of defecation and urination movements and postures contributes to knowledge of the state of the cauda equina. Thus neuritis of the cauda equina is characterized by flaccid paralysis and analgesia of the tail, anus and perineum, rectum, and bladder. There is no paresis or paralysis of the hindlimbs unless lumbosacral segments of the cord are damaged.

PALPATION OF THE BONY ENCASEMENT OF THE CENTRAL NERVOUS SYSTEM

Palpable or visible abnormalities of the cranium or spinal column are not commonly encountered in diseases of the nervous system, but this examination should not be neglected. There may be displacement, abnormal configuration, or pain on deep palpation. These abnormalities are much more readily palpable in the vertebral column and if vertebrae are fractured. Abnormal rigidity or flexibility of the vertebral column, such as occurs in atlantooccipital malformations in Arabian horses and cattle, may also be detectable by manipulation.

COLLECTION AND EXAMINATION OF CEREBROSPINAL FLUID

The collection and laboratory analysis of CSF from farm animals with clinical evidence of nervous system disease can provide useful diagnostic and prognostic information. A case series involving 102 cattle highlighted the clinical utility of CSF analysis in the antemortem diagnoses of nervous diseases.[6]

CSF is formed mostly from the choroid plexuses of the lateral, third, and fourth ventricles by the ultrafiltration of plasma and the active transport of selected substances across the blood-brain barrier; as such CSF should be regarded as a modified ultrafiltrate of plasma. A small amount of CSF is formed from the ependymal lining of the ventricular system, the pia arachnoid and meningeal blood vessels, and the central canal of the spinal cord. The rate of CSF turnover is approximately 1% per minute; accordingly, it takes many minutes for systemic electrolyte or acid-base changes (such as an increase in plasma magnesium concentration in hypomagnesemic beef cattle) to result in detectable and clinically relevant changes in CSF concentrations. CSF in the ventricular system flows caudally and diffuses out of the lateral recess in the fourth ventricle to circulate around the brain and spinal cord. The presence of CSF in the subarachnoid space separates the brain and spinal cord from the bony cranium and vertebral column, which reduces trauma to the underlying delicate nervous tissue. CSF flows within the subarachnoid space of leptomeninges, and it is primarily in this location that CSF equilibrates with the extracellular fluid (ECF) compartment of CNS parenchyma.[6] It also helps regulate intracranial pressure, maintains electrolyte and acid-base homeostasis, serves as an intracerebral transport system for neurotransmitters and hormones, and has excretory functions with the removal of products of cerebral metabolism. CSF analysis therefore provides a clinically valuable insight into diseases of the CNS.

Collection of Cerebrospinal Fluid

CSF can be collected from the **lumbosacral cistern** with sedation (horses) or restraint (ruminants) and the **atlantooccipital cistern (cisterna magna)** using injectable general anesthesia. For collection it is necessary to puncture the subarachnoid space in either the lumbosacral space or cisterna magna. Although there is no substantial difference between the composition of lumbosacral or cisternal CSF samples unless there is a compressive lesion of the spinal cord, the general policy is to sample as close to the lesion as possible, with the exception that

atlantooccipital sampling should not be attempted in animals suspected to have increased intracranial pressure. CSF should be collected into a sterile tube and there is no need to add an anticoagulant, even in samples visibly contaminated with blood. Cytology should be performed as soon as possible after collection (ideally within 15 minutes) because the cells rapidly degenerate after collection. The reason for this rapid degeneration appears to be associated with the low oncotic pressure in CSF; the addition of autologous serum to make a 11% serum solution permitted storage of bovine CSF samples for 24 hours at 4°C before cytologic examination was performed with no loss in cell integrity.[7] The addition of serum to CSF in a ratio that provides an approximate final serum solution of approximately 11% should therefore be considered if there is an unavoidable delay before cytologic examination can be performed.[8]

Collection From the Lumbosacral Cistern

The lumbosacral site is preferred because general anesthesia is not required. CSF can be collected from the lumbosacral cistern with relative ease provided that adequate restraint can be achieved and the anatomic landmarks can be identified. It can be collected from the standing or recumbent animal. If recumbent, the animal should be placed in sternal recumbency with hips flexed and the pelvic limbs extended alongside the abdomen. This widens the lumbosacral space to permit correct placement of the spinal needle. Ultrasonographic guidance has been described but is rarely needed.[9]

The site for collection is the midpoint of the lumbosacral space, which can be identified as the midline depression between the last palpable dorsal lumbar spine (L6 in cattle, goats, and horses; L6 or L7 in sheep and pigs; L7 in New World camelids) and the first palpable sacral dorsal spine (usually S2). In well-conditioned animals, these landmarks cannot always be identified; in which case the site is identified as the midpoint of a line connecting the caudal aspect of the tuber coxae. The site is clipped, surgically prepared, and 1 to 2 mL of local anesthetic is administered subcutaneously. Sterile surgical gloves should be worn. Hypodermic spinal needles with stylettes are recommended because ordinary needles commonly plug with tissue. The length and gauge of needle depends on the size of the animal, but at least 15-cm (6-inch) 18-gauge needles are needed for adult horses and cattle. These needles can bend considerably with animal movement, requiring the use of at least an 18-gauge needle; very tall horses may need a 20-cm needle because the depth needed maybe 16 to 18 cm. The following guide is recommended (Table 14-7).

Provided the animal is well restrained and care is exercised in introducing the needle, little difficulty should be encountered. For collection from the lumbosacral space the needle is slowly advanced perpendicular or up to 15 degrees caudal to perpendicular to the plane of the vertebral column. The needle must be introduced in a perfectly vertical position relative to the plane of the animal's vertebral column because of the danger of entering one of the lateral blood vessels in the vertebral canal. Changes in tissue resistance can be felt as the needle point passes sequentially through the subcutaneous tissue and interarcuate ligament; then there is a sudden "pop" caused by the loss of resistance as the needle point penetrates the ligamentum flavum into the epidural space. Once the needle point has penetrated the dorsal subarachnoid space, CSF will well up in the needle hub within 2 to 3 seconds. Failure to appreciate the changes in resistance as the needle moves down may result in puncture of the conus medullaris, which may elicit an immediate pain response and some discomfort. Movement of the pelvic limbs may dislodge the needle point, with the risk of causing local trauma and hemorrhage in the leptomeninges, which results in blood in the sample. Repeated CSF taps of the lumbosacral space may make it more difficult to obtain an adequate sample volume because of fibrosis of epidural tissue.

Table 14-7 Needle length gauge for lumbosacral cerebrospinal fluid collection

Species and body weight	Length (cm) and gauge of needle
Lambs < 30 kg	2.5 and 20
Ewes 40–80 kg	4.0 and 20
Rams > 80 kg	5.0 and 20
Calves < 100 kg	4.0 and 20
Calves 100–200 kg	5.0 and 18
Cattle > 200 kg	10.0–15.0 and 18

Careful aspiration with a syringe attached to the needle held between the thumb and index finger is usually required to obtain a sample of 2 to 3 mL, which is sufficient for laboratory analysis. This can be facilitated by firmly resting the forearms and wrists on the animal's back. Failure to obtain fluid is usually caused by incorrect direction of the needle, in which the case the bony landmarks of the lumbosacral space (depression) must be rechecked and, with the needle correctly realigned, the procedure repeated. Occasional small rotations of the needle to change the direction of the bevel can be successful in obtaining CSF, particularly in smaller animals.

In animals with a vertebral body abscess and neurologic disease confined to the hindlimbs, CSF may be difficult to obtain from the lumbosacral space because flow is occluded. In these circumstances, if a sample is obtained, the CSF protein may be increased as a result of stagnation of CSF distal to the lesion with exudation or transudation of protein from the lesion (**Froin's syndrome**).

Collection From the Atlantooccipital Cistern (Cisterna Magna)

This site is preferred for intracranial lesions because the fluid is produced in the subarachnoid space and flows caudally down the spinal cord. However, this site is rarely used because of the inherent risk of needle penetration of the brainstem. Xylazine at 0.20 mg/kg body weight (BW) intramuscularly is effective in providing adequate sedation and analgesia for this procedure in cattle. A general anesthetic (such as combined intravenous administration of xylazine and ketamine) is recommended for horses. Ultrasonographic guidance has been described but is rarely needed.

The site is prepared as with the lumbosacral cistern. Ventriflexion of the head and neck of cattle enlarges the space of the cisterna magna and allows easy entry using a styletted spinal needle inserted at a point created by the transection of the transverse line of the cranial rim of the wing of the atlas and the dorsal midline. The needle is advanced carefully and steadily, and the tip is directed rostrally toward the symphysis of the lower jaw. The needle point goes through the skin, ligamentum nuchae, and leptomeninges. In most mature cattle with a BW over 500 kg, a 20-gauge, 10-cm (4-inch) spinal needle will enter the cisterna magna at 5 to 7 cm after going through the ligamentum nuchae, which provides some increased resistance. A 20-gauge 3.8-cm (1.5-inch) needle can be used in sheep, goats, foals, and neonatal calves. The entrance to the cisterna magna is at a depth of approximately 4 to 6 cm in adult horses and 1.5 to 2.5 cm in neonatal foals. Once at the lower range of the anticipated depth to enter the cisterna magna, the spinal needle is advanced 1 to 2 mm at a time. When the needle point punctures the leptomeninges, the animal may move its head slightly. At that point the needle is advanced only 1 to 2 mm and the stylette is then removed. If the end of the needle is in the cisterna magna, CSF will flow out of the needle freely and the manometer can be attached and the pressure measured.

Cerebrospinal Fluid Pressure

CSF pressure can be determined by the use of a manometer attached to the spinal needle. Normal CSF pressures of the cisterna magna in cattle and xylazine/ketamine-anesthetized horses range from 5 to 15 cm H_2O (unknown reference point) and 28 ± 4 cm H_2O (referenced to the right atrium), respectively. When the fluid system is properly connected, occlusion of both jugular veins causes a marked rise in CSF pressure; this is called

Queckenstedt's test. This test involves bilateral jugular vein compression, which results in a sudden increase in intracranial subarachnoid pressure that is transmitted to the cranial subarachnoid space. The resultant CSF pressure wave is transmitted to the lumbar area (when obtaining CSF from the lumbosacral space) in the absence of an obstruction in the spinal subarachnoid space, resulting in an increased flow of CSF.

Variations in CSF pressure are not of much use in clinical diagnosis except in hypovitaminosis A, and measurement of CSF pressure is only indicated in animals with signs of cerebral disease (abnormal mentation) that may have cerebral edema. Care is needed in interpreting results because the pressure is greatly affected by voluntary movement such as tenesmus. CSF pressure is increased in a number of diseases, including PEM, bacterial meningitis, and hypovitaminosis A, reflecting the presence of increased intracranial pressure. Xylazine given intravenously causes a decrease in intracranial pressure in healthy conscious horses. Intracranial pressure is increased in anesthetized horses when their head is placed lower than their heart because of an increase in the hydrostatic pressure gradient.[10] Epidural pressure of cattle changes with change in position from standing to lateral recumbency to dorsal recumbency, and epidural pressure is positive in laterally recumbent animals.

Analysis of Cerebrospinal Fluid

Analysis of CSF has greater diagnostic value than hematology in animals with nervous system disease. CSF can be examined for the presence of protein, cells, and bacteria. The white blood cell count in normal animals is usually less than 5 cells/μL.[11] An increase in the CSF leukocyte count above 5 cells/μL is termed a pleocytosis and is categorized as mild (6 to 49 cells/μL), moderate (50 to 200 cells/μL), or marked (>200 cells/μL). The differential white cell count comprises mostly lymphocytes and monocytes (mononuclear cells predominate); there are no erythrocytes in the CSF of healthy animals with an atraumatic CSF tap. Cytologic examination of CSF is usually done after a Cytospin preparation that carefully concentrates the cells without destroying their architecture. This is needed because the cell count in CSF is usually very low. With bacterial infections of the nervous system, the CSF concentration of protein will be increased and the white blood cell count increased up to 2000 cells/μL with more than 70% neutrophils. A neutrophilic pleocytosis is considered 95% to 100% indicative of an inflammatory process within the CNS. Samples that show visible turbidity usually contain large numbers of cells (>500 cells/μL) and a great deal of protein.

The CSF glucose concentration is usually 60% to 80% of serum glucose concentration; this steady-state value reflects facilitated transport across the blood-brain barrier, absence of binding proteins for glucose in CSF, and nervous tissue metabolism of glucose. However, sudden changes in plasma glucose concentrations are not immediately reflected in CSF glucose concentrations, because CSF turns over at around 1% per minute. Typically, a lag time of up to 3 hours is needed for CSF glucose concentration to be in equilibrium with plasma glucose concentrations. Therefore hyperglycemia from the stress of handling and restraint may not be reflected by an increased CSF glucose concentration.

In cattle, protein concentrations range from 23 to 60 mg/dL, sodium concentrations from 132 to 144 mmol/L, potassium 2.7 to 3.2 mmol/L, magnesium 1.8 to 2.1 mEq/L, and glucose concentrations 37 to 51 mg/dL. In the horse, the reference values for CSF are similar. Neonatal foals under 3 weeks of age have higher CSF protein concentrations than do adult horses. Glucose concentrations peak in the first 48 hours after birth and then decrease to adult values by the second week of life. Concentrations of sodium and potassium are not affected by age and are similar to values reported for adult horses and ponies. In sheep, protein concentrations range from 12 to 60 mg/dL and glucose concentrations from 38 to 63 mg/dL.

Cytokine concentrations in CSF may have prognostic value,[11] and the cytokine gene expression in nucleated cells in CSF may have clinical utility in the diagnosis of specific nervous diseases.[13] The presence of one or more eosinophils in CSF is extremely unusual and should be assumed to indicate the presence of aberrant parasite migration or fungal encephalitis. Theoretically, the CSF glucose concentration will be decreased and CSF lactate concentration will be increased in animals with bacterial meningitis because of bacterial metabolism, but these are unreliable signs and usually do not provide additional information to that provided by determination of CSF leukocyte and protein concentrations. Bacteria may also be cultured from the CSF.

The creatine kinase and lactate dehydrogenase activities in CSF have been examined as an aid in the differentiation of some neurologic diseases. However, creatine kinase activity is considered to be unreliable in the horse; contamination of the sample with epidural fat and dura may increase CSF creatine kinase activity. In contrast, CSF creatine kinase activity >19.5 U/L provided an excellent prognostic test of nonrecovery in sheep with Listeriosis.[12] Insufficient information is available to evaluate the clinical utility of CSF lactate dehydrogenase activity in large animals.

Blood contamination of CSF can make interpretation difficult. A formula has been developed that "corrects" the CSF values for the degree of blood contamination, based on the red blood cell count (RBC) in CSF (RBC_{CSF}) and blood (RBC_{blood}), in which the corrected value for substance X in CSF ($X_{corrected}$, where X is a concentration or activity) is derived from the measured value of X in CSF (X_{CSF}) and blood (X_{blood}) and applying the following formula:

$$X_{corrected} = X_{CSF} - (X_{blood} \times RBC_{CSF} / RBC_{blood}).$$

Calculation of a "corrected" value rarely provides additional insight into the CSF analysis and is not commonly practiced in large animals. Xanthochromia is a slight yellow tinge to CSF that indicates previous erythrocyte lysis or more commonly increased protein concentration. A foamy appearance to the CSF is also suggestive of increased protein concentration.

Protein fractionation of CSF is not routinely performed because it requires sensitive electrophoresis methodology or species-specific radial immunodiffusion assays. Albumin (ALB) concentration in CSF can also be measured using an immunologic technique based on the detection of albumin–antialbumin immune complexes by nephelometry.[7] Calculation of the **albumin quotient** and **IgG index** may be informative in specific neurologic diseases. Theoretically, these calculations can differentiate four blood-brain permeability patterns, normal blood-brain barrier permeability (normal albumin quotient and IgG index), intrathecal IgG production with normal blood-brain barrier permeability (normal albumin quotient and increased IgG index), increased blood-brain barrier permeability without intrathecal IgG production (increased albumin quotient and normal IgG index), and increased blood-brain barrier permeability with intrathecal production of IgG (increased albumin quotient and increased IgG index). The albumin quotient is calculated from the albumin concentration in CSF (ALB_{CSF}) and serum (ALB_{serum}), in which:

$$Albumin\ Quotient = (ALB_{CSF}) \times 100 / (ALB_{serum}).$$

The normal range for albumin quotient in the adult horse is 0.6 to 2.2 for atlantooccipital CSF samples and 0.7 to 2.3 for lumbosacral CSF samples, but the mean is 0.4 to 0.5 in cattle and adult llamas. Because CSF protein is most often derived by disturbance of the blood-brain barrier and inflammation (resulting in an increased CSF albumin concentration), an increased CSF protein concentration is usually accompanied by an increased albumin quotient.

In animals suspected to have increased immunoglobulin production in the CNS (a rare occurrence, and almost always accompanied by disturbance of the blood-brain barrier), the IgG index can be calculated from the IgG concentration in CSF (IgG_{CSF}) and serum (IgG_{serum}), and the albumin

concentration in CSF (ALB_{CSF}) and serum (ALB_{serum}), in which:

$$IgG\ Index = (IgG_{CSF}/(IgG_{serum}) \times (ALB_{serum}/ALB_{CSF}/).$$

An IgG index of more than 0.3 is suspected to indicate intrathecal IgG production in the adult horse. This formula corrects the CSF IgG concentration for an increased permeability of the blood-brain barrier; therefore, theoretically it provides a more sensitive method for detecting local production of IgG within the CNS. Calculating the albumin quotient and IgG index is expensive and rarely provides additional information to that provided by CSF protein concentration alone, and for this reason is not commonly performed in large animals.

When antigen-specific titers are measured, two modified CSF indices, the **Goldmann–Witmer coefficient** (***C*-value**) and the **antibody index** (**AI**), can be calculated to distinguish intrathecal versus passively acquired antibodies in the CSF.[14,15] The *C*-value is calculated as

$$C\text{-}value = (IgG_{serum} \times reciprocal\ CSF\ titer)/(IgG_{CSF} \times reciprocal\ serum\ titer).$$

The AI is calculated as the ratio of the specific antibody quotient to the albumin quotient, in which

$$AI = (\{reciprocal\ CSF\ titer\}/\{reciprocal\ serum\ titer\})/(\{CSF\ albumin\ concentration\}/\{serum\ albumin\ concentration\}).$$

The **urine dipstick protein test** provides a useful on-farm assessment of CSF protein concentration and is underutilized in clinical practice. Most dipsticks use the following gradations of trace (<25 mg/dL), 1+ (28–75 mg/dL), 2+ (115–240 mg/dL), and 3+ (470–590 mg/dL), and a study of dog CSF samples indicated that all dogs with a urine dipstick protein of 2+ or greater had increased CSF protein concentration.[16] Similar studies do not appear to have been conducted in large animals.

The **Pandy test** also provides a useful on-farm assessment of CSF protein concentration. The basis for the test is that proteins (globulin and albumin) are precipitated by a saturated solution of phenol in water. The Pandy test uses a 10% solution of carbolic acid crystals dissolved in water (providing a saturated aqueous solution of phenol); the solution is termed Pandy's solution. One milliliter of Pandy's solution is placed in a glass tube and one drop (approximately 0.05 mL) of CSF is carefully layered on top. A turbid appearance at the interface signifies the presence of elevated concentrations of globulin or albumin in the CSF and is regarded as a positive Pandy's reaction (usually a total protein concentration greater than approximately 50 mg/dL). A variant of the test has the sample thoroughly mixed and the degree of turbidity ranked from 1+ (faint turbidity) to 4+ (dense milk-colored precipitate). A negative Pandy's reaction shows no turbidity or precipitate, and this is the expected result in normal CSF samples. A positive control (4+) can be run at the same time by adding a drop of serum or plasma to 1 mL of Pandy's solution. Because Pandy's solution contains phenol, clinicians should wear gloves and protective eyewear when handling the solution, and dispose of used reagents appropriately.

In summary, collection and analysis of CSF from the lumbosacral region provides a practical, safe, and informative diagnostic tool in conscious large animals with neurologic disease. Analysis of CSF in animals with CNS disease has greater diagnostic value than analysis of the leukon or serum biochemical analysis. Routine assessment of CSF should include total protein concentration (including the semiquantitative Pandy test and urine dipstick measurement), erythrocyte count, leukocyte count, and leukocyte differential count. Other analytical procedures on CSF can be performed in specific diseases related to the nervous system.

EXAMINATION OF THE NERVOUS SYSTEM WITH SERUM BIOCHEMICAL ANALYSIS

Arterial Plasma Ammonia Concentration

In animals suspected of having hepatic encephalopathy, measurement of the arterial plasma ammonia concentration provides a clinically useful diagnostic test and a means of monitoring the response to treatment. In monogastrics, ammonia is produced by bacterial degradation of amines, amino acids, and purines in the gastrointestinal tract, by the action of bacterial and intestinal urease on urea in the gastrointestinal tract, and by the catabolism of glutamine by enterocytes. In ruminants, ammonia is derived predominantly from bacterial metabolism in the rumen and catabolism of amino acids in tissue. Absorbed ammonia is normally converted to urea by the liver and to glutamine by the liver, skeletal muscle, and brain. In the presence of hepatic dysfunction, ammonia is inadequately metabolized, resulting in high plasma ammonia concentrations. Ammonia is a direct neurotoxin that alters inhibitory and excitatory neurotransmission in the brain.

Hyperammonemia can be used as a specific indicator of hepatic dysfunction. Normal values for arterial plasma ammonia concentration are less than 29 µmol/L in adult cattle but may reach higher values in the immediate periparturient period. Arterial values are higher than venous values and are preferred for analysis.

Blood gas analysis and serum electrolyte determination should be routinely undertaken in animals with clinical signs of encephalopathy to rule out metabolic causes of cerebral dysfunction.

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EXAMINATION OF THE NERVOUS SYSTEM WITH IMAGING TECHNIQUES

Radiography

Examination of the bony skeleton of the head and vertebral column to detect abnormalities that are affecting the nervous system of large animals is commonly used in referral centers. Conventional diagnostic radiography remains the best method for the initial evaluation of trauma to the brain and spinal cord, but usually the trauma needs to have displaced bone for the lesion to be readily visible on a radiograph. Lesions that can be identified on plain radiographs include fractured, luxated, or subluxated vertebra; intervertebral disk prolapse; discospondylitis; osteomyelitis; and neoplasia.[1] The injection of contrast media into the CSF system (**myelography**) is used for the detection of spinal cord compression but is not often performed in large animals because spinal cord depression surgery is rarely undertaken and because sensitivity and specificity estimates are low depending on criteria used for interpretation.[2] In cases of peripheral nerve injury the radiograph of the appropriate limb may reveal the presence of a fracture or space-occupying lesion that has caused dysfunction of the peripheral nerve.

Radiography has been used to diagnose lesions of the tympanic bullae in cattle (otitis interna) characterized by thickening of the bulla wall, increased soft tissue opacity within the bulla, and osteolysis of the bulla wall and trabeculations.[3] Radiography is not as sensitive as computed tomography (CT) for the diagnosis of otitis media, however, because CT provides more detailed information regarding the bony structures of the middle ear[4] and is more sensitive and specific than radiography in the diagnosis of otitis media in calves.[3]

Computed Tomography

CT of the skull has several advantages over radiography because structures are viewed in cross section without superimposition. The use of contrast agents and development of computer software and technology that permit rapid acquisition times and three-dimensional reconstruction allows a large amount of information to be obtained from a CT examination. Numerous diseases of the head of the horse, including those of the brain and cervical spine, can be diagnosed using this technique, but the limiting factors are the weight of the patient (a custom-designed table is required for adult horses and cattle), accessibility for large animals, and the need for general anesthesia.

CT provides an excellent image of skeletal cranial defects and soft tissue defects that differ considerably from surrounding tissue. CT has been used for the antemortem diagnosis of many conditions in foals, horses, and cattle, including cerebral abscess, porencephaly, meningoencephalocele, pituitary adenoma, cervical stenotic myelopathy, spinal cord rupture, and otitis interna/media, and has been used to guide brain biopsy for in vivo diagnosis of an intracranial mass.[4-7] CT provides less contrast resolution than magnetic resonance imaging (MRI), but CT provides better spatial resolution (i.e., is more able to differentiate fine anatomic features such as bone trabeculae), is more widely available, and has a shorter scan acquisition time. In a case series of 57 cases, CT was a useful diagnostic test in horses with abnormal mentation or a history of trauma followed by a period of unconsciousness. In contrast, CT did not provide clinically helpful information in horses with seizures.[8]

Magnetic Resonance Imaging

MRI scanning uses nuclear magnetic resonance to create cross-sectional images based on the magnetic properties of tissues. In general, MRI provides an excellent image of soft tissue defects and is considered superior to CT for intracranial and intraspinal lesions because MRI provides a high contrast between soft tissues and better anatomic detail. MRI can be performed in standing sedated horses; however, these MRI units (typically 0.25 T) produce low-resolution images that may not have sufficient detail to be diagnostic for many nervous diseases. Higher resolution images are produced by more expensive magnets (typically 1.0–3.0 T) that require the patient be immobile. The limiting factors for MRI use are therefore cost (MRI is more expensive than CT), the weight of the patient, accessibility for large animals, and the need for general anesthesia for higher resolution images (usually MRI has a longer imaging time than CT). Other challenges specific to MRI are that the environment provides considerable challenges for the monitoring of anesthesia and the placement of limbs to minimize postanesthetic myopathy/neuropathy syndrome, particularly in horses.[9]

MRI has been used for the antemortem diagnosis of a number of neurologic conditions in foals and horses, including brain abscess, hydrocephalus, nigropallidal encephalomalacia,[10] cerebellar abiotrophy in Arabian horses,[11] cervical stenotic myelopathy,[2] and peripheral nerve sheath tumor (PNST) in the tongue.[12] MRI has also been used to diagnose PEM and cerebellar hypoplasia in calves[13] and PEM, leukoencephalomalacia, and porencephaly and demyelination in sheep and goats.[14] More studies are required documenting the clinical superiority of MRI versus other diagnostic modalities. For instance, MRI can differentiate horses with cervical stenotic myelopathy (CSM) and cervical vertebral stenosis from healthy horses and horses with other causes for ataxia; however, MRI cannot accurately localize the site of cord compression.[2] MRI will be more widely used in the diagnosis of nervous diseases, particularly intracranial and cervical spinal cord disease, as equipment and acquisition costs decrease.

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Ultrasonography

Ultrasonography of the cricoarytenoideus lateralis muscle has been used as part of the examination of horses with suspected laryngeal hemiplegia and compared with endoscopic findings obtained at rest and during exercise. An 8.4-MHz curvilinear transducer was applied over the larynx and four acoustic windows evaluated. Subjectively assessed increased echogenicity of this muscle had a sensitivity of 94.6% and a specificity of 94.5% for detecting laryngeal hemiplegia.[1] The reported advantages of ultrasonography are that it is widely available, noninvasive, and depicts a real-time view of the tissues.

The supraspinous ligament has been evaluated in horses with and without back pathology using ultrasonography. Linear and sector array transducers (5–10 MHz) were used to obtain longitudinal and cross-sectional views of the supraspinous ligament, and lesions were identified and categorized. All 39 horses studied had at least one site of supraspinous ligament desmitis, and there was no association between desmitis lesions and clinical signs of pain that could be localized to this region.[2]

Ultrasonography has been used to diagnose syringohydromyelia and segmental hypoplasia of the lumbar spinal cord in a 4-day-old Holstein Friesian calf that had been unable to stand since birth. The calf was placed in right lateral recumbency, and lumbosacral flexion was induced to enable widening of ultrasound windows. Diagnostic images of the lumbar spinal cord were obtained in sagittal and transverse orientations at the lumbosacral junction (L6-S1), as well as the proximal lumbar intervertebral junctions up to L2-L3, using a 6- to 10-MHz linear transducer.[3]

An ultrasound imaging technique of the tympanic bullae has been developed for the diagnosis of otitis media in calves.[4] A 7.5-MHz linear probe is applied to the base of the ear without the use of coupling gel and with the calf in a standing position. The probe is applied ventral to the base of the ear and caudal to the mandible. Abnormalities detected included anechoic to hyperechoic content; trabeculae lysis; and thinning, deformation, and rupture of the bulla wall. In calves, ultrasonography has also been used to identify the femoral nerve in calves to assist in the diagnosis of spastic paresis cases that involve the quadriceps muscle (such as in Belgian Blue cattle with a cranially directed hyperextension of the limb) instead of the more common form of spastic paresis that involves the gastrocnemius muscle and a caudally directed hyperextension of the hindlimb.[5,6] Placement of a 5-MHz curved linear array transducer over the dorsal paravertebral space between the fifth and sixth lumbar transverse processes provided the best view of the femoral nerve and permitted selective blocking of the femoral nerve using 4% procaine solution.

ENDOSCOPY (RHINOLARYNGOSCOPY)

Endoscopy (rhinolaryngoscopy) is now a routine technique for the examination of horses with suspected laryngeal hemiplegia, which is a distal axonopathy of the left recurrent laryngeal nerve.

Endoscopic examination of the epidural and subarachnoid space from the atlantooccipital space to the eighth cervical nerve has been performed safely in healthy adult horses.[7] The procedure was performed under general anesthesia. The technique may have clinical utility in the diagnosis of cervical vertebral stenotic myelopathy because physical constraints do not currently permit imaging of the caudal cervical vertebral column by MRI or CT.

Endoscopy has also been used to examine the anatomic structures in the sacrococcygeal area of adult cattle. Cows were restrained and sedated with xylazine (0.03 mg/kg, intravenously). A lidocaine epidural was administered and a flexible endoscope (outside diameter, 2.3 mm) introduced through an introducer set and a small amount of air introduced. The procedure permitted visualization of blood vessels, connective tissue, fat, nerves, and the spinal dura mater.[8]

OPHTHALMOSCOPY

Ophthalmoscopy for the examination of the structures of the eye is important in the diagnosis of diseases affecting the optic nerve such as in vitamin A deficiency and the optic disc edema (papilledema) associated with diffuse cerebral edema.

ELECTROMYOGRAPHY

Electromyographic needle examination is a technique that records the electrical activity generated by single muscle fibers and the summated electrical activity of muscle fibers in individual motor units. The technique involves inserting a recording needle into the muscle of interest and recording the resultant EMG. Typically, animals are unsedated and restrained in stocks or a chute. An abnormal EMG signals include short-duration and low-amplitude motor unit action potentials, which indicate diseased muscle fibers of early or incomplete reinnervation after denervation. Other abnormalities include the presence of fibrillation potentials, positive sharp waves, and complex repetitive discharges that occur when the skeletal cell membrane becomes unstable because of denervation or myopathy.

EMG provides a more practical diagnostic test than electroencephalography (EEG) and provides a sensitive indicator of neurologic dysfunction and assists in the neuroanatomic localization of the lesion.[8] It is especially useful for evaluating peripheral nerve injury and diagnosing hyperkalemic periodic paresis in horses and should be helpful in additional studies on calving-associated paralysis and other peripheral nerve injuries in cattle. EMG can discriminate between lower motor neuron and myogenic disorders, and **nerve conduction studies** can differentiate axonal loss from demyelination. In addition, repetitive stimulation can provide information regarding neuromuscular transmission. Reference values for motor nerve conduction velocity have been developed for calves and, as expected, conduction velocities are related to the nerve fiber diameter.[10]

Somatosensory evoked potentials of the trigeminal complex using the infraorbital nerve have been used in horses to assist in the diagnosis of idiopathic head-shaking. An electrical surface stimulus is applied at a set stimulus rate but variable stimulus currents to a focal area of the buccal mucosa. Recording electrodes placed along the sensory pathway of the trigeminal complex detect the presence or absence of **sensory nerve action potentials** (SNAPs) and nerve conduction velocity.[11] The threshold current required to trigger a SNAP provides clinically useful information about the sensitivity of the anatomic location to stimuli.

EMG has been coupled with transcranial magnetic stimulation to induce magnetic **motor evoked potentials** in the horse. This provides a useful noninvasive evaluation of cervical spinal cord dysfunction in horses with radiologic abnormalities of the cervical vertebrae by detecting the presence of a neuropathy involving the descending motor tracts. However, EMG does not provide information on upper motor neurons; therefore it is not useful in the clinical evaluation of horses suspected to have hindlimb neurologic deficits caused by cervical spinal cord disease.[9]

ELECTROENCEPHALOGRAPHY

EEG has not been used to any significant degree in large animals. It requires sophisticated equipment, a quiet dim environment free from electrical interference, and a quiet patient that has minimal muscular activity. Because of the difficulty in obtaining quality recordings in a conscious large animal, it is preferred that the animal is sedated or anesthetized for the recording, which confounds interpretation of the EEG pattern depending on the anesthetic protocol. Thorough and repeated observations of simultaneously recorded EEG and video may facilitate interpretation of the EEG,[12,13] but the clinical utility of EEG remains uncertain in large animals exhibiting nervous signs consistent with an intracranial lesion. Therefore EEG has been primarily used in large animals as an antemortem or research tool, and its use will probably remain as a complementary test to other neurologic examinations and diagnostic tests at referral institutions.

Recommendations have been made to standardize EEG techniques for animals; these typically involve meticulous preparation of the recording sites on the scalp, and placement of electrodes over the left and right frontal areas, the left and right occipital areas, and the vertex area, and a reference electrode is placed behind the tip of the nose. The addition of other recording sites increases the ability to localize a focal lesion.[12] Neurologic disease is associated with changes in EEG frequency or amplitude, or both, and frequency changes are a more reliable indicator of disease. In general, focal EEG abnormalities indicate a focal lesion in the cortex, whereas diffuse EEG abnormalities indicate diffuse cortical or subcortical lesions or focal subcortical lesions.

EEG has been used to study epilepsy in goats and cattle, congenital hydranencephaly and hydrocephalus in cattle, scrapie in sheep, thiamine-responsive PEM in cattle, and BSE in cattle. When performed under controlled conditions, EEG has been shown to be a useful diagnostic tool for the early diagnosis of equine intracranial diseases, with adequate sensitivity and specificity.

ELECTRORETINOGRAPHY

Flash electroretinography (ERG) is a recording of rod and cone function of the eyes. The animal is sedated (usually with xylazine) and topical 0.5% proparacaine is applied to both eyes to permit the placement of a contact lens electrode on both eyes. Subcutaneous electrodes are then placed at the lateral canthus and midline at the nostrils to provide reference and ground electrodes, respectively. A period of dark adaptation is then implemented, and a standardized flash sequence applied.[10] Decreased B-wave amplitudes during flash ERG have been identified in horses with equine motor neuron disease and attributed to lipofuscin deposits on the retina.

BRAINSTEM AUDITORY EVOKED POTENTIALS

The brainstem auditory evoked potential (BAEP) is a recording of the electrical activity of the brainstem following an acoustic stimulation; as such, BAEP can be used to evaluate the integrity of the auditory pathway. The use of the BAEP permits differentiation of cochlear pathology (including otitis media/interna) from retrocochlear pathology (auditory nerve or brainstem).

BAEP is obtained on a sedated patient (xylazine is frequently used) by recording neuroelectrical activity from generators in the auditory pathway immediately following an acoustic click stimulus, and BAEP waveforms for horses,[14] ponies, foals,[15,16] and calves have been recorded. Such recordings can be useful in evaluating horses suspected

to have deafness, vestibular disease, brainstem disease, or temporohyoid osteoarthropathy,[17] as well as calves with otitis media and facial paralysis,[18] and to monitor the response to treatment.[17]

INTRACRANIAL PRESSURE MEASUREMENT

Intracranial pressure has been measured in neonatal foals, although the clinical utility of such measurements in foals has not been demonstrated. Increases in intracranial pressure can cause decreases in cerebral perfusion pressure and irreversible injury to the CNS.

The head-down position in the horse increases the hydrostatic pressure gradient between the heart and brain, increasing mean intracranial pressure in isoflurane-anesthetized horses from 31 to 55 mm Hg when placed in the Trendelenburg position to facilitate abdominal surgery.[19] Similar directional changes in intraocular pressure were measured in adult horses sedated with detomidine.[20] Hydrostatic pressure effects on intracranial pressure have also been observed in isoflurane-anesthetized adult cattle.[21] In other words, large animals suspected to have increased intracranial pressure should be encouraged to keep their heads elevated to prevent cerebral edema formation. In addition, head position must be standardized when intracranial pressure is measured.

KINETIC GAIT ANALYSIS

Lameness is common in large animals and usually results in asymmetric gait abnormalities; lameness caused by selected musculoskeletal abnormalities is discussed in Chapter 15. Ataxia caused by spinal cord disease also causes gait abnormalities that are usually symmetric and particularly evident in the hindlimbs. Diagnostic differentiation of lameness and neurologic causes of gait abnormalities can be challenging, even to experienced practitioners. Consequently, kinetic gait analysis offers an objective quantitative test that may assist in the differentiation of neurologic from musculoskeletal causes for a gait abnormality. Two indices appear to have the greatest clinical utility in identifying the presence of a neurologic gait abnormality: higher lateral force peak and increased variation in vertical force peak in both hindlimbs.[22]

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Diffuse or Multifocal Diseases of the Brain and Spinal Cord

There are many different causes of diffuse or multifocal nervous system disease in large domestic animals.

- Infectious causes include bacteria, viruses, fungi, and helminth, arthropod, and protozoan parasites.
- Exogenous substances such as lead, salt, selenium, organophosphate insecticides, feed additives such as urea, poisonous plants, and many other chemicals are common causes.
- Endogenous substances such as products of disease in other body systems or of abnormal metabolism such as bacterial toxins, ammonia, and carbon dioxide can cause abnormalities of the nervous system.
- Metabolic and nutritional causes include ischemia secondary to cardiopulmonary disease; hypoglycemia; hypomagnesemia; copper deficiency in pregnant animals; and hyper D-lactatemia in calves, lambs, and kids with neonatal diarrhea and adult ruminants with grain overload.
- Chronic acidemia associated with diarrhea can cause mental depression and ataxia (whereas experimentally induced acute acidemia does not cause mental depression in neonatal calves).
- Idiopathic diseases account for several diseases of the spinal cord of horses.
- Malformation occurs primarily in the developing fetus and results in congenital nervous system disease, which is usually present at birth. Many different teratogens can cause congenital defects. In some cases of inherited disease, the clinical signs do not manifest until sometime after birth.

Responses of Central Nervous System to Injury

The CNS may respond to injury by morphologic changes that include cerebral edema and brain swelling, inflammation, and demyelination. Malformations occur when the CNS is affected during fetal life.

The remainder of this chapter will present the general clinical aspects of the diseases of the nervous system according to anatomic sites and causative agent. The salient features of the etiology, pathogenesis, clinical findings, diagnosis, and treatment of these clinicoanatomic diseases are described. Cerebral hypoxia, hydrocephalus, cerebral edema, meningitis, encephalitis, myelitis, encephalomalacia, and myelomalacia are common to many diffuse or multifocal diseases of the nervous system and are described here.

CEREBRAL HYPOXIA

Cerebral hypoxia occurs when the supply of oxygen to the brain is reduced for any reason. An acute or chronic syndrome develops depending on the acuteness of the deprivation. Initially there are irritation signs followed terminally by signs of loss of function.

ETIOLOGY

All forms of hypoxia, including anemic, anoxic, histotoxic, and stagnant forms cause some degree of cerebral hypoxia, but signs referable to cerebral dysfunction occur only when the hypoxia is severe. Hypoxia of the brain may be secondary to a general systemic hypoxia or be caused by lesions restricted to the cranial cavity.

Cerebral Hypoxia Secondary to General Hypoxia

- Poisoning by hydrocyanic acid or nitrite
- Acute heart failure in severe copper deficiency in cattle
- Anesthetic accidents
- Terminally in pneumonia, congestive heart failure
- During or at birth in foals, hypoxic-ischemic encephalopathy in foals (also known as neonatal encephalopathy, perinatal asphyxia, dummy foal syndrome, or neonatal maladjustment syndrome),[1] or intrapartum hypoxia in calves and lambs caused by prolonged parturition

Cerebral Hypoxia Secondary to Intracranial Lesion

- In increased intracranial pressure
- In brain edema

PATHOGENESIS

The CNS is extremely sensitive to hypoxia, and degeneration occurs if the deprivation is extreme and prolonged for more than a few minutes. The effects of the hypoxia vary with the speed of onset and with the severity. When the onset is sudden, there is usually a transitory period during which excitation phenomena occur, and this is followed by a period of loss of function. If recovery occurs, a second period of excitation usually develops as function returns. In more chronic cases the excitation phase is not observed, and the signs are mainly those of loss of function. These signs include dullness and lethargy when deprivation is moderate and unconsciousness when it is severe. All forms of nervous activity are depressed, but the higher centers are more susceptible than medullary centers and the pattern of development of signs may suggest this.

CLINICAL FINDINGS

Acute and chronic syndromes occur depending on the severity of the hypoxia. Acute cerebral hypoxia is manifested by a sudden onset of signs referable to paralysis of all brain functions, including tetraparesis and unconsciousness. Muscle tremor, beginning about the head and spreading to the trunk and limbs, followed by recumbency, clonic convulsions, and death or recovery after further clonic convulsions is the most common pattern, although affected animals may fall to the ground without premonitory signs. In chronic hypoxia, there is lethargy, dullness, ataxia, weakness, and blindness and in some cases muscle tremor or convulsions. In both acute and chronic hypoxia, the signs of the primary disease will also be evident. Cerebral hypoxia of fetal calves is thought to be a cause of weakness and failure to suck after birth, leading to the eventual death of the calf from starvation. Such hypoxia can occur during the birth process, especially if it is difficult or delayed, or during late pregnancy.

CLINICAL PATHOLOGY AND NECROPSY FINDINGS

There is no distinctive clinical pathology or characteristic necropsy lesion other than those of the primary disease.

DIFFERENTIAL DIAGNOSIS

Clinically there is little to differentiate cerebral hypoxia from hypoglycemia or polioencephalomalacia in which similar signs occur. Irritation and paralytic signs follow one another in many poisonings including lead and arsenic and in most diffuse diseases of the brain including encephalitis and encephalomalacia. The differential diagnosis of cerebral hypoxia depends on the detection of the cause of the hypoxia.

TREATMENT

An increase in oxygen delivery is essential and can usually only be provided by removing the causative agent. A respiratory stimulant (the most effective is doxapram, 2 mg/kg BW, intravenously)[2] may be advantageous in acute cases, and artificial respiration may be necessary and effective.

INCREASED INTRACRANIAL PRESSURE, CEREBRAL EDEMA, AND BRAIN SWELLING

Diffuse cerebral edema and brain swelling usually occur acutely and cause a general increase in intracranial pressure. Cerebral edema is rarely a primary disease, but is commonly an accompaniment of other diseases. Cerebral edema is often a transient phenomenon and may be fatal, but complete recovery or recovery with residual nervous signs also occurs. It is manifested clinically by blindness, opisthotonus, muscle tremor, paralysis, and clonic convulsions.

ETIOLOGY

Diffuse cerebral edema and brain swelling may be **vasogenic**, when there is increased permeability of capillary endothelium, and **cytotoxic** when all the elements of brain tissue, glia, neurons, and endothelial cells undergo swelling. Causes include the following.

Vasogenic Edema

- Brain abscess, neoplasm, hemorrhage, lead encephalopathy, purulent meningitis
- Minor edema after most traumatic injuries, in many encephalitides and many poisonings, including propylene glycol in the horse; probably contributes to the pathogenesis
- Accidental intracarotid injection of promazine in horses
- Leukoencephalomalacia in horses caused by fumonisin consumption
- Septicemia in neonatal foals

Cytotoxic Edema

- Hypoxia
- PEM of ruminants (thiamine deficiency or sulfur toxicosis)
- Salt poisoning of swine

Interstitial Edema

- Hydrocephalus

PATHOGENESIS

Cerebral Edema and Brain Swelling

This disease is potentially life-threatening because of the limited ability for accommodation of increased volume within the confines of the dura and the cranium. CNS parenchyma does not possess a lymphatic system, and the interstitial space between cells, especially in the gray matter, is much narrower than in other tissues. When CNS edema develops, of necessity it largely accumulates within cells, although interstitial fluid will form if cells lyse or if the edema is severe.

Cerebral edema usually occurs to some degree in all pathologic states, whether degenerative or inflammatory or traumatic or neoplastic. Edema around chronic, focal lesions such as abscesses, parasitic cysts, and primary or metastatic tumors in white matter often produce marked swelling. Cerebral hemispheric swelling compresses the underlying brainstem, flattening the rostral colliculi and distorting the aqueduct. As the swollen brain expands and fills the confines of the calvaria, some regions are prone to herniation. If this occurs, the accompanying blood vessels are likely to become occluded, which may result in hemorrhage or infarction. Commonly with brain swelling the caudal lobe of the cerebellar vermis protrudes as a flattened lip over the medulla oblongata toward the foramen magnum.

In vasogenic edema the primary insult is to the wall of cerebral capillaries, allowing the escape of plasma fluid and proteins under the hydrostatic pressure of the circulation. The inciting vascular injury may be brain or spinal cord trauma, vasculitis, a neoplasm, or a cerebrovascular accident. Vasogenic edema affects predominantly the white matter, in which fluid accumulates within the cytoplasm of astrocytes and spreads in the interstitial spaces. Vasogenic edema moves over very long distances and from one hemisphere to the other via the corpus callosum. A chronic epidural abscess involving the frontal lobe can produce sufficient brain swelling from vasogenic edema to induce herniation of the occipital cortex beneath the tentorium cerebelli.

Cytotoxic edema results from an injury to a glial cell that disturbs osmoregulation of that cell by depletion of energy stores and failure of energy-dependent ionic pumps. This leads to cell swelling with fluid and differs from edema in other tissues in which fluid accumulation is interstitial. Cytotoxic edema reflects a specific cellular insult and may result from ischemia or hypoxia, nutritional deficiency, an intoxication, or an inherited metabolic abnormality. Brain swelling from cytotoxic edema is less dramatic than that seen in vasogenic edema. It may affect just the gray matter, just the white matter, or both.

The ECF volume in vasogenic edema is increased by the edema fluid, which is a plasma filtrate containing plasma protein. In cytotoxic edema it is the cellular elements themselves that increase in size. In hypoxia this is because of failure of the adenosine triphosphate (ATP)-dependent sodium pump within the cells. As a result sodium accumulates within the cells and water follows to maintain osmotic equilibrium. In PEM and salt poisoning, the edema of the

brain is primary. In salt poisoning in pigs there is an increase in concentration of cations in brain tissue with a sudden passage of water into the brain to maintain osmotic equilibrium. The cause of the edema in PEM of ruminants, associated with a thiamine inadequacy, is unknown. When promazine is injected accidentally into the carotid artery of the horse, it produces a vasogenic edema and infarction generally, but especially in the thalamus and corpora quadrigemina on the injected side. The vasogenic edema surrounding an abscess is localized and is not evident in the white matter.

Cerebral edema and cerebellar herniation have been described in neonatal foals admitted to an intensive care unit for treatment. All foals had septicemia. It was suggested that hypoglycemia, hypoxia, or the alterations in cerebral blood flow associated with septicemia might have initiated injury to cell membranes, resulting in vascular damage and subsequent edema. It is hypothesized that cerebellar herniation occurs in neonatal foals with sepsis because of the inelastic nature of the dural folds and the anatomic rigidity of the neonatal equine skull. This is in contrast to the human infant, in whom cerebral edema occurs in bacterial meningitis but cerebral or cerebellar herniation is not normally a feature. The relatively small brain of the newborn foal is only 1% of total body mass compared with the human infant, which is 12% and in which the brain is enclosed within a large but relatively thin calvarium with sutures that, in the preterm infant at least, can be separated by excess internal pressure.

An increase in intracranial pressure occurs suddenly and, as in hydrocephalus, there is a resulting ischemic anoxia of the brain caused by compression of blood vessels and impairment of blood supply. This may not be the only factor that interferes with cerebral activity in PEM and salt poisoning. The clinical syndrome produced by the rapid rise in intracranial pressure is manifested by involuntary movements such as tremor and convulsions followed by signs of weakness. If the compression of the brain is severe enough and of sufficient duration, ischemic necrosis of the superficial layers of the cortical gray matter may occur, resulting in permanent nervous defects in those animals that recover. Opisthotonus and nystagmus are commonly observed and are probably caused by the partial herniation of the cerebellum into the foramen magnum.

CLINICAL FINDINGS

Although the rise of intracranial pressure in diffuse edema of the brain is usually more acute than in hydrocephalus, the development of clinical signs takes place over a period of 12 to 24 hours and nervous shock does not occur. There is central blindness, and periodic attacks of abnormality occur in which **opisthotonus**, **nystagmus**, **muscle tremor**, and **convulsions** are prominent.

In the intervening periods, the animal is dull, depressed, and blind, and optic disc edema may be present. The involuntary signs of tremor, convulsions, and opisthotonus are usually not extreme, but this varies with the rapidity of onset of the edema. Because of the involvement of the brainstem, in severe cases muscle weakness appears, the animal becomes ataxic, goes down and is unable to rise, and the early signs persist. Clonic convulsions occur terminally, and animals that survive may have residual defects of mentality and vision.

CLINICAL PATHOLOGY

Clinicopathologic observations will depend on the specific disease causing the edema.

NECROPSY FINDINGS

Microscopically the gyri are flattened and the cerebellum is partially herniated into the foramen magnum with consequent distortion of its caudal aspect. The brain has a soft, swollen appearance and tends to sag over the edges of the cranium when the top has been removed. Caudal portions of the occipital lobes herniate ventral to the tentorium cerebelli.

DIFFERENTIAL DIAGNOSIS

Diffuse brain edema causes a syndrome not unlike that of encephalitis, although there are fewer irritation phenomena. Differentiation from encephalomalacia and vitamin A deficiency may be difficult if the history does not give a clue to the cause of the disease. Metabolic diseases, particularly pregnancy toxemia, hypomagnesemic tetany of calves, and lactation tetany, resemble it closely, as do some cases of acute ruminal impaction. In the history of each of these diseases, there are distinguishing features that aid in making a tentative diagnosis. Some of the poisonings, particularly lead, organic mercurial and arsenicals, and enterotoxemia associated with *Clostridium perfringens* type D produce similar nervous signs, and gut edema of swine may be mistaken for diffuse cerebral edema.

TREATMENT

Decompression of the brain is desirable in acute edema. The treatment will depend in part on the cause; the edema associated with PEM will respond to early treatment with thiamine. In general terms, edema of the brain responds to parenteral treatment with hypertonic solutions (mannitol and hypertonic sodium chloride are most often used) and corticosteroids (specifically dexamethasone). Hypertonic solutions are most applicable to cytotoxic edema and corticosteroids to vasogenic edema. This is in addition to treatment for the primary cause of the disease.

Hypertonic solutions open the blood-brain barrier by shrinking endothelial cells and widening the tight junctions.[3] The magnitude of the opening is dependent on the type of hypertonic solution (mannitol and hypertonic saline are used most frequently with mannitol as the first choice treatment) and the achieved plasma concentration. The magnitude of the opening is also dependent on age, with neonates having a "leakier" blood-brain barrier than adults.[3,4] This supports clinical observations that mannitol treatment appears to be more successful in treating neonates suspected to have cerebral edema than adults. The preferred treatment is mannitol given as a 20% solution in a series of bolus intravenous infusions of 0.25 to 1 g/kg BW every 4 to 6 hours. The suggested dose rate has been derived from those recommended for humans and dogs but is very expensive. There are dangers with mannitol: it should not be repeated often, it must not be given to an animal in shock, and it should be given intravenously slowly. A recent meta-analysis suggested that hypertonic saline (1.5–23.5% NaCl at 10–30 mL/kg BW total dose) may be as effective as 20% mannitol in the treatment of cerebral edema, with 7.5% NaCl as the most commonly used osmalality.[5]

Dexamethasone administration (1 mg/kg BW intravenously every 24 hours) is no longer recommended for the treatment of cerebral edema in human infants,[6] and its efficacy in large animals with cerebral edema is uncertain. Dexamethasone is thought to decrease cerebral edema and CSF production and inhibit tumor-induced angiogenesis in patients with intracranial tumors. Hypertonic glucose given intravenously is not recommended because an initial temporary decompression is followed after a 4- to 6-hour interval by a return to pretreatment CSF pressure when the glucose is metabolized.

Diuretics usually produce tissue dehydration too slowly to be of much value in acute cases, but they may be of value as an adjunct to hypertonic solutions or in early or chronic cases. The removal of CSF from the cisterna magna in an attempt to provide relief may cause complications. In some cases the removal of 25 to 75 mL of CSF provides some temporary relief, but the condition becomes worse later because portions of the swollen brain herniate into the foramen magnum. There is no published information available on how much CSF can be safely removed; therefore recommendations cannot be made.

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HYDROCEPHALUS

Obstructive hydrocephalus may be congenital or acquired and is manifested in both cases by a syndrome referable to a general increase in intracranial pressure. Irritation signs of mania, head-pressing, muscle tremor, and convulsions occur when the onset is rapid, and signs of paralysis including dullness, blindness, and muscular weakness are present when the increased pressure develops slowly.

ETIOLOGY

Obstructive hydrocephalus may be congenital or acquired, but in both instances it is caused by defective drainage or absorption of CSF. In the congenital disease, there is an embryologic defect in the drainage canals and foramina between the individual ventricles or between the ventricles and the subarachnoid space, or in the absorptive mechanism, the arachnoid villi.

Congenital Hydrocephalus

Causes include the following:

- Alone, with lateral narrowing of the mesencephalon
- Inherited defects of Hereford, Holstein, Ayrshire, and Jersey cattle
- Inherited combined defects with chondrodysplasia, or in white Shorthorn cattle combined with hydrocephalus, microphthalmia, and retinal dysplasia
- Virus infections of the fetus suggest themselves as possible causes of embryologic defects in the drainage system, but there are no verified examples of this; the cavitation of brain tissue and subsequent accumulation of fluid, hydranencephaly, which occurs after infection with bluetongue virus in lambs, and Akabane virus in calves, is compensatory, not obstructive
- Vitamin A deficiency may contribute
- Other occurrences, sometimes at high levels of prevalence, but without known cause

Acquired Hydrocephalus

Causes include the following:

- Hypovitaminosis A in young growing calves causing impaired absorption of fluid by the arachnoid villi
- Cholesteatoma in choroid plexuses of the lateral ventricles in the horse; these may produce an acute, transient hydrocephalus on a number of occasions before the tumor reaches sufficient size to cause permanent obstruction
- Other tumor or chronic inflammatory lesion obstructing drainage from the lateral ventricles

PATHOGENESIS

Increased intracranial pressure in the fetus and before the syndesmoses of the skull have fused causes hydrocephalus with enlargement of the cranium. After fusion of the suture lines the skull acts as a rigid container, and an increase in the volume of its contents increases intracranial pressure. Although the increase in volume of the contents may be caused by the development of a local lesion such as an abscess, tumor, hematoma or cestode cyst, which interferes with drainage of the CSF, the more common lesion is a congenital defect of CSF drainage.

Clinical and pathologic hydrocephalus has been produced experimentally in animals by creating granulomatous meningitis. The clinical signs included depression, stiffness of gait, recumbency, and opisthotonus with paddling convulsions. The general effects in all cases are the same, the only difference is that local lesions may produce localizing signs as well as signs of increased intracranial pressure. These latter signs are caused by compression atrophy of nervous tissue and ischemic anoxia caused by compression of blood vessels and impairment of blood supply to the brain.

In congenital hydrocephalus the signs observed are usually those of paralysis of function, whereas acquired hydrocephalus, being more acute, is usually manifested first by irritation phenomena followed by signs of paralysis. Edema of the optic papilla is a sign of increased intracranial pressure and may be detected using an ophthalmoscope. Bradycardia occurs inconstantly and cannot be considered to be diagnostic.

CLINICAL FINDINGS

In acquired hydrocephalus there is, in most cases, a gradual onset of general paresis. Initially there is depression, disinclination to move, central blindness, an expressionless stare, and a lack of precision in acquired movements. A stage of somnolence follows and is most marked in horses. The animal stands with half-closed eyes, lowered head, and a vacant expression and often leans against or supports itself on some solid object. Chewing is slow, intermittent, and incomplete, and animals are often observed standing with food hanging from their mouths. The reaction to cutaneous stimulation is reduced, and abnormal postures are frequently adopted. Frequent stumbling, faulty placement of the feet, and incoordination are evidenced when the animal moves, and circling may occur in some cases. Bradycardia and cardiac arrhythmia have been observed.

Although the emphasis is on depression and paresis, signs of brain irritation may occur, particularly in the early stages. These signs often occur in isolated episodes during which a wild expression, charging, head-pressing, circling, tremor, and convulsions appear. These episodes may be separated by quite long intervals, sometimes of several weeks' duration. In vitamin A deficiency in calves, blindness and papilledema are the early signs and an acute convulsive stage occurs terminally.

Fig. 14-2 **A,** Holstein Friesian calf with hydrocephalus caused by in utero infection with bovine viral diarrhea virus. The calf was able to suckle but appeared to have diminished responsiveness to its environment. **B,** Piglet with meningocele secondary to in utero hydrocephalus.

Congenitally affected animals are usually alive at birth but are unable to stand and most die within 48 hours. The cranium is sometimes domed, the eyes protrude, and nystagmus is often evident (Fig. 14-2). Meningocele is an infrequent accompaniment.

CLINICAL PATHOLOGY

Examination of the composition and pressure of the CSF will be of value. The fluid is usually normal biochemically and cytologically but the pressure is increased. A marked increase in serum muscle enzyme activity has been observed in calves with congenital hydrocephalus, caused probably to an accompanying muscular dystrophy. Convulsions, if they occur, may contribute to this increase.

NECROPSY FINDINGS

On necropsy the cranium may be enlarged and soft in congenital hydrocephalus. The ventricles are distended with CSF under pressure and the overlying cerebral tissue is thinned if the pressure has been present for some time.

DIFFERENTIAL DIAGNOSIS

Congenital hydrocephalus resembles vitamin A deficiency in newborn pigs, toxoplasmosis, and hydranencephaly if there is no distortion of the cranium.

Acquired hydrocephalus needs to be differentiated from other diffuse diseases of the brain, including encephalitis and encephalomalacia, and from hepatic dystrophies, which resemble it very closely. In these latter diseases, there may be other signs of diagnostic value, including fever in encephalitis and jaundice in hepatic dystrophy. In most cases it is necessary to depend largely on the history and recognition of individual disease entities.

MENINGITIS

Inflammation of the meninges occurs most commonly as a complication of a preexisting disease. Meningitis is usually associated with a bacterial infection and is manifested clinically by fever, cutaneous hyperesthesia, and rigidity of muscles. Although meningitis may affect the spinal cord or brain specifically, it commonly affects both and is dealt with here as a single entity. Meningoencephalitis is common in neonatal farm animals. Primary bacterial meningitis is extremely rare in adult farm animals, with the exception of listeriosis and *H. somni* (formerly *Haemophilus somnus*) infection, although the latter is more a vasculitis than a primary meningitis. The possibility of immunodeficiency should be considered in adult horses with bacterial meningitis. Compared with adults, bacterial meningitis is more common in neonates because their immune system is immature, the blood-brain barrier is incomplete, and umbilical infections are common, providing a nidus of infection.

ETIOLOGY

Most significant meningitides are bacterial, although most viral encephalitides have some meningitic component.

Cattle

- Viral diseases including bovine malignant catarrh, sporadic bovine encephalomyelitis
- Bacterial diseases including listeriosis, *H. somni,* chronic lesions elsewhere in the body possibly associated with meningitis in adult animals; rarely tuberculosis
- Facial paralysis syndrome of calves in the Franklin district of New Zealand[1]

Sheep

- Melioidosis, *S. aureus* (tick pyemia) in newborn lambs
- *Pasteurella multocida* in lambs
- *Mannheimia (Pasteurella) haemolytica* in lambs

Horses

- Strangles, *Pasteurella haemolytica* (also donkeys and mules), *Streptococcus suis, S. equi, Actinomyces* spp., *Klebsiella pneumonia, Staphylococcus aureus*,[2] coagulase-negative staphylococci, *Anaplasma phagocytophilum* (equine granulocytic ehrlichiosis, formerly named *Ehrlichia equi*), *Borrelia burgdorferi*,[3] *Sphingobacterium multivorum,* and *Cryptococcus neoformans.*

Pigs

- Glasser's disease, erysipelas, salmonellosis; *S. suis* type 2 in weaned and feeder pigs

Coliform and streptococcal septicemias are probably the most common causes of meningitis in neonatal farm animals. The infection may originate from omphalophlebitis, bacteremia, or bacterial translocation across the gastrointestinal tract in neonates less than 24 hours of age or with enteritis. Septicemia occurs in all species, especially calves, and may be accompanied by polysynovitis, endocarditis, and hypopyon. The causative bacteria are usually a mixed flora.

Hematogenous infection occurs from other sites also. In neonatal animals, some of the common infections include the following:

- **Calf:** *Escherichia coli*; the disease is most common in calves under several days of age and can occur in less than 24 hours after birth; failure of transfer of colostral immunoglobulins is a common contributing factor
- **Piglet:** *S. zooepidemicus, S. suis* type 1
- **Lamb:** *S. zooepidemicus*

PATHOGENESIS

Inflammation of the meninges causes local swelling and interference with blood supply to the brain and spinal cord but as a rule penetration of the inflammation along blood vessels and into nervous tissue is of minor importance and causes only superficial encephalitis. Failure to treat meningitis associated with pyogenic bacteria often permits the development of a fatal choroiditis, with exudation into CSF, and ependymitis. There is also inflammation around the nerve trunks as they pass across the subarachnoid space. The signs produced by meningitis are thus a combination of those resulting from irritation of both central and peripheral nervous systems. In spinal meningitis, there is muscular spasm with rigidity of the limbs and neck, arching of the back, and hyperesthesia with pain on light touching of the skin. When the cerebral meninges are affected, irritation signs, including muscle tremor and convulsions, are the common manifestations. Because meningitis is usually bacterial in origin, fever and toxemia can be expected if the lesion is sufficiently extensive.

Defects of drainage of CSF occur in both acute and chronic inflammation of the meninges and produce signs of increased intracranial pressure. The signs are general although the accumulation of fluid may be localized to particular sites such as the lateral ventricles.

A newly described mild nonsuppurative meningitis is associated with facial paralysis in calves in a specific geographic location in New Zealand.[1] Affected animals have a fever with unilateral or bilateral dysfunction of the facial nerve (CN VII; buccal and auriculopalpebral branches). The case–fatality rate ranges from 38% to 52%, and affected calves do not have listeriosis or *M. bovis* infection.

CLINICAL FINDINGS

Acute meningitis usually develops suddenly and is accompanied by fever and toxemia in addition to nervous signs. Vomiting is common in the early stages in pigs. There is trismus, opisthotonus, and rigidity of the neck and back. Motor irritation signs include tonic spasms of the muscles of the neck causing retraction of the head, muscle tremor, and paddling movements. Cutaneous hyperesthesia is present in varying degrees, with even light touching of the skin causing severe pain in some cases. There may be disturbance of consciousness manifested by excitement or mania in the early stages, followed by drowsiness and eventual coma.

Blindness is common in cerebral meningitis but not a constant clinical finding. In young animals, ophthalmitis with hypopyon may occur, which supports the diagnosis of meningitis. The pupillary light reflex is usually much slower than normal. Examination of the fundus of the eyes may reveal evidence of optic disc edema, congestion of the retinal vessels, and exudation.

In uncomplicated meningitis the respiration is usually slow and deep, and often phasic in the form of **Cheyne–Stokes breathing** (a breathing pattern characterized by a period of apnea followed by a gradual increase in the depth and rate of respiration) or **Biot's breathing** (an irregular breathing pattern characterized by groups of quick, shallow inspirations followed by periods of apnea). Terminally there is quadriplegia and clonic convulsions.

The major clinical finding of meningoencephalitis in calves under 2 weeks of age was depression, which progressed rapidly to stupor, but the mental state changed to hyperesthesia, opisthotonus, and seizures in unresponsive terminal cases. Meningoencephalitis should be considered in calves that have been treated for the effects of diarrhea with fluid therapy but fail to respond and remain depressed.

In a series of 32 cases of meningitis in neonatal calves, the mean age at admission was 6 days (range, 11 hours to 30 days). The major clinical findings were lethargy (32/32), recumbency (32/32), anorexia and loss of the

suck reflex (26/32), and stupor and coma (21/32). The frequencies of other clinical findings were as follows: opisthotonus (9/32), convulsions (7/32), tremors (6/32), and hyperesthesia (6/32). The case–fatality rate was 100%; this case series was accumulated before the widespread availability of third-generation cephalosporins labeled for use in food animals.

Although meningitis in farm animals is usually diffuse, affecting particularly the brainstem and upper cervical cord, it may be quite localized and produce localizing signs, including involvement of the cranial or spinal nerves. Localized muscle tremor, hyperesthesia, and rigidity may result. Muscles in the affected area are firm and board-like on palpation. Anesthesia and paralysis usually develop caudal to the meningitic area. Spread of the inflammation along the cord is usual. Reference should be made to the specific diseases cited under Etiology in this section for a more complete description of their clinical manifestations.

In newborn calves, undifferentiated diarrhea, septic arthritis, omphalophlebitis, and uveitis are frequent concurrent clinical findings. Bacterial meningitis has been reproduced experimentally in calves, resulting in typical clinical signs consisting of convulsions, depression, circling and falling to one side, ataxia, propulsive walking, loss of saliva, tremors, recumbency, lethargy, and nystagmus.

CLINICAL PATHOLOGY

Cerebrospinal Fluid

CSF collected from the lumbosacral space or cisterna magna in meningitis contains elevated protein concentrations, has a high cell count, and usually contains bacteria. The collection of CSF from the lumbosacral space of calves has been described under the section Special Examination of the Nervous System. Culture and determination of antimicrobial susceptibility is strongly recommended because of the low antimicrobial concentrations achieved in the CSF. In a series of meningitis in neonatal calves, the CSF revealed marked pleocytosis (mean 4,000 leukocytes/μL; range, 130–23,270 leukocytes/μL), xanthochromia, turbidity, and a high total protein concentration.

Hematology

Hemogram usually reveals a marked leukocytosis, reflecting the severity of the systemic illness secondary to septicemia.

NECROPSY FINDINGS

Hyperemia, the presence of hemorrhages, and thickening and opacity of the meninges, especially over the base of the brain, are the usual macroscopic findings. The CSF is often turbid and may contain fibrin. A local superficial encephalitis is often present. Additional morbid changes are described under the specific diseases and are often of importance in differential diagnosis. In neonatal calves with meningitis, lesions of septicemia are commonly present at necropsy and *E. coli* is the most common isolated organism.

DIFFERENTIAL DIAGNOSIS

Hyperesthesia, severe depression, muscle rigidity, and blindness are the common clinical findings in cerebral meningitis, but it is often difficult to differentiate meningitis from encephalitis and acute cerebral edema. Examination of the CSF is the only means of confirming the diagnosis before death. Analysis of CSF is very useful in the differential diagnosis of diseases of the nervous system of ruminants. Details are presented in the section Collection and Examination of Cerebral Spinal Fluid. Subacute or chronic meningitis is difficult to recognize clinically. The clinical findings may be restricted to recumbency, apathy, anorexia, slight incoordination if forced to walk, and some impairment of the eyesight. Spinal cord compression is usually more insidious in onset and is seldom accompanied by fever; hyperesthesia is less marked or absent, and there is flaccidity rather than spasticity.

TREATMENT

Most of the viral infections of the nervous system are not susceptible to chemotherapeutics. Some of the larger organisms such as *Chlamydia* spp. are susceptible to broad-spectrum antimicrobial agents such as the tetracyclines and chloramphenicol.

Bacterial infections of the CNS are usually manifestations of a general systemic infection as either bacteremia or septicemia. Treatment of such infections is limited by the existence of the blood-brain and blood-CSF barriers, which prevent penetration of some substances into nervous tissue and into the CSF. Very little useful data exist on the penetration of parenterally administered antibiotics into the CNS of either normal farm animals or those in which there is inflammation of the nervous system.

In humans it is considered that most antimicrobials do not enter the subarachnoid space in therapeutic concentrations unless inflammation is present, and the degree of penetration varies among drugs. Chloramphenicol is an exception; levels of one-third to one-half of the plasma concentration are commonly achieved in healthy individuals; chloramphenicol administration is now much reduced in developed countries because of the idiosyncratic occurrence of aplastic anemia in humans. The relative diffusion of gram-negative antimicrobial agents from blood into CSF in humans is shown in Table 14-8.

The most promising antimicrobial agents for the treatment of bacterial meningitis in farm animals are trimethoprim-sulfonamide combinations, the third-generation cephalosporins, and fluoroquinolones. When treating bacterial meningitis, pharmacodynamic principles suggest that CSF antimicrobial concentrations should have a peak concentration that is at least five times the minimum bactericidal concentration (MBC) of the pathogen, and concentrations above the MBC are required during the entire dosing interval for optimal bactericidal activity.

Table 14-8 Relative diffusion of gram-negative antimicrobials

Excellent with or without inflammation	Good only with inflammation
Sulfonamides	Ampicillin
Third-generation Cephalosporins	Carbenicillin
Cefoperazone, cefotaxime	Cephalothin
	Cephaloridine
Minimal or not good with inflammation	**No passage with inflammation**
Tetracycline	Polymyxin B
Streptomycin	Colistin
Kanamycin	
Gentamicin	

In most instances of bacterial encephalitis or meningitis in farm animals, it is likely that the blood-brain barrier is not intact and that parenterally administered drugs will diffuse into the nervous tissue and CSF to a greater extent than in healthy animals. Certainly, the dramatic beneficial response achieved by the early parenteral treatment of *H. somni* meningoencephalitis in cattle using intravenous oxytetracycline or intramuscular penicillin suggests that the blood-brain barrier may not be a major limiting factor when inflammation is present. Another example of an antibiotic that does not normally pass the blood-brain barrier well but is able to do so when the barrier is damaged is penicillin in the treatment of listeriosis. When cases of bacterial meningoencephalitis fail to respond to antimicrobial agents to which in vitro testing indicates that the organisms are susceptible, other reasons should also be considered. Often the lesion is irreversibly advanced or there is a chronic suppurative process that is unlikely to respond.

Intrathecal injections of antimicrobial agents have been suggested as viable alternatives when parenteral therapy appears to be unsuccessful. However, there is no evidence that such treatment is superior to appropriate parenteral therapy. In addition, intrathecal injections can cause rapid death and therefore are not recommended.

Glucocorticoids may be administered in an attempt to decrease nerve damage resulting from inflammation. Appropriate randomized clinical trials have not

been performed in large animals, but steroid administration in adult humans with meningitis was associated with decreased mortality.[4]

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ENCEPHALITIS

Encephalitis is, by definition, inflammation of the brain, but in general usage it includes those diseases in which inflammatory lesions occur in the brain, whether there is inflammation of the nervous tissue or primarily of the vessel walls. Clinically, encephalitis is characterized initially by signs of involuntary movements, followed by signs caused by loss of nervous function. The meninges and spinal cord may be involved in an encephalitis, causing varying degrees of meningoencephalomyelitis.

ETIOLOGY

Many encephalitides of large animals are associated with viruses but other infectious agents are also common. Some causes are as follows.

All Species

- Viral infections including rabies, pseudorabies, Japanese B encephalitis, West Nile virus encephalomyelitis
- Bacterial infections of neonatal farm animals
- Toxoplasmosis, which is not a common cause in any species
- Sarcocystosis
- Verminous encephalomyelitis, which is migration of larvae of parasitic species that normally have a somatic migration route, e.g., *Halicephalobus gingivalis* (previously *H. deletrix* or *Micronema deletrix*) and *Setaria* spp.

Cattle

- BSE
- Viral infections including malignant catarrhal fever, BVD virus, sporadic bovine encephalomyelitis, Akabane virus, and bovine herpesvirus-5 (BHV-5), rarely louping-ill virus,[1] and astrovirus (BoAstV-NeuroS1)[2]
- Bacterial infections including *Listeria monocytogenes, H. somni* (formerly *Haemophilus somnus*), heartwater, and clostridial infections following dehorning of calves
- Migration of *Hypoderma bovis* occasionally to brain and spinal cord
- Newborn calves with in utero protozoal infection of *Neospora caninum*[3]

Sheep

- Scrapie
- Viral infections including louping-ill, visna (associated with maedi-visna virus [MVV]), BVD virus (border disease), and Akabane virus
- Thrombotic meningoencephalitis associated with *H. somni* (formerly *H. ovis*) in lambs
- Bacterial meningoencephalitis in lambs 2 to 4 weeks of age
- Migration of *Oestrus ovis*

Goats

- Scrapie
- Caprine arthritis encephalitis (CAE) virus, Akabane virus

New World Camelids

- Viral infection caused by Eastern equine encephalitis virus[4]
- Bacterial infection caused by *L. monocytogenes*
- Verminous encephalomyelitis caused by *Parelaphostrongylus tenuis* ("meningeal worm" of white-tailed deer)

Horses

- Viral infections including infectious equine encephalomyelitis; Borna disease; equine herpesvirus-1 (EHV-1) myeloencephalopathy; equine infectious anemia; eastern, western, Venezuelan, and West Nile equine encephalomyelitis; Murray Valley encephalitis virus[5,6]; Shuni virus[7]; and rarely louping-ill virus
- Bacterial meningoencephalitis caused by *Anaplasma phagocytophilum* (equine granulocytic ehrlichiosis) and *Borrelia burgdorferi*[8]
- Protozoal myeloencephalitis caused by *Sarcocystis neurona* infection
- Verminous encephalomyelitis caused by *Strongylus vulgaris, P. tenuis* (meningeal worm of white-tailed deer), and *Draschia megastoma*; *Angiostrongylus cantonensis,* which normally migrates through the CNS of the rat, has been found as a cause of verminous encephalomyelitis in foals

Pigs

- Bacterial infections as part of the systemic infections with *Salmonella* and *Erysipelas* spp., rarely *L. monocytogenes*
- Viral infections including hog cholera, African swine fever, encephalomyocarditis, swine vesicular disease, hemagglutinating encephalomyelitis virus, and porcine encephalomyelitis virus

PATHOGENESIS

Compared with other extraneural tissues, the inflammatory response mounted by the nervous system is unique. The CNS is in a sequestered and immunologically dormant state within the body. The capillary endothelial blood-brain barrier restricts free access by blood constituents. The CNS lacks specialized dendritic antigen-presenting cells, and the intrinsic expression by CNS cells of major histocompatibility complex molecules, especially class II, is low. There is no lymphatic system within nervous tissue, but cells and antigens within the CNS drain into the circulation and into the cervical lymph nodes.

The CNS has unique populations of cells consisting of parenchymal cells, which are **neurons** and **neuroglia**. The neuroglia are supporting cells and are subdivided into macroglia and microglia. The macroglia are **astrocytes** and **oligodendrocytes**; the third glial cell type is a **microglial cell**. The brain and spinal cord are enclosed by meninges (**dura**, **arachnoid,** and **pia**), which provide protection, a compartment for CSF circulation (the subarachnoid space), support for blood vessels, and a sheath for the cranial and spinal nerves. Within the brain and spinal cord are the ventricular system and central canal, which are lined by **ependymal cells,** and the **choroid plexuses**, which produce the CSF. Circulation of the CSF moves from the lateral, third, and fourth ventricles into the central canal or through lateral apertures at the cerebellomedullary angle into the subarachnoid space of the brain. CSF in the subarachnoid space drains via specialized **arachnoid granulations** into intracranial venous sinuses, with some draining into venous plexuses associated with cranial and spinal nerves. CSF may also cross the ventricular surface into the adjacent parenchyma.

The histologic characteristics of CNS inflammation include the following:

- Perivascular cuffing
- Gliosis
- Neuronal satellitosis and neuronophagia

A perivascular compartment, actual or potential, exists around all CNS arteries, arterioles, venules, and veins. A characteristic feature of CNS inflammation is perivascular cuffing, which is the accumulation of leukocytes of one or multiple types in the perivascular space. All perivascular cuffing results in vasculitis of some degree. In bacterial diseases, polymorphonuclear cells predominate with a minor component of mononuclear cells. In general, viral diseases

are characterized by lymphocyte-rich cells with some plasma cells and monocytes; some arbovirus infections cause a polymorphonuclear cell response. In immune-mediated diseases, there are mixtures of polymorphonuclear and mononuclear cells. In thrombogenic diseases, such as thrombotic meningoencephalitis, vascular occlusion precludes the development of cuffing around injured vessels.

Gliosis is the increased prominence of glial cells, resulting from cytoplasmic swelling and the acquisition of more cell processes, from cell proliferation, or both. Either of the macroglia (oligodendrocytes or astrocytes) or microglia may participate in gliosis.

Neuronal satellitosis occurs when oligodendrocytes react and proliferate in response to degenerating neurons, which may be infected by a virus.

Neuronophagia is the progressive degeneration of the neuron characterized by its piecemeal division and phagocytosis, eventually leaving a dense nodule of glial cells and fragments of the former neuron. Details of the form, functions, and roles of astrocytes in neurologic disease have been reviewed.

Primary demyelination is characteristic of only a small number of inflammatory neurologic diseases and is associated with only a few viruses. The inflammatory neuraxial diseases of large animals include visna in sheep and caprine arthritis encephalitis. The demyelinating process may be initiated directly by the infectious agent alone or by an immunologic response initiated by the agent.

With the exception of the viruses of bovine malignant catarrh and EHV-1, which exert their effects principally on the vasculature, those viruses that cause encephalitis do so by invasion of cellular elements, usually the neurons, and cause initial stimulation and then death of the cells. Those bacteria that cause diffuse encephalitis also exert their effects primarily on vascular endothelium. *L. monocytogenes* does so by the formation of microabscesses. In some diseases, such as meningoencephalitis in cattle associated with *H. somni,* the lesions may be present in the brain and throughout the spinal cord.

Entrance of the viruses into the nervous tissue occurs in several ways. Normally the blood-brain barrier is an effective filtering agent, but when there is damage to the endothelium infection readily occurs. The synergistic relationship between the rickettsias of tick-borne fever and the virus of louping-ill probably has this basis. Entry may also occur by progression of the agent up a peripheral nerve trunk, as occurs with the viruses of rabies and pseudorabies and with *L. monocytogenes.* Entry via the olfactory nerves is also possible.

The clinical signs of encephalitis are usually referable to a general stimulatory or lethal effect on neurons in the brain. This may be in part due to the general effect of inflammatory edema and in part to the direct effects of the agent on nerve cells. In any particular case, one or the other of these factors may predominate, but the tissue damage and therefore the signs are generalized. Clinical signs are often diverse and can be acute or chronic, localized or diffuse, and progressive or reversible. Because of diffuse inflammation in encephalitis, the clinical signs are commonly multifocal and asymmetric. This is not the case in listeriosis, in which damage is usually localized in the pons-medulla. Localizing signs may appear in the early stages of generalized encephalitis and remain as residual defects during the stage of convalescence. In calves with thromboembolic meningoencephalitis caused by *H. somni,* prolonged recumbency may be associated with widespread lesions of the spinal cord. Visna is a demyelinating encephalitis, and caprine leukoencephalomyelitis is both demyelinating and inflammatory and also invades other tissues including joints and lung.

In verminous encephalomyelitis, destruction of nervous tissue may occur in many parts of the brain and in general the severity of the signs depends on the size and mobility of the parasites and the route of entry. One exception to this generalization is the experimental "visceral larva migrans" produced by *Toxocara canis* in pigs when the nervous signs occur at a time when lesions in most other organs are healing. The signs are apparently provoked by a reaction of the host to static larvae rather than trauma caused by migration. Nematodes not resident in nervous tissues may cause nervous signs caused possibly by allergy or by the formation of toxins.

CLINICAL FINDINGS

Because the encephalitides are associated with infectious agents, they are often accompanied by fever, anorexia, depression, and increased heart rate. This is not the case in the very chronic diseases such as scrapie and BSE. In those diseases associated with agents that are not truly neurotropic, there are characteristic signs, which are not described here.

The clinical findings that can occur in encephalitis are combinations of the following:

- **Subtle to marked changes in behavior**
- **Depression**
- **Seizures**
- **Blindness**
- **Compulsive walking**
- **Leaning on walls or fences**
- **Circling**
- **Ataxia**

Bacterial meningoencephalitis in lambs 2 to 4 weeks of age is characterized by lack of suck reflex, weakness, altered gait, and depression extending to stupor, but hyperesthesia to auditory and tactile stimuli. Opisthotonus is common during the terminal stages.

There may be an initial period of **excitement or mania**. The animal is easily startled and responds excessively to normal stimuli. It may exhibit viciousness and uncontrolled activity including blind charging, bellowing, kicking, and pawing. Self-mutilation may occur in diseases such as pseudorabies. Mental depression, including head-pressing, may occur between episodes.

Involuntary movements are variable in their occurrence or may not appear at all. When they do occur, they include convulsions, usually clonic, and may be accompanied by nystagmus, champing of the jaws, excessive frothy salivation, and muscle tremor, especially of the face and limbs. In cattle with malignant catarrhal fever, there is severe depression for a few days followed by the onset of tremors associated with the terminal encephalitis. Unusual irritation phenomena are the paresthesia and hyperesthesia of pseudorabies and scrapie.

Signs caused by loss of nervous function follow and may be the only signs in some instances. Excessive drooling and pharyngeal paralysis are common in rabies. In horses with equine encephalomyelitis, feed may be left hanging from the mouth, although swallowing may not be impaired. The loss of function varies in degree from paresis with knuckling at the lower limb joints, to spasticity of the limbs with resultant ataxia, to weakness and recumbency. Recumbency and inability to rise may be the first clinical finding encountered as in many cases of meningoencephalitis associated with *H. somni.* Hypermetria, a staggering gait and apprehensiveness progressing to belligerency, may occur in a disease such as BSE.

Clinical signs referable to certain anatomic sites and pathways of the brain and spinal cord are manifested by deviation of the head, walking in circles, abnormalities of posture, ataxia, and incoordination but these are more often residual signs after recovery from the acute stages. Progressive ascending spinal cord paralysis, in which the loss of sensation and weakness occur initially in the hindlimbs followed by weakness in the forelimbs, is common in rabies. Residual lesions affecting the CNs do not commonly occur in the encephalitides, except in listeriosis and protozoal encephalitis of horses, both infections predominating in the caudal brainstem.

In the horse with cerebral nematodiasis caused by *S. vulgaris*, the clinical signs are referable to migration of the parasite in the thalamus, brainstem, and cerebellum. There is incoordination, leaning and head-pressing, dysmetria, intermittent clonic convulsions, unilateral or bilateral blindness, and paralysis of some CNs. The onset may be gradual or sudden. The clinical diagnosis is extremely difficult because examination of CSF and hematology are of limited value. A pathologic diagnosis is necessary. In foals with neural angiostrongylosis, tetraparesis was the result of progressive and multifocal neurologic disease.

CLINICAL PATHOLOGY

Clinical pathology may be of considerable assistance in the diagnosis of encephalitis, but the techniques used are for the most part specific to the individual diseases.

Hemogram

In the horse, complete and differential blood counts and serum chemistry profiles are recommended for most neurologic cases.

Serology

Acute and convalescent sera can be submitted when a specific infectious disease is suspected for which a serologic diagnosis is possible.

Cerebrospinal Fluid

Laboratory examination of CSF for cellular content and pathogens may also be indicated. In bacterial meningoencephalitis, analysis of CSF obtained from the lumbosacral space reveals a highly significant increase in protein concentration with marked neutrophilic pleocytosis.

NECROPSY FINDINGS

In some of the common encephalitides there are no gross lesions of the brain apart from those that occur in other body systems and that are typical of the specific disease. In other cases, on transverse section of the brain, extensive areas of hemorrhagic necrosis may be visible, as in meningoencephalitis in cattle caused by *H. somni*. Histologic lesions vary with the type and mode of action of the causative agent. Material for laboratory diagnosis should include the fixed brain and portions of fresh brain material for culture and for transmission experiments.

DIFFERENTIAL DIAGNOSIS

The diagnosis of encephalitis cannot depend entirely on the recognition of the typical syndrome because similar syndromes may be caused by many other brain diseases. Acute cerebral edema and focal space-occupying lesions of the cranial cavity, and a number of poisonings, including salt, lead, arsenic, mercury, rotenone, and chlorinated hydrocarbons, all cause similar syndromes, as do hypovitaminosis A, hypoglycemia, encephalomalacia, and meningitis.

Fever is common in encephalitis but is not usually present in rabies, scrapie, or bovine spongiform encephalopathy; but it may occur in the noninflammatory diseases if convulsions are severe.

In general, the clinical diagnosis rests on the recognition of the specific encephalitides and the elimination of the other possible causes on the basis of the history and clinical pathology, especially in poisonings, and on clinical findings characteristic of the particular disease. In many cases a definite diagnosis can only be made on necropsy. For differentiation of the specific encephalitides, reference should be made to the diseases listed under the previous section Etiology.

Infestation with nematode larvae causes a great variety of signs depending on the number of invading larvae and the amount and location of the damage.

TREATMENT

Specific treatments are dealt with under each disease. Antimicrobials are indicated for bacterial meningoencephalomyelitis. In general, the aim should be to provide supportive treatment by intravenous fluid and electrolyte therapy or stomach tube feeding during the acute phase. Sedation during the excitement stage may prevent the animal from injuring itself, and nervous system stimulants during the period of depression may maintain life through the critical phase. Although there is an increase in intracranial pressure, the removal of CSF is contraindicated because of the deleterious effects of the procedure on other parts of the brain.

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EPILEPSY

Seizures occur most frequently in conjunction with other signs of brain disease. The syndrome of inherited, recurrent seizures, which continues through life with no underlying morphologic disease process, is true epilepsy, which is extremely rare in farm animals. Familial epilepsy has been recorded in Brown Swiss cattle and Arabian foals.[1]

Residual lesions after encephalitis may cause symptomatic epileptiform seizures, but there are usually other localizing signs. A generalized seizure is manifested by an initial period of alertness, the counterpart of the aura in human seizures, followed by falling in a state of tetany, which gives way after a few seconds to a clonic convulsion with paddling, opisthotonus, and champing of the jaws. The clonic convulsions may last for some minutes and are followed by a period of relaxation. The animal is unconscious throughout the seizure, but appears normal shortly afterward.

Some seizures may be preceded by a local motor phenomenon such as tetany or tremor of one limb or of the face. The convulsion may spread from this initial area to the rest of the body. This form is referred to as jacksonian epilepsy and the local signs may indicate the whereabouts of the local lesion or point of excitation. Such signs are recorded very rarely in dogs and not at all in farm animals. The seizures are recurrent, and the animal is normal in the intervening periods.

EEG has been performed but there are significant challenges in obtaining and interpreting the EEG from a conscious foal. It is not clear whether the EEG recording changed the initial treatment protocol for affected foals, and it should be noted that a diagnosis of epilepsy in humans is made primarily on clinical grounds.[1]

TREATMENT

Treatment is empirical. Seizures in foals can be initially controlled with intravenous diazepam (0.1–0.4 mg/kg; the large dose range suggests that some seizures are of short duration). Long-term seizure control emphasizes oral phenobarbital because of its cost and proven efficacy in humans and dogs. A loading intravenous phenobarbital dose that has been used in foals is 12 to 20 mg/kg diluted in 1 L of 0.9% NaCl and administered over 30 minutes, followed by oral phenobarbital at 6 to 12 mg/kg every 12 hours. The oral dose is adjusted based on clinical response and measured peak and trough serum phenobarbital concentrations. Therapeutic phenobarbital concentrations for horses are unknown, but the therapeutic range in humans is 15 to 40 µg/mL. Once seizure control is established with oral phenobarbital and the foal is seizure free for 6 months, the phenobarbital dose can be decreased by 20% every 2 weeks and the horse closely monitored. If phenobarbital does not provide adequate seizure control, potassium bromide can be tried at a tentative initial oral dose of 25 mg/kg every 24 hours. Clients should wear gloves during administration of potassium bromide.

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MYELITIS

Inflammation of the spinal cord (myelitis) is usually associated with viral encephalitis. Clinical signs of myelitis are referable to the

loss of function, although there may be signs of irritation. For example, hyperesthesia or paresthesia may result if the dorsal root ganglia are involved. This is particularly noticeable in pseudorabies and to a lesser extent in rabies. However, paresis or paralysis is the more usual result of myelitis. There are no specific myelitides in farm animals, with most viral infections producing an encephalomyelitis with variations on the predominance of clinical signs being intracranial or extracranial. Viral myelitis associated with EHV-1 (the equine rhinopneumonitis virus) is now commonplace, and equine infectious anemia and dourine include incoordination and paresis in their syndromes. In goats, CAE is principally a myelitis, involving mostly the white matter.

Equine protozoal myeloencephalitis (EPM) causes multifocal lesions of the CNS mostly on the spinal cord. The most accurate diagnosis is based on histologic findings:

- Necrosis and mild to severe, nonsuppurative myeloencephalitis
- Infiltration of neural tissue by mononuclear cells
- Sometimes giant cells, neutrophils, and eosinophils
- Infiltration of perivascular tissue by mononuclear cells including lymphocytes and plasma cells.

EPM is caused primarily by *S. neurona,* which has the opossum (*Didelphis virginiana*) as the definitive host, raccoons as the most likely intermediate host, and the horse acting as a dead end host. Occasional cases of protozoal myeloencephalitis in horses are associated with *Neospora hughesi.*

Myelitis associated with *N. caninum* infection in newborn calves has been described. Affected calves were recumbent and unable to rise but were bright and alert. Histologically, there was evidence of protozoal myelitis.

ENCEPHALOMALACIA

The degenerative diseases of the brain are grouped together under the name encephalomalacia. By definition encephalomalacia means softening of the brain. It is used here to include all degenerative changes. **Leukoencephalomalacia** and **PEM** refer to softening of the white and gray matter, respectively. **Abiotrophy** is the premature degeneration of neurons caused by an inborn metabolic error of development and excludes exogenous insults of neurons. The underlying cellular defect in most abiotrophies is inherited. The syndrome produced in most degenerative diseases of the nervous system is essentially one of loss of function.

ETIOLOGY

Some indication of the diversity of causes of encephalomalacia and degenerative diseases of the nervous system can be appreciated from the examples that follow, but many sporadic cases occur in which the cause cannot be defined.

All Species

- Hepatic encephalopathy is thought to be caused by high blood levels of ammonia associated with advanced liver disease. This is recorded in experimental pyrrolizidine alkaloid poisoning in sheep, in hepatic arteriovenous anomaly, and thrombosis of the portal vein in the horse. Congenital portacaval shunts are also a cause of hepatic encephalopathy.
- Abiotrophy involves multisystem degenerations in the nervous system as focal or diffuse lesions involving the axons and myelin of neuronal processes. These include a multifocal encephalopathy in the Simmental breed of cattle in New Zealand and Australia and progressive myeloencephalopathy in Brown Swiss cattle, known as "weavers" because of their ataxic gait.
- Poisoning by organic mercurials and, in some instances, lead; possibly also selenium poisoning; a bilateral multifocal cerebrospinal poliomalacia of sheep in Ghana.
- Cerebrovascular disorders corresponding to the main categories in humans are observed in animals, but their occurrence is chiefly in pigs, and their clinical importance is minor.
- Congenital hypomyelinogenesis and dysmyelinogenesis are recorded in lambs (hairy shakers), piglets (myoclonia congenita), and calves (hypomyelinogenesis congenita). All are associated with viral infections in utero. EHV-1 infections in horses cause ischemic infarcts.
- Cerebellar cortical abiotrophy occurs in calves and lambs.

Ruminants

- BSE
- Plant poisons, e.g., *Astragalus* spp., *Oxytropis* spp., *Swainsona* spp., *Vicia* spp., *Kochia scoparia*
- Focal symmetric encephalomalacia of sheep, thought to be a residual lesion after intoxication with *C. perfringens* type D toxin
- PEM caused by thiamine inadequacy in cattle and sheep and sulfur toxicosis in cattle; poliomalacia of sheep caused possibly by an antimetabolite of nicotinic acid
- Progressive spinal myelopathy of Murray Grey cattle in Australia
- Spongiform encephalopathy in newborn polled Hereford calves similar to maple syrup urine disease
- Neuronal dystrophy in Suffolk sheep
- Shakers in horned Hereford calves associated with neuronal cell body chromatolysis
- The abiotrophic lysosomal storage diseases including progressive ataxia of Charolais cattle, mannosidosis, gangliosidosis, and globoid cell leukodystrophy of sheep
- The inherited defect of Brown Swiss cattle known as weavers, and presented elsewhere, is a degenerative myeloencephalopathy
- Swayback and enzootic ataxia caused by nutritional deficiency of copper in lambs
- Prolonged parturition of calves causing cerebral hypoxia and the weak calf syndrome
- Idiopathic brainstem neuronal chromatolysis in cattle
- Bovine bonkers caused by the consumption of ammoniated forages
- Inherited neuronal degeneration in Angora goats

Horses

- Leukoencephalomalacia caused by feeding moldy corn infested with *Fusarium moniliforme,* which produces primarily fumonisin B_1 and, to a lesser extent, fumonisin B_2[1,2]
- Nigropallidal encephalomalacia caused by feeding on yellow star thistle (*Centaurea solstitialis*)[3]
- Poisoning by bracken and horsetail causing a conditioned deficiency of thiamine
- Ischemic encephalopathy of neonatal maladjustment syndrome of foals
- EDM,[4,5] which is associated with vitamin E deficiency

Ruminants and Horses

Neurotoxic Mycotoxins

Swainsonine and slaframine produced by *Rhizoctonia leguminicola* cause mannose accumulation and parasympathomimetic effects. Lolitrems from *A. lolii* and paspalitrems from *C. paspali* are tremorgens found in grasses.

Pigs

- Leukoencephalomalacia in mulberry heart disease
- Subclinical attacks of enterotoxemia similar to edema disease
- Poisoning by organic arsenicals, and salt.

PATHOGENESIS

The pathogenesis of the degenerative diseases can be subdivided into the following:

- **Metabolic and circulatory disorders**
- **Intoxications and toxic-infectious diseases**
- **Nutritional diseases**
- **Hereditary, familial, and idiopathic degenerative diseases**

Metabolic and Circulatory

Hepatic encephalopathy is associated with acquired liver disease, and the resultant

hyperammonemia and other toxic factors are considered to be neurotoxic. Disorders of intermediary metabolism result in the accumulation of neurotoxic substances such as in maple syrup urine disease of calves. Lysosomal storage diseases are caused by a lack of lysosomal enzymes, which results in an accumulation of cellular substrates and affecting cell function.

CNS hypoxia and ischemia impair the most sensitive elements in brain tissue, especially neurons. Severe ischemia results in necrosis of neurons and glial elements and areas of infarcts. Gas anesthesia–related neurologic disease occurs in animals that have been deprived of oxygen for more than 5 minutes. The hypoxia is lethal to neurons, and on recovery from anesthesia affected animals are blind and seizures may occur. The typical lesion consists of widespread neuronal damage. Postanesthetic hemorrhagic myelopathy and postanesthetic cerebral necrosis in horses are typical examples.

Hypoglycemia occurs in neonates deprived of milk and in acetonemia and pregnancy toxemia and clinical signs of lethargy, dullness progressing to weakness, seizures, and coma have been attributed to hypoglycemia. However, there are no studies of the CNS in farm animals with hypoglycemia and the effects, if any, on the nervous tissue are unknown.

Intoxications and Toxic-Infectious Diseases

A large number of poisonous substances including poisonous plants, heavy metals (lead, arsenic, and mercury), salt poisoning, farm chemicals, antifreeze, herbicides, and insecticides can directly affect the nervous system when ingested by animals. They result in varying degrees of edema of the brain, degeneration of white and gray matter, and hemorrhage of both the central and peripheral nervous system. Toxic-infectious diseases such as edema disease of swine and focal symmetric encephalomalacia of sheep are examples of endotoxins and exotoxins produced by bacterial infections, which have a direct effect on the nervous system resulting in encephalomalacia.

Nutritional Diseases

Several nutritional deficiencies of farm animals can result in neurologic disease:

- **Vitamin A deficiency** affects bone growth, particularly remodeling of the optic nerve tracts, and CSF absorption. The elevated CSF pressure and constriction of the optic nerve tracts results in edema of the optic disc and wallerian-type degeneration of the optic nerve resulting in blindness.
- **Copper deficiency** in pregnant ewes can result in swayback and enzootic ataxia of the lambs. Copper is an integral element in several enzyme systems such as ceruloplasmin and lysyl oxidase, and copper deficiency affects several organ systems. The principal defect in swayback appears to be one of defective myelination probably caused by interference with phospholipid formation. However, some lesions in the newborn are more extensive and show cavitation with loss of axons and neurons rather than simply demyelination. In the brain, there is a progressive gelatinous transformation of the white matter, ending in cavitation that resembles porencephaly or hydranencephaly. In the spinal cord the lesions are bilateral, and it is suggested that the copper deficiency has a primary axonopathic effect
- **Thiamine deficiency** in ruminants can result in **PEM** or **cerebrocortical necrosis**. Thiamine, mainly as thiamine diphosphate ([TDP]; pyrophosphate), has an important role as a coenzyme in carbohydrate metabolism, especially the pentose pathway. Diffuse encephalopathy may occur characterized by brain edema and swelling, resulting in flattening of the gyri, tentorial herniation, and coning of the cerebellar vermis. Bilateral areas of cerebral cortical laminar necrosis are widespread.

Hereditary, Familial, and Idiopathic Degenerative Diseases

A large number of neurologic diseases of farm animals are characterized by abnormalities of central myelinogenesis. In most instances, the underlying abnormality directly or indirectly affects the oligodendrocyte and is reflected in the production of CNS myelin of diminished quantity or quality or both. Many of these are inherited and manifest from or shortly after birth. They include leukodystrophies, hypomyelinogenesis, spongy degeneration, and related disorders. Neuronal abiotrophy, motor neuron diseases, neuronal dystrophy, and degenerative encephalomyelopathy of horses and cattle are included in this group.

Polioencephalomalacia and Leukoencephalomalacia

PEM appears to be, in some cases at least, a consequence of acute edematous swelling of the brain and cortical ischemia. The pathogenesis of leukoencephalomalacia appears to be related to vasogenic edema as a result of cardiovascular dysfunction and an inability to regulate cerebral blood flow. Whether the lesion is in the gray matter (PEM) or in the white matter (leukoencephalomalacia) the syndrome is largely one of loss of function, although as might be expected irritation signs are more likely to occur when the gray matter is damaged.

CLINICAL FINDINGS

Weakness of all four limbs is accompanied by the following:

- **Dullness or somnolence**
- **Blindness**
- **Ataxia**
- **Head-pressing**
- **Circling**
- **Terminal coma**

In the early stages, particularly in ruminant **PEM**, there are involuntary signs including muscle tremor, opisthotonus, nystagmus, and convulsions.

In equine leukoencephalomalacia, which may occur in outbreaks, initial signs include anorexia and depression. In the neurotoxic form, which is the most common, the anorexia and depression progresses to ataxia, circling, apparent blindness, head-pressing, hyperesthesia, agitation, delirium, recumbency, seizures, and death. An early and consistent sign in affected horses is reduced proprioception of the tongue, which manifests as delayed retraction of the tongue to the buccal cavity after the tongue has been extended. In the hepatotoxicosis form, clinical findings include icterus, swelling of the lips and nose, petechiation, abdominal breathing, and cyanosis. Horses with either syndrome may be found dead without any premonitory signs.

In many of the leukoencephalomalacias, the course may be one of gradual progression of signs, or more commonly a level of abnormality is reached and maintained for a long period, often necessitating euthanasia of the animal. For example, EDM is a diffuse degenerative disease of the equine spinal cords and caudal portion of the brainstem and primarily affects young horses. There is an insidious onset of symmetric spasticity, ataxia, and paresis. Clinical signs may progress slowly to stabilize for long periods. All four limbs are affected, but the pelvic limbs are usually more severely affected than the thoracic limbs. There is no treatment for the disease, no spontaneous recovery and, once affected, horses remain atactic and useless for any athletic function.

CLINICAL PATHOLOGY

There are no clinicopathologic tests specific for encephalomalacia, but various tests may aid in the diagnosis of some of the specific diseases mentioned in this section under Etiology.

NECROPSY FINDINGS

Gross lesions including areas of softening, cavitation, and laminar necrosis of the cortex may be visible. The important lesions are described under each of the specific diseases.

TREATMENT

The prognosis depends on the nature of the lesion. Early cases of thiamine deficiency–induced PEM can recover completely if treated with adequate levels of thiamine. Encephalomalacia caused by sulfur-induced PEM and lead poisoning is more difficult to

treat. Young calves with acquired in utero hypomyelinogenesis and horses with myelitis associated with EHV-1 infection can make complete recoveries.

DIFFERENTIAL DIAGNOSIS

The syndromes produced by encephalomalacia resemble very closely those caused by most lesions that elevate intracranial pressure. The onset is quite sudden, and there is depression of consciousness and loss of motor function. One major difference is that the lesions tend to be nonprogressive, and affected animals may continue to survive in an impaired state for long periods.

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MYELOMALACIA

Degeneration of the spinal cord (myelomalacia) occurs rarely as an entity separate from encephalomalacia. One recorded occurrence is focal spinal poliomalacia of sheep, and in enzootic ataxia the lesions of degeneration are often restricted to the spinal cord. In both instances there is a gradual development of paralysis without signs of irritation and with no indication of brain involvement. Progressive paresis in young goats may be associated with the virus of CAE and other unidentified, possibly inherited causes of myelomalacia.

Degeneration of spinal cord tracts has also been recorded in **poisoning** by *Phalaris aquatica* in cattle and sheep, by *Tribulus terrestris* in sheep,[1] by sorghum in horses, by 3-nitro-4-hydroxyphenylarsonic acid in pigs, and by selenium in ruminants; the lesion is a symmetric spinal poliomalacia. Poisoning of cattle by plants of *Zamia* spp. produces a syndrome suggestive of injury to the spinal cord but no lesions have been reported. Pantothenic acid (PA) or pyridoxine deficiencies also cause degeneration of the spinal cord tract in swine.

A spinal myelinopathy, possibly of genetic origin, is recorded in Murray Grey calves. Affected animals develop ataxia of the hindlegs, swaying of the hindquarters, and collapse of one hindleg with falling to one side. Clinical signs become worse over an extended period.

Sporadic cases of degeneration of spinal tracts have been observed in pigs. One outbreak is recorded in the litters of sows on lush clover pasture. The piglets were unable to stand, struggled violently on their sides with rigid extension of the limbs and, although able to drink, usually died of starvation. Several other outbreaks in pigs have been attributed to selenium poisoning.

Neuraxonal dystrophy is a progressive degenerative process of CNS axons characterized initially by discontinuous swellings (called spheroids) along the distal section of axons. The spheroids reflect an inability of the neuron to maintain a normal structure and function. Neuraxonal dystrophy has been diagnosed in a number of sheep breeds, including Suffolks in the United States, Coopworth and Romney lambs in New Zealand, and Merino sheep in New Zealand and Australia, where it was previously been called Murrurrundi disease or ovine segmental axonopathy. The disease is consistent with an autosomal recessive disorder.[2]

EDM (neuraxonal dystrophy) affects young horses and has been recorded in the United States, Canada, the UK, and Australia. EDM appears to be inherited with vitamin E intake during growth modifying the clinical expression and is pathologically more advanced form of neuraxonal dystrophy.[3,4] The major clinical signs are referable to bilateral leukomyelopathy involving the cervical spinal cord. There is abnormal positioning and decreased strength and spasticity of the limbs as a result of upper motor neuron and general proprioceptive tract lesions. Hypalgesia, hypotonia, hyporeflexia, muscle atrophy, or vestibular signs are not present, and there is no evidence of CN, cerebral, or cerebellar involvement clinically. Abnormal gait and posture are evident, usually initially in the pelvic limbs but eventually also in the thoracic limbs. There are no gross lesions, but histologically there is degeneration of neuronal processes in the white matter of all spinal cord funiculi, especially the dorsal spinocerebellar and sulcomarginal tracts. The lesion is most severe in the thoracic segments and is progressive.[5]

Motor neuron diseases are a group of nervous disorders characterized by selective degeneration of upper motor neurons and/or lower motor neurons. Common characteristics of motor neuron diseases are muscle weakness or spastic paralysis. Motor neuron diseases have been identified in a number of species and are currently considered incurable.[6] An inherited **motor neuron disease** has been identified in an extended family of Romney lambs. Lower motor neuron signs predominated and affected lambs were euthanized at 4 weeks of age. The disorder was inherited in a simple autosomal recessive manner.[6] **Bovine spinal muscular atrophy** is an inherited motor neuron disease of Brown Swiss cattle characterized by progressive weakness and severe neurogenic muscle atrophy with early postnatal onset and death within the first few months of life.[2]

An inherited lower motor neuron disease has been recorded in pigs. Clinical findings of muscular tremors, paresis, or ataxia developed at 12 to 59 days of age. There is widespread degeneration of myelinated axons in peripheral nerves and in the lateral and ventral columns of lumbar and cervical segments of the spinal cord. Axonal degeneration is present in ventral spinal nerve roots and absent in dorsal spinal nerve roots when sampled at the same lumbar levels.

Equine motor neuron disease is a neurodegenerative condition that affects horses from 15 months to 25 years of age of many different breeds and has been associated with oxidative stress and vitamin E deficiency.[7,8] Progressive weakness, short-striding gait, trembling, long periods of recumbency, and trembling and sweating following exercise are characteristic clinical findings. The weakness is progressive and recumbency is permanent. Appetites remain normal or become excessive. At necropsy, degeneration or loss of somatic motor neurons in the spinal ventral horns, angular atrophy of skeletal muscle fibers, and the presence of lipofuscin deposits in the ventral horns of the spinal cord and retina are characteristic.

Sporadic cases of spinal cord damage in horses include hemorrhagic myelomalacia following general anesthesia and acute spinal cord degeneration following general anesthesia and surgery. Following recovery from the anesthesia, the horse is able to assume sternal recumbency but not able to stand. A hemorrhagic infarct assumed to be caused by cartilage emboli, and a venous malformation causing spinal cord destruction, have also occurred in the horse. The disease must be differentiated from myelitis and spinal cord compression caused by space-occupying lesions of the vertebral canal and cervical, vertebral malformation/malarticulation.

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Focal Diseases of the Brain and Spinal Cord

TRAUMATIC INJURY TO THE BRAIN

The effects of trauma to the brain vary with the site and extent of the injury, but initially nervous shock is likely to occur followed by death, recovery, or the persistence of residual nervous signs. Traumatic lesions of the skull or vertebral column were the most

commonly diagnosed nervous diseases of horses at necropsy in a large case series of 4,319 horses with clinical signs of nervous disease, accounting for 34% of all diagnoses.[1]

ETIOLOGY

Traumatic injury to the brain may result from direct trauma applied externally, by violent stretching or flexing of the head and neck, or by migration of parasitic larvae internally. Recorded causes include the following:

- Direct trauma is an uncommon cause because of the force required to damage the cranium. Accidental collisions, rearing forward, falling over backward after rearing are the usual reasons.
- Periorbital skull fractures in horses are caused by direct traumatic injury commonly from colliding with gate posts.
- Cerebral injury and CN injury accounted for a large percentage of neurologic diseases in horses. Young horses under 2 years of age seem most susceptible to injuries of the head.
- Injury by heat in goat kids is achieved with prolonged application of a hot iron used for disbudding
- Pulling back violently when tethered can cause problems at the atlantooccipital junction.
- Animals trapped in bogs, sumps, cellars, and waterholes and dragged out by the head, and recumbent animals pulled onto trailers can suffer dire consequences to the medulla and cervical cord, although the great majority of them come to surprisingly little harm.
- The violent reaction of animals to lightning stroke and electrocution causing damage to central nervous tissue; the traumatic effect of the electrical current itself also causes neuronal destruction.
- Spontaneous hemorrhage into the brain is rare but sometimes occurs in cows at parturition, causing multiple small hemorrhages in the medulla and brainstem.
- Brain injury at parturition, recorded in lambs, calves, and foals, is possibly a significant cause of mortality in the former.

PATHOGENESIS

The initial reaction in severe trauma or hemorrhage is nervous shock. Slowly developing subdural hematoma, a common development in humans, is accompanied by the gradual onset of signs of a space-occupying lesion of the cranial cavity, but this seems to be a rare occurrence in animals. In some cases of trauma to the head, clinical evidence of injury to the brain may be delayed for a few days until sufficient swelling, callus formation, or displacement of the fracture fragments has occurred. Trauma to the cranial vault may be classified, from least to most severe, as **concussion**, **contusion**, **laceration**, and **hemorrhage**.

Concussion

Concussion is usually a brief loss of consciousness that results from an abrupt head injury, which produces an episode of rapid acceleration/deceleration of the brain.

Contusion

With a more violent force, the brain is contused. There is maintenance of structure but loss of vascular integrity, resulting in hemorrhage into the parenchyma and meninges relative to the point of impact. Bony deformation or fracture of the calvaria results in two different kinds of focal lesions:

- Direct (**coup**) contusions immediately below the impact site
- Indirect (**contrecoup**) contusions to the brain at the opposite point of the skull; these hemorrhages result from tearing of leptomeningeal and parenchymal blood vessels.

Laceration

The most severe contusion is laceration in which the CNS tissue is physically torn or disrupted by bony structures lining the cranium or by penetrating objects such as bone fragments. Focal meningeal hemorrhage is a common sequel to severe head injury. Subdural hematomas usually follow disruption of bridging cerebral veins that drain into the dural venous sinuses, but subarachnoid hemorrhages are more common. The importance of these hemorrhages is that they develop into space-occupying masses that indent and compress the underlying brain. Progressive enlargement of the hematoma can result in secondary effects such as severe, widespread brain edema, areas of ischemia, herniations, midline shift, and lethal brainstem compression.

In birth injuries the lesion is principally one of hemorrhage subdurally and under the arachnoid.

Experimental Traumatic Craniocerebral Missile Injury

Traumatic insult of the brains of sheep with a .22 caliber firearm results in a primary hemorrhagic wound track with indriven bone fragments and portions of muscle and skin. There is crushing and laceration of tissues during missile penetration; secondary tracks caused by bone and bullet fragments; widely distributed stretch injuries to blood vessels, nerve fibers, and neurons as a consequence of the radial forces of the temporary cavity that develops as a bullet penetrates tissue; marked subarachnoid and intraventricular hemorrhage; and distortion and displacement of the brain. The lesions are consistently severe and rapidly fatal.

CLINICAL FINDINGS

Clinical signs of neurologic disease usually follows the pattern of greatest severity initially with recovery occurring quickly but incompletely to a point where a residual defect is evident, with this defect persisting unchanged for a long period and often permanently. This failure to improve or worsen after the initial phase is a characteristic of traumatic injury.

With severe injury there is cerebral shock in which the animal falls unconscious with or without a transient clonic convulsion. Consciousness may never be regained, but in animals that recover it returns in from a few minutes up to several hours. During the period of unconsciousness, clinical examination reveals dilatation of the pupils; absence of the eye preservation and pupillary light reflexes; and a slow, irregular respiration, with the irregularity phasic in many cases. There may be evidence of bleeding from the nose and ears, and palpation of the cranium may reveal a site of injury. Residual signs vary a great deal. Blindness is present if the optic cortex is damaged, hemiplegia may be associated with lesions in the midbrain, and traumatic epilepsy may occur with lesions in the motor cortex.

Fracture of the petrous temporal bone is a classic injury in horses caused by rearing and falling over backward. Both the facial and the vestibular nerves are likely to be damaged so that at first the animal may be unable to stand and there may be blood from the ear and nostril of the affected side. When the animal does stand, the head is rotated with the damaged side down. There may be nystagmus, especially early in the course of the disease. The ear, eyelid, and lip on the affected side are also paralyzed and sag. Ataxia with a tendency to fall is common. Some improvement occurs in the subsequent 2 or 3 weeks as the horse compensates for the deficit, but there is rarely permanent recovery. An identical syndrome is recorded in horses in which there has been a stress fracture of the petrous temporal bone resulting from a preexisting inflammation of the bone. The onset of signs is acute but unassociated with trauma.

Fracture of the basisphenoid and/or **basioccipital bones** is also common. These fractures can seriously damage the jugular vein; carotid artery; and glossopharyngeal, hypoglossal, and vagus nerves. The cavernous sinus and the basilar artery may also be damaged and lead to massive hemorrhage within the cranium. Large vessels in the area are easily damaged by fragments of the fractured bones, causing fatal hemorrhage. A midline fracture of the frontal bones can also have this effect.

Other signs of severe trauma to the brain include opisthotonus with blindness and nystagmus and, if the brainstem has been damaged, quadriplegia. There may also be localizing signs, including head rotation,

circling, and falling backward. Less common manifestations of resulting hemorrhage include bleeding into the retropharyngeal area, which may cause pressure on guttural pouches and the airways and lead to asphyxia. Bleeding may take place into the guttural pouches themselves.

Newborn lambs affected by birth injury to the brain are mostly dead at birth, or die soon afterward. Surviving lambs drink poorly and are very susceptible to cold stress. In some flocks it may be the principal mechanism causing perinatal mortality.

DIAGNOSIS

Radiography of the skull is important to detect the presence and severity of fractures, which may have lacerated nervous tissue; however, CT is a much more sensitive method for detecting fractures of the calvarium and basilar bone than radiography.[1]

CLINICAL PATHOLOGY

CSF should be sampled from the cerebellomedullary cistern and examined for evidence of RBCs. Extreme care must be taken to ensure that blood vessels are not punctured during the sampling procedure because this would confound the interpretation of the presence of RBCs. The presence of heme pigments in the CSF (xanthochromia) suggests the presence of preexisting hemorrhage; the presence of eosinophils or hypersegmented neutrophils suggests parasitic invasion.

NECROPSY FINDINGS

In most cases a gross hemorrhagic lesion will be evident, but in concussion and nematodiasis the lesions may be detectable only on histologic examination.

DIFFERENTIAL DIAGNOSIS

Unless a history of trauma is available diagnosis may be difficult.

TREATMENT

The principles of treatment of animals exhibiting neurologic abnormalities after a traumatic event are derived from the results of large, controlled, multicenter clinical trials in humans. Similar studies have not been performed in large animals. The general principles are (1) stabilize the patient by ensuring a patent airway, obtaining vascular access and attending to wounds; (2) specific treatment for hyperthermia, because brain defects may result in an inability to regulate core temperature; (3) prevent or treat systemic arterial hypotension; (4) optimize oxygen delivery; (5) ensure adequate ventilation by placing in sternal recumbency whenever possible; (6) decrease pain; (7) monitor plasma glucose concentration and maintain euglycemia; and (8) prevent or treat cerebral edema by having the head elevated or by the intravenous administration of a hyperosmolar agent (20% mannitol as a series of bolus infusions of 0.25–1.0 g/kg BW every 4–6 hours, the latter is an expensive treatment; hypertonic saline, 7.2% NaCl, 2 mL/kg BW every 4 hours for five infusions). Intravenous catheterization should be confined to one jugular vein, and the neck should not be bandaged in an attempt to minimize promotion of cerebral edema by jugular venous hypertension.

Seizures should be treated when they occur by initially administering diazepam at 0.1 mg/kg intravenously. If no improvement is noticed within 10 minutes, then one or two additional doses of diazepam (0.1 mg/kg, intravenously; total dose 0.3 mg/kg, intravenously) should be administered at 10-minute intervals. Midazolam could be substituted for diazepam, but dose rates are not well defined. If this dosage protocol of diazepam does not provide adequate seizure control, then phenobarbitone (20 mg/kg intravenously over 20 minutes) should be administered to effect; the phenobarbitone can be diluted in 0.9% NaCl solution. This should provide seizure control for a number of hours. If seizures return, then oral phenobarbitone (6 mg/kg every 8 hours) can be administered to foals and horses, with a reduction in the oral dose to 3 mg/kg every 8 hours if seizures are controlled. An alternative protocol in horses is a mixture of 12% chloral hydrate and 6% magnesium sulfate to effect at an intravenous administration rate not exceeding 30 mL/min. Euthanasia should be considered to adult ruminants with seizures that are only responsive to intravenous phenobarbitone.

Many anecdotal treatments have been used in large animals, but evidence attesting to their efficacy is lacking. Among the more popular empiric antioxidant treatments are dimethyl sulfoxide (1 g/kg BW IV as a 10% solution in 0.9% NaCl) administered intravenously or by nasogastric tube every 12 hours, vitamin E (α-tocopherol, 50 IU/kg BW administered orally every day), vitamin C (ascorbic acid, 20 mg/kg BW administered orally every day), and allopurinol (5 mg/kg BW administered orally every 12 hours). Corticosteroids have also been advocated; promoted treatments include an antiinflammatory dose of dexamethasone (0.05 mg/kg BW IV every day) or a high dose of methylprednisolone sodium succinate (30 mg/kg BW initial IV bolus, followed by continuous infusion of 5.4 mg/kg BW per hour for 24–48 hours); the latter treatment is prohibitively expensive in large animals and must be given within a few hours of the traumatic event to be effective. Intravenous magnesium sulfate (50 mg/kg BW) in the first 5 to 10 L of intravenous fluids has also been advocated on the basis that it inhibits several aspects of the secondary injury cascade.

The overall short-term survival rate in one case series of 34 cases was 62%.[2] In those animals that recover consciousness within a few hours or earlier, the prognosis is favorable and little or no specific treatment may be necessary other than nursing care. When coma lasts for more than 3 to 6 hours, the prognosis is unfavorable, and slaughter for salvage or euthanasia is recommended. Horses with basilar bone fractures are 7.5 times more likely not to survive as horses without this type of fracture.[2] Treatment for cerebral edema of the brain as previously outlined may be indicated when treatment for valuable animals is requested by the owner. Animals that are still in a coma 6 to 12 hours following treatment are unlikely to improve, and continued treatment is probably not warranted.

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BRAIN ABSCESS

Abscesses of the brain are rare, but occur most commonly in young farm animals under 1 year of age and rarely in older animals. They appear to be more common in ruminants than in horses. Brain abscesses were not observed at necropsy in a large case series of 4,319 horses with clinical signs of nervous disease in France.[1] They produce a variety of clinical signs depending on their location and size. Basically the syndrome produced is one of a space-occupying lesion of the cranial cavity with some motor irritation signs. Localized or diffuse meningitis is also common, along with the effects of the abscess.

ETIOLOGY

Abscesses in the brain originate in a number of ways. Hematogenous infections are common, but direct spread from injury to the cranium or via the nasopharynx may also occur.

Hematogenous Spread

The lesions may be single, but are often multiple, and are usually accompanied by meningitis. The infection usually originates elsewhere.

- *Actinobacillus mallei* from glanders lesions in lung
- *Streptococcus zooepidemicus* var. *equi* as a complication of strangles in horses
- *Corynebacterium pseudotuberculosis* in a goat causing an encapsulated abscess in the left cerebellar peduncles
- *Actinomyces bovis* and *Mycobacterium bovis* from visceral lesions in cattle
- *Fusobacterium necrophorum* from lesions in the oropharynx of calves
- *Pseudomonas pseudomallei* in melioidosis in sheep

- *Staphylococcus aureus* in tick pyemia of lambs
- Systemic fungal infections such as cryptococcosis may include granulomatous lesions in brain.

Local Spread

- Via peripheral nerves from the oropharynx, the one specific disease is listeriosis in ruminants and New World camelids.
- Multifocal meningoencephalitis associated with lingual arteritis induced by barley spikelet clusters.
- Space-occupying lesions of facial and vestibulocochlear nerves and geniculate ganglion secondary to otitis media in calves.
- Abscesses of the rete mirabile of the pituitary gland are seen secondary to nasal septal infection after nose-ringing in cattle. *Trueperella* (*Arcanobacterium* or *Actinomyces* or *Corynebacterium*) *pyogenes* is the most common isolate, and several other species of bacteria that cause chronic suppurative lesions have been recovered. Similar abscesses, usually containing *T. pyogenes,* occur in the pituitary gland itself.
- Extensions from local suppurative processes in cranial signs are seen after dehorning from otitis media. The lesions are single and most commonly contain *T. pyogenes* and are accompanied by meningitis.

PATHOGENESIS

Infectious agents can invade the CNS by four routes:

- **Retrograde infection via peripheral nerves**
- **Direct penetrating injuries**
- **Extension of adjacent suppurative lesions**
- **By way of the systemic circulation**

Single abscesses cause local pressure effects on nervous tissue and may produce some signs of irritation, including head-pressing and mania, but the predominant effect is one of loss of function caused by destruction of nerve cells. Multiple abscesses have much the same effect. In single abscesses the signs usually make it possible to define the location of the lesion, whereas multiple lesions present a confusing multiplicity of signs and variation in their severity from day to day, suggesting that damage has occurred at a number of widely distributed points and at different times.

The pituitary abscess syndrome has an uncertain pathogenesis. The pituitary gland is surrounded by a complex mesh of intertwined arteries and capillary beds known as the rete mirabile, which has been identified in cattle, sheep, goats, and pigs but not horses. This extensive capillary network surrounding the pituitary gland makes it susceptible to localization by bacteria that originate from other sources of infection. Nose-ringing of cattle may result in septic rhinitis, which could result in infection of the dural venous sinus system, which communicates with the subcutaneous veins of the head. Bacteria may also reach the rete mirabile by way of lymphatics of the nasal mucosa and cribriform plate. CN deficits occur as a result of the extension of the abscess into the adjacent brainstem.

CLINICAL FINDINGS

General signs include mental depression, clumsiness, head-pressing, and blindness, often preceded or interrupted by transient attacks of motor irritation including excitement, uncontrolled activity, and convulsions. A mild fever is usually present, but the temperature may be normal in some cases.

The degree of blindness varies depending on the location of the abscess and the extent of adjacent edema and meningoencephalitis. The animal may be blind in one eye and have normal eyesight in the other eye or have normal eyesight in both eyes. Unequal pupils and abnormalities in the pupillary light reflex, both direct and consensual, are common. Uveitis, iris bombé, and a collection of fibrin in the anterior chamber of an eye may be present in some cases of multiple meningoencephalitis in cattle. Nystagmus is common when the lesion is near the vestibular nucleus; strabismus may also occur.

Localizing signs depend on the location of lesions and may include cerebellar ataxia, deviation of the head with circling and falling, and hemiplegia or paralysis of individual or groups of CNs often in a unilateral pattern. In the later stages, there may be papilledema. In calves with lesions of the facial and vestibulocochlear nerves and geniculate ganglion, clinical signs may include drooping of the ears and lips, lifting of the nose, slight unilateral tilting of the head, and uncontrolled saliva flow. Inability to swallow may follow and affected calves become dehydrated.

These localizing signs may be intermittent, especially in the early stages, and may develop slowly or acutely.

Pituitary gland abscesses are most common in ruminants, primarily cattle 2 to 5 years of age, but are relatively rare. The most common history includes anorexia, ataxia, depression, and drooling from the mouth with inability to chew and swallow. The most common clinical findings are depression, dysphagia, dropped jaw, blindness, and absence of pupillary light reflexes. Terminally, opisthotonus, nystagmus, ataxia, and recumbency are common. Characteristically, the animal stands with a base-wide stance with its head and neck extended and its mouth not quite closed; there is difficulty in chewing and swallowing, and drooling of saliva. Affected animals are usually nonresponsive to external stimuli. CN deficits are common, and usually asymmetric, multifocal, and progressive. These include reduced tone of the jaw, facial paralysis, strabismus, and a head tilt. There may also be ptosis and prolapse of the tongue. Bradycardia has been recorded in about 50% of cases. Terminally there is opisthotonus, nystagmus, and loss of balance, followed by recumbency.

CLINICAL PATHOLOGY

Cerebrospinal Fluid

Leukocytes, protein, and bacteria may be present in the CSF, but only when the abscess is not contained.

Hematology

In pituitary gland abscessation there may be hematologic evidence of chronic infection including neutrophilia, hyperproteinemia, and increased fibrinogen, although it is unlikely that a pituitary abscess itself is sufficiently large enough to induce these changes.

Imaging

Radiographic examination will not detect brain abscesses unless they are calcified or cause erosion of bone. CT has been used to diagnose a brain abscess in the horse. MRI is the preferred imaging modality to diagnose a cerebral abscess, with mature abscesses having an isointense to hypointense core on T1-weighted images and an isotense to hyperintense core with a hypointense capsule on T2-weighted images.[2]

Electroencephalography

Electroencephalographic assessment of central blindness caused by brain abscess in cattle has been reported.

NECROPSY FINDINGS

The abscess or abscesses may be visible on gross examination and if superficial are usually accompanied by local meningitis. Large abscesses may penetrate to the ventricles and result in a diffuse ependymitis. Microabscesses may be visible only on histologic examination. A general necropsy examination may reveal the primary lesion.

DIFFERENTIAL DIAGNOSIS

Brain abscess is manifested by signs of involuntary movements and loss of function, which can occur in many other diseases of the brain, especially when local lesions develop slowly. This occurs more frequently with tumors and parasitic cysts but it may occur in encephalitis. The characteristic clinical findings are those of a focal or multifocal lesion of the brain, which include the following:

- Localizing signs of hemiparesis and ataxia
- Postural reaction deficit
- Vestibular signs, including head tilt and positional nystagmus
- Cranial nerve deficits

There may be evidence of the existence of a suppurative lesion in another organ, and a high cell count and detectable infection in the CSF to support the diagnosis of abscess. Fever may or may not be present. The only specific disease in which abscess occurs is listeriosis, in which the lesions are largely confined to the medulla oblongata and the characteristic signs include circling and unilateral facial paralysis. Occasional cases may be associated with fungal infections, including cryptococcosis. Toxoplasmosis is an uncommon cause of granulomatous lesions in the brain of most species.

Many cases of brain abscess are similar to otitis media but there is, in the latter, rotation of the head, a commonly associated facial paralysis and an absence of signs of cerebral depression.

The pituitary gland syndrome in cattle must be differentiated from listeriosis, polioencephalomalacia, lead poisoning, other brain abscesses, and thrombomeningoencephalitis. In sheep and goats, *Parelaphostrongylus tenuis* infection and caprine arthritis encephalomyelitis syndrome may resemble the pituitary gland abscess syndrome.

TREATMENT

Parenteral treatment with antimicrobials is indicated but the results are often unsatisfactory because of the inaccessibility of the lesion, with the clear exception being listeriosis. Treatment of pituitary gland abscess is not recommended, and an antemortem diagnosis is rarely obtained. There is one successful report of recovery after surgical excision of the complete abscess in a 1-month-old alpaca.[2]

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TUMORS OF THE CENTRAL NERVOUS SYSTEM

Primary tumors of the CNS are extremely rare in farm animals. They produce a syndrome indicative of a general increase in intracranial pressure and local destruction of nervous tissue. Tumors of the peripheral nervous system are more common.

ETIOLOGY

The reader is referred to the review literature for a summary of available references on the tumors of the CNS of farm animals, which include the following:

- Meningeal tumors in cattle
- Oligodendroglioma in a cow[1]
- Ependymoblastoma in a heifer[2]
- Primitive neuroectodermal tumor with ependymal differentiation in a cow[3]
- Cerebellar medulloblastoma in a calf[4]
- Choroid plexus carcinoma in a goat[5]
- Equine papillary ependymoma
- Lymphoma confined to the CNS in a horse.[6]

PATHOGENESIS

The development of the disease parallels that of any space-occupying lesion, with the concurrent appearance of signs of increased intracranial pressure and local tissue destruction. Many lesions found incidentally at necropsy may not have had any related clinical findings.

CLINICAL FINDINGS

The clinical findings are similar to those caused by a slowly developing abscess and localizing signs depending on the location, size, and speed of development of the tumor. Clinical signs are usually representative of increased intracranial pressure, including opisthotonus, convulsions, nystagmus, dullness, head-pressing, and hyperexcitability. Common localizing signs include circling, deviation of the head, and disturbance of balance.

CLINICAL PATHOLOGY

There are no positive findings in the clinicopathologic examination, which aids in diagnosis.

NECROPSY FINDINGS

The brain should be carefully sectioned after fixation if the tumor is deep-seated.

TREATMENT

There is no treatment.

DIFFERENTIAL DIAGNOSIS

Differentiation is required from the other diseases in which space-occupying lesions of the cranial cavity occur. The rate of development is usually much slower in tumors than with the other lesions.

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CENTRAL NERVOUS SYSTEM–ASSOCIATED TUMORS

The pituitary gland (hypophysis) consists of the adenohypophysis (pars distalis, intermedia, tuberalis) and the neurohypophysis (pars nervosa). Tumors of the pituitary gland are common in older horses. Cushing's syndrome in horses almost invariably originates from an **adenoma of the pars intermedia** of the pituitary gland. Initially, these animals exhibit only one remarkable sign, namely, hirsutism. Horses with Cushing's disease only do not manifest polyuria and polydipsia. Major sequelae of an adenoma of the pars intermedia of the pituitary gland are type 2 diabetes mellitus and laminitis. Diagnosis of an adenoma of the pars intermedia of the pituitary gland in the horse mainly depends on dynamic endocrinologic function tests. The sensitivity of the adrenocorticotropin test is about 80%.

Pituitary adenomas can arise from other parts of the pituitary gland; there is a report of a nonfunctional chromophobe adenoma located in the pars distalis of an alpaca with depression and compulsive walking.[1]

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METASTATIC TUMORS OF THE CENTRAL NERVOUS SYSTEM

Many primary tumors of nonnervous tissue have the potential for metastasis or localized growth into the CNS.

- **Ocular squamous cell carcinoma** of cattle may invade the cranium through the cribriform plate
- **Lymphomas** of cattle may metastasize to the CNS with either a multicentric distribution or occasionally as the only lesion. Most commonly bovine lymphoma occurs as an epidural mass in the vertebral canal. Intracranial lymphoma usually involves the leptomeninges or the choroid plexus. Clinical signs are related to the progressive compression of the nervous tissue at the site of the mass. Lymphoma in the horse has occurred in the epidural space with spinal cord compression.
- **Thymic lymphosarcoma** rarely metastasizes to the cerebellum and intracranial extradural sites in yearling cattle.[1]
- **Rhabdomyosarcoma** invaded the thoracic spinal cord of a heifer, resulting in posterior paresis.[2]
- **Schwannomas** (also called neuromas) originate from the Schwann cells of cranial or spinal nerve roots except CNs I and II, which are myelinated by oligodendroglia. Local growth of a schwannoma into the thoracic or sacral spinal cord produced clinical signs of spinal cord dysfunction in two adult cattle.[3] Schwannomas occur in adult

horses with no apparent breed or sex predisposition. There is one report of successful treatment of a dermal schwannoma using localized radiation therapy.[4] In domestic animals, schwannomas can be difficult to differentiate from neurofibromas, and consequently, schwannomas and neurofibromas are categorized as PNSTs by the WHO.

- **Malignant melanoma** has been diagnosed in a cow with hindlimb ataxia[3] and in gray horses where they are usually metastases from skin tumors.

CENTRAL NERVOUS SYSTEM–ASSOCIATED MASSES

Cholesterinic granulomas, also known as cholesteatomas, may occur in up to 20% of older horses without any clinical effects. However, they can be associated with significant neurologic disease. Affected horses are usually obese. Cholesterinic granulomas occur in the choroid plexus of the fourth ventricle or in the lateral ventricles and mimic cerebrocortical disease. It has been suggested that cholesterol granulomas result from chronic hemorrhage into the plexus stroma, but the underlying pathogenesis is unknown.

Brownish nodular thickening of the plexuses with glistening white crystals is a common incidental finding in mature and aged horses. Occasionally, deposits in the plexuses of the lateral ventricles are massive and fill the ventricular space and cause secondary hydrocephalus caused by the buildup of CSF behind the mass. CSF may be xanthochromic with an elevated total protein.

Clinical findings include episodes of abnormal behavior such as depression and bolting uncontrollably and running into fences and walls. Some horses exhibit profound depression, somnolence, and reluctance to move. Seizures have also been reported. Other clinical findings reported include decreased performance, aggression, head tilt, incoordination, intermittent convulsions, hindlimb ataxia progressing to recumbency, intermittent circling in one direction, and spontaneous twitching along the back and flank. There are often serious changes in temperament, with previously placid animals becoming violent and aggressive. In others there are outbursts of frenzied activity followed by coma. The horse may be normal between attacks, and these may be precipitated by moving the head rapidly.

These signs are referable to cerebrocortical disease and the differential diagnosis of cholesterol granulomas must include diffuse cerebral encephalopathy caused by abscess, tumor, toxicosis, metabolic disease, encephalomyelitis, trauma, and hydrocephalus. At necropsy, large cholesterol granulomas are present in the choroid plexus.

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Plant Toxins Affecting the Nervous System

CANNABINOIDS

Cannabinoids are resinoids found in the plant *Cannabis sativa* (marijuana). The toxic principle is the alkaloid tetrahydrocannabinol. Most reports of poisoning are in dogs and humans, but cattle and horses have also been affected. Clinical signs of poisoning in horses include restlessness, hypersensitivity, tremor, sweating, salivation, dyspnea, staggering gait, and death or recovery after a few hours. No significant necropsy lesions are recorded. The toxin is detectable in stomach or rumen contents.

CYNANCHOSIDE

Cynanchoside is found in *Cynanchum* spp. (monkey rope),[1] and a very similar toxin is found in *Marsdenia rostrata* (milk vine), *M. megalantha*,[1] *Sarcostemma brevipedicellatum* (= *S. australe*; caustic vine), and *S. viminale* (caustic bush). It is associated with hypersensitivity; ataxia; muscle tremors; recumbency; tetanic and clonic convulsions; opisthotonus; and death in horses, donkeys, pigs, and ruminants.[1,2] Other less common signs include teeth grinding, dyspnea, salivation, and vomiting.

DITERPENOID (KAURENE) GLYCOSIDES (ATRACTYLOSIDE, CARBOXYATRACTYLOSIDE, PARQUIN, CARBOXYPARQUIN, AND WEDELOSIDE)

Diterpenoid glycoside toxins have been found in the following species:

Atractylis
Atractylodes
Callilepsis
Cestrum
Iphiona
Wedelia
Xanthium

Xanthium strumarium (cockleburr, Noogoora burr) includes the taxa *X. canadense, X. italicum, X. orientale, X. pungens,* and *X. chinense,* and is poisonous to pigs and ruminants. *X. spinosum* (Bathurst burr) is also toxic and assumed to contain diterpenoid glycosides. The two cotyledonary leaves, either within the spiny burrs or just after sprouting, contain the largest amount of toxin and are the usual source of poisoning. The cockleburs occur on most continents. Poisonings are reported from North America, UK, Europe, and Australia. Most deaths occur on flood plains on which the weed is allowed to grow in abundance. After heavy rain the seeds in the burrs sprout and are palatable to all species, especially calves and pigs. Mortalities are also recorded in adult cows and sheep. Burrs may contaminate feed grains and poison livestock fed on the compounded ration.

Cestrum spp. (e.g., *C. parqui, C. laevigatum*), are garden plants originating from South and Central America which, except for *C. diurnum,* also contain a carboxyatractyloside toxin.

Wedelia asperrima (yellow daisy), *W. biflora,* and *W. glauca* contain wedeloside. Severe hepatic necrosis is the principal necropsy finding, and the clinical syndrome and clinical pathology are characteristic of hepatic encephalopathy.

Poisoning by diterpenoid glycoside toxins in pigs and calves is acute, manifested by hyperexcitability, so that the entire herd appears restless, followed by severe depression, rigidity of the limbs and ears, weakness and a stumbling gait, falling easily and recumbency, and clonic convulsions with opisthotonus. Calves may be belligerent. Acute cases die during the first convulsive episode. The course may be as long as 48 hours and terminate in recovery, but death is the usual outcome. The characteristic lesion is hepatic necrosis.

Treatment is not undertaken. Control depends on keeping livestock away from pasture dominated by these weeds, especially when there are large quantities of sprouted *Xanthium* spp. seeds available.

STYPANDROL

Stypandrol (syn. hemerocallin), a binaphthoquinone (binaphthalene tetrol) is found in *Dianella revoluta* (flax lily), *Stypandra glauca* (= *S. imbricata, S. grandiflora*—nodding blue lily), and *Hemerocallis* spp. (day lily). Field cases occur only with *S. glauca* and are characterized by blindness, incoordination, posterior weakness and, eventually, flaccid paralysis and recumbency in grazing ruminants. Dilatation and immobility of the pupil, with retinal vascular congestion, hemorrhage, and papilledema visible ophthalmoscopically, are characteristic. At necropsy there is diffuse status spongiosis in the brain, general neuronal vacuolation, and axonal degeneration of optic nerve fibers and the photoreceptor cells of the retina.[3] Only the young green shoots are poisonous, so that outbreaks occur only in the spring when the plant is flowering.

TROPANE ALKALOIDS

Tropane alkaloids include atropine, hyoscyamine, hyoscine, and scopolamine, found in the following:[4,5]

Atropa belladonna (deadly nightshade)
Datura stramonium (common thorn apple, jimsonweed, gewone stinkblaar)[4]
D. ferox (large thornapple, groot stinkblaar)[4]

Duboisia leichhardtii
D. myoporoides (corkwoods)
Hyoscyamus niger (henbane).

D. stramonium grows universally but cases of poisoning are few, possibly because of its unpalatability, its high toxic dose, and because it produces ruminal atony in cattle. All parts of *Datura* spp. contain belladonna alkaloids with the highest amount in the flowers, followed by the stem, seeds, leaves, and roots.[5] The seeds of the plant are likely to contaminate grain supplies and may be associated with poisoning.[4]

Clinical signs are primarily caused by blockade of peripheral muscarinic receptors innervating smooth muscle, cardiac muscle, and exocrine glands. Ingestion of these plants in sufficient quantity is associated with a syndrome of mydriasis (pupil dilation and blindness), dry mouth, restlessness, tremor, tachycardia, hyperthermia, and frenzied actions.[5] Colic, in particular impaction colic, is reported in horses.[4] Convulsions, recumbency, and death may occur. Cholinesterase inhibitors such as physostigmine may be used to reverse the anticholinergic effects.[4] There are no significant necropsy lesions.

TUTIN

Tutin is a poisonous constituent of the *Coriaria* spp. (tutu trees) in New Zealand. It is associated with a short course of hypersensitivity, restlessness, and convulsions followed by death, with no visible lesions at necropsy.

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INDOLE ALKALOIDS

A large number of indole alkaloids occur in fungi, especially the *Claviceps* and *Acremonium* spp. In plants there are also some groups of toxins with similar toxic effects, and similar to those of the fungi. The important two are the β-carbolines and the dimethyl tryptamines; followed by the hydroxyl methyl tryptamines, and a miscellaneous group of alstonine and related toxins. Plants included in the latter group that are associated with an incoordination syndrome like phalaris staggers are *Gelsemium sempervirens* (yellow jessamine), *Alstonia constricta* (bitter bark tree), and the mushroom *Psilocybe* spp. (mad or magic mushroom). *Poa hueca* and *Urtica* spp. (stinging nettle) are associated with a more acute syndrome of convulsions and sudden death. *Phalaris* spp. are unusual in that they contain both β-carbolines and methylated tryptamines. Related indole alkaloids of the pyrrolidinoindoline type have poisoned livestock in Australia (idiospermuline in *Idiospermum australiense*) and North America (calycanthine in *Calycanthus* spp.), producing tetanic convulsions.

β-CARBOLINE INDOLEAMINE ALKALOID POISONING

β-Carboline indole alkaloids (harmala alkaloids) in plants include harmaline, tetrahydroharmine, harman, norharman, tetrahydroharman, harmine, harmol, harmalol, peganine, and deoxypeganine.[1] The mechanism of action for these alkaloids is competitive inhibition of monoamine oxidase (primarily MAO-A) resulting in increased serotonin activity.[2] Synthetic forms of these alkaloids are associated with clinical signs similar to those occurring in natural plant poisonings with *Peganum harmala* (African or Turkish rue), *P. mexicana* (Mexican rue), *Phalaris* spp., *T. terrestris* (caltrop, catshead burr), *T. micrococcus* (yellow vine), *Kallstroemia hirsutissima* (hairy caltrop, carpet weed), and *K. parviflora*.[1-3]

The characteristic syndrome, similar to that of an upper motor neuron lesion, includes hypermotility or hypomotility, sometimes sequentially in the same patient, muscle tremor, partly flexed paresis of the thoracic and/or the pelvic limb, hypermetria, a wide-based stance, crossing of the limbs, extension of the neck, swaying of the head, walking backward, sudden jumping movements, sham eating, and terminal convulsions. The net effect, seen in all farm animal species and camels, is one of easy stimulation, by stimulating gait incoordination and stumbling, fetlock knuckling, falling, and recumbency. The signs appear gradually; are similar to, but less severe than, those associated with the methylated tryptamines; and are irreversible. There is axonal degeneration in peripheral nerves. Long-term cases of *T. terrestris* poisoning pivot on their front limbs while their hindlimbs trace a circle. The pivoting is related to the unilateral muscle atrophy of limbs of one side or the other.

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INDOLIZIDINE ALKALOID TOXICOSIS (LOCOISM, PEASTRUCK)

The two indolizidine alkaloids of plant origin are castanospermine and swainsonine and both of them affect cellular enzyme activity.

CASTANOSPERMINE POISONING

Castanospermine, an indolizidine alkaloid found in the seeds of *Castanospermum australe* (Moreton Bay chestnut tree), is structurally and functionally similar to swainsonine.[1] It inhibits α-glucosidase activity so that affected cattle have been misdiagnosed as heterozygotes for generalized glycogenosis type II (Pompe's disease). The seeds are also associated with hemorrhagic gastroenteritis with myocardial degeneration and nephrosis in cattle and sheep if eaten in large quantities.[1]

SWAINSONINE POISONING

SYNOPSIS

Etiology Poisoning by some plants in the genera of *Astragalus, Oxytropis,* and *Swainsona*. It is associated with induced mannosidosis.

Epidemiology Grazing toxic plants for 2–6 weeks is associated with signs, reversible if pasture is changed.

Clinical pathology Urine content of mannose-containing oligosaccharides is elevated.

Lesions Vacuolation of neurons.

Diagnostic confirmation Swainsonine can be detected in serum, urine, or animal tissues; the endophyte may be detected in the plant.

Treatment No treatment is available.

Control Restrict both the amount of plant and time animals allowed to graze infected pastures.

ETIOLOGY

Swainsonine is an indolizidine alkaloid found in many *Astragalus* spp., *Oxytropis* spp., and *Swainsona* spp. legumes.[2,3] Some *Ipomoea* spp.[4] as well as *Turbina cordata*[5] and *Sida carpinifolia*[6,7] contain swainsonine either alone or in combination with mixtures of other alkaloids. Ingestion of the toxic plants over a long period is associated with an induced lysosomal storage disease in all animal species. Not all plants in a particular species contain swainsonine. In North America there are over 354 different species of *Astragalus* and 22 species of *Oxytropis,* yet only 20 of them are known to contain swainsonine or are associated with locosim.[2] The common plants in which the alkaloid's

presence has been identified include the following:

- *Astragalus lentiginosus, A. mollisimus, A. wootonii, A. emoryanus.*[2] Other plants of this genus that are associated with a similar disease, and in which the presence of swainsonine is assumed, are *A. northoxys, A. lentiginosus* var. *waheapensis, A. lusitanicus,* and *A. thurberi.*
- *Oxytropis sericea, O. ochrocephala.*[2] Other plants of this genus that are associated with a similar disease, and in which the presence of swainsonine is assumed, are *O. besseyi, O. condensata, O. lambertii,* and *O. puberula.*
- *Swainsona canescens, S. galegifolia, S. brachycarpa, S. greyana, S. luteola, S. procumbens, S. swainsonioides.*[3]

Undifilum oxytropis (formerly *Embellisa* spp.), a fungal endophyte present in the seeds, has been identified in the genera of *Astragalus* spp. and *Oxytropis* spp. as well as in *S. canescens* and is currently thought to be responsible for the production of swainsonine.[6,8,9] Swainsonine is also synthesized by the fungus *R. leguminicola,* but the disease associated with this fungus is caused by its slaframine content.

EPIDEMIOLOGY

Occurrence

Poisoning is most common in North America (as locoism associated with *Astragalus* spp. and *Oxytropis* spp.) and in Australia as Darling pea or peastruck (*Swainsona* spp.), but it occurs worldwide.[2,3,8] Toxicity from *Oxytropis* spp. has been reported in China, *Ipomea* spp. in goats in Brazil,[4] *T. cordata* in goats in Brazil,[5] *S. carpinifolia* in horses in Brazil,[10] and unknown swainsonine source in a horse in Belgium.[7]

Risk Factors

Animal Risk Factors

All animal species are affected, and experimental administration of the alkaloid to monogastric, farm, and laboratory animals is associated with the typical neuronal *A. lentiginosus* lesions. Horses are highly sensitive to swainsonine and develop clinical signs when fed 0.2 mg swainsonine/kg BW for 60 days followed by cattle and sheep at 0.25 mg/kg BW for 30 to 45 days.[7,11]

Grazing animals must ingest the plants for at least 2 weeks, and more often 6 weeks, before clinical signs appear.[7] The plants are not addicting, but animals appear to have a preference for them over other plants. It may be that the plants are more palatable to them at certain times of the year compared with what other forage is available.[2]

Swainsonine is excreted in the milk and may intoxicate nursing animals.[2]

PATHOGENESIS

Swainsonine is a specific inhibitor of lysosomal α-mannosidase causing accumulation of mannose in lysosomes and thus widespread neurovisceral cytoplasmic vacuolation.[2,3,7] The vacuoles are accumulations of mannose-rich oligosaccharides, including abnormal glycoproteins. Vacuolation reaches its greatest intensity in the CNS, and this is probably related to the predominance of nervous signs in the disease. Vacuolation of the chorionic epithelium may be related to the occurrence of abortion, and a transient infertility is suspected in rams to be the result of a similar lesion in the epithelium of the male reproductive tract. The lesion appears quickly and is reversible if the swainsonine intake ceases. In addition, swainsonine inhibits mannosidase II resulting in an alteration of glycoprotein synthesis, processing, and transport. The net result is a dysfunction of membrane receptors and circulating insulin, as well as impairment of cellular adhesion.[2,7]

CLINICAL FINDINGS

After several weeks of grazing affected pasture adult animals begin to lose condition and young animals cease to grow. The appetite is diminished, and the coat becomes dull and harsh.[2,7,10,11] Several weeks later nervous signs of depression; gait incoordination; muscle tremor; and difficulty in rising, eating, and drinking become apparent. Sheep commonly adopt a "star-gazing" posture, and horses may show nervousness, excitation, rearing over backward when handled, tremors, colic, recumbency, and death.[7,11] Cases may become overexcited if stressed or stimulated. Recovery is likely if the animal is removed from the source of the toxin soon after signs appear. Recovery may be complete or there may be a residual gait incoordination if the animal is excited. Advanced cases may show no improvement, and others become recumbent and die. Calves at high altitudes fed *A. lentiginosus* or *O. sericea* develop a higher incidence of congestive heart failure than calves not fed on the plants.

Pregnant ewes ingesting *Astragalus* spp. plants may abort or produce abnormal offspring with contractures. The defects take the form of small, edematous, or dead fetuses or skeletal deformity.[2,12] There are no such abnormalities recorded with *Swainsona* spp.

CLINICAL PATHOLOGY

Vacuolation in circulating lymphocytes occurs in poisoning caused by *Swainsona* spp., and may have diagnostic significance. Serum levels of α-mannosidase are significantly reduced and swainsonine levels increased. Swainsonine levels reflect the amount being ingested and not the duration of exposure, and quickly return to normal when ingestion of the plants ceases.[7] The urine content of mannose-containing oligosaccharides is greatly increased during the period of intake of swainsonine.

NECROPSY FINDINGS

The characteristic microscopic lesion is fine vacuolation of the cytoplasm in neurons throughout the CNS. Similar vacuolation is present in cells of other organs, especially the kidney, and the fetus in animals poisoned by *Astragalus* spp. High blood and tissue levels of swainsonine are detectable, including in frozen material.

In aborted calves, lambs, and foals there is extensive vacuolation of the chorionic epithelial cells. The skeletal deformities include arthrogryposis and rotation of the limbs about their long axis.

Diagnosis is made by documenting exposure to a swainsonine-containing plant, identifying the clinical signs, and swainsonine serum or tissue concentrations. Recently a quantitative polymerase chain reaction (PCR) method was identified that can measure fungal endophytes in the *Astragalus* spp. and *Oxytropis* spp.[13]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis list

- *Conium* spp. piperidine alkaloids
- Inherited mannosidosis
- *Lupinus* spp. quinolizidine alkaloids
- *Nicotiana* spp. alkaloids

TREATMENT

There is no effective treatment for Swainsonine poisoning. Removal of the affected animals from access to source plants may result in partial or complete recovery, provided the cases are not too advanced.

CONTROL

Pregnant animals should not be exposed to sources of swainsonine, but other stock may be grazed on the plant without ill effect for short, specified periods, namely 4 weeks for sheep and cattle and 2 weeks for horses. The most important factor is the amount of plant material ingested and the amount of time the animal is exposed to the toxin. Animals should not be allowed to graze when toxic plants are palatable and other forage is in short supply. In the western part of the United States, cattle should not be allowed to graze on locoweed-infected pastures until late May or early June, when other grasses have begun to grow. Pastures should not be overstocked because a lack of adequate forage will force animals to graze on locoweed. Animals grazing on locoweed pastures should be monitored closely and moved to a different pasture if they begin to show signs of poisoning. Herbicides may be used to control *Astragalus* spp. and *Oxytropis* spp., but the endophyte is contained in the seeds and they are drought resistant and able overwinter, allowing only for control and not elimination. Attempts to reduce consumption of the toxic plants by creating conditioned reflex aversion, to reduce absorption

of ingested swainsonine or by supplementing the diet with bentonite, have not been rewarding.

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NEUROGENIC QUINOLIZIDINE ALKALOIDS (*LUPINUS* SPP.)

ETIOLOGY

Alkaloids causing the nervous syndrome include sparteine, lupinine, lupanine, hydroxylupanine, spathulatine, and thermopsine. These vary widely in their toxicity and their concentration in plant species, and within the same species between years, depending largely on the climate. Species of lupin known to contain them are *Lupinus angustifolius* and *L. cosentinii* (synonym *L. digitatus*). Species that are associated with the characteristic nervous syndrome and in which the presence of the alkaloids in the plant is assumed include the following:

L. argenteus
L. caudatus
L. cyaneus
L. greenei
L. laxiflorus
L. leucophyllus
L. leucopsis
L. onustus
L. pusillus

EPIDEMIOLOGY

The alkaloids are present in all parts of the plant but are in their greatest concentration in the seeds and pods; most outbreaks of poisoning occur when livestock graze mature, standing lupins, carrying many pods. Sheep eat the plant more readily and are more commonly affected than cattle or horses. The mortality rate in sheep is high. In cattle, it is usually low but may be as high as 50%.

Other plants in which the alkaloids occur and which are associated with the nervous disease include the following:

Cytisus (synonym *Laburnum*, *Sarothamnus* spp.)
Baptisia spp.
Sophora spp.
Spartium junceum (Spanish broom)
Thermopsis spp.

CLINICAL FINDINGS

In the nervous disease, affected animals may develop dyspnea and depression, followed by coma and death without a struggle. More acute cases have convulsive episodes in which they are dyspneic and staggery, and show frothing at the mouth, clonic convulsions, and grinding of the teeth. A more prolonged disease is reported in cattle poisoned experimentally with *Thermopsis montana*. There is anorexia, depression, edematous swelling of the eyelids, tremor, a stilted gait, arching of the back and a tucked-up abdomen, rough hair coat, and prolonged recumbency.

PATHOLOGY

Severe myopathy results in high aspartate aminotransferase (AST), creatine kinase (CK) and lactic acid dehydrogenase (LDH) activities. The possibility of a myopathy being associated with lupins has been raised because the prevalence of enzootic muscular dystrophy appears to be much higher on lupin than on other pasture. Lupins are low in selenium and vitamin E content, and classical white muscle disease may also occur. Histologic and biochemical examination of affected calves discount myopathy as the primary lesion. In poisoning by *Cytisus* spp., both *C. laburnum* (laburnum) and *C. scoparius* (broom) are associated with fatalities.

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NITROCOMPOUND PLANT TOXICOSIS (MILK VETCH)

SYNOPSIS

Etiology Several different toxins; miserotoxin in certain *Astragalus* spp. is the most important.

Epidemiology Limited to geographic distribution of the toxic plants; mostly North America but other countries affected depending on specific plant.

Clinical pathology Nonspecific; methemoglobin values >20%.

Lesions Degenerative lesions in peripheral nerves and spinal cord.

Diagnosis confirmation Associated with isolation of nitrotoxins in tissues and fluids.

Treatment None.

Control Management of pasture to avoid grazing pasture when relevant plants are abundant.

ETIOLOGY

Nitrocompounds (nitrotoxins) poisonous to animals occur in a number of plants, especially in some species of *Astragalus*. They are all glycosides of 3-nitropropionic acid (NPA) or of 3-nitro-ropanol (NPOH). Miserotoxin is the most common and well known toxin; other toxins include cibarian, corollin, coronarian, coronillin, and karakin.[1] The best known occurrences of the nitrocompounds include the following:

- *A. canadensis* (Canadian milk vetch), *A. emoryanus* (Emory's milk vetch), *A. miser* (forest or woody milk vetch), *A. pterocarpus* (winged milk vetch), *A. tetrapterus* (four-wing milk vetch), and others; contain miserotoxin.[1]
- *Corynocarpus laevigatus* (karaka tree); contains karakin.[2]
- *Oxytropis* spp., a plant genus very similar botanically to *Astragalus* spp., is associated with the same diseases as the latter but its toxic agent has not been identified.
- *Securigera varia* (*Coronilla varia*), contains cibarian and others.[1]
- *Indigofera linnaei* (Birdsville indigo), contains karakin and other nitrocompounds.[3]

EPIDEMIOLOGY

Occurrence

The occurrence of these plant poisonings is determined by the presence and ingestion of the specific plants. *Astragalus* and *Oxytropis* spp. are, for the most part, limited in distribution to North America, but poisoning of sheep by *A. lusitanicus* is recorded in Morocco, and of all species by *O. puberula* in Kazakhstan. *Corynocarpus* spp. occur in New Zealand and *Indigofera* spp. are widespread, occurring in North America, Australia, Africa, and Southeast Asia.

Astragalus and *Oxytropis* spp. are herbaceous legumes, most of them are perennial, and they dominate the desert range over large areas of the United States. They provide excellent forage. Only some species contain miserotoxin, but this makes them very destructive and very heavy losses of sheep and cattle may occur.

Risk Factors

Animal Risk Factors

Cattle are the more susceptible. Lactating animals are more susceptible than dry animals. There are reports of the disease in horses in North America and a similar disease in horses in China after grazing *O. kansuensis*

Human Risk Factors

Miserotoxin and its metabolic end products may be excreted in the milk of cows eating these plants.

PATHOGENESIS

In ruminants the glycosides are hydrolyzed in the rumen to NPOH and NPA. Both are absorbed from the rumen and once in the liver, NPOH is further biodegraded to NPA. Nitrous dioxide (NO_2) formed during biodegradation may account for methemoglobinemia.[1] Some nitrite may also be formed resulting in methemoglobinemia in horses and ruminants. The onset of clinical signs is associated with the accumulation of NPA and a resulting neurologic syndrome, characterized principally by nervous signs and the development of degenerative lesions in the CNS. In experimental animals the dose rate and length of exposure to the toxin determine whether the acute or chronic disease occurs. Typically, animals must have consumed nitrotoxin plants for a week or more before showing signs. Morbidity is 10% to 15%; case–fatality rate may be up to 30%.[1]

CLINICAL FINDINGS

Acute Poisoning

Death may occur as soon as 3 hours after the commencement of signs, but the course is usually about 24 hours. Common signs include ataxia or a staggering walk, recumbency, and death from respiratory or cardiac arrest.

Chronic Poisoning

The syndrome in cattle is often referred to as "cracker heels," because of the noise made when rear hooves strike each other.[1] Affected animals lose weight, and develop a poor hair coat, nasal discharge, and poor exercise tolerance. Respiratory distress, with loud stertor (roaring), is more marked in sheep than in cattle and knuckling of the fetlocks and incoordination, followed in some by paraplegia, is more common in cattle. Temporary blindness and drooling of saliva may also be evident. The mortality rate is very high, with the course lasting over several months. Animals that recover have a long convalescence. Death may occur suddenly if affected animals are stressed.

I. linnaei poisoning in horses (synonym Birdsville horse disease) is associated with weight loss, gait incoordination, easy falling, toe dragging, dyspnea, and convulsions.[3] The plant is equally poisonous when dry or green, although most cases occur in the spring when the plant is succulent. Horses need to graze the plant for about 10 days before signs appear. Characteristic signs include segregation and somnolence, with the animal often standing out in the open in the hot sun, apparently asleep when unaffected horses have sought the shade. There is marked incoordination, with the front legs being lifted and extended in an exaggerated manner. The hocks are not flexed, causing the fronts of the hind hooves to be dragged on the ground. The head is held in an unnaturally high position and the tail is held out stiffly. There is difficulty in changing direction, and incoordination increases as the horse moves. The horse commences to sway and at the canter there is complete disorientation of the hindlegs so that the animal moves its limbs frantically but stays in the one spot with the legs becoming gradually abducted until it sits down and rolls over. Terminally there is recumbency with intermittent tetanic convulsions, which may last for up to 15 minutes and during which death usually occurs.

A chronic syndrome may develop in some horses subsequent to an acute attack. Affected animals can move about, but there is incoordination and dragging of the hindfeet with wearing of the toe, and inspiratory dyspnea (roaring) may also occur. No lesions have been described in the nervous system of affected animals. *I. linnaei* contains the toxic amino acid, indospicine, an analog of arginine, and NPA.[3] Poisoned horses may not always develop the liver damage typical of intoxication by indospicine[3]; however, supplementation of the diet with arginine-rich protein feeds prevents development of the disease.[4] Peanut meal (0.5–1 kg/day) and gelatin provide readily available and cheap sources of arginine.

CLINICAL PATHOLOGY

Methemoglobinemia concentrations greater than 20% may occur in cattle and horses. Laboratory procedures for the determination of blood levels of miserotoxin, some other nitrotoxins, and NPOH and NPA are available.

NECROPSY FINDINGS

Brown discoloration of the blood, and extensive petechiation in tissues, are common findings in the acute form of the disease. In the chronic disease, there are degenerative changes in the spinal cord and peripheral nerves, especially the sciatic nerve, as well as areas of necrosis in the thalamus and Purkinje cells in some cerebellar folia, white matter spongiosis in the globus pallidus, and distension of the lateral ventricles.[1] Nonspecific gross lesions include pulmonary emphysema and pneumonia, abomasal ulceration, and pericardial/pleural fluid.

Diagnosis confirmation depends on the identification of the poisonous plants in the environment and the toxins in the plants and animal tissues

DIFFERENTIAL DIAGNOSIS

Differential diagnosis list (chronic form)

- Chronic cyanide poisoning
- Paspalum staggers
- Phalaris staggers
- Ryegrass staggers

TREATMENT

Treatment includes removing animals from the suspected pastures and providing an alternate food source. The use of injectable thiamine has not shown to be of any value. There is no specific treatment for the chronic form of the disease, and some animals may ultimately recover.

CONTROL

Control of the growth of the plants by stimulating growth of competitive grasses, or the widespread use of selective herbicides, is recommended but unlikely to be a practicable procedure in many of the situations in which the plants occur. Experimentally, the use of some herbicides significantly reduces the content of miserotoxin in *A. miser* var. *oblongifolia* in pasture. Variations between species of *Astragalus* spp. in their capacity to produce miserotoxin and store selenocompounds (some of them, e.g., *A. toanus*, do both) provides opportunities to manipulate the grazing of particular fields to best advantage.

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PIPERIDINE ALKALOID PLANT TOXICOSIS

ETIOLOGY

The important, identified piperidine alkaloids include coniine, cynapine, nicotine,

and lobeline. These alkaloids are primarily neurotoxins; some alkaloids present in *Conium maculatum* and *Nicotiana* spp. are also teratogens and are dealt with separately in Chapter 18.

CONIUM

C. maculatum (poison hemlock) contains five major acetate-based piperidine alkaloids—coniine, *N*-methylconiine, conhydrine, pseudoconhydrine, and γ-coniceine—and a number of other, lesser, alkaloids. γ-Coniceine is likely a precursor of the others and is much more toxic.[1] The concentration of each of the alkaloids in different parts of the plant, in different climates, and at different times of the year is quite variable. For example, the concentration of the γ-coniceine is high in the fruits when they are formed, but there is no significant content in the roots. In the dormant stage, the toxicity of the roots is very high.

EPIDEMIOLOGY

Poison hemlock occurs in most parts of the world. All animal species are affected, with cattle, sheep, goats, horses, and pigs showing the nervous form of the disease. Poisoned cattle, pigs, and sheep also produce deformed offspring, with ewes being much less susceptible than cows and sows. Grazing animals are poisoned by eating the standing plant, the seeds, or roots at the appropriate time of their development. The plant may also be fed in hay or green feed or the seeds may contaminate harvested grain. Milking cows secrete the alkaloids in their milk.

PATHOGENESIS

The alkaloids are associated with two modes of poisoning, paralysis of skeletal muscle by blocking transmission at neuromuscular junctions and by acting as teratogens. All of the major alkaloids are associated with the acute disease. Only coniine and γ-coniceine are known to be teratogenic.

CLINICAL FINDINGS

Clinical signs in the acute, neurologic form of poisoning include tremor, staggering gait, knuckling of fetlocks, belching, vomiting, frequent urination and defecation, drooling of saliva, tachycardia, and pupillary dilation.[2,3] In cows and sows, prolapse of the nictitating membrane occurs, and in affected cows, a characteristic mousy odor of the milk and urine is described. The course in cattle, goats, and horses is only a few hours and terminates in recumbency and death by respiratory paralysis, without convulsions. Sheep are least affected and recovery is common.

CYNAPINE

Cynapine, a piperidine alkaloid found in *Aethusa cynapium* (fool's parsley, lesser hemlock) is associated with dyspnea and gait incoordination in cattle, goats, and pigs.

NICOTIANA

The most common poisonous members of the tobacco family of plants include the following:

Nicotiana tabacum (commercial tobacco)
N. attenuata (wild tobacco)
N. exigua
N. glauca (tree tobacco)
N. megalosiphon
N. trigonophylla (wild tobacco)
N. velutina

The principal toxins include nicotine, anabasine, and anagyrine.[4] Other alkaloids occurring in *Nicotiana* spp., but which are not recorded as having poisoned animals, are nornicotine and anatabine. *Duboisia hopwoodii* (pituri) is another plant with these alkaloids. Several alkaloids may be present in the one plant, but most plant species have a particular alkaloid that predominates. The concentration of the alkaloid varies between parts of the plant and between different stages of growth.

Acute poisoning of livestock ingesting *Nicotiana* spp. or *D. hopwoodii* is associated with muscle tremor, weakness, incoordination, pupil dilation, and recumbency with limb paddling progressing to paralysis. Diarrhea may be present. The alkaloid anabasine is teratogenic.

Tobacco-specific nitrosamines, formed from *Nicotiana* spp. alkaloids, are known to be carcinogenic to laboratory animals, but there is no record of this association in agricultural animals.

LOBELINE

The piperidine alkaloid lobeline is found in the plant *Lobelia berlandieri*. Ingestion of the plant is associated with mouth erosions, salivation, and diarrhea. Necropsy lesions are limited to the lesions of enteritis.

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CORYNETOXINS (TUNICAMINYLURACILS) (ANNUAL RYEGRASS STAGGERS, FLOOD PLAIN STAGGERS, STEWART RANGE SYNDROME)

SYNOPSIS

Etiology Corynetoxins (tunicaminyluracils) present in infected grass (*Lolium rigidum, Lachnagrostis filiformis, Polypogon monspeliensis*) eaten by all species. A similar tunicaminyluracil has been isolated from water-damaged wheat eaten by pigs.

Epidemiology Outbreaks in Australia (summer to early fall) and South Africa when grazing animals ingest infected seedhead galls. Occurs anytime of the year in animals fed infected hay.

Clinical pathology Increased activity of hepatic enzymes in serum; prolonged prothrombin and activated partial thromboplastin time.

Lesions Perivascular edema in meninges and brain; hemorrhages in multiple tissues.

Diagnosis confirmation Tunicaminyluracil in pasture seed heads.

Treatment Magnesium sulfate in horses or small herds. Removal of animals from infected fields or hay; reduce stress.

Control Keep animals off infected pastures; decrease prevalence of infection by various methods (see text); test hay before purchasing.

ETIOLOGY

Nematode larvae infest and are associated with galls in the seedheads of *Lolium rigidum* (Wimmera or annual ryegrass), *Polypogon monspieliensis* (annual beard grass), and *Lachnagrostis filiformis* (formerly *Agrostis avenacea* and commonly referred to as blown or blowaway grass).[1,2] Nematodes in the genus *Anguina* (*A. agrostis, A. funesta, A. paludicola*) transport the corynetoxin producing bacteria *Rathayibacter toxicus* into the cuticle of grass seeds.[1,3,4] Bacteriophages were originally felt to play an integral part, but that may no longer be the case.[2] Corynetoxins (tunicaminyluracils) are glycolipid tunicaminyluracil antibiotics produced in the seedhead gall and sheep, cattle, and horses grazing the pasture are poisoned when they are ingested.[1,3,5] Animals eating corynetoxin-infected hay are poisoned.[1,2]

Other outbreaks have been recorded. In the 1960s, sheep and cattle in the northwestern United States developed a similar neurologic condition when fed fescue infected with *A. agrostis* and *Rathayibacter*-like organisms.[1] Tunicaminyluracil has been isolated from water-damaged wheat, which when fed to pigs is associated with clinical signs and deaths similar to those associated with the tunicaminyluracil on grasses.[1]

EPIDEMIOLOGY

Occurrence

Poisoning that occurs in livestock pastured on *L. rigidum* (termed annual ryegrass toxicity or ARGT) or in those grazing *L. filiformis* (flood plain staggers) has become a very important cause of death losses on farms in western and southern Australia, southern New South Wales, and also in South Africa.[1,3,5] Toxicity associated with ingestion of *P. monspieliensis* (termed Stewart range syndrome) is found in flood-prone portions in southeastern South Australia.[1] Typically, in Australia, infected seed heads are toxic beginning with the dry summer period and continuing until the onset of fall rains.[1,2] Clinical signs do not occur until the stock has been on pasture for several days or up to 12 weeks.[1] Forced exercise and high ambient temperatures precipitate or exacerbate clinical signs.[1,5]

Risk Factors

Animal Risk Factors

The oral dose of tunicamycins in sheep associated with the onset of clinical signs following investigational intraduodenal administration is 150 µg/kg.[6] The subcutaneous lethal dose is much smaller, 30 to 40 µg/kg as a single dose or a set of small sequential doses. The toxins are cumulative if the interval between doses are few days.

Plant Risk Factors

Pasture improvement based on annually alternating crop-pasture rotations seem to predispose to the disease, with the worst outbreaks occurring after the end of a cropping year. This can be avoided by burning the pasture in the autumn. The organism is introduced onto farms by the introduction of infested grass seed or contaminated agricultural implements.[2] *L. rigidum* has become a weed in southern Australia and herbicide-resistant strains have evolved, complicating control measures. Hay made from infested grass remains poisonous for 5 to 6 years. Poisoning associated with *L. filiformis* has occurred in cattle on extensive pasture recently subjected to severe flooding, hence the name flood plain staggers.[1]

PATHOGENESIS

Corynetoxins are similar structurally to tunicamycin antibiotics originally isolated from an actinomycete (*Streptomyces lysosuperificus*).[1] Collectively the group, including corynetoxins, is referred to as tunicaminyluracil antibiotics. They are potent inhibitors of lipid linked *N*-glycosylation of glycoproteins[1] and capable of causing cerebral vascular lesions in experimental animals. Interference with cardiovascular function and vascular integrity leads to interference with oxygenation of tissues, particularly the brain.

CLINICAL FINDINGS

Signs appear when the cattle or sheep are disturbed or stressed, especially by driving. The animals fall in a convulsion with paddling of limbs, nystagmus, opisthotonus, jaw champing and salivation, head nodding, tetanic extension of limbs and, in sheep, posterior extension of the hindlimbs.[1-3] Death may occur during a convulsion or, if left alone, the animal may recover to the point of being able to stand, but there may be gait incoordination caused by hypermetria, stiff gait, a broad-based stance, head swaying, rocking backward and forward, and loss of balance. Intermittent convulsive episodes recur and the animals soon go down again. Death occurs in up to 24 hours. Further cases occur for up to 10 days after affected animals are removed from the pasture.[2] Morbidity and mortality rates may reach as high as 100% in sheep flocks. In surviving ewes, abortion may occur in up to 10% of pregnant sheep.[1]

Poisoning occurs less frequently in horses and stress is often a precipitating factor.[5] Colic with tachycardia, borborygmi, and congested mucous membranes, is often the first sign observed followed by hypermetria, ataxia, muscle tremors, recumbency, convulsions with limb paddling, and death.[5]

CLINICAL PATHOLOGY

Blood levels of liver enzymes, bilirubin, and bile acids are elevated. Prothrombin time and activated partial thromboplastin time are prolonged.[1]

NECROPSY FINDINGS

Necropsy findings are inconsistent and nonspecific. The liver may be enlarged and pale or icteric. There may be hemorrhages in a range of tissues. Histologically, there may be perivascular edema in the brain, particularly in cerebellar meninges. Other lesions may include significant liver damage.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis list:

- Lead poisoning
- Perennial ryegrass staggers
- Phalaris staggers
- Poisoning by any one of a large number of plants in which the toxic agent has not been identified.

TREATMENT

Affected flocks or herds should be removed from a toxic pasture as slowly and as quietly as possible to good-quality feed with shade and water in a place free of disturbance.[1,5] Stress should be kept to a minimum.

No specific antidote or antitoxin is available.[1,5] An antidote was developed by CSIRO in Australia for use early in outbreaks of poisoning, but field trials were disappointing.[7] Pharmacologic measures are impractical in herd situations, although intravenous administration of magnesium sulfate could be used for individual animals. Horses have been treated successfully with an intravenous injection of magnesium sulfate (approximately 100 mg/kg BW; range of 60–200 mg/kg) and supportive measures including flunixin meglumine, dimethyl sulfoxide, and intravenous fluids.[5] Doses of 25 to 150 mg/kg intravenously have been used for hypomagnesemia in horses and may be useful in managing equine cases.[8] It is recommended that magnesium not be administered concurrently with calcium-containing intravenous fluids. Used in combination, calcium is used preferentially at the neuromuscular junction, limiting the effectiveness of magnesium in preventing muscle contractions.[5]

CONTROL

Pasture management in endemic areas should aim to reduce exposure of livestock to mature pastures with seedheads. This may be achieved by a variety of measures such as heavy stocking during winter and spring, harvesting pasture for silage or hay before seeding followed by heavy grazing to remove ryegrass seedlings, burning crop and pasture residues, and herbicide application.[2]

Methods exist for testing hay and are used for hay exported from Australia.[2,9] Recent improvements in testing have shortened the turnaround time considerably.[10] Hay purchased for use within Australia should be tested and accompanied by a declaration stating that testing occurred and the hay is safe for use.[2]

Two cultivars of *L. rigidum* (Guard and Safeguard) resistant to *A. funesta* have been developed that significantly reduce the number of galls per kilogram of hay and the risk of developing ARGT.[2] Pasture application of *Dilophospora alopecuri,* a fungal pathogen of *A funesta,* has been studied, but the results are mixed and may be uneconomical.[11] Immunization against the toxin is promising but difficult as glycolipids are poor immunogens.[1]

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MISCELLANEOUS PLANT TOXINS AFFECTING THE NERVOUS SYSTEM (UNIDENTIFIED TOXINS)

Plants with ingestions resulting in signs of gait incoordination, with or without recumbency, convulsions, or lesions of nervous system include the following:

Ageratina altissima
Araujia hortorum (cruel vine)
Berula erecta
Brachychiton populneus (kurrajong tree)
Brachyglottis repanda (rangiora)
Catharanthus spp.
Centella uniflora
Combretum platypetalum
Craspedia chrysantha
Doronicum hungaricum (wild sunflower)
Echinopogon spp. (roughbearded grass)[1]
Ervum spp.
Euphorbia mauritanica
Gomphrena celosioides (soft khaki weed)
Hoya spp. (wax flower)[1]
Idiospermum australiense
Melanthrium hybridum
M. virginicum (bunchflower)
Melica decumbens (dronkgras)
Melochia pyramidata
Modiola caroliniana (creeping mallow)
Pennisetum clandestinum (kikuyu grass)[2,3]
Rhodomyrtus macrocarpa (finger cherry; also is associated with blindness).

E. mauritanica is associated with hypersensitivity, stiffness, tremor, incoordination, recumbency, and convulsions in sheep.[1] *Echinopogon ovatus* poisoning in calves and lambs is characterized by stress-induced episodes of stiff-legged incoordination and easy falling and bellowing followed by spontaneous recovery.

G. celosioides is associated with outbreaks of incoordination in horses in northern Australia. Spontaneous recovery follows removal from the pasture.

P. clandestinum poisoning was originally attributed to rumen acidosis, but the current suggestion is that it is a poisoning associated with the fungi *Fusarium torulosum* growing on the grass, which is an unlikely association in some outbreaks.[2,3] Epidemiologically, the disease occurs concurrently with circumstances conducive to fungal growth, including warmth, moisture, and litter under the grass, often caused by the depredations of heavy infestations of sod webworms (grass caterpillars), African black beetles, leaf hoppers, and armyworm caterpillars (*Pseudoletia separata, Pseudocalymma elegans, Spodoptera exempta*).[2]

Cattle, sheep, and to a lesser extent, goats, show signs of poisoning in late summer and autumn.[2] Clinical signs include depression, hypersalivation, abdominal pain, ruminal tympany and stasis, paralysis of the tongue and pharynx, sham drinking, muscle tremors, incoordination, recumbency, diarrhea, dehydration, and death.[2] In the forestomachs there is distension, mucosal reddening, and extensive microscopically visible necrosis in the rumen and abomasum.

Plant ingestions associated with paralysis in ewes and horses, with lesions of a lysosomal storage disease and prominent neuronal pigmentation in the brain and spinal cord include the following:

Romulea spp. (onion weed)[1]
Solidago chilensis
Stachys arvensis (stagger weed)
Stephania spp.
Trachyandra spp.
T. laxa
T. divaricata.

Romulea bulbocodium is associated with a high incidence of phytobezoars, a level of fertility in ewes as low as 20%, and a severe gait incoordination when stimulated to move.[1] Affected sheep walk with their heads held high, fall easily, struggle momentarily, then relax and get up and walk normally. If they are left on the same pasture for 3 or 4 weeks, they become permanently recumbent.

Plant ingestions resulting in signs of mania (e.g., wild running, hyperexcitability, incoordination, circling, aimless wandering, blindness) include the following:

Burttia prunoides
Pisum sativum

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Fungal Toxins Affecting the Nervous System

Diplodia maydis (synonym *D. zeae, Stenocarpella maydis*) is associated with a serious disease of maize crops called corn cob rot. Infected cobs fed to cattle, sheep, goats, and horses are associated with diplodiosis, a neuromycotoxicosis, reported in Australia, Argentina, Brazil, and most often in South Africa.[1] The toxin has been identified as diplonine; a second toxin, diplodiatoxin, has been identified but may not be related to poisoning.[1] The fungus develops its toxin only after a prolonged (more than 6 weeks) period of growth. This may explain frequent reports that the fungus is not poisonous. The same applies to cultured fungus used to produce the disease experimentally; it must be a culture that is at least 8 weeks old.

Clinical signs in adults include lacrimation, salivation, tremor, ataxia, paresis, and paralysis, but signs disappear when the corn is removed from the diet. If the subjects are females in the second and third trimesters of pregnancy, there may be a very high mortality rate (up to 87%) in stillborn or newborn lambs or calves; many of the dead neonates have widespread degeneration of the CNS. Affected animals recover if feeding of the infected grain is stopped.

At postmortem, a status spongiosus lesion may occur in the brain of affected animals, but in most cases there are no necropsy lesions. Fetuses are much more susceptible, and spongiform lesions in the brain are present in most. Their BWs are less than normal, and the gestation period is also reduced.

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TREMORGENIC MYCOTOXINS

Tremorgenic mycotoxins are produced by fungi belonging to the *Penicillium, Aspergillus, Claviceps,* and *Neotyphodium* genera.[1] Over 20 different mycotoxins, all containing a tryptophan indole moiety, affect many different mammals including cattle, sheep, goats, and horses. The fungi grow on a wide variety of foodstuffs including spoiled food, garbage, stored grains, forages (grasses and legumes), malt (beverage) residues, and compost piles.[2,3] Despite the different fungi and mycotoxins, the common neurologic signs of prolonged muscle tremors, ataxia, and stress-exacerbated weakness are similar in most species.[2] Hyperexcitability or depression, tetanic seizures, recumbency, paralysis, and rarely death may occur.[2,4]

Tremorgenic mycotoxins are rapidly absorbed from the gastrointestinal tract, and signs occur anywhere from a few hours to several days, depending on the species and particular mycotoxin. Age is important with younger animals more susceptible than older.[5] They are lipid soluble and easily move across the blood-brain barrier and into the CNS. Excretion is primarily biliary and fecal; little hepatic metabolism occurs.[6]

The mechanism of action is unknown, but generally tremorgenic mycotoxins interfere with inhibitory neurotransmitters

(γ-amino butyric acid [GABA] and glycine) and stimulate excitatory neurotransmitters. Treatment is supportive and symptomatic.

Aspergillus-Associated Mycotoxins

Aspergillus clavatus, other Aspergillus spp., and Penicillium spp. produce several tremorgenic mycotoxins associated with outbreaks in cattle and sheep. Verruculogen is the most widely recognized mycotoxin; less recognized mycotoxins produced by these fungi include tryptoquivaline, territrems A and B, and aflatrem. *A. clavatus*–associated mycotoxins have been incriminated in several neurologic outbreaks in sheep and cattle.[2,7,8] Common clinical signs included tremors, posterior paresis, knuckling at the fetlocks, recumbency, and death. The specific mycotoxin may be patulin, although that was not present in all cases.[2]

Bermudagrass Staggers

Cattle in California, Oklahoma, and Texas have developed tremors and neurologic signs after grazing on mature bermudagrass (*Cynodon dactylon*) infected with *C. cynodontis.* Analysis of infected seedheads showed high concentrations of the tremorgens paspalitrems and paspaline-like indole-diterpenes and low concentrations of ergine and ergonovine.[1]

Claviceps-Associated Mycotoxins (*Paspalum* or Dallis Grass Staggers)

Cattle, sheep, and horses may develop "grass staggers" after several days after grazing on mature Bahia grass (*Paspalum notatum*) or Dallis grass (*P. dilatatum*) infected with *C. paspali.*[2,4,8,9] The tremorgenic mycotoxins paspaline and paspalitrems A, B, and C are present in the sclerotia (ergots); paspalitrem B is most commonly associated with the onset of signs in cattle and sheep. Affected animals develop exercise-induced nervousness, odd facial expressions, tremors, ataxia, seizures, and death.

Neotyphodium-Associated Mycotoxins (Perennial Ryegrass Staggers)

Horses, deer, cattle, alpacas, and in particular, sheep grazing on perennial ryegrass (*L. perenne*) in the northwestern United States, Australia, New Zealand, and some parts of Europe have developed neurologic signs similar to other stagger-producing grasses.[2,5,10] Lolitrems A, B, and D and other lolitrem precursors produced by the endophyte *Neotyphodium lolii* are the tremorgenic mycotoxins most involved.[9,10] Lolitrem B (maximum tolerable dose 2 mg/kg BW) is the predominant mycotoxin associated with the onset of signs in sheep and cattle.[2] Signs most often occur in the late summer/early fall when animals are on overgrazed pastures. Tremors begin in the head, progress to the neck and shoulder, and finally include the extremities. Affected animals are uncoordinated and become recumbent or develop seizures when stressed. If removed from infected grasses and not stressed, affected animals recover in 7 days or so.

Penicillium-Associated Mycotoxins

Penitrem A and roquefortines, produced by *Penicillium* spp., are the most common mycotoxins associated with tremors. In general, toxicosis with these mycotoxins are more common in small animals ingesting spoiled food (meats, cheese, nuts, eggs, etc.) and garbage, but cases have occurred in horses, cattle, and sheep. Janthitrem A, B, and C produced by *P. janthinellum* have been associated with outbreaks of staggers in sheep grazing on ryegrass.

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MISCELLANEOUS FUNGAL TOXINS AFFECTING THE NERVOUS SYSTEM (UNIDENTIFIED TOXINS)

BLACK SOIL BLINDNESS

This is a mycotoxicosis of grazing cattle, associated with the fungus *Corallocytostroma ornicopreoides* growing on Mitchell grass (*Astrebla* spp.) in pastures on heavy basalt (black soil) soil in tropical northwest Australia. The disease has occurred only once, in a year marked by heavy seasonal rainfall and a longer than usual growing season. Morbidity and mortality were high at the peak of the outbreak. Clinical characteristics include blindness and death within 24 hours. Necropsy lesions include renal tubular nephrosis, rumenoreticulitis, and moderate liver cell damage.

NERVOUS SIGNS

Nervous signs of tremor, gait incoordination, recumbency, and convulsions are the primary toxic effects present after ingestion of *Trichothecium roseum* and *Penicillium cyclopium.*

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Other Toxins Affecting the Nervous System

INORGANIC TOXINS AFFECTING THE NERVOUS SYSTEM

LEAD TOXICOSIS (PLUMBISM)

SYNOPSIS

Etiology Accidental ingestion of lead metal or lead-containing substances, ingestion of lead-contaminated feed, or grazing pastures containing excessive lead in the soil.

Epidemiology Occurs in all age groups. One of the most common poisonings of farm livestock, especially in young calves after turn out in spring. In cattle, usually sporadic and caused by ingestion of a single source of lead but outbreaks occur when feed is contaminated. High case–fatality rate if untreated. Sources include discarded lead batteries, lead-based paints, industrial sources of lead, ash residues, pastures near motor vehicle highways, and smelters. Occurs in sheep and horses grazing contaminated pastures.

Clinical pathology Lead levels in blood, feces, liver, kidney; elevated porphyrins in blood.

Lesions Encephalopathy, degeneration of liver and kidney; pale musculature, brain laminar cortical necrosis, intranuclear renal inclusion bodies.

Diagnostic confirmation Toxic levels of lead in blood and tissues.

Treatment Supportive care, removal of large amounts of lead from the gastrointestinal tract, chelation therapy.

Control Identify and prevent access of animals to sources of lead.

ETIOLOGY

Lead poisoning is associated with the accidental ingestion of lead metal or lead-containing compounds; ingestion of feed, usually forage, containing lead; or grazing lead-contaminated pastures.[1,2] The latter two are often associated with environmental pollution. Both organic and inorganic lead are toxic, with organic lead the most bioavailable followed by inorganic lead and then metallic lead.[1,3]

EPIDEMIOLOGY

Where groups of animals have access to the same source of lead, outbreaks occur and the morbidity rate ranges from 10% to 30%. The case–fatality rate may reach 100% but

early intensive therapy can be successful and reduce the figure to less than 50%. In one recorded outbreak, in which a discarded 24-V battery was accidentally mixed and ground up into the feed of 80 heifers, 55 of the animals died or were euthanized.

Occurrence

Lead is one of the most common poisonings in farm animals, especially young cattle.[1] Sheep and horses are also affected but not as often.[3,4] Pigs, because of housing conditions, are not often exposed to lead and appear to be more tolerant than other species.

Risk Factors

Animal Risk Factors

Cattle

Data from diagnostic toxicology laboratories illustrate that lead poisoning is one of the most common toxicosis in cattle. In Alberta, Canada, over a period of 22 years, lead poisoning was the most frequently diagnosed toxicoses of cattle, representing 0.68% of all bovine submissions to the provincial diagnostic laboratories. Most cases of poisoning occur during the summer months from May to August, when the cattle have ready access to lead-containing materials such as crankcase oil and batteries that are being changed in agricultural machinery. In many countries the incidence of the disease is highest in cattle in the spring of the year a few days after the animals have been turned out onto pasture.[5] Poisoning is most common in younger cattle, with 52% of the cases reported in animals 6 months of age or less.[6] Younger animals are more susceptible to lead toxicosis presumably because of a higher rate of gastrointestinal tract absorption. In addition, young cattle are especially curious and seem to seek out and find sources of lead. Confined housing of calves with or without overcrowding is often followed by the appearance of pica, which may be associated with boredom and an increase ingestion of lead-containing objects.

Lead poisoning in cattle is usually acute and caused by accidental ingestion of a toxic quantity of lead over a short period of time.[7] The natural curiosity, licking habits, and lack of oral discrimination of cattle makes any available lead-containing material a potential source of poisoning. Cattle will readily drink motor oil; lick older machinery grease, peeling paint, and paint ashes; and chew lead-based batteries. Many countries currently ban leaded gasoline, and in these areas used motor oil may not contain lead as well as motor oil from diesel engines or present-day machinery grease.[8] In ruminants, there is a tendency for metallic lead particles to settle in the reticulum, and poisoning results from the gradual conversion of lead particles to soluble lead acetate. Several epidemics of lead poisoning in domestic animals have been recorded throughout the world in which the source of the metal was contamination of pasture or crops by nearby lead mining or industrial lead operations.[9,10] Animals eating vegetation in these areas may accumulate amounts of lead sufficient to produce clinical signs of lead poisoning.

Buffalo

Lead poisoning in buffalo has been reported and provides interesting comparative data; they may have a higher tolerance to lead than cattle.

Sheep

Sheep are usually affected by eating soil or forage contaminated by environmental sources of lead.

Horses

Horses are much more selective in their eating habits. They usually do not lick old paint cans, lead storage batteries, and peeling paint, and they do seem to find the taste of used motor oil attractive. Lead poisoning in horses is most common when they graze lead-contaminated pastures rather than by the accidental ingestion of a toxic amount of lead.[2,4,10] Young horses are particularly more susceptible than older horses and cattle grazing on the same pasture.

Environmental Risk Factors

Environmental pollution with lead is a common occurrence in cities and surrounding suburbs. For farm animals, significant pollution is more likely to occur near smelters or other industrial enterprises or near major highways where pasture is contaminated by exhaust fumes of automobiles if leaded gasoline is still used in the region. Much of the poisoning is subclinical because of the low level of absorption, but lead-intoxicated animals have served as sentinels for human lead exposure.[11]

Lead is still commonly found in pastures near highways. The lead levels in the whole blood of sheep grazing near main highways in three areas of the Nile delta region of Egypt were 0.062, 0.067, and 0.083 parts per million (ppm). Pasture adjacent to heavily used roads may carry as much as 390 mg/kg of lead, in contrast to 10 mg/kg on lightly used roads.[9,10] The concentration of lead on pasture varies markedly with proximity to the traffic, falling rapidly the greater the distance and with the time of the year. Pastures contaminated by smelters are recorded as carrying 325 mg/kg of lead (equivalent to a daily intake for an animal of 6.4 mg/kg BW).[12] In some locations near lead smelters, lead poisoning is considered to be a predictable occurrence in horses that are allowed to graze on local pastures.[4] As a result horses are either not raised in these areas or hay is imported from other areas. Although ingestion is the principal method of poisoning of animals, inhalation may also be a significant method of entry for cattle grazing close to smelters or highways.

Lead as an environmental contaminant is often combined with cadmium, which has some effects similar to those of lead, thus the effects may be somewhat additive. Experimental poisoning with both elements is associated with reduced weight gain in calves at dose levels up to 18 mg/kg BW of each contaminant, and clinical signs appear at levels above 18 mg/kg BW of each. Lead is also combined with chromate for industrial purposes. The combination is nontoxic when combined with lead at lead intake levels of less than 100 mg/kg BW.

Environmental pollution in the vicinity of lead and zinc-ore processing factories can result in varying degrees of poisoning with lead, zinc, and cadmium.[13] These can be monitored by the analysis of blood, hair, and tissues obtained at necropsy.

Farm or Premise Risk Factors

The relationship between lead concentrations in blood of cattle with lead poisoning and those in the milk is exponential.[14] The lead level in milk is relatively constant up to a blood level of 0.2 to 0.3 mg/L, and increases sharply at higher blood levels. The biological half-life of lead excretion in cattle is between 6 and 14 weeks.[15] Studies in six affected dairy herds reported a variable half-life ranging from 48 to 2507 days.[2] One probable reason for this great variance is the ability of the ruminant to retain variable amounts of metallic lead in the rumen, which acts as a continuing reservoir. Half-life studies do not account for variable intake and retention of a persistent reservoir of toxicant, so the concept of using half-life excretion in dealing with lead-poisoned cattle is not likely accurate. Owners of such cattle should be advised of the potentially long withdrawal period. It may be advisable to test periodically and allow marketing based on actually measured levels or to estimate the costs of such a plan and consider salvage. This recent work casts doubt on the economic utility of holding recovered animals. In acutely sick cows that were emergency slaughtered, the range of lead levels in edible muscle tissue was 0.23 to 0.50 mg/kg. The concentrations in the kidneys ranged from 70 to 330 mg/kg and in the livers 10 to 55 mg/kg.

Human and Public Health Risk Factors

The source of lead intoxication in animals must be identified so humans are not inadvertently poisoned. In one recent study, investigations involving cattle deaths from lead poisoning led to elevated blood levels in a pregnant woman, dog, cat, and remaining cattle.[11]

A major concern with the treatment of lead-poisoned animals, particularly food-producing animals, is the assurance that the edible tissues of recovered animals do not contain toxic levels of lead. The length of time required after successful treatment of

cattle with typical clinical lead poisoning before such animals can be sent to slaughter or before the milk can be used safely is not known. It is suggested that treated animals should be appropriately identified[6] and blood lead levels determined once or twice monthly for several months. When the blood lead levels have dropped to background levels for three consecutive samplings at least 2 weeks apart, the animals are assumed to be safe for slaughter. Undocumented field observations suggest that at least 6 months are necessary for background levels to be achieved. Decisions about reaching acceptable residue levels will depend on national or local regulations as well as the economics of maintaining a herd for long periods without sales of milk or meat, and appropriate food safety and public health officials should be consulted in this decision. The lead concentrations in blood and milk from periparturient heifers 7 months after an episode of acute lead poisoning revealed no lead in the milk. Animals that had been severely affected by lead poisoning experienced a transient increase in whole-blood lead concentration at parturition that was not high enough to be considered toxic.

Transmission (Sources of Lead)

Lead poisoning is most common in cattle on pasture, particularly if the pasture is poor and the animals are allowed to forage in unusual places, such as trash dumps.[15,16] Phosphorus deficiency may also be a predisposing factor, because affected animals will chew solid objects as a manifestation of osteophagia. However, cattle on lush pasture may also seek out foreign material to chew. Discarded lead batteries are one of the most common sources of lead poisoning in cattle.[13] In Alberta, Canada, over a period of 22 years, discarded batteries or used crankcase oil accounted for more than 80% of cases for which the source of lead was determined: batteries, 39.5%; used crankcase oil, 31.6%. The batteries are commonly placed in garbage dumps on the farm and, in temperate climate countries, the batteries freeze during the winter months and break open, exposing the plates, which are attractive and palatable for cattle to lick and chew.

The contamination of forage supplies with shotgun lead pellets used in hunting and shooting exercises can serve as a source of lead for cattle grazing the pasture or consuming haylage or silage made from the contaminated field.[1,6] Automobile batteries have been accidentally added to feed mixers in which they are ground by powerful augers and mixed into the feed supply of cattle. Discarded lead-based paint cans are particularly dangerous but fences, boards, the walls of pens, painted canvas, and burlap are also common sources in calves. Painted silos may cause significant contamination of the ensilage. One outbreak of lead poisoning in cattle was associated with silage containing 1200 mg/kg dry matter lead, which had become contaminated by ash and debris left after burning an old lead-containing electrical cable in the silo before it had been filled.

Metallic lead in the form of lead shot, solder, or leaded windows has been associated with mortalities, although, experimentally, sheet lead is not toxic.[1,2,4] Lead sheeting that has been exposed to the weather or subjected to acid corrosion appears to be more damaging, possibly because of the formation of a fine coating of a soluble lead salt. Lead poisoning can be a major hazard in the vicinity of oil fields, and engine sump oil may contain over 500 mg lead per 100 mL. Automotive and other mineral oils are very palatable to young beef calves. As lead use becomes restricted in many countries, grease and lead-contaminated engine oil have become less common sources of lead.[8] Less common but still potent sources of lead are linoleum, roofing felt, putty, automobile oil filters, and aluminum paint. Some of the latter paints contain large quantities of lead, and others none at all. Only lead-free aluminum paint should be used on fixtures to which animals have access.

Lead parasiticide sprays, particularly those containing lead arsenate, were once associated with heavy losses in cattle grazing in recently sprayed orchards or vegetable crops. These are not commonly used now, except in some countries, but cattle may accidentally ingest old stores of the compound.

PATHOGENESIS

The absorption, distribution, and elimination of lead vary depending on the chemical form of lead, amount ingested, age and species of animal, and other physiologic factors. Deficiencies in calcium, iron, and zinc are associated with increased lead absorption and increased toxicity. Lead from salts such as lead sulfate are absorbed more than metallic lead from battery plates.[13] Regardless of the chemical form of the ingested lead, only a small proportion (2%–10%) is absorbed because of the formation in the alimentary tract of insoluble lead complexes, which are excreted in the feces.[1,15] Once absorbed, 60% to 90% of lead is found in erythrocytes and the rest bound to albumin and other proteins.[3] Very little lead is found unbound in the serum. Lead is distributed to first to the soft tissues, especially kidneys and liver, and ultimately to bone, which serves as a storage or "sink" for excess lead. Excretion is slow and primarily through bile and the milk of lactating animals with little excreted in the urine.[1,3,14]

Blood lead concentrations are an excellent marker of exposure in animals. In cows, blood-level concentrations greater than 0.35 ppm have been associated with poisoning[1] and blood lead levels less than 0.1 ppm with normal background exposure. In horses, blood lead levels greater than 0.2 to 0.35 ppm have been associated with poisoning[4] and blood lead levels less than 0.2 ppm with background exposure. Correlation between blood lead levels and milk levels is good; correlation between blood lead levels and the presence or severity of clinical signs is often poor.[14,17]

Lead is transferred across the placental barrier,[17] and high liver levels occur in the lambs of ewes fed more than normal amounts of lead. Calves born from cows experimentally poisoned with lead have elevated levels of lead in bone, kidney, and liver. In a naturally occurring case of lead poisoning in a pregnant heifer, the blood and liver concentrations in the fetus were 0.425 and 4.84 ppm, respectively, which was 72% and 84% of the same tissue lead concentrations of the dam. Hepatic lysosomes of the fetus contained metallic electron densities, which may have been lead.

Several biochemical processes are affected by lead. Lead is a neurotoxicant and at elevated doses it disrupts the blood-brain barrier allowing albumin, water, and electrolytes to enter, resulting in edema. The complete mechanism of action associated with lead's neuropathy is unknown, but its ability to substitute for calcium and/or zinc is involved.[3] Lead mimics or inhibits the action of calcium altering the release of neurotransmitters and activating protein kinases.[3] It also binds to a sulfhydryl group on proteins resulting in inhibition of enzymes, conformational changes in proteins, and alterations in calcium/vitamin D metabolisms.[16] Lead inhibits δ-aminolevulinic acid dehydratase (D-ALAD) and ferrochelatase activity, thus decreasing heme synthesis and hemoglobin production.[2,3,18] This not only plays a role in lead-associated anemia but results in decreased oxygen carrying capacity with the nervous system susceptible to the resulting tissue ischemia.

CLINICAL FINDINGS

Lead is toxic to a number of organ systems including the nervous, gastrointestinal, hematologic, cardiovascular, renal, musculoskeletal, and reproductive systems.[3] The major effects of lead toxicity are often manifested in three main ways[7]:

- Lead encephalopathy
- Gastroenteritis
- Degeneration of peripheral nerves

Clinical signs vary depending on the species, type and amount of lead involved, and duration of exposure. Typically, acute nervous system involvement occurs following the ingestion of large doses in susceptible animals such as calves, alimentary tract irritation following moderate doses, and peripheral nerve lesions following long-term ingestion of small amounts of lead. The nervous signs of encephalopathy and the lesions of peripheral nerve degeneration are caused by the degenerative changes of nervous system tissue. Gastroenteritis is

associated with the caustic action of lead salts on the alimentary mucosa.

Cattle

The signs of acute lead poisoning are more common in calves and younger cattle and have a sudden onset and short duration, usually lasting only 12 to 24 hours. Many animals, especially those on pasture, are found dead without any observable signs. Staggering and muscle tremors particularly of the head and neck, with champing of the jaws (chewing gum fits) and frothing at the mouth are obvious. Snapping of the eyelids, rolling of the eyes, and bellowing are common. Blindness and cervical, facial, and auricular twitching are consistent in acute lead poisoning of cattle.[15] The animal eventually falls and intermittent tonic-clonic convulsions occur and may continue until death. Pupillary dilation, opisthotonus, and muscle tremors are marked and persist between the convulsive episodes (Fig. 14-3). There is hyperesthesia to touch and sound, and the heart and respiratory rates are increased. In some cases, particularly in adults, the animal remains standing, is blind, maniacal, charges into fences, attempts to climb or jump over walls, and head-presses strongly against walls or fences. Frenzy is common and some animals appear to attack humans, but the gait is stiff and jerky and progress is impeded. Death usually occurs during a convulsion and is caused by respiratory failure.

The subacute form is more common in adult cattle, and in this form the animal remains alive for 3 to 4 days. Gastrointestinal tract dysfunction is one of the most common abnormalities. Ruminal atony is accompanied by constipation in the early stages. Later a fetid diarrhea occurs in most cases. Grinding of the teeth is common, and hypersalivation may occur. Neurologic signs include dullness, blindness, and some abnormality of gait including incoordination and staggering, and sometimes circling. The circling is intermittent and not always in the same direction and usually occurs when the animal is confined in a small space like a box stall. Muscle tremor and hyperesthesia are common but not as pronounced as in the acute form.

Sheep

Lead poisoning in sheep is usually manifested by a subacute syndrome similar to that seen in adult cattle. There is anorexia and scant feces followed by the passage of dark, foul-smelling feces. Weakness and ataxia follow, often with abdominal pain, but there is no excitement, tetany, or convulsions. Polyuria occurs when the intake of lead is small but with large amounts there is oliguria.

Chronic toxicity is rare, but two syndromes of posterior paresis have been described in young lambs in old lead-mining areas, and tissue levels of lead are abnormally high in both instances. In both syndromes there is gait impairment. Osteoporosis is present in one but in the other there is no suggestion of skeletal changes. In the osteoporotic disease the signs occur only in lambs 3 to 12 weeks of age and never in adults. There is stiffness of gait, lameness, and posterior paralysis. Affected lambs are unthrifty and the bones, including the frontal bones, are very fragile. The paralysis is caused by lesions of the vertebrae, usually affecting one or more of the lumbar bones, resulting in compression of the spinal cord. In the other form, gait abnormalities occur in the same lamb age group and are manifested initially by incomplete flexion of the limb joints so that the feet drag while walking. In a later stage the fetlocks are flexed, the extensor muscles paretic, and the lamb soon becomes recumbent. Recovery is common, although many lambs die of concurrent disease.

Horses

Acute and chronic lead poisoning occurs in horses and ponies, although more rarely than other species. Signs occur most often in horses ingesting contaminated forage or soil found near old lead mines, smelters, and battery recycling depots.[3,4] The clinical findings are extremely variable, but include ataxia, weakness, hypotonia, muscle tremors, rough hair coat, dysphagia, weight loss, dyspnea, roaring or stridor, seizure like movements, colic, and maniacal behavior.[3] A roughened hair coat, pharyngeal dysfunction, and weight loss were the most common clinical findings in 10 case reports involving a total of 68 animals. Some horses died without any previous clinical illness but where clinical signs are apparent they were usually distinct and dramatic rather than subtle. Inspiratory dyspnea associated with paralysis of the recurrent laryngeal nerve is the most common finding. This may be accompanied by pharyngeal paralysis in which recurrent choke and regurgitation of food and water through the nostrils occur. Aspiration pneumonia may result after inhalation of ingesta through the paralyzed larynx. Paralysis of the lips occasionally accompanies the other signs.

Pigs

Early signs include squealing as though in pain, mild diarrhea, grinding of the teeth, and salivation. The disease is usually a prolonged one and listlessness, anorexia, and loss of weight develop followed by muscle tremor, incoordination, partial or complete blindness, enlargement of the carpal joints, and disinclination to stand on the front feet. Convulsive seizures occur in the terminal stages.

CLINICAL PATHOLOGY

Hematology

In chronic lead poisoning, hematologic examination may reveal a normocytic, normochromic anemia in some, and, although basophilic stippling does not occur often enough to be diagnostic, it is recorded in some experimental poisonings.[3] It is recorded as occurring in lead-exposed pigs and a horse. In some, poikilocytosis and anisocytosis were marked. The CSF is approximately normal with slightly elevated leukocyte numbers but no increase in protein or other biochemical components.

Fig. 14-3 Holstein Friesian steer with acute lead toxicity. Notice the abnormal mentation, contraction of facial muscles, and marked dilatation of the pupils. The bandage around the neck protected an intravenous catheter that was used for daily intravenous Ca-EDTA treatment. The steer recovered following treatment.

Blood Lead

Whole-blood levels are generally the best sample for determining the lead status of the animal. Bovine blood lead reference materials are available and have been certified for many years. Whole-blood levels of lead in normal ruminants are usually below 0.05 to 0.25 ppm; poisoned animals, including horses, usually have levels above 0.35 ppm and deaths begin at 1.0 ppm.[1,3,4] Buffalo may have blood levels above 1.0 ppm and still survive, which suggests that they have a higher tolerance level than cattle. Blood lead concentrations also fluctuate markedly after administration of lead and, consequently, the clinical importance of blood lead concentrations is often questionable and a diagnosis based on this single determinant is equivocal.

Blood lead concentration also has limited value for assessing the effectiveness of therapy for lead poisoning. Blood level concentrations may change rapidly during chelation therapy, often decreasing by 50% or more within 24 hours after initiation of treatment despite certain body tissues still containing high concentrations of lead. Thus the evaluation of biochemical indicators such as **aminolevulinic acid dehydratase (ALA-D)** may be useful. The blood and liver levels of fetuses from pregnant cattle with lead poisoning may be higher than what are considered toxic levels in adults, which suggests concentration in the fetus.

Milk Lead

Only limited information is available on the concentrations of lead that occur in cattle affected with field cases of lead poisoning. Lead levels of 0.13 mg/L of milk have occurred in natural cases with a half-life of 4.6 days. The regulatory limit for lead in bovine milk in the Netherlands is 0.05 mg/L milk. In acute lead poisoning in lactating buffalo pastured near smelters in India, the lead concentrations in milk were 1.13 ppm compared with 0.24 ppm in the milk from buffalo in unpolluted areas. The mean lead concentrations in the forage of poisoned animals were 706 ± 73.0 ppm, compared with the unpolluted area of 78 ± 12 ppm.

Fecal Lead

Fecal levels of lead represent unabsorbed and excreted lead deriving from the bones, and are of limited value unless considered in conjunction with blood levels because ingested lead may have been in an insoluble form and harmless to the animal. When fecal levels are high, it can be assumed that the lead has been ingested in the preceding 2 to 3 weeks, but high blood levels may be maintained for months after ingestion. Thus high blood and low fecal levels indicate that the lead was taken in some weeks previously, but high blood and high fecal levels suggest recent ingestion and significant absorption.

Urinary Lead

Urine lead levels are variable, rarely high (0.2–0.3 mg/L), and although elevated urine levels are usually associated with high blood levels, this relationship does not necessarily hold.

δ-ALA-D

Because of some of the limitations of blood lead, other indirect measurements of lead poisoning, such as the levels of δ-ALA-D in blood, are used to supplement blood lead determinations. For example, the best method of detecting the presence of lead poisoning in its early stages, except in the horse, is the estimation of δ-ALA-D in the blood. The evaluation of δ-ALA-D and blood lead concentrations together can assist in resolving diagnostic situations in which the blood lead concentration is in the questionable range of 0.25 to 0.35 ppm.

δ-ALA-D is important in the synthesis of heme and is probably the most sensitive enzyme in the heme pathway. Inhibition of the enzyme results in a block in the utilization of δ-ALA, a subsequent decline in heme synthesis and a marked increase in the urinary excretion of δ-ALA.[17] In cattle, sheep, and pigs affected with chronic lead poisoning, the plasma levels of δ-ALA-D are decreased, and the urinary levels of δ-ALA are increased before clinical signs are detectable. In sheep, erythrocyte δ-ALA-D is recommended as the most sensitive diagnostic test available.

The disadvantages of the assay for blood δ-ALA-D include age-related variations, particularly in calves[12,18]; the methods used for analysis are not yet uniform and blood must be collected in polystyrene or polyethylene tubes rather than glass tubes and an anticoagulant other than ethylenediaminetetraacetic acid (EDTA) must be used. The levels of δ-ALA-D increase in calves from birth to 10 weeks of age and age-matched controls should be evaluated simultaneously when conducting the test in calves of younger than 6 months of age. In cattle under 1 year of age, δ-ALA-D values of less than 200 mmol of porphobilinogen (PBG)/mL of RBC/h should raise suspicion of their having ingested lead. In this same age range values below 100 mmol would confirm ingestion of lead. In cattle equal to or less than 2 years of age, values of δ-ALA-D of less than 100 mmol of PBG/mL of RBC/h would indicate ingestion of lead.

The dδ-ALA-D is so sensitive to lead that it remains inhibited even after lead exposure has ceased. Following treatment with a chelating agent the blood lead levels will often decline giving a false indication of a positive treatment effect. If the δ-ALA-D levels do not decrease following therapy, it indicates that there is sufficient lead present to continue to suppress the enzyme.

Erythrocyte Protoporphyrin

The levels of free erythrocyte zinc protoporphyrin increase in lead poisoning, and this is indicative of the chronic metabolic effect of lead on the erythroid cells being released from bone marrow into the peripheral circulation. A mean value of 22 μg coproporphyrin per 100 mL of erythrocytes has been determined. It may be of some value along with determinations of blood lead and δ-ALA-D. The use of δ-ALA-D activity and erythrocyte protoporphyrin content as cumulative lead exposure indicators in cows environmentally exposed to lead is recommended.

Plasma δ-Aminolevulinic Acid

In human beings, δ-ALA is suggested as a sensitive marker of trace exposures to lead.[18] Plasma δ-aminolevulinic acid has been evaluated in cattle as a biomarker for acute lead poisoning and the results showed it to be a promising tool.[2,18] Further work is necessary, however, to establish concentrations in unexposed, intermittently exposed, and chronically exposed animals.

NECROPSY FINDINGS

In most acute cases there are no gross lesions at necropsy. In cases of longer standing there may be some degree of abomasitis and enteritis, diffuse congestion of the lungs, and degeneration of the liver and kidney. Epicardial hemorrhages are common. Congestion of meningeal and cerebral vessels may also be observed and hemorrhages may be present in the meninges. An increase in CSF is often recorded but is of minor degree in most cases.

In chronic cases, gross lesions in cattle include cerebrocortical softening, cavitation, and yellow discoloration with the most severe lesions in the occipital lobes. Histologic lesions were most severe at the tips of the gyri. Similar lesions were produced experimentally. Acid-fast inclusion bodies deep in the renal cortex have diagnostic significance. Examination of the contents of the reticulum in ruminants for particulate lead matter is essential. Flakes of paint, lumps of red lead, or sheet lead usually accumulate in this site. Their absence is not remarkable, especially if animals have licked fresh paint, but their presence does give weight to the provisional diagnosis.

Liver and Kidney Lead

The submission of alimentary tract contents and tissues for analysis forms an important part of the diagnosis of lead poisoning, but results must be interpreted with caution.

Cattle

In the kidney cortex 25 mg/kg (ppm) of lead wet weight (WW) is diagnostic and is a more reliable tissue for assay than liver, which may contain 10 to 20 mg/kg WW. The concentrations in the kidney are always much higher

than in the liver. A diagnostic laboratory found mean levels in livers of poisoned cattle of 93 µg/g WW, and 438 µg/g WW in kidneys. Tissue lead levels in cattle from industrial areas are significantly higher (liver 0.23 mg/kg WW, kidney 0.42 mg/kg WW) than in cattle from clear air zones (liver and kidney less than 0.1 mg/kg WW).

Horses

Levels of lead at 4 to 7 mg/kg (ppm) WW have been found in the livers of horses dying of chronic lead poisoning but 25 to 250 mg/kg are more likely, and 40 mg/kg WW may occur in the livers of affected pigs.

Samples for Confirmation of Diagnosis

- **Toxicology:** 50 g liver, kidney, and reticulum content (determine lead concentration)
- **Histology:** formalin-fixed cerebral cortex, kidney (light microscopy)

DIFFERENTIAL DIAGNOSIS

In all cases, the possibility of access to lead and the environmental circumstances that may arouse suspicion of other poisonings or errors in management should be considered. Estimation of the lead content of blood and feces should be performed at the earliest opportunity and tissues for necropsy specimens submitted for analysis.

Differential diagnosis list

Cattle (see Table 14-12)

Arsenic poisoning

Claviceps paspali toxicity

Diseases resulting in blindness (hypovitaminosis A, ophthalmitis, polioencephalomalacia)

Hypomagnesemic tetany

Meningoencephalitis

Nervous acetonemia

Sheep

Enzootic ataxia caused by copper deficiency

Enzootic muscular dystrophy

Polyarthritis caused by bacterial infection

Horses (see Table 14-11)

Botulism

Equine degenerative myeloencephalopathy

Equine motor neuron disease

Equisetum spp. (horsetail toxicosis)

Fumonisin toxicosis (equine leukoencephalomalacia)

Hepatoencephalopathy caused by hepatotoxic plants

Laryngeal hemiplegia

Protozoal encephalomyelitis

Rabies

Viral encephalomyelitides, including West Nile virus

TREATMENT

Treatment in most animals includes supportive care, preventing further exposure to lead, surgical removal of large amounts of lead from the gastrointestinal tract, and chelation therapy. Supportive care should include the use of tranquilization for those animals with neurologic signs and intravenous fluids to prevent and treat dehydration. Chelation therapy may be used to lower blood level concentrations but may not remove it completely from tissues or affect tissue damage. Large amounts of lead left in the gastrointestinal tract before chelation may result in enhanced or increased absorption of lead. Lead mobilized from tissue sites during chelation may transiently increase blood lead levels and exacerbate clinical signs.

Calcium Versenate

Calcium versenate (calcium disodium EDTA [CaEDTA]) has been used successfully in cases of lead poisoning produced experimentally in calves and in natural cases in cattle and horses.[3,4,14] Cattle may be treated with 73.3 mg/kg/day slow intravenously divided two to three times a day for 3 to 5 days.[19] If necessary, after a rest period of 2 days, an additional 3 to 5 days of treatment may be used. Other doses and dosage regimens are available.[14,19] Horses may be treated with CaEDTA at 75 mg/kg BW divided two to three times a day by slow intravenous infusion for 4 to 5 days.[4,19] If necessary, after a rest period of 2 days, an additional 4 to 5 days of therapy may be used.

The disadvantages of CaEDTA is that it must be given intravenously and there are side effects. Renal and gastrointestinal toxicity may occur with long-term therapy, and essential minerals such as copper and iron may be removed with multiple treatments.[3] Severe neurologic signs and dyspnea occurred in a horse receiving a second round of CaEDTA therapy.[4]

Succimer (Dimercaptosuccinic Acid)

Dimercaptosuccinic acid has been used for many years in human medicine as a specific chelator for arsenic, lead, and mercury. Published doses are available for dogs, cats, and birds but not large animals.[19] Succimer has the advantages of heavy metal specificity, oral administration, and lack of nephrotoxicity.[3]

Thiamine Hydrochloride

When used in combination with CaEDTA, thiamine is a valuable agent for the treatment of lead poisoning. Thiamine hydrochloride reduced the deposition of lead in most tissues, especially liver, kidney, and the central and peripheral nervous system of experimentally poisoned calves. The recommended dose is 2 mg/kg BW intramuscularly, given at the same time as CaEDTA, with a total daily dose not to exceed 8 mg/kg BW.[19]

Magnesium Sulfate

Oral dosing with small amounts of magnesium sulfate has been used on the basis that soluble lead salts will be precipitated as the insoluble sulfate and excreted in the feces.[14] However, the lead is often present in large quantities and in the form of particles, which are only slowly dissolved.

Rumenotomy

Rumenotomy to remove the ingested lead has been used but may be unsatisfactory because of the difficulty in removing particulate material from the recesses of the reticular mucosa. However, it may be appropriate when a valuable animal is affected and it is known that the animal ingested a certain compound of lead, which may be removable from the reticulum and rumen.

TREATMENT AND CONTROL

Cattle

Calcium versenate (73 mg/kg/day slow IV divided two to three times a day for 3–5 days. Rest × 2 days. Repeat 4–5 days of therapy if need be) (R-2)

Thiamine HCl (2 mg/kg BW IM, given at the same time as CaEDTA; max 8 mg/kg BW/day) (R-2)

Horses

Calcium versenate (75 mg/kg BW divided two to three times a day slow IV for 4–5 days. Rest × 2 days. Repeat 4–5 days of therapy if need be) (R-2)

Thiamine HCl (2 mg/kg BW IM, given at the same time as CaEDTA; max 8 mg/kg BW/day) (R-2)

BW, body weight; CaEDTA, calcium disodium ethylenediaminetetraacetic acid; IM, intramuscular; IV, intravenous.

CONTROL

The following practices are recommended to reduce the incidence of lead poisoning:

- Limit grazing on pastures near lead mines, smelters, or battery recycling depots.
- Use phosphate rock treatment on contaminated pastures (phosphate salts bind to lead yielding low solubility lead phosphates).[4]
- Keep trash out of pastures.
- Do not burn wood or other substances in pastures, and keep animals away from ashes.
- Provide adequate nutrition and consistent feeding practices to minimize pica or abnormal feeding behavior in livestock.
- Consider temporarily adding calcium phosphate to the diet to decrease lead absorption.[4]
- Dispose of or store used lead batteries, motor oil, and leaded petroleum products in areas animals cannot access.

- Use vehicle service and machinery storage areas separate from areas used by livestock.
- Use only lead-free paints on fencing, boards, and buildings.
- Dispose of contaminated carcasses according to Environmental Protection Agency regulations.
- Identify the source of lead intoxication.

FURTHER READING

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MERCURY TOXICOSIS

SYNOPSIS

Etiology Ingestion, inhalation, or dermal exposure to mercury compounds including fungicides, phenylmercury treated grain, contaminated ashes, etc.

Epidemiology Generally organic preparations used in seed grain fed accidentally to livestock.

Clinical pathology High levels of mercury in all tissues; elevated serum urea nitrogen and creatinine concentration; decreased osmolarity, glycosuria, proteinuria, and phosphaturia.

Lesions
- Inorganic salts: acute, gastroenteritis; chronic, nephrosis.
- Organomercurials: neuronal necrosis in brain and spinal nerves.

Diagnostic confirmation High blood, urine, tissue, hair levels of mercury.

Treatment Supportive and symptomatic care; judicious use of chelation in acute cases; treatment of chronic intoxication generally unrewarding.

Control Care in the handling of agricultural and pharmaceutical mercury compounds.

ETIOLOGY

Mercury is a naturally occurring element (heavy metal) that occurs in three different forms.[1] Metallic mercury, an environmental pollutant, comes from sources such as mining, smelting, fossil fuels, volcanoes, and forest fires.[2] It is used in a variety of products including thermometers, button batteries, barometers, and dental fillings. Inorganic mercury (mercury salts) is produced when mercury is combined with a salt such as sulfur or chlorine. Fungicides, disinfectants, antiseptics, and older anthelmintics may contain inorganic mercurial compounds. Organic mercury (organomercurials) is formed when mercury combines carbon to form, among others, methylmercury, ethylmercury, and phenylmercury.

EPIDEMIOLOGY

Occurrence

Stringent state and national standards have made mercury poisoning in animals a rare occurrence. Toxicosis, when it occurs, is most often associated with oral ingestion of an organic mercury compound. In general, this is chronic and caused by accumulation of grain contaminated with mercury in the form of phenylmercury.[3] Acute or chronic poisoning can occur from either inorganic or organic mercury compounds but is generally accidental in nature.[4]

Because of the availability of fungicidal agents other than mercury it is possible to limit the use of mercuric agents by legislation to those excreted rapidly by animals, the phenylmercury compounds, and prohibit those that are most highly retained in animal tissues, the ethyl and methyl compounds.[5] Worldwide use of mercurial fungicides has declined, and poisoning is much less common than in the past. The most common products, when used, are dusts of 5.25% methoxyethylmercury silicate or methylmercury dicyandiamide. These and ethylmercuric chloride are toxic when fed to pigs at the rate of 0.19 to 0.7 6 mg of mercury per kilogram BW per day for 60 to 90 days. Methylmercury dicyandiamide fed to pigs at the rate of 5 to 15 mg/kg is associated with illness, and 20 mg/kg is associated with some deaths with a delay of 3 weeks between dosing and illness.

Treated seed is usually not harmful if it comprises only 10% of the ration and must be fed in large amounts for long periods before clinical illness occurs. A single feeding even of large amounts of grain is thought to be incapable of causing mercury poisoning in ruminants, but horses may be susceptible.

Accidental administration of medicines containing mercury, licking of skin dressings (e.g., mercuric oxide), and absorption from liberally applied skin dressings or combined with dimethyl sulfoxide may be associated with sporadic cases that may occur in horses after application of mercury-containing "blisters." Inorganic mercury salts contaminating lakes or other anaerobic ecologic areas can be reduced and converted to methylmercury and serve as a source of organic mercurial poisoning or food contamination through accumulation in fish or fish meal.

Risk Factors

Animal Risk Factors

The toxicity of mercury compounds depends on their solubility and the susceptibility of the animals. Cattle are highly susceptible, with toxicosis occurring on an average daily intake of mercury, in organic mercury form, of 10 mg/kg BW/day, whereas toxic effects are only obtained in sheep with intakes of 17.4 mg/kg BW/day. In horses, the acute toxic dose inorganic mercury is 5 to 10 g.[5] Chronic ingestion of inorganic mercuric chloride (0.8 g/kg BW/day) for 14 weeks resulted in mercury toxicity.[5]

Human Risk Factors

Meat, liver, and kidneys from animals poisoned by mercury are unsuitable for human consumption. Depending on the form of mercury, milk may not be safe.

PATHOGENESIS

The toxicokinetics of mercury depends on the form and route of exposure. Metallic mercury is primarily absorbed through the respiratory tract with very little by ingestion.[1] It is lipophilic and once distributed to the kidneys it crosses both the blood-brain and placental barriers in which it can remain for extended periods of time. Excretion is via urine and feces and a small amount in milk. Inorganic mercury has limited gastrointestinal absorption (<40%), is not lipophilic, is distributed to several body organs, and accumulates in the kidney.[5] Excretion is via urine and feces with very small amounts in the milk. Organic mercury is almost completely absorbed from the gastrointestinal tract (90%–95%). It is rapidly distributed to the circulatory system, is lipophilic, and crosses both the blood-brain and placental barriers in which it is trapped and accumulates in the brain and fetus, accumulates in RBCs, and undergoes further distribution to body tissues, reaching equilibrium in approximately 4 days. Excretion is very slow and primarily fecal, although some urine and milk excretion occurs.

The mechanism of action relates to the specific form of mercury. Metallic mercury and organic mercury accumulate in the brain and are potent neurotoxicants.[1,5,6] Toxicity from methylmercury is multifactorial. It inhibits protein synthesis in the brain by interfering with aminoacyl tRNA synthetase enzymes, generates excess free radicals, and inhibits antioxidant enzymes resulting in cell death. All forms of mercury accumulate in the kidney, concentrating in the proximal renal tubular cells, producing cell membrane permeability, excess free radical formation,

inhibition of antioxidant enzymes, and induction of glutathione and glutathione-dependent enzymes.[1,5] Acute toxicity results in acute tubular necrosis and renal failure; chronic toxicity results in renal interstitial fibrosis and renal failure.[5]

CLINICAL FINDINGS

The toxic effects of mercury depend on the form, route of exposure, dose, and duration of exposure.[1,5] The target organs of both inorganic and organic mercury are the brain and kidney, and this is where the most damage occurs.[1,6,7]

Acute inorganic mercury toxicosis occurs when large amounts of inorganic mercury are ingested. There is an acute gastroenteritis with vomiting of bloodstained material and severe diarrhea.[4] Death occurs within a few hours from shock and dehydration. In less acute cases the patient survives several days. The syndrome includes salivation, a fetid breath, anorexia, oliguria, tachycardia, hyperpnea, and, in some cases, posterior paralysis and terminal convulsions.

Chronic inorganic mercury toxicosis occurs when small amounts of inorganic mercury are ingested over longer periods. Damage to the kidney and nervous system in addition to the gastrointestinal tract is likely to occur.[4] Signs include depression, anorexia, emaciation, a stiff, stilted gait that may progress to paresis, alopecia, scabby lesions around the anus and vulva, pruritus, petechiation and tenderness of the gums and shedding of the teeth, persistent diarrhea, weakness, incoordination, and convulsions.

Chronic organic mercurial poisoning is associated with neurologic syndromes.[4,5] In pigs blindness is accompanied by staggering, gait instabilities, lameness, recumbency, and inability to eat, although the appetite is good. Cattle poisoned in this way show ataxia, neuromuscular incoordination, paresis, recumbency, convulsions, evidence of renal failure, and death. Clinical signs may not develop until 20 days after feeding is commenced. Sheep are similar to cattle, although signs of tetraplegia may occur. Horses show renal disease, neurologic abnormalities, colic, and laminitis.

CLINICAL PATHOLOGY

Mercury can be detected at higher levels than normal in the blood, urine, feces, milk, tissues, and hair of affected animals and in the toxic source material.[1,4,8] Urine is the best source for metallic and inorganic mercury and hair for organic mercury. Generally, blood is useful only for the first 3 to 5 days postexposure as distributed to other tissues occurs.[1] Creatinine and serum urea nitrogen concentrations will be elevated and urinalysis may show reduced osmolarity, glycosuria, proteinuria, and phosphaturia. Less than 0.2% of ingested mercury is excreted in cow's milk.

NECROPSY FINDINGS

In acute cases, there is severe gastroenteritis with edema, hyperemia, and petechiation of the alimentary mucosa. The liver and kidneys are swollen, and the lungs are congested and show multiple hemorrhages. There may be an accompanying catarrhal stomatitis. A crusting focus of dermatitis may be identified if exposure was percutaneous.

Histologically, the renal tubular epithelial cells are swollen and vacuolated, and proteinuria is evident. An ulcerative colitis may also be visible. In chronic toxicity associated with organic mercury compounds there are also degenerative changes in nerve cells in the cortex of the cerebrum, brainstem, and spinal cord. The lesions include neuronal necrosis, neuronophagia, cortical vacuolation, and gliosis. Fibrinoid necrosis of leptomeningeal arterioles may be seen. Other common microscopic changes include degeneration of granular cells of the cerebellar cortex and of Purkinje cells of the myocardium.

Mercury reaches its greatest concentration in the kidney, and this tissue should be submitted for assay. In horses with acute mercury toxicosis, renal tissue with mercury at more than 10 µg/g of mercury is diagnostic.[4] Concentrations of 100 mg/kg may be present in the kidney of animals poisoned with inorganic mercury. With chronic organic mercurial poisoning in swine, levels of mercury up to 2000 mg/kg may be present in the kidney.

Samples for Confirmation of Diagnosis

- **Toxicology:** 50 g kidney, brain is half fresh and half in formalin, 500 g of suspect feed (ASSAY [Hg]); muscle tissue for potential residues in food animal edible tissues
- **Histology:** formalin-fixed kidney, heart, oral and/or skin lesions; half of midsagittally sectioned brain (LM)

DIFFERENTIAL DIAGNOSIS

Differential diagnosis list

- Arsenic toxicosis (especially organic arsenicals in swine)
- Lead toxicosis

TREATMENT

Treatment should be aimed toward removal of the source and providing supportive care. Activated charcoal followed by mineral oil or another laxative should be used in acute cases. Further care includes intravenous fluids to enhance hydration, promote excretion, and correct electrolyte abnormalities, gastrointestinal protectants, and pain medications. Antioxidants, including selenium, have been used in human beings.[9]

There is no true antidote, and the use of chelation agents is controversial. In acute toxicity in horses, intramuscular dimercaprol (BAL) at 3 mg/kg BW every 4 hours × 2 days, followed by 3 mg/kg BW every 6 hours on day 3, and then 3 mg/kg BW twice a day × 10 days has been used.[4] Penicillamine, 3 mg/kg BW orally every 6 hours has also been used effectively.[4] In cattle and swine, intramuscular dimercaprol at 3 mg/kg BW every 6 hours for 4 days, followed by every 12 hours for 10 days has been recommended.[10]

CONTROL

Seed grains dusted with mercury compounds should not be fed to animals.

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BORON TOXICOSIS

Boron, an essential element for plant growth, is added to many agricultural fertilizers and presents yet another toxic chemical in the list of farm hazards for animals. Boron compounds such as boric acid or sodium borate are generally of low toxicity and reports of poisoning in cattle rare. In some fertilizers, a solubilized form of boron is used to increase availability thus increasing its toxicity and palatability. Cattle accidentally ingesting a boron-containing fertilizer developed depression, weakness, tremor, and ataxia; other reported signs include short periods of gait spasticity, dorsiflexion of the head, and flutter of the periorbicular muscles, followed by stumbling backward and sternal recumbency, then lateral recumbency, and a quiet death. The case–fatality rate is 100%. There are no gross lesions on necropsy examination.

Experimental dosing with the fertilizer in goats is associated with the previously mentioned syndrome plus head-shaking, ear-flicking, star-gazing (staring), phantom dodging, oral champing, restless weight shifting from foot to foot, sawhorse stance,

mild diarrhea, and frequent urination. The goats do not eat or drink but paw food and water as though they are hungry but unable to prehend.

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BROMIDE TOXICOSIS

Bromide salts are available in several forms including sodium bromide, potassium bromide, and methyl bromide.[1-3] Potassium bromide has been added to horse feed and studied in horses for treatment of epilepsy.[1,2] Sodium bromide is commonly used in swimming pools as an alternative to chlorine and in the petroleum industry around oil wells. Methyl bromide is a soil fumigant once commonly used worldwide. Because of its effect on the ozone layer, a planned phase out of methyl bromide will be complete in 2015.[3]

Ingestion of methyl bromide–contaminated oat hay by horses, goats, and cattle and sodium bromide–pelleted feed by cattle has resulted in toxicosis. Clinical signs are neurologic in nature and include ataxia, weakness, and lethargy.

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ORGANIC TOXINS AFFECTING THE NERVOUS SYSTEM

ANTHELMINTIC TOXICOSIS

Anthelmintics are drugs used to treat infections with parasitic worms. This includes both flat worms (e.g., flukes and tapeworms) and round worms (i.e., nematodes). Poisoning associated with most of the newer anthelmintics is rare and usually caused by an accidental overdose in individual animals or a mixing error when added to feed. Older anthelmintics carry the burden of higher toxicity, but fortunately their use has declined dramatically.

COMMONLY USED ANTHELMINTICS

Commonly used anthelmintics include the following groups:

- Amino-acetonitrile derivatives (monepantel)
- Benzimidazoles and probenzimidazoles (albendazole, fenbendazole, etc.)
- Cyclic octadepsipeptides (emodepside)
- Imidazothiazoles (levamisole)
- Macrocyclic lactones ([MLs] ivermectin, moxidectin, doramectin)
- Miscellaneous (Piperazine, clorsulon)
- Praziquantel/epsiprantel
- Salicylanilides/substituted phenols (closantel, rafoxanide, oxyclozanide)
- Tetrahydropyrimidines (pyrantel and morantel)

OLDER ANTHELMINTICS

Older, rarely used anthelmintics include:

- Carbon tetrachloride
- Hexachloroethane
- Hexachlorophene
- Nicotine
- Phenothiazines
- Sumicidin (fenvalerate)
- Tetrachlorethylene

CURRENTLY USED ANTHELMINTICS

Amino-Acetonitrile Derivatives (Monepantel)

Amino-acetonitrile derivatives (ADD) are a group of synthetic compounds with activity against intestinal nematodes. Anthelmintics in this group work by binding to an MPTL-1, nematode-specific acetylcholine receptor.[1] Monepantel, an ADD, was originally marketed in New Zealand as a drench for sheep, but it is now used in Australia, South America, Europe, and other countries.[1,2] Oral administration to sheep at 5× the recommended dose every 3 weeks × 8 treatments did not result in any adverse effects.[1] No adverse effects were noted in ewes when given 3× the recommended dose every 5 days for their entire reproductive cycle.[2]

Benzimidazoles (Albendazole, Fenbendazole, and Thiabendazole) and Probenzimidazoles (Febantel, Netobimin, etc.)

The benzimidazoles are generally not water soluble and thus poorly absorbed from the gastrointestinal tract. Probenzimidazoles must be absorbed and metabolized into their respective active compounds. The mechanism of action of this group is inhibition of parasitic β-tubulin, which generally makes them safe drugs.[3] Many of them, however, are contraindicated in pregnancy because of antimitotic activity with resultant embryo toxicity and teratogenicity.[3,4]

Albendazole, Cambendazole, and Parbendazole

Albendazole at four times the standard dose produces some fetal abnormalities if given early in pregnancy. Cambendazole and parbendazole are teratogens and are specifically contraindicated in pregnant animals, especially during the first third of the pregnancy and at dose rates higher than normal. The safety margin is small, and their use at any dose level is not recommended in these females. Defects produced include rotational and flexing deformities of the limbs, overflexion of the carpal joints, abnormalities of posture and gait, vertebral fusion and asymmetric cranial ossification, cerebral hypoplasia, and hydrocephalus.

Fenbendazole

A dose of fenbendazole and the flukicide bromsalans to cattle either simultaneously or within a few days of each other may be accompanied by deaths. Because fenbendazole and the other tertiary benzimidazoles, oxfendazole and albendazole, are extremely valuable in removing dormant *Ostertagia ostertagi* larvae, it is suggested that Fascol (bromsalans) should not be used when this is an important problem or if 2 weeks should elapse between treatments.

Thiabendazole

At an oral dose rate of 800 mg/kg BW in sheep, transient signs of salivation, anorexia, and depression appear. There are similar signs at larger dose rates, and death is likely at a dose rate of 1200 mg/kg BW. Toxic nephrosis is the cause of death and is reflected in the clinical and pathologic findings of hypokalemia, hypoproteinemia, and uremia.

Cyclic Octadepsipeptides (Emodepside)

Currently emodepside is the only commercially available member of this group, and it is registered in the United States and Europe for use in dogs and cats.[1] It has been used experimentally in sheep and cattle and found to be effective and safe.[1,5] Anthelmintics in the groups have a dual mechanism of action, binding to a SLO-1, calcium-activated potassium channel SLO-1 and binding to am HC110R, latrophilin-like receptor. The result is inhibition of pharyngeal muscle activity in parasites resulting in death.[1,5]

Imidazothiazoles (Levamisole)

All commercial preparations of levamisole consist of the levo isomer. Its mechanism of action is similar to nicotine by causing prolonged depolarization and neuromuscular junction blockade resulting in parasympathetic stimulation and cholinergic type signs.[6,7] The absorption of levamisole is rapid regardless of the route of administration. Elimination is rapid with an elimination half-life of 2.34 hours (intramuscularly) and 5.44 hours (orally) in sheep, 1.44 hours (orally) in goats, and 6.9 hours (intramuscularly) and 9.3 hours (orally) in swine.[8]

There are some human health implications because levamisole may be found in meat, milk, and cheese especially in toxic situations. The withdrawal period of sheep is 13 days, goats 9 days, swine 11 days, and beef

and milk from dairy cows 48 hours.[8] A recent study involving six dairy cows receiving levamisole at 5 mg/kg BW and oxyclozanide at 10 mg/kg BW showed levamisole residues greater than 0.83 µg/kg for the first 10 milkings and concentration of levamisole residues in soft, hard, and whey cheeses.[9]

Accidental injection of pigs caused vomiting, salivation, ataxia, recumbency, and a high mortality within a few minutes of injection. In pigs, concurrent treatment with levamisole and pyrantel tartrate resulted in enhanced toxicity of the levamisole.[6]

Sheep accidentally receiving a double dose of levamisole as a drench developed depression, head-shaking, muscle tremors, spastic movements, and diarrhea.[7] Levamisole used during the breeding season has an adverse effect on the semen quality in rams when used as an anthelmintic and on pregnancy in ewes when used as an immunomodulatory agent.[10]

Double doses in goats produce mild depression and ptosis, whereas higher doses produce, in addition, head-shaking, twitching of facial muscles, grinding of teeth, salivation, tail-twitching, increased micturition, and straining.

Following treatment at standard doses, some cattle show signs of lip-licking, increased salivation, head-shaking, skin tremors, and excitability. The excitability is more marked in calves; when released they tend to raise their tails and run around the paddock. Coughing may commence within 15 to 20 minutes, but this is from the death and expulsion of lung worms and stops in 24 hours. With higher doses, the signs are more pronounced, defecation is frequent, and hyperesthesia in the form of a continuous twitching of the skin may be seen.

Macrocyclic Lactones (Ivermectin, Moxidectin, and Doramectin)

Macrocyclic lactones are insecticides, acaricides, and nematicides in a number of species and are covered in a separate chapter.

Miscellaneous (Piperazine and Clorsulon)

Piperazine

Piperazine acts to block neuromuscular transmission in the parasite resulting in flaccid paralysis and rapid expulsion of parasites. Piperazine should not be used in animals with a heavy parasite load, in particular foals, because it may result in an ascarid-impaction colic or intestinal perforation.

Piperazine compounds are relatively nontoxic but poisoning can occur in horses on normal or excessive doses. Signs follow a delay of 12 to 24 hours and include incoordination, pupillary dilation, hyperesthesia, tremor, somnolence, and either swaying while at rest or lateral recumbency. Recovery follows in 48 to 72 hours without treatment.

Clorsulon

Clorsulon is a sulfonamide used primarily in the treatment of liver flukes in cattle and sheep. It has a high margin of safety and few reports of toxicosis. Infected sheep treated with 100 mg/kg showed no adverse effects and neither did uninfected sheep treated with 200 mg/kg and 400 mg/kg. No acute toxic dose is recorded for cattle, although cows treated with 25× the label dose showed no changes in weight gain or feed consumption.[11] Uninfected goats treated with 35 mg/kg every other day for three doses showed no adverse effects.[11] Clorsulon is distributed to muscle and secreted into milk so appropriate precautions need to be taken both with normal use and in overdose situations.

Praziquantel/Epsiprantel

Praziquantel and epsiprantel are effective against cestode parasites in most species of animals and humans.[12] Both products have a wide margin of safety, and reports of toxicity in large animals are scarce.

Salicylanilides/Substituted Phenols (Closantel, Rafoxanide, and Oxyclozanide)

Closantel, rafoxanide, and oxyclozanide are halogenated salicylanilides effective against *Fasciola* spp. in sheep and have approximately the same low level of toxicity if dosed appropriately. They are capable of causing CNS signs including temporary or permanent blindness if overdosed, especially in small rumianants.[13,14] Overdosed sheep and goats developed retinal lesions characterized by necrosis, loss of the photoreceptor layer, and retinal separation.[14] Status spongiosus of the cerebral and cerebellar white matter were consistent findings at postmortem.[14]

All three drugs are highly protein bound and have very long terminal half-lives (closantel, 14.5 days; rafoxanide, 16.6 days; oxyclozanide, 6.4 days) in sheep. Associated with their use are tissue residues and the need for long withholding times.

Tetrahydropyrimidines (Pyrantel and Morantel)

Pyrantel, either as pamoate or tartrate salt, is widely used in horses and pigs and, to a lesser extent, ruminants. Morantel tartrate, the methyl ester, is more widely used in ruminants. There are two mechanisms of action.[15] The first mechanism is inhibition of fumarate reductase, whereas the second mechanism is a direct action on acetylcholine receptors at the neuromuscular junction. It is the second mechanism that is responsible for paralysis and death of the parasite.

All of these drugs have been on the market for over 30 years and are considered safe in most species studied. Pyrantel pamoate is labeled for administration to mares a month before foaling; no adverse reactions were reported when it was administered at the recommended dose to pregnant mares or breeding stallions. No adverse reactions were reported when pyrantel tartrate was administered at the recommended dose to pregnant mares or breeding stallions. Horses dosed with pyrantel tartrate at 100 mg/kg BW developed incoordination, sweating, and an increased respiratory rate. Cattle dosed at 200 mg/kg morantel tartrate (20× the recommended dose) did not exhibit any adverse effects. Morantel tartrate has a 14-day meat withdrawal in cattle, but no milk withholding time.

OLDER ANTHELMINTICS

Carbon Tetrachloride

Carbon tetrachloride is sometimes accidentally administered in excessive quantities but deaths are more common when sheep are given standard doses or cattle are dosed by mouth instead of by injection. Standard doses of 2 mL per sheep to kill adult *Fasciola hepatica* or 1 mL/10 kg BW to obtain efficacy against immature forms, have been widely used but in some circumstances these doses can be highly toxic. Doses as low as 0.5 mL/10 kg BW can be associated with liver damage in calves, and clinical effects are apparent at 1 mL/10 kg BW in goats.

Inhalation of carbon tetrachloride is associated with an immediate and acute depression of the CNS and peripheral and circulatory collapse. Diffuse pulmonary edema occurs and sheep that survive show hepatic and renal damage. Ingestion of toxic doses may result in death within 24 hours because of anesthetic depression and severe pulmonary edema, or may occur 3 to 7 days later resulting from renal and hepatic insufficiency. Deaths are associated with almost complete liver and kidney failure.

In gross overdosing or inhalation there is an immediate onset of staggering, falling, progressive narcosis, collapse, convulsions, and death caused by respiratory failure. Animals that survive this stage or, as in the most common form of carbon tetrachloride poisoning in which animals absorb insufficient dose to produce narcosis, additional signs may be manifested in 3 to 4 days. These include anorexia, depression, muscle weakness, diarrhea, and jaundice. After a further 2 to 3 days affected sheep go down and mild-to-moderate clonic convulsions may occur, but death is always preceded by a period of coma. Survivors are emaciated and weak, and may develop photosensitization or shed their wool. They are very susceptible to environmental stresses, particularly inclement weather, and isolated deaths may occur for several months.

Animals dying after inhalation of the drug show marked pulmonary, hepatic, and renal damage. Those dying of massive oral overdosing may show abomasitis and inflammation of the duodenum. In addition acute hepatic swelling, pallor, and mottling accompanied by centrilobular necrosis and fatty degeneration, and renal lesions of extensive

tubular necrosis and degeneration, are observed in animals that die after the ingestion of small doses.

Hexachloroethane

Hexachloroethane is preferred to carbon tetrachloride for the treatment of fascioliasis in cattle, but it is not completely without danger. Deaths are rare (1 in 20,000) cattle treated and in sheep (1 in 40,000), but nonfatal illness is not uncommon. Susceptible groups may show narcosis, muscle tremor, and recumbency after administration of the standard dose (cattle, 15 g per 6 months of age up to a maximum of 60 g; sheep, 0.4 g/kg BW); such animals should be given half this dose on two occasions at 48-hour intervals.

Animals with large overdoses show ataxia, dullness, anorexia, dyspnea, ruminal tympany, and sometimes abdominal pain, diarrhea, and dysentery. Necropsy lesions include acute abomasitis and enteritis, edema of the abomasal mucosa, and hepatic centrilobular necrosis. Treatment with calcium borogluconate as in milk fever elicits a good response.

Hexachlorophene

At high dose rates (25–50 mg/kg BW) hexachlorophene is associated with atrophy of seminiferous epithelium of the testis of young adult rams. Repeated dosing is associated with periportal fatty changes in liver.

Nicotine

Nicotine poisoning seldom occurs in animals except in lambs and calves in which nicotine sulfate is still incorporated in some vermifuges. Doses of 0.2 to 0.3 g nicotine sulfate have been toxic for lambs weighing 14 to 20 kg. Animals in poor condition are more susceptible than well-nourished animals. Animals are affected within a few minutes of dosing and show dyspnea with rapid shallow respirations, muscle tremor and weakness, recumbency, and clonic convulsions. Animals that survive the acute episode may show abdominal pain, salivation, and diarrhea. At necropsy there may be abomasitis and inflammation of the duodenum.

Phenothiazine

Exposure to phenothiazine has occurred in the past from its extensive use as an anthelmintic. Keratitis, a noteworthy sign of poisoning, is most common in calves, rarely in pigs and goats, and usually after a heavy single dose of phenothiazine, but it can occur in a program of daily intake in a dietary premix. Phenothiazine is absorbed from the rumen as the sulfoxide, conjugated in the liver and excreted in the urine as leukophenothiazine and leukothionol. As urine is voided, further oxidation turns the metabolic products to a red-brown dye, phenothiazine and thionol, which may be confused as hematuria or hemoglobinuria.

Cattle are unable to detoxify all the sulfoxide and some escapes into the circulation and can enter the aqueous humor of the eye, causing photosensitization. Other photodynamic agents that cannot enter the eye may also be produced, and they, with the sulfoxide, are associated with photosensitization of light-colored parts of the body. Hyperlacrimation with severe blepharospasm and photophobia commences 12 to 36 hours after treatment and is followed by the development of a white opacity on the lateral or dorsal aspects of the cornea, depending on which is exposed to sunlight. Most animals recover within a few days, particularly if kept inside or in a shaded paddock. If the animals continue to be exposed, a severe conjunctivitis with keratitis may result.

Sumicidin

Sumicidin (fenvalerate) is a synthetic pyrethroid anthelmintic capable of causing nonfatal restlessness, yawning, frothing at the mouth, dyspnea, ear and tail erection, pupillary dilation, ruminal tympany, regurgitation of ruminal contents, staggering, tremor, clonic convulsions, and recumbency after a single oral dose. Single oral doses of >450 mg/kg are lethal. Repeated daily dosing (113 mg/kg BW or 225 mg/kg BW) also causes death after 5 to 15 days.

Tetrachlorethylene

Tetrachlorethylene rarely produces incoordination, which may be evident for 1 or 2 hours after dosing in cattle or sheep. Treatment is not usually necessary.

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MACROCYCLIC LACTONE (IVERMECTIN, MOXIDECTIN, ETC.) TOXICOSIS

SYNOPSIS

Etiology Exposure to any of the macrocyclic lactone compounds including abamectin, doramectin, eprinomectin, ivermectin, and moxidectin.

Epidemiology Wide application as insecticides, nematicides, and ascaricides. Ivermectin is most popular because of safety and efficacy. Agricultural uses include miticides, ascaricide, and insecticide.

Clinical pathology Nonspecific changes in CBC and elevations in liver enzymes; increases in plasma and milk concentrations of specific compound.

Lesions Nonspecific postmortem lesions.

Diagnostic Confirmation Clinical signs, history of exposure, analysis of tissue or body fluids.

Treatment No antidote, supportive care; intravenous intralipid emulsion in individual cases.

Control Use appropriate dose for size and weight of animal; keep agricultural and crop products stored where animals cannot access them.

CBC, *complete blood count.*

ETIOLOGY

Ivermectin, the most widely recognized of the group, is a semisynthetic ML originally obtained from *Streptomyces avermitilis*.[1] It is approved for oral or injectable use as an endectocide in horses, cattle, sheep, goats, swine, and many other species but not lactating cattle, sheep, and goats.[1,2] Abamectin is a mixture of ivermectin B_{1a} and B_{1b} used primarily as an injectable product in cattle. Other ML endectocides used in livestock include doramectin (injectable and pour-on), eprinomectin (pour-on), and moxidectin (oral, injectable, pour-on).[3-7] They are

also agricultural products used on crops and fields as miticides, ascaricides, and insecticides.[8]

EPIDEMIOLOGY

The MLs have a wide margin of safety in most species when used at the recommended doses and according to label directions. Clinical signs of toxicosis in all species involve neurologic dysfunction as well as some gastrointestinal disturbances.[9] Many of the case reports involve younger animals and are caused by an incomplete blood-brain barrier, failure to adequately estimate weight, or massive overdoses.[5,10] There have been case reports of adult horses developing neurologic signs when administered the recommended dose of ivermectin. These may be caused by the presence of a toxic plant, other medications, low body fat, or other physiologic reasons.

Eight-month-old Jersey bull calves receiving 600 µg/kg BW either intravenously or subcutaneously developed neurologic signs including depression, ataxia, and miosis. Calves receiving 8 mg/kg BW developed neurologic signs and became recumbent 24 hours after dosing with ivermectin.[11] Horses receiving 6 to 10 times the recommended dose of ivermectin developed ataxia, depression, and vision impairment within 24 hours of dosing. Three horses displayed classic signs of ivermectin toxicosis after receiving the normal recommended dose and consuming toxic plants in the *Solanum* family.[12]

Occurrence

Poisoning associated with MLs has been reported worldwide in a large number of animal species most often secondary to an inadvertent overdose or misuse of the product. Agricultural use of the product as a miticide, insecticide, or ascaricide opens the door to herd problems should animals be exposed to bulk quantities.

Risk Factors

Animal Risk Factors

Reports of toxicosis are most common in horses and often in foals. In general, a dosing error has occurred and the animal has received several times the recommended dose.[9,10] Signs of toxicosis have been reported with normal doses, but these often occur in conjunction with another compound or substance.[11]

Environmental Risk Factors

MLs are excreted in the feces of treated animals and may contaminate the field or act as a poison to nontarget species either directly through defecation or when manure is spread in a pasture or field.[13,14]

PATHOGENESIS

The pharmacokinetic properties of MLs depend on the dose, specific formulation, and route of administration. In general, MLs are slowly absorbed, widely distributed throughout the body to fat and liver, poorly metabolized, and excreted primarily unchanged in the feces.[1,5] Up to 90% of ivermectin and 77% of moxidectin are excreted via bile into the feces.[1,6] At normal doses they do not cross the blood-brain barrier of healthy, adult large animals, which his due primarily to action of the P-glycoprotein transporter system.[5,6] They are lipophilic, in particular moxidectin, and thus the lack of body fat may play a role in the elimination half-life and toxicity in debilitated animals.[5] In the absence of body fat, MLs concentrate in the serum and may reach levels high enough to overcome the blood-brain barrier.[5]

They exert their toxic effects by binding to GABA and glutamate-gated chloride channels. Binding to glutamate-gated chloride channels results in hyperpolarization and paralysis of the parasite's pharyngeal pump musculature.[1,5,6] Glutamate-gated chloride channels are present only in nematodes and arthropods. In animal species, GABA-gated channels are only found in the CNS and poisoning does not occur unless the P-glycoprotein transporter is overwhelmed or compromised and MLs are allowed to enter.

CLINICAL FINDINGS

Clinical signs in horses are primarily those of neurologic dysfunction.[9,10,12,15] Intoxicated horses are ataxic and stand base wide with the head down. Muscle tremors, head-pressing, impaired vision, and facial nerve abnormalities including ptosis. have been reported. Mydriasis is commonly reported. Other signs include hyperthermia, colic, seizures, and recumbency. Similar signs have been reported in other species including cattle and pigs.[1]

NECROPSY FINDINGS

Postmortem findings are nonspecific. Tissues and body fluids (serum and milk) may be analyzed for the presence of ML compounds using high-performance lipid chromatography.[16] Gastrointestinal contents, feces, fat, and liver are the best specimens to submit for postmortem analysis.[6]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis list

- Blue-green algae toxicosis
- Central nervous system trauma
- Encephalitis
- Hepatic encephalopathy
- Organophosphorus compound or carbamate toxicosis

TREATMENT

There is no antidote for ML toxicosis and treatment is symptomatic and supportive. Activated charcoal should be administered in recent overdoses when the animal is stable; multiple doses are recommended because MLs undergo enterohepatic recirculation. Methocarbamol has been recommended for tremors, diazepam or phenobarbital for seizures, and intravenous fluids for rehydration.[9,10,12] Physostigmine is no longer recommended because of the incidence of seizures. Sarmazenil, a benzodiazepine agonist effective at GABA receptor sites, at 0.04 mg/kg BW intravenously every 2 hours × 6 doses has been used with equivocal success.[5,10]

An intravenous intralipid emulsion (ILE) containing 20% soybean oil in water has been used successfully in the treatment of ivermectin and moxidectin overdoses in dogs[17,18] and was successful in treating a large overdose in a miniature Shetland pony.[10] The mechanism of action of ILEs in drug overdoses is not completely understood. When associated with lipophilic drug overdoses, it may act as a vascular "lipid sink," pulling drugs from the CNS back into the systemic circulation in which they can be metabolized and/or excreted.[10] There currently is no specified dose in large animals; the recommended small animal dose is a bolus of 1.5 mL/kg BW slowly over 1 to 3 minutes, followed by an infusion of 0.25 to 0.5 mL/kg BW over 30 to 60 minutes.[19] The dose (0.25 mL/kg BW) may be repeated in 4 to 6 hours if there is no evidence of lipemia in the serum.[10]

TREATMENT AND CONTROL

Sarmazenil (0.04 mg/kg BW IV every 2 hours × 6 doses) (R3)

Intralipid emulsion (20% soybean oil) (1.5 mL/kg BW as IV bolus over 1–3 minutes, followed by an infusion of 0.25–0.5 mL/kg BW over 30–60 minutes) (R2)

BW, body weight; IV, intravenous.

CONTROL

Careful attention should be paid to administration as most of the case reports revolve around errors in administration, primarily because of miscalculation of an animal's weight or failure to read and follow directions. As with all anthelmintics and insecticides, MLs should be kept in an area where animals cannot access them.

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ORGANOPHOSPHORUS COMPOUNDS AND CARBAMATE INSECTICIDES

SYNOPSIS

Etiology Poisoning by accidental exposure or overdosing with any one of the very large number of insecticides in these two groups of organic compounds.

Epidemiology Outbreaks occur from overdosing, use of oil-based preparations formulated for use on nonanimal surfaces, dehydrated animals, drift of spray from orchards, field crops to pasture.

Clinical pathology Marked depression of blood cholinesterase levels.

Lesions
Acute disease: no diagnostic lesions.
Delayed neurotoxicity: degenerative lesions in peripheral nerves and spinal cord.

Diagnostic confirmation Depressed cholinesterase levels in blood; organophosphate or carbamate in feed or environment.

Treatment Atropine in large doses to effect or atropine plus 2-PAM; remove residual toxin from hair coat; prevent absorption from gastrointestinal tract with activated charcoal and cathartics.

Control Avoid use in stressed, especially dehydrated, animals. Special constraints with chlorpyrifos.

ETIOLOGY

Organophosphorus (OP) compounds and carbamates act in essentially the same manner therapeutically and toxicologically, but bonding of the compound to the esterase enzyme is irreversible in the OP compounds and spontaneously degradable with the carbamates, rendering the carbamates potentially less dangerous. A large number of compounds are included in the group, and those used for the direct treatment of animals have been selected for their low toxicity. A vast amount of information is available on the relative toxicities of the many compounds but it is not possible to provide details here and the information does not lend itself to summarization.[1]

EPIDEMIOLOGY

Occurrence

All animal species are affected. OP compound and carbamate poisoning in animals may occur less frequently as safer insecticides are developed.[2]

Source of Toxin

- Grazing in recently sprayed areas, particularly orchards in which the most toxic compounds are frequently used
- Spray used on cereal crops and in orchards carried by wind onto pasture fields
- Hay or cubes made from plants sprayed with organophosphate compounds
- Inadvertent access to granular insecticides intended for crops
- Use of old insecticide containers as feeding utensils
- Contamination of water supplies
- Too high a concentration of the insecticide in a spray
- Storage toxicity of some compounds appears to increase with storage
- Application to animals of products containing oily bases designed specifically for spraying on walls or plants

Risk Factors

Animal Risk Factors

Susceptible groups include the following:

- Young animals (but with some compounds adults are more so), stressed, water-deprived, and chilled animals; the increased susceptibility caused by restriction of water intake is noted especially after oral treatment to control warble fly infestations.
- Pregnant females in that congenital defects occur in their offspring.
- Brahman and Brahman-cross cattle appear to be more susceptible to some compounds than other cattle.
- Dorset Down sheep may be especially susceptible.
- Chlorpyrifos is more toxic for male animals with high blood levels of testosterone and is not recommended for use in bulls over 8 months of age.

Environmental Risk Factors

The introduction of these compounds into animal therapeutics as treatments for nematode, botfly, sheep nasal botfly, and warble fly infestations and as insecticidal sprays on plants and soil has increased their importance as possible causes of poisoning and as causes of pollution of milk, meat, and eggs. They also have a role in the poisoning of native birdlife and other nontarget animals.[2]

Transmission

- Formulation used, especially the solvent or vehicle used and droplet size
- Method of application, e.g., the toxicity of pour-ons is delayed by 24 hours compared with sprays

PATHOGENESIS

OP compounds are highly toxic and readily absorbed by ingestion, inhalation, and by percutaneous and perconjunctival absorption. Once absorbed, sulfur-containing OPs (phosphorothioates and phosphorodithioates) are metabolized by mixed function oxidases (MFOs) and sulfur is exchanged for oxygen, thus increasing toxicity. There are two forms of toxicity: cholinesterase inactivation and an OP-induced, delayed neurotoxicity.

Cholinesterase Inactivation

The inactivation of cholinesterase by these OP compounds is associated with an increase in acetylcholine in tissues and increased activity of the parasympathetic nervous system and of the postganglionic cholinergic nerves of the sympathetic nervous system. The toxic effects thus reproduce the muscarinic and nicotinic responses of acetylcholine administration. Differences between the toxicities of compounds depend on the stability of this bonding between esterase and compound, and the toxicity of the substance formed by the bonding.

The muscarinic effects of acetylcholine are the visceral responses of the respiratory system and include marked respiratory distress caused by a decrease in dynamic lung compliance and arterial oxygen tension and an increase in total pulmonary resistance; there is bronchial constriction and increased mucous secretion by bronchiolar glands. In the alimentary tract there is increased peristalsis and salivation. Effects in other systems include hypotension and bradycardia, pupillary constriction, sweating, and abortion.

The nicotinic effects are the skeletal muscle responses of twitching, tremor and tetany, convulsions, opisthotonus, weakness, and flaccid paralysis. There is a difference in the relative muscarinic and nicotinic responses between species, and the visceral effects are more marked in ruminants and the muscular effects more evident in pigs in which posterior paralysis is the common manifestation.

Organophosphorus-Induced Delayed Neurotoxicity

This form of toxicity is manifested by distal axonopathy commencing 1 or 2 weeks after the poisoning incident. There is a dieback of neurons causing regional flaccid paralysis,

especially in long neurons. The pathogenesis of this lesion is the toxic end product produced by the interaction between some OP compounds and the esterase, a phosphorylated neurotoxic esterase. The most severe effects are associated with industrial OP compounds. Typical examples include the following:

- Congenital defects in young carried by poisoned pregnant females.
- Bilateral laryngeal hemiplegia in horses.
- Paralytic ileus may possibly be associated with chlorpyrifos toxicosis.

Haloxon, in particular, has this neurotoxic effect because it is associated with only a slight depression in cholinesterase levels, but a neurotoxic response in the form of hindlimb ataxia has been reported in a proportion of treated sheep and pigs. The susceptibility of sheep is determined by each individual's genetic ability to metabolize this class of OP compound.

CLINICAL FINDINGS

Acute Poisoning

In general, signs of acute toxicity in animals may occur within minutes of inhalation or ingestion of solutions of the more toxic compounds and deaths 2 to 5 minutes later. After cutaneous application of dichlorvos to calves clinical signs appear within 30 minutes, peak at about 90 minutes, and disappear in 12 to 18 hours. With less toxic compounds in solid form, signs may not appear for some hours and deaths may be delayed for 12 to 24 hours.

Cattle, Sheep, and Goats

Acute Toxicosis

In acute cholinesterase inactivation the premonitory signs, and the only signs in mild cases, are salivation, lacrimation, restlessness, nasal discharge, cough, dyspnea, diarrhea, frequent urination, and muscle stiffness with staggering. Grunting dyspnea is the most obvious, often audible from some distance because of the number affected. Additional signs include protrusion of the tongue, constriction of the pupils with resulting impairment of vision, muscle tremor commencing in the head and neck and spreading over the body, bloat, collapse, and death with or without convulsions or severe respiratory distress. In sheep and goats, the signs also include abdominal pain. Signs disappear at 12 to 18 hours.

Delayed Neurotoxicity

In these cases, the signs do not appear for at least 8 days and up to 90 days after the poisoning. Signs include posterior incoordination and paralysis. Chlorpyrifos is a specific example of this kind of poisoning. It should not be applied to adult dairy cattle or to mature bulls. The signs include anorexia, depression, recumbency, a distended abdomen, ruminal stasis and diarrhea, and fluid splashing sounds on percussion of the right flank. Severe dehydration develops and may result in death.

Pigs

Acute Toxicosis

In pigs acute cholinesterase inactivation visceral effects (except vomiting) are less pronounced than in ruminants and salivation, muscle tremors, nystagmus, and recumbency are characteristic. In some instances, the syndrome is an indefinite one with muscle weakness and drowsiness the only apparent signs. Respiratory distress and diarrhea do not occur.

Delayed Neurotoxicity

Outbreaks of posterior paralysis occur 3 weeks after dosing with an OP anthelmintic; clinical signs vary in severity from knuckling in the hindlimbs to complete flaccid paralysis. The hindlimbs may be dragged behind while the pigs walk on the front legs. Affected pigs are bright and alert and eat well.

Horses

Acute Toxicosis

Signs include abdominal pain and grossly increased intestinal sounds, a very fluid diarrhea, muscle tremors, ataxia, circling, weakness, and dyspnea. Increased salivation occurs rarely. In foals, fluid diarrhea, which is a transient sign in moderate intoxication, may be expanded to a severe gastroenteritis with heavier dose rates.

Delayed Neurotoxicity Syndrome

Bilateral laryngeal paralysis develops in foals after dosing with an OP anthelmintic.

Miscellaneous Signs of Organophosphorus Poisoning

- Piglets with congenital defects of the nervous system manifested clinically by ataxia and tremors are produced by sows dosed with OP compounds during pregnancy. Teratogenicity may be a characteristic of only some OP compounds, e.g., trichlorfon is teratogenic and dichlorvos is not.
- A significant drop in conception rate when the administration is at the beginning of estrus.
- Most OP compounds are associated with only temporary interference with cholinesterase and are not associated with any permanent effects in recovered animals. With some compounds, especially coumaphos and ronnel, the recovery period may be quite long (up to 3 months in the case of ronnel) because of slow excretion of the compound and the combined compound-esterase complex.
- Absorption of an OP compound may also be associated with significant changes in the patient's cholinesterase status without causing clinical signs.
- Potentiation of the action of succinylcholine chloride can occur for up to 1 month after the administration of the OP compound in horses; the administration of the relaxant to a sensitized horse can be followed by persistent apnea and death. This, and a number of other interactions with drugs that may themselves have toxic effects, means that the manufacturer's instructions for OP compounds must be followed explicitly.

CLINICAL PATHOLOGY

The estimation of cholinesterase in body tissues and fluids is the most satisfactory method of diagnosing this poisoning, but it is essential that proper methods and standards of normality be used. Convincing figures are of the order of 50% to 100% reduction from normal controls. The degree and the duration of the depression of blood cholinesterase levels varies with the dose rate and the toxicity of the compound used. Blood cholinesterase levels are depressed for much longer than clinical signs are apparent, e.g., after dichlorvos poisoning the depression of cholinesterase level in the blood does not reach bottom until 12 hours after application, and the return to normal levels takes 7 to 14 days. Similarly, cholinesterase levels in cattle poisoned with terbufos, an agricultural insecticide, do not commence to rise toward normal until 30 days and are not normal for 150 days after the poisoning incident. Unlike organophosphate insecticides, carbamate insecticide cholinesterase inhibitors may spontaneously reverse binding, and cholinesterase depression may not be detectable in recently poisoned animals.

Suspected food material can be assayed for its content of OP compounds but assays of animal tissues or fluids are virtually valueless and may be misleading.

NECROPSY FINDINGS

There are no gross or histologic lesions at necropsy in acute cholinesterase inactivation cases, but tissue specimens could be collected for toxicologic analysis. Material sent for laboratory analysis for cholinesterase should be refrigerated but not deep frozen.

Distinctive degenerative lesions in peripheral nerves and spinal cord can be seen in delayed neurotoxicity cases, and hypoplasia is visible in the cerebrum, cerebellum, and spinal cord in congenitally affected piglets.

DIFFERENTIAL DIAGNOSIS

Outbreaks of a syndrome of dyspnea, salivation, muscle stiffness, and constriction of the pupils after exposure plus a history of exposure and depressed blood levels of cholinesterase suggest intoxication with these organophosphorus compounds, but diagnostic confirmation requires positive assay results on

Continued

suspected toxic materials. In cattle the morbidity and case–fatality rates are approximately 100%, but in pigs the recovery rate is good and all pigs may recover if intake has been low and access is stopped. With the other poisons listed next, death is much more common in pigs, and residual defects, including blindness and paralysis, occur in a proportion of the survivors.

Differential diagnosis list

Cattle

- Early stages of nicotine poisoning
- Groups of cattle affected by acute bovine pulmonary emphysema and edema (fog fever)
- Sporadic cases of anaphylaxis

Horses

- Lead toxicosis

Pigs

- Arsenic toxicosis
- Avitaminosis A
- Mercury poisoning
- Sodium chloride (salt) poisoning

TREATMENT

Animals that have been dipped or sprayed should be washed with water to which soap or a detergent is added to remove residual OP material. When oral intake has occurred, activated charcoal will adsorb residual toxin in the gut.

Primary treatment is urgent and critical, especially in cattle because of the usually high case–fatality rate. Atropine is the antidote for muscarinic effects, but does not reverse the nicotinic effects of the OP compound, i.e., tremors, spasms, and convulsions. The recommended dose in sheep and goats is 0.5 mg/kg BW with ¼ given intravenously and the remainder intramuscularly or subcutaneously.[3] This should be repeated every 3 to 4 hours for 1 to 2 days with salivation and heart rate guiding therapy. Atropine appears to have low efficacy in sheep. This is not a serious drawback because sheep are much less susceptible than cattle to larger doses of atropine. The recommended dose of atropine in horses is 0.02 to 0.2 mg/kg BW intravenously to effect,[3] but it needs to be given with care because horses are very susceptible to the gastrointestinal effects of atropine.

Oximes, if available and economically feasible, may be useful in the early treatment of poisoning from OP compounds. Their usefulness as antidotes declines rapidly with the passage of time after the poisoning occurs, and they are of doubtful use after 24 hours. The most common oxime is pralidoxime chloride (2-PAM). The recommended dose rate for 2-PAM in ruminants is 25 to 50 mg/kg BW given intravenously as a 20% solution over 6 minutes.[4] In horses 2-PAM at doses of 20 mg/kg BW has given good results.[4] Treatment may need to be repeated for up to 10 days to counteract slower acting compounds such as coumaphos.

TREATMENT AND CONTROL

Ruminants

Atropine sulfate (0.5 mg/kg BW with ¼ given IV and the remainder IM or SC; repeat every 3–4 hours for 1–2 days) (R1)

Pralidoxime chloride (2-PAM) (25–50 mg/kg BW IV as a 20% solution over 6 minutes. Repeat as needed) (R2, depending on economics; not for herd use)

Horses

Atropine sulfate (0.02 to 0.2 mg/kg BW IV to effect; repeat judiciously SC every 1.5–2 hours) (R1, only if needed)

Pralidoxime chloride (2-PAM) (20 mg/kg BW IV; repeat every 4–6 hours as needed) (R2)

BW, body weight; IM, intramuscularly; IV, intravenously; SC, subcutaneously.

CONTROL

Most outbreaks occur after accidental access to compounds. Animals to be treated orally with OP insecticides should be permitted ample fresh drinking water beforehand. Use of chlorpyrifos is restricted to beef cattle and not in calves less than 12 weeks old or in bulls over 8 months of age.

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INDUSTRIAL ORGANOPHOSPHATES

Principal industrial uses of organophosphates are as fire-resistant hydraulic fluids, as lubricants, and as coolants. A number of compounds including tri-*o*-tolyl phosphate, tri-*o*-cresyl phosphate (TOCP), and triaryl phosphates (TAP) have come to veterinary notice as being associated with poisoning in animals. TAPs contain a number of isomers as well as TOCP (e.g., *m*-cresol, *p*-cresol, *o*-cresol), and all of them are more poisonous than TOCP. Poisoning may occur by ingestion or cutaneous absorption.

Clinical signs of delayed neurotoxicity do not occur until several weeks after contact and include irreversible neurologic signs of respiratory stertor, dyspnea, dysuria, knuckling, leg weakness, and posterior paralysis.

Diagnostic confirmation depends on evidence of exposure to the toxicant, signs referable to the nervous system lesions, and a positive assay for the toxicant in the animal's tissues. Necropsy lesions characteristically include neuronal degeneration in the spinal cord and peripheral nerves.

ROTENONE TOXICOSIS

Rotenone has been extensively used in the past to control bovine *Hypoderma* larvae (cattle grubs). It is a neurotoxicant; chronic exposure results in degeneration of neuronal cells, especially dopaminergic neurons.[1] Use as a pesticide and insecticide in the United States is being phased out, in part because of its link to Parkinson's disease in humans.[2]

It has a reputation for low mammalian toxicity but relatively high toxicity to aquatic life. The mammalian oral LD_{50} is 100 to 300 mg/kg, whereas the LD_{50} for fish is less than 100 µg/L of water. Oral absorption in mammals is limited but enhanced by fat in the diet.

Ingesta at necropsy may contain as much as 2000 ppm of rotenone. Signs include salivation, muscle tremor, vomiting, ascending paralysis, incoordination, quadriplegia, respiratory depression, coma, and death. Accidental oral exposure may be treated with activated charcoal, and an osmotic cathartic for decontamination followed by control of seizures is needed. Phenothiazine tranquilizers are contraindicated in rotenone toxicosis.

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ORGANOCHLORINE INSECTICIDES

SYNOPSIS

Etiology Poisoning by any of the group of insecticides including aldrin, hexachloride, chlordane, DDT, dieldrin, endrin, heptachlor, isodrin, lindane, methoxychlor, or toxaphene.

Epidemiology Accidental or misinformed overdosing. Usage on animals now

superceded by other less toxic compounds. Stored or leftover products may accidentally be accessed by animals. It is important because of residues in animal products used in the human food chain.

Clinical pathology Assay of compounds in animal tissues.

Lesions No consistent significant lesions; some animals show pale musculature.

Diagnostic confirmation Chemical assay of liver or brain for acute poisoning; fat or other animal tissue for chronic poisoning.

Treatment. Supportive care only; control hyperthermia and seizures. Removal of residual chemical; activated charcoal for oral detoxification.

Control Do not use these insecticides and store them appropriately.

DDT, *dichlorodiphenyltrichloroethane.*

ETIOLOGY

This group of poisons includes dichlorodiphenyltrichloroethane (DDT), benzene hexachloride (and its pure gamma isomer, lindane), aldrin, dieldrin, chlordane, toxaphene, methoxychlor, dichlorodiphenyldichloroethane, isodrin, endrin, and heptachlor. Methoxychlor is less toxic than DDT, and isodrin and endrin are more toxic than aldrin and dieldrin. Camphor (2-bornanone) is chemically similar to toxaphene and is associated with a similar syndrome when fed accidentally.

EPIDEMIOLOGY

Occurrence

Poisoning with these compounds has been recorded in all animal species. The chlorinated hydrocarbons have come under so much criticism as environmental contaminants that they are rarely used directly on animals, so outbreaks of clinical illness associated with them are much less common than they were.

Risk Factors

Animal Risk Factors

The compounds vary in their ability to pass the skin barrier. Benzene hexachloride, aldrin, dieldrin, and chlordane are readily absorbed. Species susceptibility to skin absorption also varies widely. Very young animals of any species are more susceptible than adults, and lactating and emaciated animals also show increased susceptibility.

Farm or Premise Risk Factors

Many outbreaks are associated with the application to animals of products intended for crops, e.g., endosulfan, and labeled specifically "Not For Animal Use." These insecticides may contaminate soil and persist there for many years. Rooting animals such as pigs are particularly susceptible to this source of poisoning. These compounds are also sometimes fed accidentally and in large amounts in lieu of feed additives, and are associated with acute poisoning. In feedlot animals, signs may continue for as long as a year because of repeated contamination from the environment. Insect baits, e.g., grasshopper baits containing toxaphene and chlordane, used on pasture and for leaf-eating insects on market gardens can be associated with poisoning in livestock, which may eat large quantities of them. These insecticides, especially heptachlor, are incorporated in the soil before the crop of potatoes or maize is sown to control soil pests. Subsequent grazing of the field will cause contamination of the livestock for several years.

Environmental Risk Factors

Organochlorines are closely regulated and banned in many countries primarily because of their persistence in the environment, but some are still widely used in agriculture, principally on growing plants to control insect pests and on stored seed grain to control fungi. If the plants or grain, even milled and by-products, e.g., bran, are fed to animals, they can be associated with problems of tissue residues; if they are fed in sufficient quantities they can be associated with clinical illness.

Human Risk Factors

Because the compounds are soluble in fat and accumulate in body stores they are formidable threats to the meat industry. They are also excreted in significant amounts in milk and enter the human food chain at this point. They are concentrated still further in cream and butter.

Transmission

Ingestion, inhalation, aspiration, and percutaneous absorption are all possible portals of entry so that contamination of feed and application of sprays and dips can all be associated with poisoning.

Method of Application

Dipping of animals is the most hazardous method of application because entry may occur through all portals. Spraying is safer because percutaneous absorption and inhalation are the only portals of entry. The small particle size of the compound and concentration of animals in confined spaces while spraying increase the possibility of poisoning. Oily preparations are not used for animal treatment but are used inadvertently and are readily absorbed through the skin.

Formulation Used

Concentrations of insecticide in formulations used for spraying barns are much higher than those used for animals. Among spray preparations simple solutions are most dangerous followed by emulsions and, least of all, suspensions of wettable powder. Dusting is safest and is preferred to other methods. Preparations for use on plants are often unstable emulsions, which come out of suspension quickly when they reach the plant. If these preparations are used in animal dips, the first few animals through the dip can be heavily contaminated and suffer acute, lethal toxic effects. Although the treatment of pastures to control their insect pests is usually safe to animals grazing, the treated pasture or hay made from it can cause contamination of animal products. This contamination can be avoided by incorporating the insecticide into superphosphate granules ("prills") instead of applying it as sprays or dusts.

PATHOGENESIS

The mechanism of action of organochlorines is to induce repetitive discharge of motor and sensory neurons by interference with axonal transmission of nerve impulses. After absorption, cyclodiene insecticides are activated by the MFO system, and any prior chemical or environmental exposures that increase the MFO system may exacerbate the onset of poisoning. The diphenyl aliphatic (DDT) organochlorines affect sodium channels, prolonging sodium influx and inhibiting potassium efflux at the nerve membrane. The cyclodiene organochlorines competitively inhibit the binding of GABA at receptor sites, resulting in loss of GABA inhibition and resultant stimulation of the neuron. In all organochlorine poisonings recovery may occur, but with smaller animals paralysis follows and finally collapse and death ensue.

Most of the substances accumulate in the fat depots, where they are a potential source of danger in that sudden mobilization of the fat may result in liberation of the compound into the bloodstream and the appearance of signs of poisoning.

CLINICAL FINDINGS

The speed of onset of illness after exposure varies from a few minutes to a few hours, depending on the portal of entry and the compound and its formulation, but it is never very long.

The toxic effects produced by the members of this group include complete anorexia, increased excitability and irritability followed by ataxia, muscle tremor, weakness and paralysis, and terminal convulsions in severe cases. Salivation and teeth grinding occur in large animals and vomiting occurs in pigs. Variations on this clinical syndrome, which is common to all organochlorine intoxications, include the following:

- DDT and methoxychlor chronic poisoning may be associated with moderate liver damage.
- Benzene hexachloride, lindane, chlordane, toxaphene, dieldrin, endrin, aldrin, and heptachlor are associated with an exaggerated syndrome including teeth grinding, champing of jaws, dyspnea, tetany, snapping of the eyelids,

auricular spasms, opisthotonus, frequent micturition, frenzied movements, walking backward, climbing walls, violent somersaults, and aimless jumping. Fever of 5% to 7% above normal may occur, possibly as a result of seizure activity. Seizures may persist for 2 or 3 days if the animal does not die.

CLINICAL PATHOLOGY

Blood, hair, and ingesta can be assayed chemically for specific toxins. The removal of a biopsy from the fat pad near the cow's tail offers a satisfactory means of providing samples for tissue analysis. Organochlorine residues in acutely poisoned animals may reach 4 to 7 ppm in brain or liver.

NECROPSY FINDINGS

At necropsy there are no specific major lesions in the nervous system, but toxic hepatitis and tubular nephritis appear in some cases. Tissue levels need to be high to be good indicators of recent intoxication. If possible, the specimens should be deep frozen, and the suspected compound should be nominated because assay procedures are long and involved.

Samples for Postmortem Confirmation of Diagnosis

- Specimens of hair, if the portal is percutaneous
- Ingesta, if oral intake is probable

DIFFERENTIAL DIAGNOSIS

Differential diagnosis list

- Lead poisoning
- Rabies
- Pseudorabies of cattle
- Polioencephalomalacia
- Thromboembolic meningoencephalitis
- Salt poisoning in pigs

TREATMENT

There is no specific primary treatment. Activated charcoal (2 g/kg) given early by stomach tube will bind pesticide in rumen and reduce further absorption. The use of mineral oil should be avoided because it will increase the absorption of lipid organochlorines. Residual chemical should be removed from the coat with a degreasing soap and copious water rinse. Supportive treatment includes sedation with diazepam or pentobarbital sodium until signs disappear, monitoring and treating hyperthermia, and replacing fluid losses.

Treatment to reduce the contamination of tissues is unsuccessful and in most cases the time required for the contamination to subside varies between compounds but is lengthy, taking 3 to 6 months or longer. For example, cows fed DDT prepartum need an average of 189 days from parturition for the level in the milk fat to decline to 125 ppm. After the source of contamination is removed, drenching of cows with up to 2 kg of activated charcoal followed by daily incorporation in their feed for 2-week intervals has been recommended for this purpose. Neither of these procedures is really practical in the average farm operation. The common procedure for reducing the level of tissue contamination in animals is to put them in a feedlot without any contact with pasture and feed them on energy-intensive rations. Sheep decontaminate much more quickly than cattle, and animals on a high plane of nutrition eliminate the toxins more quickly.

CONTROL

Avoidance of the use of the compounds is recommended.

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SODIUM FLUOROACETATE (COMPOUND 1080) TOXICOSIS

ETIOLOGY

Sodium fluoroacetate in the form of compound 1080 is used as a potent rodenticide in agriculture. It is currently used in the United States against coyotes and in Australia and New Zealand against introduced species such as possums.[1,2] It is also formed naturally by fluoride uptake from the soil and water in many plants that are native to Africa, Australia, and Brazil. The toxic dose level for domestic animals including sheep is 0.3 mg/kg BW,[3] and 0.4 mg/kg BW is lethal for cattle. Sublethal doses may be cumulative if given at sufficiently short intervals.

EPIDEMIOLOGY

The use of fluoroacetate in agriculture poses a hazard for grazing farm animals because it is usually spread out across fields combined with cereals, carrots, or bread as bait and is attractive to ruminants.

PATHOGENESIS

Fluoroacetate in the body is converted to fluorocitrate, which inhibits the enzymes aconitase and succinate dehydrogenase in the tricarboxylic acid cycle (Krebs cycle) leading to the accumulation of significant amounts of citrate in tissues and to irreversible cardiac damage. Two actions are manifest: CNS stimulation producing convulsions and myocardial depression with ventricular fibrillation. In sheep the predominant effect with acute poisoning is on the myocardium and the pulmonary system; in pigs and dogs it is the nervous system.

CLINICAL SIGNS

Clinical signs vary widely among species. In herbivores, sudden death in acute cases typically occurs. The animals are found dead without evidence of a struggle, or there are tetanic convulsions and acute heart failure with the animals showing weakness and dyspnea accompanied by cardiac arrhythmia, a weak pulse, and electrocardiographic evidence of ventricular fibrillation.

In sheep with subacute poisoning, the signs are similar but are not apparent when the animal is at rest. When they are disturbed, the nervous signs of tremor and convulsions appear but disappear when the sheep lies down.

Pigs manifest the nervous form of the disease, including hyperexcitability and violent tetanic convulsions. In all cases there is a period of delay of up to 2 hours after ingestion before signs appear.

CLINICAL PATHOLOGY/ NECROPSY FINDINGS

There are no specific lesions, but the tissues contain elevated levels of citrate.

TREATMENT/CONTROL

No specific treatment is available. In cats, calcium gluconate and sodium succinate have been used successfully in the treatment of experimental intoxication.[4] Care in the disposition of baits and highly dependable retrieval of uneaten baits before allowing livestock access to baited fields preempts most mortalities.

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MOLLUSCICIDE TOXICOSIS

Metaldehyde

Metaldehyde is the active ingredient in products used to control slugs and snails (mollusks), mites, and insects.[1-3] It is often used in combination with a carbamate, such as methiocarb, and historically with calcium

arsenate.[3] Metaldehyde is often bran based with molasses frequently added to attract snails and slugs. It is a neurotoxicant to all mammals by inhalation, ingestion, and dermal exposure. The mechanism of action is unknown, but it may be related to changes in the concentration of neurotransmitters in the brain. Outbreaks have occurred in cattle, goats, sheep, and horses.[1-3] The acute lethal dose in adult cattle is 0.2 g/kg BW and less in calves[3]; in horses it is 0.1 g/kg BW. The onset of signs varies depending on the concentration and amount ingested, but in cattle it is reported to be 15 minutes to 24 hours postingestion.[3] Prolongation may be caused by delayed rumen absorption.

Ingestion of a toxic amount of metaldehyde causes CNS stimulation with profound muscle tremors and hyperthermia. Other reported signs in ruminants include incoordination, hyperesthesia, hypersalivation, dyspnea, diarrhea, partial blindness, unconsciousness, cyanosis, and death caused by respiratory failure.[2,3] All the signs are exacerbated by excitement or activity. A mortality rate of 3% may be expected. Signs in horses are similar plus heavy perspiration and death in 3 to 5 hours.

There is no antidote, and treatment is largely supportive. Mineral oil and activated charcoal (1–3 doses) may be used to decrease absorption. Muscle tremors and seizures should be controlled with a tranquilizer and/or muscle relaxant. Intravenous fluids should be used to replace and restore fluids and electrolytes. Rumenotomy may be effective if performed before the onset of clinical signs.

Methiocarb

Methiocarb is a carbamate molluscicide used alone or in combination with metaldehyde. It has anticholinesterase and nicotinic and muscarinic activities.[4] The compound is usually in pellet form and dyed blue or yellow so that affected animals can be detected by the blue/yellow staining of their mouths.[3,4]

The signs can vary widely depending on the degree of receptor stimulation. Poisoning of sheep is associated with depression, hypersalivation, diarrhea, dyspnea, aimless wandering, and ataxia. Death is caused by pulmonary edema. Horses show sweating, lacrimation, urine dribbling or polyuria, muscle tremor, hypersalivation, and finally recumbency and death caused by pulmonary edema.[4]

Binding to acetylcholinesterase is reversible so recovery can occur with supportive care. Atropine is an effective antidote but likely will need to be repeated several times, especially if the amount ingested is large. Additional treatment is supportive and aimed toward specific system involvement.

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STRYCHNINE

Strychnine has been used for years as a rodenticide and avicide. Historically it has been used as an appetite stimulant and laxative and most recently, as a contaminant in LSD and other street drugs. It is an alkaloid derived primarily from seeds and bark of the *Strychnos nux-vomica* tree, although it is found in various amounts in many *Strychnos* spp.

Strychnine poisoning is an uncommon occurrence in large animals and usually associated with accidental overdosing with strychnine preparations or accidental access to strychnine treated bait meant for rodent control. Cattle are particularly susceptible to parenteral administration (30–60 mg of strychnine hydrochloride may be fatal) but less susceptible to oral administration because of destruction of the drug in the rumen. Lethal doses by parenteral injection are 200 to 250 mg in horses, 300 to 400 mg in cattle, and 15 to 50 mg in pigs.

Strychnine is rapidly absorbed from the gastrointestinal tract in monogastric animals and less so by ruminants. Distribution to tissues is rapid as is hepatic metabolism. In most animals, 50% of strychnine is eliminated in 6 hours following a sublethal dose.

It is a potent neurotoxicant and convulsant, exerting its action at the postsynaptic membrane. In the spinal cord, strychnine interferes with the inhibition of motor cell stimulation resulting in simultaneous muscle contraction. In the brain, it interferes with inhibitory responses of the motor neurons resulting in neuronal excitation. The convulsant effects of strychnine are caused by interference with glycine-mediated postsynaptic inhibition. The net effect is that all skeletal muscles become hyperexcited, and tetanic seizures may be provoked by the application of minor external stimuli. In these convulsive episodes there is extension of the limbs, opisthotonus, and protrusion of the eyeballs. The seizures may last for 3 to 4 minutes and are followed by periods of partial relaxation, which become progressively shorter as the disease develops. Hyperthermia may be extreme. Respiratory arrest leads to death.

There is no antidote and treatment is supportive. Animals should be kept in a dark, calm area and not stimulated in any manner. Seizures should be treated with diazepam or a barbiturate. If seizures can be adequately controlled, animals may survive.

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Diseases of the Cerebrum

PSYCHOSES, NEUROSES, AND STEREOTYPY

Psychoses or neuroses are rarely documented in farm animals, whereas **stereotypy** is common, particularly in horses. Stereotypic behavior is repetitive behavior induced by frustration, repeated attempts to cope, or CNS dysfunction. Primary equine stereotypies include crib-biting, weaving, box walking, tongue rolling, and lip movement.

Crib-Biting and Windsucking

Crib-biting or "cribbing" is an oral stereotypic behavior in which the horse grasps an object, usually the feed box or any solid projection, with the incisor teeth, then arches the neck and, by depressing the tongue and elevating the larynx, pulls upward and backward and swallows air, emitting a loud grunt at the same time. This results in erosion of the incisor teeth and intermittent bouts of spasmodic colic and flatulence. Crib-biting must be distinguished from chewing wood from boredom and from pica caused by a mineral deficiency. **Windsucking** (aerophagia) is an oral stereotypic behavior in which the horse flexes and arches the neck and swallows air and grunts, but there is no grasping of objects.

Crib-biting is viewed as a vice and potentially "contagious" problem and affected horses are usually not welcome in stables. Once established, crib-biting is primarily postprandial. Treatments include environmental enrichment (move horse to a stall where they can view more activity; change stall door/walls so that other horses can be seen) and feeding more hay and less concentrate so that feeding takes longer. More aggressive treatments include placement of a crib-strap (a strap placed around the neck of the horse that has two pieces of metal hinges at the ventral area; during arching of the neck the crib-strap tightens around the pharynx) or neurectomy or myectomy. Weaning in a box stall appears to increase the risk of developing crib-biting.

Weaving

Weaving is a locomotor behavior during which the horse moves its head and neck laterally while its weight is moved to the contralateral forelimb, usually while the horse is positioned at the stall door with its head over the stable door into the aisle. There is no specific treatment and closing the top half of the stable door merely moves the activity back into the stall. Feeding hay ad libitum may decrease the time devoted to this activity (anecdotal reports).

Box Walking

The term **box walking** refers to persistent walking around the perimeter of the stall in a circular, repetitive manner. There is no specific treatment, but anecdotal reports suggest that feeding hay ad libitum may decrease the time devoted to this activity. Other stereotypical behavior includes persistent kicking of the stall, in the absence of pruritic lesions of the lower limbs, and cutaneous and subcutaneous mutilation by self-biting.

Farrowing Hysteria in Sows

Hysteria in sows at farrowing is a common occurrence. This syndrome is most common in gilts. Affected animals are hyperactive and restless and they attack and savage their piglets as they approach the head during the initial teat sucking activity after birth. Serious and often fatal injuries result. Cannibalism is not a feature.

When the syndrome occurs, the remaining piglets and freshly born piglets should be removed from the sow and placed in a warm environment until parturition is finished. The sow should then be tested to see if she will accept the piglets. If not, ataractic or neuroleptic drugs should be administered to allow initial sucking, after which the sow will usually continue to accept the piglets.

Azaperone (2 mg/kg BW IM) is usually satisfactory, and pentobarbital sodium administered intravenously until the pedal reflex is lost has been recommended. Promazine derivatives are effective but subsequent incoordination may result in a higher crushing loss of piglets. The piglets' teeth should be clipped.

Affected gilts should be culled subsequently because the syndrome may recur at subsequent farrowing. Where possible, gilts should be placed in their farrowing accommodation 4 to 6 days before parturition and the farrowing environment should be kept quiet at the time of parturition.

Tail-Biting, Ear-Chewing, and Snout-Rubbing in Pigs

The incidence of cannibalism has increased with intensification of pig rearing, and it is now a significant problem in many pig-rearing enterprises. Tail-biting is the most common and occurs in groups of pigs, especially males, from weaning to market age.

Ear-chewing is less common and is generally restricted to pigs in the immediate postweaning and early growing period, although both syndromes may occur concurrently. The incidence of ear-chewing has increased with the practice of docking piglet tails at birth. The lesions are usually bilateral and most commonly involve the ventral part of the ear. Lesions from bite wounds may also occur on the flanks of pigs. There is frequently an association with mange infestation with both of these vices.

A syndrome of snout-rubbing to produce eroded necrotic areas on the flanks of pigs has been described. Affected pigs were invariably colored, although both white and colored pigs acted as agonists.

The causes of these forms of cannibalism in pigs are poorly understood, but they are undoubtedly related to an inadequate total environment. Affected groups are usually more restless and have heightened activity. Factors such as a high population density, both in terms of high pen density and large group size; limited food and competition for food; low protein and inadequate nutrition; boredom; and inadequate environment in terms of temperature, draft, and ventilation have been incriminated in precipitating the onset of these vices.

When a problem is encountered, each of these factors should be examined and corrected or changed if necessary. **Prevention** is through the same measures. Chains or tires are frequently hung for displacement activity but are not particularly effective.

The problem may recur despite all attempts at prevention. Also for economic reasons it is not always possible to implement the radical changes in housing and management that may be necessary to avoid the occurrence of these vices. Because of this, the practice of tipping or docking the piglets' tails at birth has become common as a method of circumventing the major manifestation of cannibalism.

HEAD-SHAKING IN HORSES

Head-shaking by horses is a troubling syndrome associated with hypersensitivity of the trigeminal nerve in most affected horses. The disorder is characterized by repeated, sudden shaking or tossing of the head. It is proposed that a subgroup of horses with defined trigeminal hypersensitivity be classified as having trigeminal-mediated facial dysesthesia.[1]

ETIOLOGY

The etiology is complex and often unclear and conditions associated with head-shaking include the following[2]:

- Ear mites
- Otitis interna/externa
- Ophthalmic disease (uveitis)
- *Trombicula autumnalis* (chiggers) infestation of the muzzle
- Guttural pouch disease (mycosis)
- Stylohyoid arthropathy
- Osteitis of the petrous temporal bone
- Dental disease (wolf teeth, ulceration, periodontal disease, periapical abscess)
- Behavioral abnormalities
- Trigeminal neuralgia
- Optic neuritis
- Photic head-shaking (optic-trigeminal summation)
- Neck pain
- Rhinitis or sinusitis (including fungal sinusitis)[3]
- Ethmoidal disease including hematoma
- Infraorbital neuritis
- Excessive neck flexion by rider
- Equine protozoal myeloencephalitis
- Ill-fitting tack including bit and bridle
- Obstructive airway disease (heaves, laryngeal hemiplegia, epiglottic cysts, etc.)
- Fractures of the nuchal crest[4]
- Surgery of the paranasal sinuses[5]

Most cases of the disease are idiopathic despite intensive investigation of affected horses. Photic head-shaking is a common cause of the disease. Most cases have some seasonal distribution, although the reason for this is undetermined. Trigeminal neuralgia is considered an important cause of the disease. It is not associated with EHV-1 infection of the trigeminal ganglia.[6]

EPIDEMIOLOGY

The epidemiology of the disease is not well defined. The syndrome occurs in horses throughout the world. The syndrome is sporadic, usually affects only one horse on a farm, and does not occur as outbreaks. It has a seasonal occurrence in approximately 60% of horses with the majority first demonstrating head-shaking, or being most affected, during spring and summer. Head-shaking is worst on sunny days, and less severe on cloudy days, in approximately 60% of horses. Sunshine and windy weather worsen the condition in many horses.[7] Seventy-five percent and 80% of affected horses have less severe signs at night or when ridden indoors, respectively.

Affected horses are usually mature adults with onset of head-shaking at 7 to 9 years of age in over half of the cases, although signs can occur in horses as young as 1 year.[2] The disease is reported twice as often in geldings as in mares. There is an apparent predisposition to the disease in Thoroughbreds, but this is not consistently reported. Most affected horses are used for general riding, although this might represent an age effect because the syndrome tends to occur in older horses that are not used for racing. There is no apparent association of temperament and risk of head-shaking.

PATHOGENESIS

The pathogenesis of head-shaking depends on the cause, but it is increasingly persuasive that the majority of cases involve hypersensitivity of the trigeminal nerve.[1,8-10] The trigeminal nerve provides sensory function of the nose and nasal mucosa. Horses affected by head-shaking have low stimulus thresholds for the trigeminal nerve than do healthy horses, although once stimulated nerve conduction is not different between the groups.[9] The lower stimulus threshold likely makes affected horses more sensitive to noxious stimuli. A method is also described for assessment of the trigeminocervical reflex in normal horses.[11] This technique might be useful in head-shaking horses.[10-12]

Head-shaking is related to exposure to bright light in some animals. This is a condition referred to as photic or optic-trigeminal summation because of its similarity to a syndrome in people. Trigeminal neuralgia is thought to cause acute, sharp, and intense pain in the face. Although this cannot be definitively diagnosed in horses, its presence is inferred from the horse's behavior and response to analgesia of the infraorbital or posterior ethmoidal nerves.

CLINICAL FINDINGS

The **clinical signs** of head-shaking are unmistakable. Movements of the head are sudden and apparently spontaneous and involve lateral, dorsal, ventral, or rotatory movement of the nose usually during exercise. Horses rarely have the behavior only at rest, with most affected both at rest and during exercise and about 10% exhibiting signs only during exercise. The action often resembles that of a horse trying to dislodge something from its nose. Approximately 90% of horses have vertical movement of the head (as if flipping the nose). The head-shaking can be so severe it causes lateral, dorsal, or ventral flexion of the neck to the level of the caudal cervical vertebrae, although more commonly only the rostral one-third of the neck is involved, if it is involved at all. Some horses rub their nose on objects, the ground, or their front limbs, sometimes during exercise. Affected horses often snort or sneeze. There can be twitching of the facial muscles and flipping of the upper lip. The movements are sudden and at times appear to catch the horse by surprise. The frequency and/or severity of movements are usually increased during exercise. Severely affected horses can stumble and fall if head-shaking occurs during exercise, rendering the horse unsafe to ride.

A grading system to classify the severity of signs is as follows:

0 No signs of head-shaking
1 Intermittent and mild clinical signs: facial muscle twitching; rideable
2 Moderate clinical signs: definable conditions under which head-shaking occurs; rideable with some difficulty
3 Rideable to unpleasant to do so: difficult to control
4 Unrideable and uncontrollable
5 Dangerous with bizarre behavior patterns

This system might be useful for assessing response to therapy and concisely describing the severity of the signs.

Ancillary testing involves radiography of the skull; endoscopic examination of both nostrils and ethmoidal regions, nasopharynx, larynx, and guttural pouches; otoscopic examination of the external auditory canal and tympanic membrane (difficult to achieve in a conscious horse, a small endoscope is necessary); desensitization of the infraorbital and posterior ethmoidal nerves; biopsy of the nasal mucosa (in horses with suspected rhinitis); radiographic examination of the head and neck; measurement of stimulus threshold for action potentials in the trigeminal nerve,[9] and therapeutic trials including application of contact lenses or masks, or administration of medications (see the following section Treatment).

CLINICAL PATHOLOGY

There are no characteristic hematologic or serum biochemical abnormalities.

NECROPSY FINDINGS

There are no characteristic findings on necropsy, apart from those of any underlying disease. Evidence of lesions in the trigeminal nerve is lacking.

DIFFERENTIAL DIAGNOSIS

The disease must be differentiated from the stereotypic weaving that occurs during stabling and not during exercise.

TREATMENT

The principles of treatment include relief of specific underlying diseases, removal of management or environmental conditions that cause head-shaking, and administration of medications. There is the potential for an important placebo effect, in the owners, for treatment of head-shaking.[13]

If underlying conditions are detected, such as ear mites, dental disease, and other conditions listed in the previous section Etiology, then these conditions should be treated effectively. Effective treatment will alleviate head-shaking, if in fact the condition was the cause of the disease. However, most horses with head-shaking have seasonal or photic disease and treatment is more difficult. A survey of owners of 254 horses with head-shaking revealed that only 129 horses had been treated by a veterinarian and, of those, only 6% had complete resolution of head-shaking, whereas 72% had no response to treatment. Other treatments used were on the advice of lay "back specialists," homeopathy, alternative therapies, or face or head masks. Success rates for these interventions varied between 6% and 27%, with the most success obtained by use of a nose net (27%). Nose nets provided better control of signs than did face or eye masks. These figures on the success of treatment illustrate the refractory, and therefore frustrating, nature of the disease.

Fitting of **nose masks** alleviates or lessens head-shaking in some horses. The design of the nose mask does not appear to be important regarding whether it covers the entire rostral face or just the nostrils. The nose masks were most effective for treatment of up-and-down head-shaking, but not for side-to-side or rubbing behavior.

Blue-tinted **contact lenses** have been suggested for use in horses with photic head-shaking. Others have not found this intervention useful. Administration of sodium cromoglycate eye drops has demonstrated potential in a small number of horses for treatment of seasonal head-shaking, presumably because of the amelioration of the effects of seasonal allergy.[14]

Sclerosis of the infraorbital or posterior ethmoidal nerves is performed in those horses that have reduced or eliminated head-shaking after injection of local anesthetic into the infraorbital foramen or around the posterior ethmoidal nerve. Sclerosis is achieved by injection of 5 mL of 10% phenol in oil. Care must be taken to ensure that the phenol is deposited only around the nerve. The procedure should be done under general anesthesia.

Cyproheptadine (0.3 mg/kg, orally every 12 hours) improved head-shaking in 43 of 61 horses, based on owner-reported efficacy. Responses were usually observed within 1 week of the start of therapy. Others have not replicated this success but found that the combination of **carbamazepine** (4 mg/kg orally every 6 to 8 hours) and cyproheptadine improved clinical signs in seven horses within 3 to 4 days of starting treatment.

Acupuncture and **chiropractic** manipulation appear to be minimally effective.

Prevention of exposure to bright light is an obvious recommendation, but not practical for most horse owners.

Caudal compression of the infraorbital nerve with platinum coils provides a surgical treatment option for horses that do not respond to medical treatment or environmental modification.[15] Of 58 horses treated using caudal compression of the infraorbital nerve a successful outcome was initially achieved in 35 of 57 (63%) horses, but recurrence occurred between 9 and 30 months later in 9 (26%). Surgery was repeated in 10 of 31 (32%) horses. Final success rate, considering only response to the last performed surgery, was 28 of 57 (49%) horses with median follow-up time of 18 months (range 266 months). Nose-rubbing was reported postoperatively in 30 of 48 (63%) horses and resulted in euthanasia of four horses.[16]

Administration of dexamethasone in a pulsed dose schedule (60 mg orally every 24 hours × 4 days, every 3 weeks for 4 months) to 12 horses did not result in improvement of clinical signs in a randomized, placebo-controlled, blinded field trial.[7]

Addition of an unspecified feed supplement to the diet of 44 affected horses in a randomized, blinded placebo controlled study did not detect a beneficial effect of the supplement.[13]

CONTROL

There are no recognized measures for preventing development of the disease.

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TAIL-BITING IN SWINE

Tail-biting, which is the chewing or biting or sucking of a tail of a fellow pig, is an example of cannibalism. It is a very complex problem that is widespread and has demanded more attention with time. It is an intractable problem[1,2] that is very unpredictable. It has a high economic impact because of euthanasia, medical costs, other infections, and condemnations. This has increased with intensive farming and is the most serious of the vices of the domestic pig. It is much more important than flank-biting, nosing, or ear-biting. It has been seen in outdoor pigs and on organic units. About 60% of farms in the UK have at one time or another experienced tail-biting in single pigs or as a group problem. It is a serious welfare issue because it often leads to systemic infections from a whole variety of opportunist bacteria, principally *Trueperella pyogenes* and *Streptococcus* spp., which lead to septicemias and particularly spinal abscessation. Both ear-chewing and tail-biting have also increased in recent years.[3] It is assumed that contented pigs do not tail-bite.

Three stages of tail-biting have been recognized[3]:

1. Two-stage initial phase that includes predamage and damage probably related to having no substrates or play items
2. A second stage called sudden or forceful in which there are probably inadequate resources
3. An obsessive phase that includes many of the factors described in stages 1 and 2, principally those associated with genetics, attraction to blood, and protein metabolism upsets

The diagnosis of the condition is very difficult. It occurs under all conditions including outdoors. Possibly 0.5% to 0.7% of docked pigs are bitten and 2% to 4% of undocked pigs. A recent survey in the UK suggested that 90% of farms had pigs that were not bitten, 6% had small problem, and 4% had big problems. Most abattoirs do not record pigs bitten, and many bitten pigs are sent to small abattoirs. There are probably three mild lesions to every one serious lesion and these are probably not recorded.

ETIOLOGY

There are said to be three basic scenarios: (1) gentle chewing that escalates; (2) two-stage biting; and (3) sudden forceful biting, which may be sudden frustration over a lack of a resource.[5,6]

Tail-biting usually begins with one pig doing the biting and one pig being bitten in an environment that for some reason has caused stress. It then spreads rapidly through the whole group as the bitten tail becomes more attractive.

The inadequate total environment for an animal that naturally requires the opportunity to socially interact and demonstrate its natural behavior of inquisitiveness and rooting is often the underlying cause. Abnormal foraging behavior has been suggested as the underlying cause.[6] Abnormalities of ventilation, particularly drafts, appear very unsettling to pigs. The normal pig group is probably under 20 and over that number the individual's place in the hierarchy is probably lost.

EPIDEMIOLOGY

"Belly-nosing" may be one of the behavior patterns that predispose to tail-biting. It is often associated with early weaning and is the persistent rubbing of the snout on the belly of another pig. It may be misdirected suckling behavior.[7] This behavior is not eliminated by providing environmental enrichment, suckling devices, of extra drinkers or nipple feeders. There is a genetic linkage with Landrace pigs[8] and with weight for age.[9]

The condition is found worldwide. It is often more prevalent in males than females and may be part of natural aggressiveness. The real cause is still unknown but is probably a mental reaction on the part of the pig to unsavory living conditions. Under normal circumstances happy pigs root for 18% of the time and probably doze for about 82% of the time. They are really the "couch potatoes" of the domesticated farm animals. If they have nothing to do, they cause trouble. Recent studies have suggested that the "troublesome" pig may be lighter, more active, and possess more "nosing" behavior patterns.[10] Others have suggested that it is the heavier pigs that are bitten.

The causes for tail-biting are multifactorial, but it has to be considered that there may be a bad "psychologically disturbed pig." Once the behavior has started it behaves like an epidemic. Recent studies have suggested that the way the tail is held has a very considerable influence on whether it is bitten or not.

Anal biting may or may not be related to tail-biting. It has certainly been a feature of a few cases of anal irritation in response to oral dosing with Lincocin.

RISK FACTORS

These have been reviewed.[4,5] Traits related to foraging, exploration feeding, motivation to feed, and sociability are heritable.[11,12]

Because of modern genetics, pigs grow faster and are more aggressive. Aggression is also heritable.[13] Some of the breeds may be more heavily bitten, but Hampshires are less frequently bitten. Some pigs may be unable to use food properly because of a metabolic deficiency.

There is a subset of pigs called the fanatical biters who are generally small males with low lightweight gain. These biters have a low growth rate from weaning to finishing. They spend more time chewing than they do rooting. In a poor environment, they will chew other pigs rather than root. Some of these biters have respiratory or alimentary diseases or porcine circovirus type 2 (PCV2) infections. There are other types of pigs that bite.

The tail-biting hypothesis suggests that there may be a big protein demand that is not being met, so there is a protein deficiency as a result of poor intake of food. There may be a dysfunctional autonomic nervous system regulation involving the general sense responses, interrelated illnesses, and suppressed thyroid hormone T_3 production. It may be that there is a lack of tyrosine for serotonin production, which is an important neurotransmitter. Pigs with higher levels of serotonin spend more time rooting, and in the "bit tail blood model" it is found that serotonin-deficient pigs do more biting.

- There may be breed, line, or family predispositions.
- White pigs have more of a problem than colored breeds.
- There is a genetic tendency to be a biter or to bitten.
- Tail-biting is associated with lean tissue growth and backfat thickness

FACTORS INCREASING BITING

- Tails are bitten more frequently when there is a low weight gain (nutrition).
- Males may be more predisposed, but there is less biting in single sex rearing.
- When there are no interests provided and there are no toys with which to play.
- High-density stocking.
- Over stocking.
- Large group sizes.
- Mixing and moving.
- Space postweaning.[14]
- If you move pigs from a straw-based system to a slatted system they will bite much more.
- Insufficient trough space, if feeders are blocked then pigs will bite to get at the feeder.
- Insufficient drinkers.
- Inadequate nutrition.
- Change in ration formulation leading to food sensing.

- Low-protein diets encourage biting and chewing.
- Not enough amino acids (lysine, tryptophan, but true position unknown).
- Low salt.
- Nonsatisfying environments, particularly those with a poor layout, on nonstraw systems are badly affected.
- Boredom (lack of toys).
- Inadequate environment.
- Low temperatures: cold and damp is bad on straw-based systems, and poor-quality straw is a problem.
- High temperatures.
- Fluctuating temperatures.
- Drafts.
- Too high a humidity.

Variable tail docking length is also a factor. The variation in tail anatomy and position is also important.[15]

Concurrent disease, particularly PCV2 infection and skin, disease may predispose to biting.

In a summary, overstocking was thought to be important in 60% of cases, inadequate ventilation in 50%, wrongly positioned ventilation in 50%, and cold drafts in 40%. Sick pigs that are not moved promptly were thought to be important in 60% of outbreaks and boredom in 50%. The other factors were considered to be of lesser importance (below 20%).

CLINICAL FINDINGS

At the start there is no effect on the bitten pig because the end of the tail is relatively insensitive, but as the bitten area extends toward the anus it becomes more painful and the bitten pig shows signs of distress. With continuation the pig may be reluctant to feed, reluctant to move, and eventually become paralyzed as spinal abscessation becomes the reality.

CLINICAL PATHOLOGY

There may be chewed, gnawed, and partially or completely removed tails. In an early study at an abattoir 19.9% of the lesions on the carcasses were related to tail-biting and 61.75 of carcass abscesses were associated with tail-biting.

NECROPSY

At necropsy or in the abattoir it is a bitten tail as well as the abscessation that is most noticeable along the length of the spine as infection tracts along lymphatics and longitudinal spinal veins. In some cases, the carcass is so badly affected that the whole carcass is condemned. In some cases, there will be evidence of flank-biting and ear-biting (sometimes the ear is completely bitten off), which are part of the same disturbed pig syndrome.

TREATMENT

Remove affected pigs to hospital accommodation, pen separately, and treat the wounds by cleaning, disinfection, and topical palliatives and possibly parenteral broad-spectrum antibiotics. Shoot badly affected or paraplegic pigs. Casualty slaughter is not very useful because of the carcass damage.

CONTROL

There is no really successful plan for control that will work all the time. There is a husbandry advisory tool with 100 possible risk factors. The spreadsheet lists 83 factors. Weighted for risk factors the tool shows that a quarter of the farms have no problems and a quarter of the farms have a serious problem. Attend to all the listed factors and even then you will not always remove the problem, but it will certainly be reduced. Nothing is ever completely effective.

First, observe pigs several times a day and remove the biter as soon as it is seen to bite and put it into separate accommodation.

Elevating the salt level to 0.8% often works even though there is already 0.4% in the diet, which is thought to be sufficient. Make sure there is plenty of water available.

The improved environment is one of the most important items, particularly the application of negative pressure systems. Lowering light levels reduces the "glowing effect" of blood-covered surfaces similar to housing broiler birds in infrared lights to reduce "vent pecking."

The provision of an improved environment by providing "playthings" that satisfy the desire of the pig to sniff, inquire, taste, and chew is most important. These items should be malleable, which is why straw or peat, or spent mushroom compost or rubber cords, or even tires[16] are more satisfying than chains. The chains are no good because they slap other pigs and increase the restlessness. Straw provision has the ability to keep pigs occupied for longer than other substrates,[17,18] and it is better if it is provided daily.[19] Housing systems that have had ad libitum feeding systems with multiple feed spaces have had a reduced prevalence of the problem.

This attention to sucking and chewing is the basis of all the saliva tests that have been developed to detect viruses such as porcine reproductive and respiratory syndrome (PRRS) and PCV2 and antibodies to them. Hanging a set of cotton cords in a pen that will soon be sucked by most pigs as part of play will provide a readily accessible sample source for saliva antigens antibodies and many other substances such as acute phase proteins. This does not involve disturbing the pigs or requiring handling and invasive techniques for the individual pig for investigating herd profiles.

The provision of straw is no guarantee that tail-biting will be stopped.[20]

Tail docking is the only technique that does reduce the presence of tail-biting. The conditions attached to use of this practice vary from country to country and often mean that the technique has to be prescribed by a veterinarian only after the presence of a tail-biting problem has been established on that farm. Even tail-docked pigs have evidence of being tail-bitten.[21]

The ideal length of tail docking is not really known. One of the major problems is that tails differ in thickness and length before any consideration of the length to be cut off. Too short a tail, i.e., cut very short, interferes with the nervous control around the anus, may lead to fecal incontinence, and exposes the anus itself to being bitten.

Tail docking produces a neuroma at the site of nerve transection, which results in the formation of many sensitive nerve endings that enable the pig to react more sensitively to any nosing of its tail.

In a recent survey,[18] 62% thought that docking was effective in preventing tail-biting, 47% thought adding straw was helpful, 46% thought that playthings were effective, but only 18% thought reducing stocking density was helpful. The latter may be because of the economic implications of reducing stocking. All in all, reducing stocking density and adding straw together was considered to be the best option.[22]

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Bacterial Diseases Primarily Affecting the Cerebrum

ENTEROTOXEMIA ASSOCIATED WITH *CLOSTRIDIUM PERFRINGENS* TYPE D (PULPY KIDNEY, OVEREATING DISEASE)

SYNOPSIS

Etiology An acute toxemia of ruminants associated with the proliferation of *Clostridium perfringens* type D in the intestines and the liberation of ε-toxin that produces vascular damage and the damage to the nervous system typical of this disease.

Epidemiology Lambs 3–10 weeks of age and lambs and calves after weaning. Goats of all ages. Affected animals in good condition and on a rising plane of nutrition.

Clinical findings The disease in lambs and calves and young goats has a rapid course with diarrhea, depression, and convulsions. At this age animals are often found dead. Adult goats show more chronic disease with abdominal pain and bloody diarrhea.

Clinical pathology Hyperglycemia and glycosuria in sheep.

Necropsy findings None specific to all cases. Sheep and some goats may have gross or histologic areas of malacia in internal capsule, lateral thalamus, and cerebellar peduncles.

Diagnostic confirmation Epidemiology, clinical and necropsy findings, demonstration of ε-toxin

Treatment Anti-ε antitoxin.

Control Feed restriction, antitoxin, vaccination.

ETIOLOGY

Enterotoxemia results from the proliferation of *C. perfringens* type D in the small intestine. This organism produces a number of toxins, of which the epsilon toxin is the most important and results in vascular damage and the damage to the nervous system typical of this disease. The presence of *C. perfringens* type D in the intestine does not in itself result in disease unless other factors intercede that promote proliferation and the production of toxin. The natural habitat of the organism is in the intestine and in soil contaminated by feces, although it does not persist in soil for long periods of time.

EPIDEMIOLOGY

Occurrence

Enterotoxemia associated with *C. perfringens* type D is a disease of ruminant animals, primarily of lambs, and is worldwide in its distribution. The common practice of vaccination against this disease has reduced its prevalence, but it is still a common disease.

Although most common in lambs, it is also an important disease of calves and goats. It occurs rarely in adult cattle, deer, domesticated camels, and possibly horses. In pastured sheep, it causes heavy losses, particularly in flocks managed for the production of lamb and mutton. The prevalence in flocks varies a great deal but seldom exceeds 10%. The case–fatality rate approximates 100%. In North America enterotoxemia ranks as one of the main causes of loss among feedlot lambs. In a survey in two feedlots the disease had an annual prevalence of 3.1% and 1.5%; it ranked third in importance as a cause of death despite a policy of vaccination, and the costs of prevention programs were the largest expenditure of all disease prevention programs in the feedlots.

Experimental Reproduction

The disease can be produced experimentally in susceptible sheep, goats, and cattle by the injection into the duodenum of whole culture of *C. perfringens* type D and dextrin or starch. Clinical disease occurs as early as 30 minutes and usually within 6 to 8 hours of the start of duodenal infusion and death 1 to 9 hours following the onset of clinical signs. The disease has also been reproduced by intravenous infusion of epsilon toxin.

Animal and Management Risk Factors

C. perfringens type D normally inhabits the alimentary tract of sheep and other ruminants but only in small numbers. The extent to which it occurs in the alimentary tract varies widely between flocks, although this accounts only in part for the variable prevalence. The organism does not persist for more than 1 year in the soil.

Under certain conditions, the organisms proliferate rapidly in the intestines and produce lethal quantities of epsilon toxin. In most, if not all circumstances, the affected animals are on **highly nutritious diets** and are in very good condition. The husbandry conditions in which the disease occurs include grazing on lush, rapidly growing pasture or young cereal crops, and heavy grain feeding in feedlots. Lambs on well-fed, heavy-milking ewes are particularly susceptible. The occurrence of the disease under these conditions has given rise to the name "overeating disease."

Sheep

The highest incidence of the disease is in suckling lambs between 3 and 10 weeks of age, although lambs as young as 1 to 5 days old can be affected.[1] The risk for disease in this age group is highest when ewes are grazed on lush pastures that result in profuse lactation. The disease can occur following rain in set stocked flocks, and in flocks newly introduced to lush pastures it is often manifested 5 to 14 days after introduction. Larger and more rapidly growing single lambs are more susceptible than twins. Weaned lambs up to 10 months of age are the second most susceptible age group, and again the occurrence of disease is associated with highly nutritious diets. Feeder lambs are most commonly affected soon after they are introduced into feedlots.

Calves

Enterotoxemia in calves is most common between 1 and 4 months of age and the same risk factors pertain as for lambs. Veal calves are particularly at risk. Feeder cattle may develop disease shortly after introduction to the lot. It is a common belief among cattlemen and veterinarians that many unexplained sudden deaths in feeder cattle after the period of acclimatization are caused by this type of enterotoxemia. However, there is no laboratory evidence to support such field observations, and a controlled trial found no protective effect of vaccination.

Goats

Enterotoxemia is a common disease in goats under intensive or extensive grazing systems, occurring in many countries, and is particularly important in countries with a large goat population.[2] The peracute disease in goat kids has the same age occurrence as in lambs, but less acute and chronic forms of enterotoxemia occur in adult goats. Sudden changes in diet appear to be the most common predisposing factor. Disease can occur in vaccinated goats because vaccination is poorly protective against the enteric and chronic form of the disease in this species.[2]

Outbreaks in sheep and goats have followed the administration of phenothiazine and other anthelmintics, and a high incidence has been observed in association with heavy tapeworm infestation.

Horses

Type D enterotoxemia is rare in horses, but it has been suspected in mature horses fed concentrates during a drought. *C. perfringens* type D can be isolated in high numbers from gastric reflux of horses with anterior enteritis.

PATHOGENESIS

In the normal course of events, ingested *C. perfringens* type D are destroyed in large numbers in the rumen and abomasum, although some survive to reach the duodenum, in which multiplication occurs and toxin is produced. Toxemia does not occur because the movement of ingesta keeps the bacterial population and toxin content down to a low level. In certain circumstances, this does not hold and multiplication of the organisms and the production of toxin proceeds to the point in which toxemia occurs.

One of the circumstances has been shown to be the passage of large quantities of starch granules into the duodenum when sheep overeat on grain diets or are changed suddenly from a ration consisting largely of roughage to one consisting mainly of grain. Other factors such as heavy milk feeding may have the same effect. A slowing of alimentary tract movement has also been thought to permit excess toxin accumulation and it may be that any factor that causes intestinal stasis will predispose to the disease. The importance of diet in the production of ruminal stasis has been discussed in diseases of the forestomachs of ruminants.

The epsilon toxin of *C. perfringens* type D is a pore-forming protein that increases the permeability of the intestinal mucosa to this and other toxins, facilitating its own absorption.[3]

A receptor for epsilon toxin has been identified on vascular endothelial cells, and the clinical signs and pathologic findings can be explained by the widespread vascular damage and increase in vascular permeability.

Acute cases are characterized by the development in the brain of degeneration of vascular endothelium; perivascular and intercellular edema; and microscopic foci of necrosis in the basal ganglia, thalamus, internal capsule, substantia nigra, subcortical white matter, and cerebellum. The damage to the vascular endothelium leads to the accumulation of protein-rich fluid effusions observable in heart, brain, and lung. The postmortem autolysis of kidney tissue that occurs so rapidly and is the characteristic of "pulpy kidney" has the same basis.

There is a pronounced hyperglycemia caused by the mobilization of hepatic glycogen; severe hemoconcentration; and elevation of blood concentrations of pyruvate, lactate, and α-ketoglutarate.

In contrast to sheep, goats with enterotoxemia produced by *C. perfringens* type D also have a hemorrhagic enterocolitis that is present in both the natural and the experimental disease. The genesis of this lesion is uncertain, but it is responsible for the major clinical signs that present in goats with this disease.

A degree of natural immunity may be attained by nonlethal exposure to the toxin. Because a proportion of lambs, calves, and kids appear to be exposed to subclinical but antigenic levels of *C. perfringens* toxin, they become immune without having shown signs of illness or without having been vaccinated.[4]

CLINICAL FINDINGS

Lambs

The course of the illness is very short, often less than 2 hours and never more than 12 hours. Many lambs are found dead without previously manifesting signs. In closely observed flocks the first signs may be dullness, depression, yawning, facial movements, and loss of interest in feed. Acute cases may show little more than severe clonic convulsions with frothing at the mouth and rapid death. Cases that survive for a few hours show a green, pasty diarrhea, staggering, recumbency, opisthotonus, and severe clonic convulsions. The temperature is usually normal but may be elevated if convulsions are severe. Death occurs during a convulsion or after a short period of coma.

Adult Sheep

These usually survive for longer periods of up to 24 hours. They lag behind the flock and show staggering and knuckling; champing of the jaws; salivation; and rapid, shallow, irregular respiration. There may be bloat in the terminal stages. Irritation signs, including convulsions, muscle tremor, grinding of the teeth, and salivation, may occur but are less common than in lambs.

Calves

The syndrome is similar to that seen in adult sheep, with nervous signs predominating. Peracute cases are found dead without having shown premonitory signs of illness and with no evidence of struggling. The more common, acute cases show a sudden onset of bellowing, mania, and convulsions, with the convulsions persisting until death occurs 1 to 2 hours later. Subacute cases, many of which recover, do not drink, are quiet and docile, and appear to be blind, although the eye's preservation reflex persists. They may continue in this state for 2 to 3 days and then recover quickly and completely. In an outbreak of the disease in calves all three forms of the disease may be seen. Experimental inoculation of whole or washed cultures of *C. perfringens* type D into the duodenum of 9-month-old calves produced severe clinical signs within 2 to 5 hours of inoculation.[5]

Goats

Diarrhea is a prominent sign in affected goats, especially in those that survive for more than a few days.[2] In the peracute form, which occurs most frequently in young kids, there are convulsions after an initial attack of fever (40.5°C, 105°F) with severe abdominal pain and dysentery; death occurs in 4 to 36 hours. In the acute form, which is more common in adults, there is usually no fever, and abdominal pain and diarrhea are prominent with death or recovery within 2 to 4 days. In chronic cases, the goats may be ill for several weeks and show anorexia, intermittent severe diarrhea and, in some cases, dysentery and the presence of epithelial shreds in the feces. Chronic wasting, anemia, and eventual emaciation also occur with chronic disease in goats.

CLINICAL PATHOLOGY

A high plasma glucose concentration of 8.3 to 11.1 mmol/L (150 to 200 mg/dL) and marked glycosuria are characteristic of the terminal stages of enterotoxemia in sheep, and are supportive for a diagnosis but are not pathognomonic.[6] Hyperglycemia and glycosuria are variably present in goats with the disease and calves with experimentally induced disease.[5]

NECROPSY FINDINGS

The body condition of the animal is usually good, but there is often fecal staining of the perineum and rapid decomposition of the carcass. In peracute cases there may be no gross lesions. More frequently, there is an excess of clear, straw-colored pericardial and thoracic fluid that clots on exposure to air. Many petechiae are present in the epicardium and endocardium, and there is pulmonary edema. Patchy congestion of the abomasal and intestinal mucosae is usual, and the small intestine often contains a moderate amount of thin, creamy ingesta. The content of the large intestine may be watery and dark green.

The characteristic finding of soft, pulpy kidneys is only useful in animals necropsied within a few hours after death because it is nonspecific and merely correlates to a more rapid rate of autolysis. Microscopy of experimentally induced ovine type D enterotoxemia cases confirms that the renal changes represent autolysis and not a true nephrosis.

The liver is dark and congested. The rumen and abomasum of feedlot lambs may be overloaded with concentrates. In goats there is acute fibrinonecrotic and hemorrhagic enterocolitis, although microscopic examination may be needed to detect this change.

In sheep that have not died acutely there may be symmetric areas of hemorrhage, edema, and liquefaction in the brain, especially in the area of the basal nuclei. Again, microscopic evaluation of the tissue is critical.

Gram-stained smears of ingesta from several levels in the small intestine should be examined. In affected animals the short, fat, gram-positive rods dominate the slide to the almost complete exclusion of other bacteria. Bowel filtrates can be tested for toxicity by injection into mice. If the filtrate is toxic, the type of toxin can be determined by protection of the mice with specific antisera. This does not determine the type of clostridia, but detection of β-toxin indicates the presence of types B or C, and ε-toxin indicates the presence of B or D.

The time taken for diagnosis by mouse neutralization tests, as well as humanitarian considerations, has promoted the development of alternative tests. Commercial enzyme-linked immunosorbent assay (ELISA) kits and multiplex PCR assays have become available for toxin detection and require minimal amounts of intestinal content.[6] Nevertheless, it is important to base

a diagnosis on epidemiologic, clinical, and pathologic information, not just the detection of toxin at postmortem.

ε-Toxin is stable if frozen, but at average temperatures it is possible to identify the toxin from the intestine of a sheep dead for up to 12 hours. The addition of one drop of chloroform to each 10 mL of ingesta will stabilize the toxin for up to 1 month. Alternatively, intestinal contents can be absorbed on filter paper and shipped at environmental temperatures, with little loss of activity for as long as 74 days as detected by immunoassay. Hyperglycemia and glucosuria may also be detected in necropsy material.

Samples for Confirmation of Diagnosis

- Bacteriology: 20 to 30 mL of intestinal content, frozen in a leak-proof glass or plastic container (ELISA, latex agglutination, bioassay, anaerobic culture, PCR); air-dried smears of ingesta from several levels of gut (cyto-Gram stain)
- Clinical pathology: urine (assay–glucose) (best performed at time of necropsy)
- Histology: fixed colon, ileum, jejunum, entire brain

DIFFERENTIAL DIAGNOSIS

Lambs
- Acute pasteurellosis
- Septicemia associated with *Histophilus somni* (formerly *Haemophilus agni*)
- *Clostridium sordellii*
- Polioencephalomalacia
- Rumen overload

Sheep
- Hypocalcemia
- Hypomagnesemia
- Focal symmetric encephalomalacia (chronic enterotoxemia)
- Rabies
- Pregnancy toxemia
- Louping-ill

Calves
- Lead poisoning
- Polioencephalomalacia
- Hepatoencephalopathy
- *H. somni* (formerly *Haemophilus somni*)

Goats
- Salmonellosis
- Coccidiosis

In lambs, but not in goats, a history of vaccination against the disease is a significant consideration in the ranking of a list of differential diagnoses.

TREATMENT

In general, the clinical course of the disease is too acute for effective treatment. Hyperimmune serum, an efficient short-term prophylactic, is unlikely to be of much value in sick animals because of the acute nature of the disease. In goats the course is longer, and antitoxin in combination with orally administered sulfadimidine may be effective in treatment.[2]

CONTROL

There are three major control measures available: reduction of the food intake, administration of antitoxin, and vaccination. These may be used individually or in combination.

Reduction in Food Intake

Reduction in food intake is the cheapest but least effective in control and is used as a short-term control while waiting for immunity to develop after vaccination. Reduction in food intake will cause a setback in the growth of the lambs and for this reason farmers tend to rely more on vaccination as a control measure. However, exercise of lambs, by mustering or herding around the paddock, may help slow the course of an outbreak.

Antitoxin

Antitoxin can be administered to all sheep as soon as an outbreak commences. The administration of ε-antitoxin 200 IU/kg BW will provide for protective circulating antitoxin levels for 21 to 29 days. Immediate losses are prevented, and in most instances the disease does not recur. Toxoid is cheaper, but to administer it alone at such times may result in further serious losses before active immunity develops.

Vaccination

Immunity in sheep is readily produced by suitable vaccination. A blood level of 0.15 Wellcome unit of ε-antitoxin per milliliter of serum is sufficient to protect sheep. Vaccines available are toxoids, and adjuvants generally improve the antigenicity. Activated alum-precipitated toxoid is the common vaccine in use. A recombinant *C. perfringens* type D toxoid has been shown to induce antibody titers comparable to a traditional toxoid and may offer a more consistent or cost-effective method of vaccine production.[7]

Vaccination of maiden **ewes** twice at an interval of at least 1 month and with the last vaccination approximately 4 weeks before lambing will result in good passive immunity in young lambs, with 97% of lambs having protective antibody levels at 8 weeks of age and a significant proportion at 12 to 16 weeks of age. This is sufficient to protect lambs during their highest risk period. Older ewes that have been vaccinated the previous year receive a single booster vaccination 4 weeks before lambing. Sheep vaccinated for 3 consecutive years can be considered to be permanently immune and to require no further vaccination.

When faced with an outbreak in lambs, the recommended procedure is to administer antiserum and toxoid immediately and repeat the toxoid in a month's time. The simultaneous administration of hyperimmune serum with this vaccine does not interfere with the stimulation of antibody production, nor does the presence of passively derived colostral immunity.

Lambs can be vaccinated with toxoid when 4 to 10 weeks of age and again a month later.

Any vaccination of sheep is not without risk of precipitating blackleg or other clostridial disease, and if these are a severe problem in an area it may be wise to vaccinate a portion of the flock as a pilot test and proceed with vaccination of the remainder only when no complications arise. A multivalent bacterin-toxoid containing antigens to all of the clostridial diseases is commonly used in sheep in these circumstances or where all of these diseases are likely to occur. Vaccination should not be done in sheep with wet fleeces.

Vaccination with toxoid is effective in calves but is not highly effective in goats, having a limited effect in preventing the disease although reducing its incidence and severity.[2] The anti-ε titer in goats following vaccination is variable, sometimes equivalent, but often lower or of shorter duration to that induced in sheep. The reasons for decreased protection following the use of commercial vaccines against type D infections in goats are not fully understood.[2] Thus, goat owners should be advised that vaccination with the current commercial vaccines often provides limited protection against type D infections, even if multiple booster vaccines are given at 3- to 6-month intervals. This occurs especially when a high level of concentrate feeding occurs, such as in dairy production. The use of hyperimmune serum must also be performed with caution in goats, particularly Saanens, which are very prone to anaphylactic reactions. Despite the limitations of protection against the enteric manifestations of the disease, vaccination is protective against the peracute form of the disease and kids should be vaccinated twice, a month apart, commencing at 4 weeks of age with booster vaccinations at 6-month intervals.

Local reactions to vaccination are common in both sheep and goats and may be visible for at least 6 months. In sheep these are generally hidden by the wool, but the vaccination site should be high on the neck and close to the base of the ear to minimize carcass blemish. With goats, especially show goats, the owner should be warned of this occurrence. Goats, especially show goats, should be vaccinated under the loose skin of the axilla, where local reactions will be hidden by the elbow.

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FOCAL SYMMETRIC ENCEPHALOMALACIA

SYNOPSIS

Etiology The disease is a chronic neurologic manifestation of enterotoxemia associated with *Clostridium perfringens* type D ε-toxin, with vascular damage and damage to the nervous system.

Epidemiology Sporadic disease in weaners and mature sheep, usually following a change of pasture, anthelmintic treatment, or supplementary feeding with grain and incomplete vaccination regimens.

Clinical findings Aimless wandering, an inability to eat, and a dummy syndrome are predominant findings

Clinical pathology None reported.

Necropsy findings Gross or histologic areas of malacia in internal capsule, lateral thalamus, and cerebellar peduncles.

Diagnostic confirmation Epidemiology, clinical and necropsy findings.

Treatment Supportive.

Control Complete vaccination.

ETIOLOGY

Lesions of focal symmetric encephalomalacia have been produced in experimental enterotoxemia and by infusion with ε-toxin of *C. perfringens* type D. Similar brain lesions have been described in an experimentally induced case of enterotoxemia in a 9-month-old calf that survived for 8 days.[1]

EPIDEMIOLOGY

Focal symmetric encephalomalacia occurs most often in lambs, weaners, and mature sheep, but lesions consistent with focal symmetric encephalomalacia have also been reported in calves and goats.[2] In grazing sheep. It has the same seasonal occurrence as enterotoxemia but may occur in sheep of poor body condition. In weaners and mature sheep, there is often a history of supplementary feeding of highly fermentable carbohydrate, such as cereal grains, a move to fresh pasture, or of anthelmintic administration 5 to 14 days preceding the occurrence of initial cases. This is often combined with an incomplete history of vaccination, and outbreaks have been associated with the grazing of young green cereal crops. The morbidity is usually low but may approach 15%. The case–fatality rate is high.

CLINICAL FINDINGS

Most often, because of infrequent observation of sheep of this age, the finding of dead sheep is the first indication of the disease. Clinically affected sheep are separate from the group or can be detected by slow movement of the flock. They show no fear of humans or dogs and can be examined without restraint. Blindness, aimless wandering, head-pressing, and incoordination are the predominant findings. More severely affected sheep lie quietly in lateral recumbency with moderate dorsiflexion of the head and show infrequent nystagmus with paddling convulsions. The sheep are unable to eat and most cannot drink, although some affected lambs may still retain a suck reflex. The clinical course varies from 1 to 14 days, with the majority of affected sheep surviving for 5 to 7 days.

NECROPSY FINDINGS

Lesions are confined to the brain, and formalin-fixed samples of this tissue are required for confirmation of the diagnosis. In many cases the characteristic lesions can be detected on macroscopic examination and consist of areas of hemorrhage and softening in the internal capsule, lateral thalamus, and cerebellar peduncles. Malacia, edema, and hemorrhage are visible histologically. Glycosuria is not a feature, and toxin cannot be demonstrated in gut contents.

TREATMENT AND CONTROL

There is no treatment. Less severely affected cases may recover if they are maintained with fluids and nutrients given by stomach tube. Outbreaks cease if the sheep are vaccinated with pulpy kidney vaccine.

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CEREBROSPINAL ANGIOPATHY

Cerebrospinal angiopathy is a sporadic disease of recently weaned pigs manifested primarily by neurologic signs and wasting. It is probably a form of edema disease. It affects only one or a few pigs within a litter up to 5 weeks after weaning, although a similar condition has been reported in finishing and adult pigs. The disease is characterized by the variety of neurologic signs that it presents. Incoordination and a decreased central awareness are common presenting signs but abnormal head position, aimless wandering, and persistent circling may also be observed. There is usually apparent impairment of vision. Fever is not a feature, and the clinical course may last for several days. Affected animals may die but are often euthanized because of emaciation. Wasting without neurologic disorder may also occur. They are also prone to savaging by unaffected penmates.

Histologically, the disease is characterized by an angiopathy that is not restricted to the CNS. The similarity of the angiopathy to that seen in chronic edema disease has led to postulation that this disease is a sequel to subclinical edema disease. The disease has been reported occurring in pigs 15 to 27 days after experimental *E. coli* infection. The characteristic feature is the presence of perivascular eosinophilic droplets.

The main differential diagnosis is that of spinal or brain abscess and the porcine viral encephalomyelitides. Affected pigs should be housed separately as soon as clinical signs are observed. In view of the nature of the lesion, therapy is unlikely to be of value; however, recovery following treatment with oxytetracycline has been reported.

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Viral Diseases Primarily Affecting the Cerebrum

RABIES

SYNOPSIS

Etiology *Lyssavirus* of family Rhabdoviridae

Epidemiology Occurs in all farm animals worldwide except Australia and New

Continued

Zealand. Major zoonoses. Transmitted by bites of infected animal. Different animals are vectors depending on geographic location: foxes in Europe and North America, skunks and raccoons in North America, mongoose in Africa, vampire bats in South America.

Signs Incubation period varies from 2 weeks to several months.

Cattle: *Paralytic form:* bizarre mental behavior (yawning, bellowing), incoordination, decreased sensation of hindquarters, drooling saliva, recumbency, and death in 4–7 days. *Furious form:* hypersensitive, belligerent, then paralysis and death as in paralytic form.

Sheep: Outbreaks common; sexual excitement, wool pulling, attacking, incoordination, and then paralysis.

Horses: Abnormal postures, lameness or weakness, depression, ataxia, pharyngeal paralysis, recumbency, hyperesthesia, biting, loss of anal sphincter tone, death in 4–6 days.

Pigs: Excitement, attack, twitching of nose, clonic convulsions, paralysis.

Clinical pathology No antemortem test.

Lesions Nonsuppurative encephalomyelitis.

Differential diagnosis list

- **Cattle:** Lead poisoning, lactation tetany, hypovitaminosis A, listerial meningoencephalitis, polioencephalomalacia, nervous acetonemia.
- **Sheep:** Enterotoxemia, pregnancy toxemia, louping-ill, scrapie.
- **Horse:** Viral encephalomyelitis, herpes viral paralysis, cerebrospinal nematodiasis, equine degenerative myeloencephalopathy, protozoal encephalomyelitis, neuritis of cauda equina, horsetail poisoning, Borna, Japanese encephalitis, botulism.
- **Pig:** Pseudorabies, Teschen disease, Glasser's disease, and other meningitides (*Escherichia. coli* and *Streptococcus suis*).

Diagnostic confirmation Fluorescent antibody test of brain. Negri bodies histologically.

Treatment None. All rabies cases are fatal.

Control Prevention of exposure. Vaccination of domestic animals and wildlife. Quarantine and biosecurity to prevent entry of virus into country.

ETIOLOGY

Rabies is caused by single-stranded RNA viruses in the genus *Lyssavirus* of the family Rhabdoviridae. The Lyssavirus genome contains about 12 kb, and five separate genes encode for two membrane-associated proteins: matrix (M); glycoprotein (G); and three structural proteins, nucleoprotein (N), phosphoprotein (P), and polymerase (L).[1]

Currently, seven distinct genetic lineages are identified in the genus *Lyssavirus:* classical rabies virus (RABV, genotype 1, which includes a number of variants), Lagos bat virus (LBV, genotype 2), Mokola virus (MOKV, genotype 3), Duvenhage virus (DUUV, genotype 4), European bat lyssavirus (EBLV, subdivided into genotype 5 and genotype 6), and the Australian bat lyssavirus (ABLV, genotype 7). It was recognized long ago that the strain of virus known as the "street" rabies virus differed in some way from "fixed" strains that had been cultivated for vaccine production (grown in cell culture or passaged through serial generations of laboratory animals). A large number of rabies virus strains are adapted to particular host species but remain infective for any mammal.

EPIDEMIOLOGY

Occurrence

Rabies occurs in all warm-blooded animals. The disease occurs in cattle, sheep, horses, and pigs, in most countries, except the insular countries that exclude it by rigid quarantine measures or prohibition of the entry of dogs. However, the genus *Lyssavirus* can still cause surprises. In 1996 and 1998, two women died in Queensland, Australia, from infections with a newly discovered rabies-related virus (Australian bat lyssavirus). In 2002 a man died in Scotland after contracting European bat lyssavirus rabies indicating that after a century of apparent freedom from rabies, the disease is now enzootic in the UK.

Europe

In Europe, sylvatic rabies is a major problem for which the **red fox** is the principal vector. The disease is still spreading from a focal point that developed in Poland in the mid-1930s. It is endemic in Yugoslavia and Turkey, and has spread westward to Germany, Denmark, Belgium, Czechoslovakia, Austria, Switzerland, and France. Spread continues at the rate of about 30 to 60 km (18–37 miles) per year, and the threat to the UK increases each year.[2] Finland had been free of rabies since 1959, but in 1988 sylvatic rabies occurred with the raccoon dog as the vector.

United States

Information on rabies surveillance in the United States is published annually by the Centers for Disease Control and Prevention (CDC). In 2013, 92% of cases occurred in wild animals, 4.2% in cats, 1.5% in cattle, and 1.5% in dogs. The disease occurred in raccoons, bats, skunks, foxes, sheep and goats, horses and mules, mongoose, rodents and lagomorphs, and humans.

The most frequently reported rabid wildlife cases occurred in raccoons, skunks, bats, and foxes. The relative contributions of those species continue to change in recent decades because of fluctuations in enzootics of rabies among animals infected with several distinct variants of the rabies virus. Endemic raccoon rabies occurs in the Appalachian mountain range and the entire eastern seaboard of the United States. Endemic skunk rabies occurs mainly in three geographic regions: the north central United States and the Canadian provinces of Manitoba, Saskatchewan, and Alberta; south central United States; and California. Within these broad areas, the disease persists in enzootic foci and erupts every 6 to 8 years. Experimental studies suggest that the species specificity of endemic rabies is caused by differences in the pathogenicity of variants of rabies virus. Skunk rabies peaks in the spring and early winter, which is probably a reflection of certain life history events within the skunk population.

The prevalence of rabies in bats in the United States is about 7%, and transmission to humans is rare even though sensational journalism has caused many people to consider bats as a serious threat to health. Trends in national surveillance for rabies among bats in the United States from 1993 to 2013 have consistently found a diffuse geographic pattern of rabies in bats throughout the continental United States. Although spillover infection of bat variants of rabies among terrestrial animals such as dogs and cats are rare, these variants of rabies virus have been associated with 92% of the indigenously acquired human rabies infections in the United States since 1990.

Canada

The arctic fox variant of rabies invaded most of Canada south of 60°N and east of the Rocky Mountains in the early 1950s largely by the migration of **arctic foxes** into the populated areas. It died out in most of that range, but persisted for over 40 years in southern Ontario with sporadic incursions into narrow adjacent strips in western Quebec and northern New York. The principal vectors were red foxes (*Vulpes vulpes*) and, to a lesser extent, striped skunks (*Mephitis mephitis*). From 1957 to 1989, Ontario experienced more animal rabies cases than almost every North American jurisdiction almost every year, and over 95% of those cases were limited to the southernmost 10% of the province's land area.

A second major outbreak, involving striped **skunks**, progressed from North Dakota into the Prairie Provinces during the late 1950s and 1960s. In the 1990s, the endemic areas in Canada are southern Ontario, which accounts for 85% of the Canadian diagnoses, and the Prairie Provinces where rabies is endemic in skunks. In western Canada, the main reservoirs of the rabies virus are skunks, bats, and foxes.

Africa

Rabies occurs in most countries in the African continent, but the reported incidence is surprisingly low for an area with such a high population of wild carnivores. The incidence of rabies, and the range of species involved, is increasing in Africa, and a number of wildlife

hosts has been identified, including wild dogs, jackals, and mongoose.

In South Africa over a 4-year period, of all the domestic animal rabies cases reported, cattle accounted for half of the rabies cases in domestic animals. The **mongoose** accounted for 70% of the wild animal cases reported. Widespread distribution of the rabies virus occurs when the young mongooses are evicted from their parents' territory during the winter months, forcing them to scatter over a wide area. This increases the probability of domestic animals coming in contact with rabid animals.

South America, Latin America, and the Caribbean

Rabies in cattle is a major economic and public health problem in South America, where vampire bat–transmitted rabies results in cyclic outbreaks. Bovine paralytic rabies is endemic in the tropical regions extending from northern Mexico, to northern Argentina, and on the island of Trinidad.

Distribution of Virus Variants

The *Lyssavirus* genus belongs to the Rhabdoviridae family of the Mononegavirales order and includes unsegmented RNA viruses causing rabies encephalomyelitis. They are well fitted to vectors belonging to the orders Carnivora (flesh-eating mammals including skunks) and Chiroptera (the order which comprises all of the 178 genera in 16 families of bats). Seven genotypes have been delineated within the genus. These genotypes are divided into two immunopathologically and genetically distinct phylogroups. Phylogroup I includes two African genotypes: *Mokola virus,* which has been isolated from shrews and cats, although its reservoir remains unknown, and *Lagos bat virus,* which has been found mainly in frugivorous bats but also in an insectivorous bat. Phylogroup II has five genotypes: *DUUV* (Africa), EBLV-1 (Europe), EBLV-2 (Europe), *Australian bat lyssavirus* (Australia), and the classical RABV (worldwide). Members of the genotypes *Duvenhage virus,* EBLV-1, and EBLV-2 are exclusively found in insectivorous bats, members of the genotype *Australian bat lyssavirus* are found in both insectivorous and frugivorous bats, and members of the genotype RABV are found in carnivorous and American bats (insectivorous, frugivorous, and hematophagous). The fact that lyssaviruses are well established in two ecologically distinct mammal orders may very likely be the consequence of successful host switching.

Analysis of 36 carnivoran and 17 chiropteran lyssaviruses representing the main genotypes and variants strongly supports the hypothesis that host switching occurred in the history of the lyssaviruses. In fact, lyssaviruses evolved in chiroptera long before the emergence of carnivoran rabies, very likely following spillover from bats. Using dated isolates, the emergence of carnivoran rabies from chiropteran lyssaviruses is estimated to have occurred 888 to 1459 years ago. In Europe, bat rabies is associated with two specific virus strains: European bat lyssavirus type 1 and European bat lyssavirus type 2. European bat lyssavirus type 1 isolates have been found in serotine bats in France. European bat lyssavirus type 2 has now been found in Daubenton's bats in England and Scotland.

In North America, variants of rabies virus are maintained in the wild by several terrestrial carnivore species, including raccoons, skunks, and a number of bat species. Each antigenically and genetically distinct variant of the virus in mammalian species occurs in geographically discrete areas and is strongly associated with its reservoir species. Within each area, a spillover of rabies into other species occurs, especially during epidemics. Temporal and spatial analysis of skunk and raccoon rabies in the eastern United States indicated that epidemics in raccoons and skunks moved in a similar direction from 1990 to 2000. However, there is no evidence that the raccoon rabies virus variant is cycling independently in the skunk population of the eastern United States or that the variant has undergone any genetic adaptations among skunks.

Within broad geographic regions, rabies infections in terrestrial mammals can be linked to distinct virus variants, identified by panels of monoclonal antibodies or by genetic analysis. These analyses have demonstrated substantial differences between isolates from various parts of the world and conventional vaccines do not fully protect against some of the naturally occurring antigenic variants that exist in nature. Most outbreaks of rabies tend to be host species specific. Each variant is maintained primarily by **intraspecific transmission** within a dominant reservoir, although spillover infection of other species may occur within the region. Geographic boundaries of the currently recognized reservoirs for rabies in terrestrial mammals have been established. Reservoirs for rabies virus are found worldwide. The virus is maintained at endemic and epidemic levels in a wide variety of Carnivora and Microchiroptera (bats) species.

The geographic boundaries of the currently recognized reservoirs for rabies in terrestrial species in North America are as follows:

- Raccoons in the southeastern United States
- Red and arctic foxes in Alaska, resulting in spread across Canada as far east as Ontario, Quebec, and the New England states
- Striped skunks in California, the north central states, and the south central states
- Gray foxes in small reservoirs in Arizona
- Coyotes in south Texas as a result of spread from domestic dogs in a long-standing reservoir at the Texas–Mexico border

In Ontario, wildlife rabies persists in two predominant species: the red fox and the striped skunk. Molecular epidemiology studies indicate that there is no host specificity, but there are very clear and consistent differences in the virus from distinct geographic regions. In Canadian studies, two major antigenic groups can be distinguished among the rabies virus isolates examined. One group is found in Ontario, Quebec, and the Northwest Territories and is represented in the wild by endemic red fox and striped skunk rabies that originated in northern Canada. The second group is found in Manitoba where striped skunk rabies is endemic.

Overlying the disease in terrestrial mammals are multiple, independent reservoirs for rabies in several species of insectivorous bats. Distinct viral variants can be identified for different bat species, but geographic boundaries cannot be defined for rabies outbreaks in the highly mobile bat species.

Methods of Transmission

The source of infection is always an infected animal, and the method of spread is almost always by the **bite** of an infected animal, although contamination of skin wounds by fresh saliva may result in infection. Not all bites from rabid animals result in infection because the virus is not always present in the saliva; the virus may not gain entrance to the wound if the saliva is wiped from the teeth by clothing. The virus may appear in the milk of affected animals, but spread by this means is unlikely as infection. The rabies virus is relatively fragile, susceptible to most standard disinfectants, and dies in dried saliva in a few hours.

One of the most important parameters in rabies models is the transmission rate, or the number of susceptible animals infected by a diseased animal per unit of time. In a population of 19 raccoons feeding at a concentrated, common food source available during the summer in rural eastern Ontario, raccoons bite and are bitten an average of 1.0 to 1.3 times per hour, respectively.

Because of the natural occurrence of rabies in animals in caves inhabited by infected insectivorous bats, inhalation as a route of infection came under suspicion. It is now accepted that interbat spread, and spread from bats to other species is principally by bites, but that infection by inhalation also occurs. That infection can occur by ingestion has been put to use in devising systems of vaccinating wildlife by baiting them with virus-laden baits.

Animal Vectors

Traditionally, the dog, and to a minor extent the cat, have been the main source animals.

However, native fauna, including foxes, skunks, wolves, coyotes, vampire, insectivorous and fruit-eating bats, raccoons, mongoose, and squirrels provide the major source of infection in countries where domestic Carnivora are well controlled. In general, foxes are less dangerous than dogs, because foxes tend to bite only one or two animals in a group, whereas dogs will often bite a large proportion of a herd or flock. Raccoons and skunks are major reservoirs of rabies in North America.

Bats are the most important species in which subclinical carriers occur. Multiplication of the virus without invasion of the nervous system is known to occur in fatty tissues in bats and may be the basis of the "reservoiring" mechanism in this species. Violent behavior is rare in rabid animals of this species, but it has been observed. Bats represent a serious threat of spread of rabies because of their migratory habits. Most spread is within the species, but the threat to humans and animal species by bats cannot be completely disregarded. Although rodents can be infected with the rabies virus they are not thought to play any part in the epidemiology of rabies, either as multipliers or simply as physical carriers of the virus. Many of the viruses they carry are rabies-like rather than classical rabies.

Rabies has occurred in swine herds where the skunk population is high, where farms were settled from rough terrain resulting in considerable interface between wildlife and domestic animals, and in which the management system allows the pigs to run free on the premises. The disease has occurred in pigs reared in a closed feeder barn where access by wildlife was very unlikely.

There is a difference in the role between vectors. For example, in Europe it is thought that foxes carry the infection into a new area, but other species disseminate it within an area. Foxes are the principal vectors and, as in Canada, cattle are the principal receptors. In western Canada, the main reservoirs of infection are skunks, bats, and foxes. This would have important consequences for control programs based on wildlife surveillance.

Domestic livestock like cattle are rarely a source of infection, although chance transmission to humans may occur if the mouth of a rabid animal is manipulated during treatment or examination. The virus may be present in the saliva for periods up to 5 days before signs are evident.

Seasonal Spread

Spread of the disease is often seasonal, with the highest incidence in the late summer and autumn because of large-scale movements of wild animals at mating time and in pursuit of food. In Canada, the frequency of rabies infection in livestock populations increases in the fall when adolescent foxes mature, begin mating behavior, and travel over large areas.

Latent Infection

Because of rapid developments in virologic techniques, especially serologic screening of animal populations to obtain presumptive diagnoses of the presence of a virus in the population, the question of latent infection and inapparent carriers of rabies has assumed some importance. The presence of rabies antibodies in animals in a supposed rabies-free area is likely to arouse concern. Inapparent carriers do occur in bats and there is some evidence that latent infections can occur in other species.

Zoonotic Implications

The disease in unvaccinated and untreated humans has always been considered **fatal**. The prime importance of rabies is its transmissibility to humans, with veterinarians being at special risk. European data indicate that by far the greatest proportion of humans requiring pretreatment for rabies have been exposed to a rabid domestic animal, and not a wild one. Human rabies is extremely rare in countries where canine rabies is controlled by regular vaccination.

Economic Importance

Rabies is not of major economic importance in farm animals, although individual herds and flocks may suffer many fatalities. The economic costs of rabies in a country are associated with pet animal vaccinations, animal bite investigations, confinement and quarantine of domestic animals that bite humans or that are suspected of exposure to rabid animals, salaries of animal control officers, laboratory diagnosis, the costs of preexposure and postexposure prophylaxis and treatment and consultation, public education, staff training, and clerical costs.

PATHOGENESIS

Following the deep introduction of rabies virus by the bite of a rabid animal, initial virus multiplication occurs in striated muscle cells at the site. The neuromuscular spindles then provide an important site of virus entry into the nervous system, which may also occur at motor end plates. In the olfactory end organ in the nares, neuroepithelial cells are in direct contact with the body surface, and these cells extend without interruption into the olfactory bulb of the brain. Following entry of the virus into nerve findings, there is invasion of the brain by passive movement of the virus within axons, first into the spinal cord, and then into the brain. The immune response during this phase of the infection is minimal and explains why neutralizing antibody and inflammatory infiltration are usually absent at the time of onset of encephalitic signs. Antibody titers reach substantial levels only in the terminal stages of the disease. Following entry of rabies virus to the CNS, usually in the spinal cord, an ascending wave of neuronal infection and neuronal dysfunction occurs.

The primary lesions produced are in the CNS, and spread from the site of infection occurs only by way of the peripheral nerves. This method of spread accounts for the extremely variable incubation period, which varies to a large extent with the site of the bite. Bites on the head usually result in a shorter incubation period than bites on the extremities. The severity and the site of the lesions will govern to a large extent whether the clinical picture is primarily one of irritative or paralytic phenomena. The two extremes of the paralytic or dumb form and the furious form are accompanied by many cases that lie somewhere between the two. Gradually ascending paralysis of the hindquarters may be followed by severe signs of mania, which persist almost until death. Destruction of spinal neurons results in paralysis, but when the virus invades the brain, irritation of higher centers produces manias, excitement, and convulsions. Death is usually caused by respiratory paralysis. The clinical signs of salivation, indigestion and pica, paralysis of bladder and anus, and increased libido all suggest involvement of the autonomic nervous system, including endocrine glands. At death, there are viral inclusions and particles in almost all neurons in the brain, spinal cord, and ganglia, but none in the supportive cells of the CNS. Electron microscopic examination also shows the presence of the virus in the cornea, which it reaches centrifugally along the peripheral nerves.

Virus reaches the salivary glands and many other organs in the same way, but the highly infective nature of saliva arises from passage of the virus along the olfactory nerve to taste buds and other sensory end organs in the oropharynx, rather than from the salivary glands. Experimentally, infection of nonnervous tissues in skunks and foxes has been reproduced in the adrenal medulla, cornea, and nasal glands. The virus may be found in milk, in some organs and in fetuses, but the virus cannot be demonstrated in the blood at any time.

Variations in the major manifestations as mania or paralysis may depend on the source of the virus. Virus from vampire bats almost always causes the paralytic form. "Fixed" virus that has been modified by serial intracerebral passage causes ascending paralysis in contrast to "street" virus, which more commonly causes the furious form. The site of infection and the size of the inoculum may also influence the clinical course. There is also a geographic difference in the proportion of animals affected by the furious or paralytic form of the disease. In the Americas most cases are paralytic. In Africa and India most cases in farm animals are the furious form.

The disease is always fatal, but infrequently an experimentally infected animal shows clinical signs of the disease but recovers. There are two recent records of

spontaneous recovery in man, and the occurrence of nonfatal rabies in all species has been reviewed. There appears to be no field occurrence in domestic animals of the finding in experimentally infected mice that some strains of virus invade only peripheral nerves and spinal ganglia leaving a number of survivors with permanent nervous disability. The pathogenesis of recovery from rabies is important relative to vaccination and serologic testing to determine the incidence and prevalence of the disease.

CLINICAL FINDINGS

Among farm animals, cattle are most commonly affected. The incubation period in naturally occurring cases is about 3 weeks, but varies from 2 weeks to several months in most species, although incubation periods of 5 and 6 months have been observed in cattle and dogs.

Cattle

Experimentally, in cattle the average incubation period was 15 days and the average course of the disease was 4 days. Unvaccinated cattle had shorter incubation and clinical duration of disease than vaccinated cattle. Major clinical findings included excessive salivation (100%), behavioral change (100%), muzzle tremors (80%), vocalization (bellowing 70%), aggression, hyperesthesia and/or hyperexcitability (70%), and pharyngeal paralysis (60%). The furious form occurred in 70%.

In the **paralytic form**, knuckling of the hind fetlocks, sagging and swaying of the hindquarters while walking, and often deviation or flaccidity of the tail to one side, are common early signs. Decreased sensation usually accompanies this weakness and is one of the best diagnostic criteria in the detection of rabies. It is most evident over the hindquarters. Tenesmus, with paralysis of the anus, resulting in the sucking in and blowing out of air, usually occurs late in the incoordination stages just before the animal becomes recumbent. This is a characteristic finding but it may be transient or absent. Drooling of saliva is one of the most constant findings. The **yawning movements** are more accurately described as voiceless attempts to bellow, and voiceless bellowing is considered a helpful clinical sign for distinguishing rabid cows from nonrabid cows, and when sound is generated in rabid cattle, the bellowing is of a higher pitch than normal.[3] When paralysis occurs, the animal becomes recumbent and unable to rise. Bulls in this stage often have paralysis of the penis. Death usually occurs 48 hours after recumbency develops and after a total course of 6 to 7 days.

In **furious rabies,** the animal has a tense, alert appearance, is hypersensitive to sounds and movement, and is attracted to noise so that it may look intently or approach as though about to attack. In some cases, it will violently attack other animals or inanimate objects. These attacks are often badly directed and are impeded by the incoordination of gait. Frequently, loud bellowing is usual at this stage. The sound is characteristically hoarse and the actions are exaggerated. Sexual excitement is also common, with bulls often attempting to mount inanimate objects. Multiple collections of semen for artificial insemination have been made during very short periods from bulls that later proved to be rabid. With this violent form of the disease, the termination is characteristically sudden. Severe signs may be evident for 24 to 48 hours and the animal then collapses suddenly in a paralyzed state, dying usually within a few hours.

There is no consistent pattern in either the development or the range of signs. Body temperatures are usually normal but may be elevated to 39.5°C to 40.5°C (103°F-105°F) in the early stages by muscular activity. Appetite varies also. Some animals do not eat or drink, although they may take food into the mouth. There is apparent an inability to swallow. Others eat normally until the terminal stages. The course may vary from 1 to 6 days. So wide is the variation in clinical findings that any animal known to be exposed and showing signs of spinal cord or brain involvement should be considered rabid until proved otherwise.

Sheep and Goats

In sheep experimentally infected, the average incubation period was 10 days, and the average course of the disease was 3 days. Major clinical findings included muzzle and head tremors (80%); aggressiveness, hyperexcitability, and hyperesthesia (80%); trismus (60%); salivation (60%); vocalization (60%); and recumbency (40%). The furious form occurred in 80% of sheep. In one large-scale outbreak in sheep, deaths occurred 17 to 111 days after exposure.

Rabies often occurs in a number of animals at one time because of the ease with which a number of sheep can be bitten by a dog or fox. Clinically, the picture is similar to that seen in cattle. The minority of animals show sexual excitement, attacking humans or each other, and vigorous wool pulling; sudden falling after violent exertion, muscle tremor, and salivation are characteristic. Excessive bleating does not occur. Most sheep are quiet and anorectic. Goats are commonly aggressive, and continuous bleating is common.

Horses

Most recorded cases in horses are lacking in distinctive nervous signs initially, but incline to the paralytic form of the disease. Experimentally, the average incubation period was 12 days and the average duration of disease was 6 days. Unvaccinated animals had shorter incubation periods and duration of clinical disease. Muzzle tremors were the most frequently observed and most common initial signs. Other clinical findings included pharyngeal paresis (71%), ataxia or paresis (71%), and lethargy or somnolence (71%). The furious form occurred in 43% of cases, some of which began as the dumb form. The paralytic form was not observed.

In naturally occurring cases, the initial clinical findings may include abnormal postures, frequent whinnying, unexplained aggressiveness and kicking, biting, colic, sudden onset of lameness in one limb followed by recumbency the next day, high-stepping gait, ataxia, apparent blindness, and violent head-tossing. Lameness or weakness in one leg may be the first sign observed, but the usual pattern of development starts with lassitude, then passes to sternal recumbency and lateral recumbency, followed by paddling convulsions and terminal paralysis.

In a series of 21 confirmed cases in horses, the clinical findings at the time of initial examination included ataxia and paresis of the hindquarters (43%), lameness (24%), recumbency (14%), pharyngeal paralysis (10%), and colic (10%). The major clinical findings observed over the course of hospitalization included recumbency (100%), hyperesthesia (81%), loss of tail and anal sphincter tone (57%), fever ~38.5°C (52%), and ataxia and paresis of the hindquarters (52%). Mean survival time after the onset of clinical signs was 4 days (range, 1–7 days). Clinical findings of the furious form of rabies, such as aggressiveness (biting), compulsive circling, and abnormal vocalization, were evident in only two horses. Supportive therapy, given to nine horses, had no effect on survival time and did not correlate with the detection of Negri bodies at necropsy. Horses developing the furious form show excitement, become vicious, and bite and kick. Their uncontrolled actions are often violent and dangerous and include blind changes, sudden falling, and rolling and chewing of foreign material or their own skin. Hyperesthesia and muscular twitching of the hindlimbs followed by crouching and weakness are also recorded in the horse.

Pigs

Pigs manifest excitement and a tendency to attack, or dullness and incoordination. Affected sows show twitching of the nose, rapid chewing movements, excessive salivation, and clonic convulsions. They may walk backward. Terminally, there is paralysis and death occurs 12 to 48 hours after the onset of signs. The clinical findings in pigs are extremely variable, and individual cases may present in a variety of ways and only one or two of the classical findings may occur.

CLINICAL PATHOLOGY

No antemortem laboratory examination is of diagnostic value, but tests for lead on blood, urine, and feces may help to eliminate lead poisoning as a possible diagnosis. Virus

neutralization tests are available, but the presence of antibodies is not diagnostic. Other available tests are passive hemagglutination, complement fixation, radioimmunoassay, and indirect fluorescent antibody staining. These are used to determine immune status rather than as a diagnostic aid. An ELISA is available for measurement of rabies-specific antibody in the sera of major domestic and wildlife reservoirs in North America.

NECROPSY FINDINGS

Confirmation of a diagnosis of rabies depends on careful laboratory examination of fresh brain. The recommended laboratory procedure includes the following tests and it is recommended that at least two of them be used on all specimens.

- The most widely used test is the fluorescent antibody test (**FAT**) on impression smears from the brain. Current recommendations include sampling of the hippocampus, **medulla oblongata**, cerebellum, or gasserian ganglion.[4] However, a recent publication stipulates that the hippocampus and cerebellum are less desirable samples than the thalamus, pons, or medulla for the detection of viral antigen, and that the current sampling recommendations stem from the visibility of Negri bodies, rather than the true distribution of viral antigen. An FAT can be completed in approximately 2 hours and is accurate when done routinely by experienced personnel because it detects all genotypes if a potent conjugate is used.[5] The reliability of FAT confirmed by the mouse inoculation test is over 99%. Those specimens that are negative on FAT, and have contact with humans, are inoculated into experimental mice. The incubation period in mice before clinical signs are seen averages 11 to 12 days (range of 4–18 days), and death occurs in 7 to 21 days. The mouse brain is harvested as soon as signs appear and is submitted to the same tests described earlier. Thus a positive result can be obtained as soon as 4 to 7 days after inoculation. Some mice must be left for the full 21 days because only a negative result at that time can give a complete negative to the test. A tissue culture infection test is now available, which allows demonstration of the virus in stained tissue culture cells within 4 days. This may replace the mouse inoculation test.
- A dot **ELISA** is available for the detection of rabies antigen in animals. It is rapid, simple, economical and, in comparison with the FAT, the agreement is 95%.
- A **histologic search** for Negri bodies in tissue sections has results available in 48 hours. Because of false-positive diagnoses the technique is in some disrepute.
- An **immunohistochemical (IHC)** test for rabies can be used on formalin-fixed, paraffin-embedded brain tissues of domestic animals and wild animals when fresh tissues are not available. In some cases, the brain tissue may be negative for the rabies virus using standard diagnostic techniques, but IHC tests may detect the presence of antigen.
- A **reverse transcriptase** (RT-)**PCR** test has been found of value in detecting rabies infection in decomposed brain samples that were negative by the direct FAT.

The histopathologic changes of rabies infection include a nonsuppurative encephalomyelitis and ganglioneuritis, with neuronal necrosis and the formation of glial nodules. Negri bodies are most commonly found in the Purkinje cells of the cerebellum in ruminants. Spongiform change has also been reported in the brain of a heifer infected with rabies virus.

Samples for Confirmation of Diagnosis

- **Histology:** half of midsagittally sectioned brain, cervical spinal cord (including root ganglia), gasserian ganglion, parotid salivary gland (LM, IHC)
- **Virology:** half of midsagittally sectioned brain, cervical spinal cord (FAT, BIOASSAY).

Note the zoonotic potential of this organism when handling carcass and submitting specimens.

DIFFERENTIAL DIAGNOSIS

The diagnosis of rabies is one of the most difficult and important duties that a veterinarian is called on to perform. Because in most cases there is a probability of human exposure, failure to recognize the disease may place human life in jeopardy. It is not even sufficient to say that if rabies occurs in the area one will classify every animal showing nervous signs as rabid, because nervous signs may not be evident for some days after the illness commences. In addition, many animals suffering from other diseases will be left untreated. The best policy is to handle all suspect animals with extreme care but continue to treat them for other diseases if such treatment appears to be indicated. If the animal is rabid, it will die and the diagnosis can then be confirmed by laboratory examination.

Several diseases are characterized by signs of abnormal mental state or paralysis, or a combination of both (see Table 14-9 for the horse; Table 14-10 for cattle). Rabies must be differentiated from the following common diseases affecting the nervous system, according to species.

Cattle and sheep

- Lead poisoning. In acute and subacute lead poisoning in cattle the clinical findings are similar to those of furious and dumb rabies. In acute lead poisoning, the common clinical findings are blindness, convulsions, champing of the jaws with the production of frothy saliva, and twitching of the eyelids and ears. In subacute lead poisoning in cattle there is blindness, stupor, head-pressing, grinding of the teeth, and almost no response to treatment. Rabid cattle are usually not blind, and signs of motor irritation such as convulsions and twitching of the facial muscles usually do not occur. However, there are signs of bizarre mental behavior, such as wild gazing, bellowing, yawning, attacking, and compulsive walking.
- Lactation tetany occurs in lactating cattle on lush pasture in the spring during cold wet and windy weather, and is characterized by hyperesthesia, tremors, convulsions, recumbency, and rapid death.
- Vitamin A deficiency occurs in groups of young cattle from 6 months to 18 months of age not receiving adequate carotene intake or vitamin A supplementation and is characterized by blindness in the ocular form and episodes of tremors and convulsions.
- Polioencephalomalacia in cattle and sheep is characterized by blindness, nystagmus, opisthotonus, and convulsions; bellowing, loss of sensation, and tenesmus do not occur.
- Listeriosis in cattle and sheep is manifested by localizing signs of circling and facial nerve paralysis.
- Enterotoxemia in sheep is usually confined to lambs on heavy carbohydrate diets.
- Pregnancy toxemia is a disease of pregnant ewes and is readily differentiated by the presence of ketonuria.
- Louping-ill in sheep is transmitted by insects, has a seasonal occurrence, and a localized geographic distribution.

Horses

In horses, rabies must be differentiated from several diseases of the nervous system (summarized in Table 14-11).

The most common include diseases include viral encephalomyelitis, herpes virus myeloencephalopathy, cerebrospinal nematodiasis, equine degenerative myeloencephalopathy, equine protozoal myeloencephalitis, neuritis of the cauda equina, horsetail poisoning, Borna, Japanese encephalitis, and botulism.

Pigs

In pigs, rabies must be differentiated from pseudorabies, Teschen disease, and involvement of the brain in several other diseases of the pigs, such as hog and African swine fever, meningitis associated with *Streptococcus suis* type II, *Haemophilus* spp., Glasser's disease, *Escherichia coli,* septicemia, and erysipelas.

Text continued on p. 1237

Table 14-9 Diseases of horses characterized by signs of intracranial or disseminated lesions of the central nervous system

Disease	Etiology and epidemiology	Clinical and laboratory findings	Treatment and control
Infection causes			
Viral encephalomyelitis (WEE, EEE, VEE)	Summer season Insect vector, usually mosquitoes Young nonvaccinated horses at greatest risk, outbreaks may occur	Stage of slight hyperexcitability and mild fever initially, impaired eyesight, circling and walking Stage of mental depression, somnolence, leaning, feed hanging from mouth, unsteady Stage of paralysis, unable to swallow, weakness, recumbency; dies 2–4 days after onset Serology for diagnosis	Supportive therapy, thick bedding Recovery rate 60%–75% Vaccinate foals at 6 months of age and other horses for the first time, twice 2 weeks apart and once or twice annually thereafter
Rabies	All age groups, knowledge of disease in area, wildlife Usually single animal affected Not common	Ascending paralysis, hypersalivation, will bite Ataxia and paresis of hindlimbs, lameness, recumbency, pharyngeal paralysis, colic, loss of tail and sphincter tone, fever Dies in 1 week Immunofluorescent antibody testing on brain for positive diagnosis	No treatment All die Vaccinate horses if anticipate outbreak
Herpesvirus myeloencephalopathy (EHV-1)	Can occur as outbreaks Neurologic disease usually preceded by fever Mature horses	Symmetric ataxia and paresis, bladder paralysis, recumbency may occur, spontaneous recovery possible, CSF (hemorrhage or xanthochromia) Vasculitis with subsequent focal malacia in gray and white matter of brain and spinal cord	No specific therapy Antiinflammatory drugs may be useful Use of corticosteroids is controversial Recovery may occur spontaneously
WNE	West Nile virus Late summer in temperate regions Can occur as epizootics Now enzootic in most of North America	Fever, muscle fasciculations, weakness, ataxia, depression, cranial nerve disease, recumbency Prominent signs of spinal cord precede sign of intracranial disease in most cases	Supportive Antiserum Interferon Antiinflammatory. drugs including corticosteroids Prevention by vaccination
Borna	Virus Direct transmission Germany and other European countries Disease is recorded in Japan Low morbidity, high case–fatality rate	Pharyngeal paralysis, muscle tremor, flaccid paralysis, course 1–3 weeks Viral encephalomyelitis with inclusion bodies	No treatment
Japanese encephalitis	Japanese encephalitis virus Sporadic Asia including Japan and China, parts of Oceania including New Guinea and Torres Strait Pig is mammalian amplifying host Vector mosquitoes, birds infected	Fever, lethargy, jaundice, dysphagia, incoordination, staggering, recovery in 1 week Serology	Spontaneous recovery Vaccination in endemic areas
Protozoal myeloencephalitis	*Sarcocystis neurona* Single animal affected Infectious but not contagious	Any central nervous system disorder. Usually causes ataxia but can cause cerebral and cranial nerve disease	Antiprotozoal medications (pyrimethamine + sulphonamide, ponazuril, or nitazoxanide) Vaccine available in the United States, but not recommended
Cerebrospinal nematodiasis (verminous encephalitis)	Migration of larval stages of *Strongylus vulgaris, Habronema* sp., and *Filaroides* *Micronema deletrix* (*Helicephalobolus*) *deletrix* Not common	Clinical signs referable to gray matter lesions are common Hypalgesia, hyporeflexia, hypotonia, muscle atrophy and cerebral, cerebellar and cranial nerve involvement Progressive encephalitis, incoordination, sensory deficits, blindness in one or both eyes, course of several days Pleocytosis of CSF Hemorrhage and malacia of thalamus, brainstem, cerebellum	Ivermectin or moxidectin at usual doses High dose benzimidazole Antiinflammatory drugs Parasite control
Brain abscess	Sporadic Often a complication of strangles	Obtunded mentation, variable signs of intracranial disease Leukocytosis Variable pleocytosis and increased protein concentration in CSF CT scan	Antimicrobials Surgical drainage Prognosis is poor

Continued

Table 14-9 Diseases of horses characterized by signs of intracranial or disseminated lesions of the central nervous system—cont'd

Disease	Etiology and epidemiology	Clinical and laboratory findings	Treatment and control
Physical			
Traumatic injury to the brain	History of traumatic injury (falling, rearing-up and falling backward)	Coma, depression, hemorrhage from nose and ears, blindness, cranial nerve deficits Often rupture of longus capitus muscle	Antiinflammatory drugs, mannitol Fair to poor prognosis
Facial nerve paralysis	Associated with prolonged surgical recumbency and compression of facial nerve	Facial nerve paralysis lasting several days Paralysis of ear, eyelid, lip, nostril on one side No alteration in sensation or vestibular function	Supportive
Lightning strike	Observed lightning strike or history of recent thunderstorm activity	Death is most common Horses that survive strike often have prominent signs of vestibular disease	Supportive Recovery is possible
Fracture or arthritis of the temporal-stylohyoid articulation, otitis media	Sporadic in older horses	Acute onset circling, head tilt, nystagmus, unilateral facial paralysis, dysphagia	Antibiotics, antiinflammatory drugs, supportive care
Intoxications			
Horsetail poisoning (*Equisetum arvense*)	Ingestion of plants mixed with hay Not common	Incoordination, swaying from side to side, muscle tremor recumbency, bradycardia, cardiac arrhythmia	Thiamine parenterally. Good response
Equine leukoencephalomalacia (fumonisin toxicosis)	Horses eating moldy corn grain contaminated with *Fusarium moniliforme* fungus	Muscle tremor, weakness, staggering gait, dysphagia, depression	None
Hepatoencephalopathy associated with hepatotoxic plants (*Crotalaria, Senecio* and *Amsinckia*)	Horses on inadequate pasture forced to eat poisonous plants More than one animal may be affected Geographic distribution	Develops slowly, commonly ill for 2–3 weeks previously, depression, pushing, ataxia, hypertonic face and lips, yawning, compulsive walking, loss of weight, icterus, photosensitization occasionally Serum liver enzymes elevated and liver function tests abnormal Hyperammonemia Gross and histopathologic liver lesions	No treatment Prevent access to poisonous plants
Lead poisoning	Grazing on pastures contaminated by atmospheric lead from nearby factories, not common now	Usually a chronic disease Inspiratory dyspnea caused by paralysis of recurrent laryngeal nerve Pharyngeal paralysis, dysphagia, aspiration pneumonia, paralysis of lips, weakness and recumbency Ingestion of large amounts causes subacute form similar to that seen in cattle	Calcium versenate
Yellow-star thistle poisoning (*Centaurea* sp., anigropallidal encephalomalacia of horses)	Ingestion of yellow-star thistle in California and Australia Summer months on weedy pasture	Difficult prehension, fixed facial expression with mouth held half open, hypertonic face and lips, persistent chewing movements and rhythmic protrusion of tongue, yawning and somnolence but easily aroused, aimless walking, slight stiffness of gait, high mortality Malacia of globus plants pallidus and substantia nigra	No treatment Prevent access to poisonous plants
Botulism	Ingestion of preformed toxin of *Cl. botulinum* in decaying grass or spoiled silage, hay or grain. Sporadic in horses. Endemic in foals in some areas of North America	Flaccid paralysis of skeletal muscles leading to weakness, stumbling and recumbency. Mentation normal. Skin sensation normal. Paralysis of tongue and thoracic muscles. Die in 2–4 days. Some recover. Filtrates of intestinal tract into laboratory animals	Supportive therapy, antitoxins. Vaccination in enzootic areas. Prevent contamination of feed by animal carcasses
Tetanus	Wounds infected with *Clostridium tetani* Sporadic	Generalized tetany of all skeletal muscles Fever, hyperesthesia, protrusion of third eyelid, trismus, recumbency followed by tetanic convulsions, die in 5–10 days	Prognosis unfavorable Dark stall, penicillin, muscle relaxants, supportive therapy and antitoxin parenterally or into subarachnoid space Toxoid vaccination
Metabolic and idiopathic			
Lactation tetany	Lactating mares, suckling foals Hypocalcemia	Acute onset of generalized stiffness, trismus, no hyperesthesia, no prolapse of third eyelid, diaphragmatic flutter, soft heart sounds Serum hypocalcemia	Rapid response to calcium borogluconate intravenously

Table 14-9 Diseases of horses characterized by signs of intracranial or disseminated lesions of the central nervous system—cont'd

Disease	Etiology and epidemiology	Clinical and laboratory findings	Treatment and control
Idiopathic epilepsy of Arabians	Single horse First noticed from shortly after birth up to 6 months of age Etiology unknown	Recurrent episodes of typical clonic-tonic convulsions lasting 10–15 minutes, loss of consciousness, sweating, tachycardia, spontaneous defecation No lesions	Control seizures with phenobarbital or potassium bromide Spontaneous recovery as foals mature
Idiopathic epilepsy of adult horses	Sporadic disease Unknown cause Can be associated with brain lesions detectable on EEG or CT	Tonic-clonic convulsions Variable periodicity and intensity	Control seizures acutely with diazepam and in the long term with phenobarbital and/or potassium bromide Spontaneous recovery unlikely
Cerebellar hypoplasia of Arabian and Swedish Gotland foals	Inherited Signs noticeable from 2–6 months of age	Defective eye blinks, ataxia, head-nodding, slight tremor of head and neck, intention tremor of the head, high-stepping gait, difficulty in rising, legs wide apart, difficulty in jumping over obstacles, fall backward if dorsiflex head and neck Cerebellar hypoplasia grossly or histologically	Eliminate carrier animals
Lower motor neuron disease	Associated with stabling and no access to pasture Sporadic North America and Europe Low serum vitamin E concentrations	Weight loss, weakness, muscle fasciculations, maintained appetite Normal mentation Low serum vitamin E concentration Diagnosis by muscle biopsy	No definitive cure Some cases stabilized with administration of oral vitamin E Poor prognosis for return to function

Note: Other less common diseases affecting the nervous system of horses include space-occupying lesions (cholesteatomas of old horses, tumors), intracranial myiasis caused by migration of Hypoderma bovis*, hydrocephalus in young horses, the accidental injection of an ataractic drug into the carotid artery, and bacterial meningitis in young horses as a sequel to streptococcal infection.*
CSF, cerebrospinal fluid; CT, computed tomography; EEE, eastern equine encephalitis; EEG, electroencephalogram; EHV-1, equine herpesvirus-1; VEE, Venezuelan equine encephalitis; WEE, western equine encephalitis; WNE, West Nile encephalomyelitis.

Table 14-10 Differential diagnosis of diseases of cattle with clinical findings referable to brain dysfunction

Disease	Epidemiology	Clinical findings	Clinical pathology and pathology	Response to treatment
Lead poisoning	All ages of calves and cows on pasture with access to dumps Discarded lead batteries, used crankcase oil, lead-based paint common sources Case–fatality rate high	Acute in calves Blindness and "chewing gum" champing of jaws, convulsions, charging, rapid death Subacute in adults: blindness, stupor, head-pressing, grinding teeth, rumen static, protozoa dead	Blood and tissue for lead Encephalomalacia	Will respond favorably to treatment in early stages if not too severe but most cases do not return to normal Calcium versenate and thiamine hydrochloride Must be concerned about disposition of meat and milk of treated animals
Polioencephalomalacia	Grain-fed rapidly growing feedlot cattle May occur on pasture containing plants and water high in sulfates Outbreaks occur	Sudden onset, blindness, tremors and shaking of head, twitching of ears, head-pressing, opisthotonus, nystagmus, strabismus, rumen contractions normal, CSF pressure increased	Blood biochemistry (see text) Brain for histopathology	Responds to thiamine in early stages Cases caused by sulfate toxicity may not respond
Hypovitaminosis A	Calves 6–8 months of age most commonly but mature cows too off dry summer pasture (CSF form) Young rapidly growing cattle fed deficient ration for several months (ocular form)	CSF form: sudden onset; syncope and convulsions followed by recovery, eyesight and pupils normal Nyctalopia CSF pressure increased Ocular form: blindness in daylight, pupils dilated and fixed, optic disc edema Syncope and convulsions may also occur Usually preceded by nyctalopia but missed by owner	Plasma and liver vitamin A Optic nerve constriction Squamous cell metaplasia of parotid ducts	CSF form: recover in 48 hours following treatment with vitamin A injections Ocular form: will not recover because of optic nerve degeneration

Continued

Table 14-10 Differential diagnosis of diseases of cattle with clinical findings referable to brain dysfunction—cont'd

Disease	Epidemiology	Clinical findings	Clinical pathology and pathology	Response to treatment
Haemophilus meningoencephalitis (thromboembolic meningoencephalitis)	Feedlot cattle (8–12 months), outbreaks, preceded by respiratory disease in group High case fatality if not treated early	Found down, fever common, ataxic, not usually blind, fundic lesions, irritation signs uncommon, weakness and paresis common, synovitis, laryngitis, pleuritis May die in 8–10 hours Myocardial abscesses may also occur	Neutrophilia CSF contains neutrophils Typical gross lesions in brain Pleuritis, pneumonia, synovitis, myocardial abscesses	Respond favorably to antimicrobials if treated early Later, high case–fatality rate
Listeria meningoencephalitis	Sporadic Fed silage Yearlings and adults	Unilateral facial paralysis, deviation of head and neck, mild fever, endophthalmitis, may be recumbent	CSF for cells Brain for histopathology	Recovery may occur. Antimicrobials Residual signs in survivors common
Nervous signs with coccidiosis (see text)	In 20% of young cattle affected with dysentery caused by coccidiosis Case fatality may exceed 50%	Tonic-clonic convulsions, normal eyesight, hyperesthesia, normal temperature, dysentery, may live 2–4 days	Oocysts in feces	Unfavorable response to treatment Must control coccidiosis
Rabies	Cattle exposed to wildlife, one or more affected, all ages, incubation 3 weeks to few months	Quiet and dull (dumb form) or excitable and easily annoyed (furious form) Bellowing, yawning, drooling, saliva, eyesight normal, tenesmus, ascending paralysis beginning with anesthesia over tail head, progressive course, dies in 4–6 days, usually no gross muscular tremors or convulsions, mild fever early	Hemogram normal Brain for laboratory diagnosis	None
Bovine spongiform encephalopathy (BSE)	Mostly in dairy cattle; epizootic began in Britain in 1986; long incubation period; caused by scrapie-like agent in protein concentrate made from sheep carcasses following change in processing procedures	Insidious onset, clinical course several weeks, change in behavior, hyperesthesia, ataxia, loss of body weight, stare, agnostic behavior, kick during milking, knuckling, falling, progressive weakness leading to recumbency	None	None
Pseudorabies	Disease of pigs transmitted to cattle by bites	Intense, local pruritus at site of bite, excitement, bellowing, convulsions, paralysis, death 2–3 days	Tissues for injection into rabbit Histopathology of brain	None
Hypomagnesemic tetany (lactation tetany)	Lactating dairy cows on lush pasture, late pregnant beef cows, cold, windy weather in spring May be precipitated by long transportation or deprivation of feed and water Outbreaks occur Seen in yearlings too Case mortality can be high	Acute: sudden onset of irritability, hyperesthesia; convulsions, recumbency, loud heart sounds, tachycardia, polypnea. Subacute: gradual onset (2–4 days), hyperirritable, difficult to handle, stilted gait, falling, stumbling, sudden movement may precipitate convulsion	Serum magnesium level slow	Responds to magnesium sulfate early
Nervous acetonemia	2–6 weeks postpartum High-producing cow Single animal	Sudden onset, bizarre mental behavior, chewing, licking, bellowing, hyperesthesia, sweating	Ketonuria, hypoglycemia	Responds to glucose parenterally and/or propylene glycol orally
Bovine bonkers (bovine hysteria)	Mature cattle and calves consuming ammoniated feeds (lucerne hay, bromegrass hay, fescue hay, wheat hay, maize stalks or silage) May also occur when animals have access to molasses-urea-protein blocks Toxic agent may be substituted imidazole formed by combination of soluble carbohydrates and ammonia Usually occurs when high-quality forage treated with ammonia concentrate of more than 3% dry matter by weight Can occur in nursing cows fed ammoniated feedstuffs	Periodic episodes of hyperexcitability, bellowing, running, charging, circling, convulsions, weaving, episodes last 30 seconds and may recur every 5–10 minutes Some die Most recover following removal of feed	Information not available	Recover spontaneously following removal of feed source

Table 14-10 Differential diagnosis of diseases of cattle with clinical findings referable to brain dysfunction—cont'd

Disease	Epidemiology	Clinical findings	Clinical pathology and pathology	Response to treatment
Hepatic encephalopathy (i.e., ragwort poisoning)	Cattle with access to plants containing pyrrolizidine alkaloids Many cattle may be affected	Loss of body weight, gradual onset of aggressive behavior, ataxia, muscular tremors, recumbency, convulsions, tenesmus and bellowing	Hyperbilirubinemia, decreased excretion of bromsulphthalein (BSP) Liver lesions	No treatment
Brain abscess	Sporadic, young cattle (6 months to 2 years of age) may have history of previous infections	Localizing signs, rotation or deviation of head and neck, loss of equilibrium, circling, mild fever, may be blind in one eye, nystagmus one eye	Neutrophilia, neutrophils in CSF	Unfavorable response to therapy
Enterotoxemia caused by *Clostridium perfringens* type D	Calves 2–4 months of age sucking high producing cows grazing on lush pastures Outbreaks occur Uncommon	Peracute: found dead. Acute: bellowing, mania, convulsions, blindness, death in 1–2 hours Subacute: dull, depressed, blind	Hyperglycemia (150–200 mg/dL), glycosuria marked Smear intestinal contents Recover toxin (mouse protection tests)	Hyperimmune serum Most die Vaccination effective
Whole-milk hypomagnesemic tetany of calves	Calves 2–4 months of age on whole milk Also in calves on milk replacers, concentrates and hay and occasionally in nursing calves on pasture	Sudden alertness, hyperesthesia, head-shaking, opisthotonus, muscular tremors, frothing at mouth, convulsions, heart rate 200–250 beats/min	Serum magnesium levels usually below 0.8 mg/dL	Magnesium sulfate intravenously gives good response, must follow up daily because of previous depletion of bone reserves

TREATMENT

No treatment should be attempted after clinical signs are evident. If the bite is seen, immediately after exposure, irrigation of the wound with 20% soft soap solution or a solution of benzalkonium chloride for at least 5 minutes may prevent the establishment of the infection. The area exposed to potential infection should be doused with iodine solution or a 40% to 50% alcohol solution if iodine is unavailable.[2] Immediate and thorough washing of all bite wounds and scratches with soap and water is perhaps the most effective measure for preventing rabies in veterinarians bitten by rabid animals. In experimental animals, simple local wound cleansing has been shown to markedly reduce the likelihood of rabies. Postexposure vaccination is unlikely to be of value in animals, because death usually occurs before appreciable immunity has had time to develop. Euthanasia of suspect animals must be avoided, particularly if human exposure has occurred, because the development of the disease in the animals is necessary to establish a diagnosis. Antirabies serum may become available for animal treatment at some future date. **In some countries, cases of rabies in farm animals are notifiable to the animal health and disease regulatory bodies.**

CONTROL

The major goal of rabies control in domestic and wild animals is the reduction or elimination of human rabies. The most rational approach to reducing human rabies is to reduce the prevalence and incidence of disease in animals. In developed countries, this has been accomplished by vaccination of dogs and cats, leaving much rabies in wildlife to be controlled. In countries without wildlife reservoirs, such as the Philippines, it would be economically advantageous to eliminate dog rabies. In Africa, where the incidence of rabies as well as the range of species involved is increasing, there is a need to develop new and economical methods of vaccinating domestic animals.

Dogs remain the major vector for transmission to humans in developing countries and are responsible for an estimated 59,000 human deaths worldwide annually.[6,7] Preexposure immunization for individuals, like veterinarians, who are at high risk to rabies, has been recommended by the World Health Organization (WHO), because it reduces risk and provides a more rapid anamnestic response, eliminating the need for human globulin should exposure occur. Rabies preexposure vaccination is now mandatory in many veterinary colleges. Despite some mild adverse reactions, immunization against rabies is an important prophylaxis measure well accepted by veterinary students.

For farm animals, there are two useful control techniques: the **prevention of exposure** and **preexposure vaccination**.

Prevention of Exposure to the Virus

This can be achieved by controlling access of wildlife species that are likely to come into contact with the farm livestock in particular areas or through vaccination of the wildlife. Foxes accounted for a very large proportion (85% in Europe) of wildlife rabies, and a control program aimed at reducing their population using poison or traps was attempted until the 1970s. This method of population reduction failed to control outbreaks or reduce enzootic rabies.

Point infection control has been shown to be highly successful in controlling raccoon rabies**.** This involves the use of three tactics: population reduction, trap-vaccinate-release, and oral vaccination with baits to control the spread of raccoon rabies.

Preexposure Vaccination of Humans

The most successful form of rabies prevention is preexposure vaccination. In human medicine, there are no reported cases of rabies deaths in anyone who has had preexposure vaccination followed by a booster vaccination if exposed. The CDC has published the recommendations of the Advisory Committee on Immunization Practices (ACIP) for human rabies prevention, which indicate that rabies preexposure vaccination should be offered to persons more likely to be exposed to rabies virus than the population of the United States at large. The recommendations of the ACIP for preexposure prophylaxis and maintenance of a detectable antibody titer differ depending on the estimated degree of risk of exposure to the virus. Four risk categories have established: continuous, frequent, infrequent, and rare. The classification depends on factors such as the occupation of the individual and geography.

With directed continuing education, common sense, first aid, and the availability of modern biologic agents, human rabies is nearly always preventable. Rabies

preexposure vaccination is recommended for anyone at increased risk of exposure to rabies, including veterinarians, veterinary students who work in university veterinary teaching hospitals, laboratory staff working with rabies, vaccine producers, animal and wildlife control personnel, and zoologists. The standard preexposure regimen is three doses of vaccine intramuscularly or intradermally on days 0, 7, and 28 (or 21). A booster dose after 1 year increases and prolongs the antibody response. This preexposure vaccination permits postexposure vaccination to consist of two doses of vaccine on days 0 and 3 instead of five doses on days 0, 3, 7, 14, and 28 and avoids the need for postexposure of administration of human rabies immunoglobulin.

Postexposure Vaccination of Humans

Modern postexposure treatment is highly successful if done adequately. Wound care with infiltration of the wound with human rabies immunoglobulin and active rabies immunization is essential, especially after severe exposure. Postexposure treatment is assumed to neutralize or inactivate virus while it is still in the wounds, before it gains access to the nervous system where it is protected from the immune system. Therefore treatment after exposure to rabies virus is very urgent, even if the patient was bitten months before.

Postexposure Vaccination of Domestic Animals

An effective postexposure protocol for unvaccinated domestic animals exposed to rabies includes immediate vaccination against rabies, a strict isolation period of 90 days, and administration of booster vaccinations during the third and eighth weeks of the isolation period. The protocol has been effective in dogs, cats, cattle, and horses.

Vaccination of Domestic Animals

A *Compendium of Animal Rabies Control* is published annually by the National Association of State Public Health Veterinarians in the United States and Canada. It provides recommendations for immunization procedures in domestic animals and the vaccines licensed and marketed in the United States. Detailed information is provided on preexposure vaccination, management of dogs and cats and livestock, postexposure management, and control methods in wild animals. Such publications should be consulted when necessary. In general, for cattle, sheep, and horses, the primary vaccination is given at 3 months of age and boosters given annually. Farm livestock in endemic areas where clinical cases of rabies occur are common should be vaccinated.

In countries where vampire bats are a major vector for rabies in farm livestock, vaccination of livestock is necessary, but in countries such as Argentina vaccination does not support a cost-benefit analysis.

Vaccines

Almost all rabies vaccines for domestic animals are inactivated. Inactivated tissue culture cell vaccines given to cattle result in neutralizing antibodies in 1 month after the primary vaccination. A booster given 1 year later increases the titers, which are detectable 1 year after the booster. A vaccine inactivated with binary ethylenimine, and containing aluminum hydroxide adjuvant, provides excellent protection for up to 3 years and is very useful for the control of rabies in cattle in Latin America where the vampire bat is the main vector.

Vaccinal antibodies are present in the colostrum of vaccinated cows and it is recommended that, where cattle are vaccinated annually, calves be vaccinated at 4 months of age and again when 10 months of age, but vaccination should be delayed 6 months for calves born to and receiving colostrum from previously vaccinated dams.[8] However, in areas with endemic and epizootic rabies, calves can be vaccinated as early as 2 months of age and be protected in the presence of passive immunity from colostral antibodies provided they are revaccinated 4 months later.[9] Calves from unvaccinated dams can be protected by vaccinating them at 17 days of age. Postvaccinal paralysis does not occur after its use. Coadministration of levamisole (6 mg/kg, subcutaneously) with vaccination does not increase the vaccine titer; however, the effect on cell-mediated immunity was not specifically evaluated in that study.[10]

Vaccination of Wildlife

Mass oral vaccination of terrestrial wild animals is a rabies control method that is feasible, effective, and internationally accepted. It is based on the concept of applied herd immunity. The vaccines are efficacious when fed as vaccine baits. The factors affecting acceptance of baits for delivery of oral rabies vaccine to raccoons have been examined.

The oral immunization of foxes has resulted in a substantial decrease in the number of rabies cases in Europe. As a result of oral vaccination of the red fox (*V. vulpes*) against rabies, using hand and aerial distribution of vaccine-laden baits, the rabies virus has almost been completely eradicated from Western and Central Europe. The same dramatic decrease occurred in southern Ontario, Canada. In most countries, vaccine baits were distributed twice yearly during the spring (March to May) and autumn (September to October). Several European countries have become rabies free: Belgium, Luxembourg, France, Italy, Switzerland, Finland, and the Netherlands.

Progress has been made in applying oral rabies vaccination to contain and eliminate some strains of terrestrial rabies in North America. Raboral V-RG is the only rabies vaccine licensed for use in the United States. It has not produced sufficient levels of population immunity in skunks in the wild at the current dose, and it may be less effective in skunks than in other species. Skunks are a major contributor to rabies in North America and this has raised concerns about an independent maintenance cycle for raccoon rabies in skunks. The national rabies management goals of virus containment and elimination will likely remain elusive until an oral vaccine is licensed that is immunogenic in all terrestrial rabies reservoir species. Vaccination will succeed in reducing or eradicating rabies only if a sufficient proportion of the target population can be immunized. Mathematical modeling techniques are now being tested to examine the population biology of rabies in wildlife species such as raccoons and skunks.

It is notable that no practical vaccination methods have been developed for bats. Phylogenetic analyses of viruses from bats and carnivores suggest a historical basis for still existing viral origins caused by interactions between these taxa. Thus the possibility for pathogen emergence resulting from transmission by rabid bats with subsequent perpetuation among other animals cannot be discounted easily on any continent.

Quarantine and Biosecurity

The most effective method of preventing the entry of rabies into a country free of the disease is the imposition of a quarantine period of 4 to 6 months on all imported dogs. This system has successfully prevented the entry of the disease into island countries, but has obvious limitation in countries that have land borders. The occurrence of the disease in two dogs in the United Kingdom in 1969 to 1970 in which the incubation period appeared to last 7 to 9 months suggests that the more usual period of 6 months may give incomplete protection. Therefore vaccination on two occasions with an inactivated vaccine while the animal is still in quarantine for 6 months is the current recommendation. To require a longer period of quarantine would encourage evasion of the law by smuggling. The situation in the UK, and in any country where the disease does not occur, is a vexed one. It is possible to rely chiefly on quarantine and act swiftly to stamp the disease out if it occurs. The shock eradication program would include quarantine of, and vaccination in, a risk area, ring vaccination around it, and destruction of all wildlife. This procedure is likely to be adopted in countries where the risk is small, such as Australia. Where the risk is great, consideration must be given to mass vaccination of wildlife by baits, because wildlife are the cracks in the defense armor. The use of combined vaccines containing rabies vaccine in other vaccines used in dogs would be an

effective and panic-free way of increasing the immune status of the pet population.

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PSEUDORABIES (AUJESZKY'S DISEASE)

The disease was first described in cattle and was known then as pseudorabies because of the similarity to rabies and thereafter Aujeszky's disease after the Hungarian physician who first isolated the virus.

SYNOPSIS

Etiology Aujeszky's disease virus (suid herpesvirus 1) (SuHV-1).

Epidemiology Found in pigs worldwide and major economic importance in swine-raising areas. High prevalence of infection; lower incidence of disease. Infected pig source of infection; latent infection is characteristic; spread occurs within herds, between herds, and from infected carriers; long-distance aerosol transmission occurs from area to area; immunity follows infection or vaccination.

Signs Fever, incoordination, recumbency, convulsion, and death in piglets. Coughing, nasal discharge, sneezing, and dyspnea in older growing pigs. In cattle and sheep, intense pruritus at site of bite, excitement, circling, convulsions, fever, recumbency, paralysis, and death in 48 hours or less.

Clinical pathology Serology for virus-neutralizing antibodies. Detection of virus in tissues.

Lesions Viral encephalitis.

Diagnostic confirmation Detection of virus in tissues; serology; inclusion bodies in nervous tissue and respiratory tract.

Differential diagnosis

Swine
- Viral encephalomyelitis (Teschen disease)
- Rabies
- Streptococcal meningitis
- Hog cholera
- African swine fever
- Glasser's disease
- Septicemias (*Escherichia coli*, erysipelas, salmonella)
- Bowel edema
- Salt poisoning
- Reproductive insufficiency (parvovirus).

Cattle and sheep
- Nervous form acetonemia
- Rabies C
- Acute lead poisoning.

Treatment None.

Control Depopulation and repopulation, test and removal, segregation of progeny, and vaccination with subunit vaccines that distinguish between infected and vaccinated pigs.

ETIOLOGY

Pseudorabies is caused by porcine herpesvirus-1 (SuHV-1), Aujeszky's disease virus, or pseudorabies virus (PRV), of the genus *Varicellovirus*, a member of the family of Herpesviridae,[1] subfamily Alphaherpesvirinae. It exists as a single serotype. Many cell lines are used for PRV culture. There are four major genome types; Type 1 is found in the United States and Europe; Type 2 is found in central Europe, Type 3 is found in Eastern Europe, and Type 4 is found only in Asia.

EPIDEMIOLOGY

Occurrence

PRV primarily affects pigs and occurs incidentally in other species. It has a worldwide distribution except for Norway, Australia, and most of the islands of Southeast Asia. Control programs have eliminated the condition in many countries,[2] leaving isolated pockets in Northern Ireland and in France. It is still endemic in eastern and southeastern Europe, Latin America, Africa, and Asia. For example, in Poland from 2005 to 2009 around 0.4% of the population was infected.[3] In countries where the disease has been eradicated vaccination is not allowed.

The disease persists in feral pigs, wild boar, and hybrids[4,5] at quite high levels in many European countries and also in the United States[2] and these permanently threaten the domestic pig population.

The reservoir of Aujeszky's disease has shifted from domestic pigs to wild and feral pig populations and circulates unchecked in many countries.[6] Thus the identification of reservoirs and the epidemiologic surveillance is becoming more difficult.

PRV is primarily a disease of pigs, and naturally occurring cases in cattle, sheep, dogs, cats, rats, and horses are rare and usually fatal. Many other species have also been affected, but only pigs survive the infection. Infection in other species often occurs when pigs cohabit with other species.

Morbidity and Case Fatality

Typically, the disease spreads rapidly in infected herds over a period of 1 to 2 weeks, and the acute stage of the outbreak lasts 1 to 2 months. In sucking pigs, the morbidity and mortality rates approach 100%, but in mature swine there may be no clinical signs, and affected animals usually recover. The highest morbidity occurs initially in unweaned piglets, but as the outbreak continues and piglets become passively immunized through the sow's colostrum, the major incidence may occur in weanlings.

In recent years, there has also been an increase in the morbidity and case–fatality rates in older pigs associated with the intensification of pig rearing and the dominance of more virulent strains.

Risk Factors

Animal Risk Factors

The seroprevalence of infection varies widely between herds, and between breeding and finishing pigs within herds. The most important animal risk factors of virus persistence are herd size and the population density of the sows in the herd. Endemic infection is more likely in herds of breeding sows with more than 66 sows. In breeding herds, spread of infection is positively associated with increasing size of the herd, having the gilts in the same barn as the sows (gestation barn), and serologic evidence of infection in the finishing pigs. The seroprevalence of infection is low in quarantined breeding herds, which makes them prime candidates for elimination of the disease by test and removal.

In the early period of a compulsory vaccination program with gI-deleted vaccines, in an area endemically infected with the disease, the seroprevalence of infected breeding females is higher in farrow–finish than farrow–feeder herds. Mandatory vaccination is beneficial in both herds but the pattern is linear in farrow–feeder herds and curvilinear in farrow–finish herds, and is more rapid in the early period of the program. In the farrow–finish herds, the odds of infected breeding females were associated positively with seropositivity in the finishing pigs of the herd and with the density of the pigs in the county in which the herd is located. In Belgium the presence of finishing pigs in the same herd increased the chances of being infected. The spread and transmission of the virus between herds can be reduced by a reduction in the contact rate between the herds and their size and by a reduction of the transmission within the herd.

The factors associated with circulation of the virus within herds include confinement of finishing pigs, concurrent infection with *Actinobacillus pleuropneumoniae*, the length of time since the herd has been under quarantine, and the presence of clinical disease.

In general, PRV does not increase the susceptibility of animals to infection with other pathogens.

The primary risk factors associated with seroprevalence of the virus in 500 swine herds in Illinois included total confinement and density of infected herds in the geographic area. It was calculated in Belgium that if there were over 455 pigs per squared kilometer, then there was a 10-fold increase in the risk of PRV. Total confinement is associated with higher seroprevalence, presumably because of increased density of population and increased risk of transmission. Seroprevalence is higher in vaccinated herds, increases over the course of the eradication program, and decreases with an increased time between quarantine and the development of a herd plan. In the Netherlands, the risk factors contributing to seroprevalence of infection in breeding herds included the presence of finishing pigs, production type (producers of finishing pigs had a higher prevalence than producers of breeding stock), vaccination of sows during nursing (compared with vaccinating all sows simultaneously at 5-month intervals, or vaccination during the second half of gestation), pig density in the municipality in which the herd was located (seroprevalence increased with higher pig density), herd size of fewer than 100 sows, average within-herd parity (seroprevalence increased with higher within-herd parity), replacement pigs raised on the premises, and vaccine strain administered to the sows.

Environmental Risk Factors

The virus is resistant to environmental conditions depending on pH, humidity, and temperature. The virus may survive for 2 to 7 weeks in an infected environment and for up to 5 weeks in meat. The infectivity of the virus in an aerosol decreases by 50% in 1 hour. Environments at 4°C supported the survival of the virus in aerosol better than at 22°C. The virus is lipophilic and sensitive to several commonly used disinfectants. Sodium hypochlorite (5.25%) is the most desirable and practical disinfectant. Suspensions of the virus in saline G solution and on the solid fomites, whole corn, and steel remained infectious for at least 7 days. Loam soil, straw, and concrete supported survival of the virus at 25°C for up to 1 week. During shipment of pigs, bedding material and surfaces in contact with pigs may become contaminated. Rinsing a needle between sampling may reduce the probability of mechanically transmitting the disease.

Pathogen Factors

Field strains of the virus differ in virulence. Numerous genomically different strains of the virus exist, and restriction endonuclease (RE) analysis can distinguish between virus isolates, which is useful for identifying new isolates of the virus as they appear in pig populations. In Denmark, restriction fragment analyses of older clinical isolates, and of isolates from all the virologically confirmed outbreaks since 1985, indicated the introduction of foreign strains. Strain variation in virulence has been observed in field isolates and produced by laboratory attenuation. Virulence also affects the tropism of the virus. Many of the highly virulent strains are neuroinvasive; many of the moderately virulent or mild strains are not neuroinvasive but affect the respiratory tract. The highly adapted or vaccinal strains often acquire a tropism for the reproductive systems. Inactivation of several genes that are not essential for viral replication can reduce the virulence of the virus.

Some field strains of the virus from Poland and Hungary have been identified by restriction fragment pattern analysis as derivatives of conventionally attenuated vaccine strains. This is considered a rare event but must be considered in relationship to trade in semen from vaccinated boars or trade in live animals between disease-free areas and areas in which vaccination with live attenuated strains is practiced.

Methods of Transmission

Pseudorabies is not very contagious and large quantities of the virus are required to infect pigs except very young piglets. Larger doses of virus are needed for oral infection than nasal infection. In feral pig and wild boar populations it appears to be venereal transmission that is more important.[7] It can be transmitted transplacentally, especially in the last third of gestation. It can also be passed through the colostrum. In milk excretion of virus takes place for 2 to 3 days following infection. Virus can be transmitted for up to 12 days in semen following infection. Venereal transmission of latent infection in sows and boars has been suspected, but there is no direct evidence. The virus cannot usually be isolated from urine.

In a study of PRV in wild swine in the United States it was found that the virus was found in the oral cavity of feral pigs and was widely distributed in the tonsils, salivary glands, taste buds, and even mucosa in the region of the tusks.[8]

Infected swine shed virus in large quantities from all body excretions, secretions, and aerosols. Virus shedding starts 1 to 2 days after infection, reaches a peak at 2 to 5 days, and may last up to 17 days. Virus can be isolated from the oropharynx for 18 to 25 days.

Pigs, and possibly rodents, appear to be the primary host for the virus. The virus is present in the nasal discharge and in the mouth of affected pigs on the first day of illness and for up to 17 days after infection. This suggests that short-length aerosol transmission is a common occurrence within buildings or units but long distance transmission is still doubted. After infection and recovery pigs may be regarded as carriers.

Within Herds

Transmission within herds occurs by direct oral–nasal contact between infected and susceptible pigs and aerosols from projection of discharges during sneezing, but it may also occur via contaminated drinking water and feed. Transmission within herds is independent of the size of the population.

The transmission of virus decreases rapidly following the start of a vaccination program, but extensive spread can still occur even among finishing pigs vaccinated twice. Vaccinated pigs may shed more virulent virus but there are no significant differences in magnitude of transmission. Mixing of chronically infected pigs with seronegative pigs may not result in seroconversion in the seronegative pigs until a clinical outbreak of disease occurs.

Between Herds

Transmission between herds is caused by the introduction of infected animals, and the virus may still be introduced into vaccinated breeding herds. Other methods of transmission have been suggested, including farm laborers, vehicles, feedstuffs, rodents, and wild or domestic animals, the carcasses of dead infected animals, and infected food and water.

Within an Area

Transmission within an area is a major problem and not well understood. Some evidence indicates that area spread may be associated with markets and the frequency of delivery of pigs to market per year. In France, it has been suggested that the presence of an infected herd within 1 km is an important factor in the spread of PRV. The concurrent occurrence of an outbreak of disease on many farms in the same area in Denmark suggested long-distance airborne transmission of the virus.

Infection is spread by airborne transmission. Sneezing probably generates the airborne virus. In a series of outbreaks in Britain between 1981 and1982, 7 of 11 were found likely to have been transmitted by aerosol on meteorologic grounds. Airborne spread occurred between herds 2 to 9 km apart. An epidemic in Denmark in 1987 to 1988, associated with foreign strains of the virus, suggests that airborne transmission occurred across the German–Danish border, especially as a southerly wind was blowing during the period of transmission.

Computer modeling based on the mean dose of virus received by an animal at a farm downwind can be used to predict the airborne spread of the virus.

The virus is inactivated in meat after 35 days of storage at −18°C (0.5°F). Meat from infected pigs may cause infection when fed to dogs.

Latency

Pigs that recover from infection are latent carriers of the virus for life. Reactivation, followed by shedding and spreading the virus, may occur following stress such as transport or farrowing, or by the administration of

corticosteroids. Serologic testing of latent carriers detects the antibody response to the whole virus or to a PRV virus glycoprotein. During natural infection, the virus replicates at the site of infection, usually in the oronasal areas. The virus gains entry into the nerve endings and ascends by retrograde axonal transport to the cell body in the trigeminal ganglion. Viral components can be found in both the trigeminal ganglion and the tonsils. The tonsil is a primary site of virus replication and serves as an area for monitoring virus shedding during acute infection and reactivation. The virus can be isolated from tissue fragments of pigs clinically recovered from disease for up to 13 months and followed by a challenge with the live virus, which may be shed by sows for up to 19 months after initial infection. Virus gene products can be found in the trigeminal ganglia and tonsils for many weeks following acute infection. Latent infection can also occur in vaccinated pigs.

Other Species

The rarity of spread to other species is caused by scanty nasal discharge and the improbability of the discharge coming into contact with abraded skin or nasal mucosa of animals other than pigs. The disease has occurred in sheep and cattle following the use of a multidose syringe previously used in infected swine. It may spread from normal or clinically affected pigs to animals of other species, but does not usually spread between animals of the other species. For example, sheep and calves can be infected experimentally, but there is no evidence that they excrete the virus. The disease may occur in pigs, sheep, and cattle on the same farm. Brown rats may be a minor source of infection but are unlikely to be an important reservoir; they are capable of spreading the disease to dogs. The wild Norway rat is thought to have only a minor role in the transmission of the disease to farm animals. The virus causes fatal disease in dogs, which are usually infected from close association with infected pigs. The raccoon can be infected experimentally, but is not considered to be a long-term subclinical carrier of the virus. The possible role of wild animals in transmission of PRV in swine has been examined with inconclusive results. It has been seen in Kodiak, polar, and Himalayan bears fed on a diet of raw pig's heads. Five viral isolates were recovered from latently infected wild boar originating from two regions of East Germany, but in the Netherlands the wild boar were said to be rarely affected. The PRV infections in the wild boar in Germany are said to exist in the country as an endemic infection and persist completely separately from the domestic population and also do not appear to affect it. The sacral ganglia and trigeminal ganglia of wild pigs were said to be a source of infection. The latency was shown in 9/16 sacral ganglia, 7/16 trigeminal ganglia, and 5/13 tonsils from feral swine in the United States, but even so most of the transmission in feral swine is expected to be venereal. The experimental infection of wild boars and domestic pigs with different strains has been performed and the clinical signs depended on the strain but the wild boar could infect the domestic strains and vice versa. The low virulence strains were highly adapted to the wild boar.

Immune Mechanisms

When infected with a virulent strain of the virus, pigs develop an immune response that can completely, or almost completely, prevent the virus from replicating after the pig becomes reinfected. Following natural infection, sows acquire immunity, which is transferred to their piglets in the colostrum and persists in the piglets until 5 to 7 weeks of age. Following intranasal challenge, piglets with colostral immunity from naturally infected sows are protected from clinical disease, but not against subclinical infection.

Vaccination of pigs with attenuated PRV virus prevents clinical disease and death that may otherwise follow exposure to the virulent virus. Vaccination does not, however, prevent either acute or latent infection with virulent virus. Consequently, vaccinated pigs, as well as nonvaccinated pigs that survive infection with the virulent virus, can become virus carriers and a source of the virus following reactivation of a latent infection. This is of vital importance in eradication programs in which it is necessary to identify infected pigs regardless of their vaccination status. Maternal immunity interferes with inactivated virus vaccination much more than with live virus vaccination.

Vaccination of pregnant sows induces a maternal immunity, which protects piglets from experimental disease. However, latent infection of young pigs with highly virulent virus can develop in the absence of clinical signs. The virus can reach the uterine and fetal tissues, via infected mononuclear cells, which is the presence of circulating antibodies induced on vaccination. Vaccination of piglets before challenge exposure has little or no effect on the rate of establishment of virus latency, but vaccination does reduce shedding after subsequent experimental reactivation of the virus with dexamethasone. Attenuated tyrosine kinase-negative vaccine strains of the virus can also establish a reactivatable, latent infection.

In growing and finishing pigs in quarantined herds, the serologic status is unpredictable because the infection may continue to spread, may cease temporarily, or may cease altogether. Evaluation of the serologic status of the boars in a breeding herd does not accurately reflect the serostatus of the herd.

It has been suggested that the T cells are more important than the B cells in the clearance of PRV from the host, and it has been shown that strong T-cell–mediated responses after challenge produce the best protection.

Economic Importance

The economic losses associated with pseudorabies in swine are caused by clinical disease and the costs of serologic analysis and vaccination programs. Economic loss estimates must include the measurement of losses during and immediately after clinical outbreaks of disease and the indirect losses incurred until after eradication of the disease. Losses have been estimated at $25 to $50 per sow per year; these include only losses during the period of the outbreak and the direct losses attributable to death and abortions. When expanding the observations of economic losses to 3 months after the termination of the outbreak, estimated losses may be as high as $145 per sow per year. Economic analyses of the losses in a commercial farrow–finish herd of 240 breeding-age sows in the United States revealed that the major part of the loss was caused by death of suckling pigs at 76% of total loss, nursery pig mortality accounted for 12.6% of total net loss, sow culling and deaths accounted for 9.4% of net loss, and market pig deaths accounted for 1.2% of net losses.

The costs of eradicating PRV vary depending on the methods used. Depopulation–repopulation is the most expensive method because it requires culling of animals, clean-up costs, and downtime, which represents the largest proportion of expense. In addition, the probability of reinfection following repopulation is a risk.

Test and removal is the most inexpensive, and segregation of offspring is an intermediate cost. The cost of eradicating the virus from a swine herd can be in excess of $220 per inventoried sow; some estimates are much higher. In large breeding herds or finishing herds with the continual influx of susceptible pigs, the disease may become endemic. PRV may also be a significant cause of reproductive inefficiency in pig herds, and infection within the herd may be initially manifested by abortions in the sow herd, followed later by the more typical occurrence of neurologic disease in suckling and growing pigs. The economic losses from the disease can be very high because of mortality in young pigs, decreased reproductive performance, and the necessity to depopulate to eradicate the disease from a herd. An economic assessment of an epidemic of PRV in a 150-sow farrow–finish operation on selected production and economic variables has been made. The mean litter size remained the same throughout the period of observation, but there was a twofold increase in suckling pig mortality and 3.5-fold increase in stillbirths during the months of the epidemic compared with the period before the epidemic. Following the epidemic, suckling pig mortality was 14% greater and stillbirth rate was 71% greater than during the months preceding the outbreak. The major economic

losses (88% of the total loss) were related to breeding herd removal/depopulation and production downtime.

PATHOGENESIS

The portal of entry is through abraded skin, oral mucosa, or via the intact nasal mucosa. Strain differences in the effect of historical PRV strains in porcine respiratory nasal mucosa explants shows that there were differences in the strains.[8] The virus is pantropic and affects tissues derived from all embryonic layers. Receptor and receptor-binding virion proteins that can mediate the virus entry into the cell and cell-to-cell spread have been described. The various glycoproteins of the virus are required for various stages of virion morphogenesis. For example, deletion of glycoproteins gE, gI, and gM inhibits the virion maturation. Pseudorabies glycoprotein gK is a virion structural component involved in virus release from the cell but not viral entry, and its presence is important to prevent immediate reinfection. Viremia occurs with localization of the virus in many viscera, but with multiplication occurring primarily in the upper respiratory tract. Viral and cell interactions have been described in detail.[9] Spread to the brain occurs by way of the olfactory, glossopharyngeal, or trigeminal nerves, i.e., via the autonomic nerves. It can pass across synapses and infect higher level neurons.[10] Cells with the common leukocyte antigen CD45+ populate the CNS-infected areas from the local capillaries, and the number of cells is increased in proportion to the number of infected neurons. Virus disappears from the brain by the eighth day, coinciding with the appearance of neutralizing antibody in the blood. When the virus gains entry through a skin abrasion, it quickly invades the local peripheral nerves, passing along them centripetally and causing damage to nerve cells. It is this form of progression that causes local pruritus in the early stages of the disease, and encephalomyelitis at a later stage when the virus has invaded the CNS. In pigs, pruritus does not develop after intramuscular injection, but a local paralysis indicative of damage to low motor neurons occurs before invasion of the CNS in some pigs. In cattle, pruritus of the head and neck is usually associated with respiratory tract infection, whereas perianal pruritus is usually caused by vaginal infection.

The inoculation of PRV into the nasal cavities or brain results in signs of encephalitis instead of local pruritus. With oral inoculation, there is an initial stage of viral proliferation in the tonsillar mucosa, followed by systemic invasion, localization, and invasion of the CNS along peripheral and autonomic nerve trunks and fibers. Lesions of Auerbach's myenteric plexus and the skin may also occur. The peripheral blood mononuclear cells, tonsils, lymph nodes, and bone marrow are a poor source of virus after experimental infection. The trigeminal ganglia and olfactory bulb are good sources of virus. The virus may be present in the trigeminal ganglion of a naturally infected sow without any history of clinical disease. Experimental inoculation of the virus into young pigs can result in a mild pneumonia, which may progress to a severe suppurative bronchopneumonia.

The virus can invade the uterus and infect preimplantation embryos, which can lead to degeneration of the embryo and reproductive failure. Virulent PRV virus can cause lesions in the uterine endothelium and ovarian corpora lutea of pigs in early pregnancy, and gene-deleted mutant virus vaccine given intravenously during estrus can cause ovarian lesions, which may affect fertility. Through the use of embryo transfer procedures, infected embryos may disseminate the virus from donors to recipients.

In other species the virus tends to be restricted to the nervous system.

CLINICAL FINDINGS

Pigs

The incubation period in natural outbreaks is about 1 day but may be from 1 to 8 days. The major signs are referable to infection of the respiratory, nervous, and reproductive systems. There is considerable variation in the clinical manifestation, depending on the virulence and tropism of the infecting strain. Nervous system disease is the major manifestation, but with some strains, respiratory disease may be the initial and prime presenting feature. There is also strain variation in the pattern of age susceptibility.

Young pigs a few days to a month old are most susceptible. Very young sucklings develop an indistinct syndrome, but prominent nervous signs occur in older piglets. A febrile reaction, with temperatures up to 41.5°C (107°F), occurs before the onset of nervous signs. Incoordination of the hindlimbs causing sideways progression is followed by recumbency, fine and coarse muscle tremors, and paddling movements. Lateral deviation of the head, frothing at the mouth, nystagmus, slight ocular discharge, and convulsive episodes appear in a few animals. A snoring respiration with marked abdominal movement occurs in many, and vomiting and diarrhea in some affected pigs. Deaths occur about 12 hours after the first signs appear. In California, a consistent sign has been blindness caused by extensive retinal degeneration.

In growing and adult pigs, the disease is much less severe but there is considerable variation depending on the virulence of the infecting strain. In growing pigs, mortality falls with increasing age and is generally less than 5% in pigs at 4 to 6 months of age. With some strains, fever is a prominent sign, whereas depression, vomiting, and sometimes marked respiratory signs, including sneezing, nasal discharge, coughing, and severe dyspnea are common. Trembling, incoordination, and paralysis and convulsions follow, and precede death. With others, the disease may be manifested at this age by mild signs of posterior incoordination and leg weakness. In adults, fever may not be present, and the infection may cause only a mild syndrome of anorexia, dullness, agalactia, and constipation. However, virulent strains may produce acute disease in adults, characterized by fever, sneezing, nasal pruritus, vomiting, incoordination and convulsions, and death. Infection in early pregnancy may result in embryonic death, or abortion, and early return to estrus. An abundant vaginal discharge may occur. Infection in late pregnancy may result in abortion, or in the subsequent birth of mummified fetuses, which may involve all or only part of the litter. Abortion may result from the effects of fever or from viral infection of the fetus.

Concurrent infection has been described with PCV2, and PRRS and swine influenza virus, and in these cases the resultant disease is more likely to be a severe proliferative and necrotizing pneumonia.[11]

Cattle, Sheep, and Goats

There may be sudden death without obvious signs of illness. More commonly, there is intense, local pruritus with violent licking, chewing, and rubbing of a particular body part. Itching may be localized to any part of the body surface, but is most common about the head, the flanks, or the feet, which are the sites most likely to be contaminated by virus. There is intense excitement during this stage, and convulsions and constant bellowing may occur. Maniacal behavior, circling, spasm of the diaphragm, and opisthotonus are often evident. A stage of paralysis follows in which salivation, respiratory distress, and ataxia occur. The temperature is usually increased, sometimes to as high as 41°C to 41°C (106°F-107°F). Final paralysis is followed by death in 6 to 48 hours after the first appearance of illness. A case of nonfatal PRV in a cow is recorded. There is also a report of PRV occurring in feedlot cattle in which there were nervous signs, bloat, and acute death, but no pruritus. In young calves, it is characterized clinically by encephalitis, no pruritus, erosion in the oral cavity and esophagus, and a high case–fatality rate. An outbreak in sheep was associated with skin abrasions acquired at shearing. Affected ewes were dull, inappetent, and had a fever of 41.1°C. About 23 of 29 affected sheep developed the "mad itch," with nibbling of their fleece and frenzied attempts to bite one area of the skin and rub it against the wall and bars of their pen. Terminally, recumbency, tremors, and opisthotonus were common, and death occurred within 12 to 24 hours after onset. Five farm cats also became ill and died; the virus was isolated from the brain of one cat. In goats, rapid deaths, unrest, lying down and rising frequently, crying plaintively,

profuse sweating, and spasms and paralysis terminally are characteristic. There may be no pruritus.

The clinical findings in dogs and cats are similar to those in cattle, with death occurring in about 24 hours. In France, cases in dogs have been linked to strains of virus from wild boars.

CLINICAL PATHOLOGY

Serology

The commonly used serologic tests for PRV-specific antibodies are the serum neutralization (SN) and ELISA tests.

Serum Neutralization Test

The SN test using the Shoppe strain has been the gold standard against which other serologic tests are compared and has been most widely used because of its sensitivity and specificity. Specific virus-neutralizing (VN) antibodies are detectable in the serum of recovered pigs, and this test is in routine use for herd diagnosis and survey purposes. Antibody is detectable on the seventh day after infection, reaches a peak about the 35th day, and persists for many months. Paired serum samples taken as early as possible, and about 3 weeks later, show a marked antibody rise. However, the SN test lacks the sensitivity necessary for detection of pigs with low levels of humoral titers of specific SN antibodies, which can be enhanced by using the Bartha gIII strain.

Some herds may have no serologic evidence of previous infection or current spread of the virus but have single reactors in the herd that may be infected with the virus. Such singleton reactors may be found in herds being monitored serologically for presence of infection. These singleton reactors may be infected with strains of the virus that are relatively avirulent.

Enzyme-Linked Immunosorbent Assay

The ELISA test is more sensitive than the SN test, especially early in the immune response to PRV antigens. However, because of its high sensitivity, screening ELISAs yield some false positives, which must be confirmed by another test, such as another ELISA, SN test, or latex agglutination test. False positives are unlikely to be caused by infection with other herpesviruses. ELISA has also been used as a meat juice test with high sensitivity (93%) and specificity (98%).

The indirect ELISA is a more rapid and convenient procedure, offering many advantages over the SN test for routine serodiagnostic work. An indirect ELISA, using whole blood collected onto paper disks, is a rapid and convenient test and eliminates the costs of using vacutainer tubes and separating the blood. An indirect ELISA based on recombinant and affinity-purified glycoprotein E of PRV to differentiate vaccinated from naturally infected animals has been developed. An indirect ELISA has been developed in the Czech Republic that can be used because of its high sensitivity and specificity for blood serum on frozen pork samples. It has allowed the demonstration of PRV in meat juice with only marginal titers in the blood.

Commercial ELISA kits are available and some are more specific than others. A highly sensitive and specific competitive ELISA based on baculovirus-expressed PRV glycoprotein gE and gI complex has been described. This allows detection as early as 2 weeks postinfection and can handle large numbers of tests without the need to handle live virus.

In countries where vaccination is regularly used for control of the disease, an assay to serologically distinguish infected from vaccinated pigs is critical. Although a vaccination program will reduce the circulation of virus in the field, it will not eliminate the virus from the pig population. To eradicate the virus, the ability to differentiate infected from vaccinated pigs is crucial. Several commercial ELISA kits can differentiate between vaccinated and naturally infected pigs. Differentiation is possible when vaccine virus strains have either a natural, or a genetically engineered, deletion that encodes for either gI, gIII, or gX genes. Commercial ELISA kits that specifically detect antibody responses to gI of the virus offer considerable advantages as diagnostic tests for the virus, with a sensitivity of 99.2% and specificity of 100%. The gI ELISA is able to distinguish infected pigs from those vaccinated with gI-negative vaccines. The field strains of the virus produce antibodies to gI when inoculated into pigs. Unvaccinated pigs, or pigs vaccinated with gI-negative vaccines, that become subclinically infected with field strains of the virus may be detected with the gI–ELISA for a long time after infection. Thus pigs that are seropositive in the gI–ELISA have either been infected with PRV or have been vaccinated with gI-positive vaccines; gI-seronegative pigs can be considered to be uninfected. Eradication of the virus from swine herds is possible by gI–ELISA testing, and culling gI-seropositive pigs in herds using gI-negative vaccines.

Detection of pigs in the latent phase of infection can be done serologically. Pigs of any age that survive the acute infection phase become latent carriers for life, and serologic testing consistently detects animals in the latent phase of infection if the test detects the antibody response to the whole virus or to a reliable PRV glycoprotein. Of several serologic tests examined, the gI and gIII marker systems, which performed with similar sensitivity as the screening tests, were superior to the gX marker system in detecting antibodies in infected pigs.

Detection of Virus

In infected pigs the virus is usually present in nasal secretions for up to 10 days. A common method for the diagnosis of PRV in sows is to take swabs from the nasal mucosa and vagina. Polyester and wire swabs shipped in 199 tissue culture medium supplemented with 2% fetal bovine serum (FBS) buffered with 0.1% sodium bicarbonate and HEPES will yield optimum recovery of the virus. Wooden applicator sticks with cotton wool have antiviral activity and recovery of the virus may not be possible after 2 days, which is of practical importance if the samples are shipped by mail. The virus can be demonstrated in nasal cells by immunofluorescence and immunoperoxidase techniques. It can be detected by direct filter hybridization of nasal and tonsillar specimens from live pigs. The virus survives on tonsil swabs taken with Dacron-tipped applicators for up to 72 hours in cell culture medium under transport.

New PCR techniques have been used and they can differentiate between true and false serologic positives when single reactor pigs have been found. A molecular beacon RT-PCR for the detection of PRV, African swine fever (ASF), PCV2, and Porcine Parvovirus has been described[12] and for the detection of PRV, ASF, and PRRS.[13] A multiplex PCR for PRV, porcine respiratory coronavirus, and PCV2 has been described.[14]

Loop-mediated isothermal amplification (LAMP) for rapid detection and differentiation of wild-type PRV and gene-deleted virus vaccines was described.[15]

NECROPSY FINDINGS

There are no gross lesions typical and constant for the disease, and in some cases lesions are absent or minimal and diagnosis must rely on laboratory examination. When pruritus has occurred, there is considerable damage to local areas of skin and extensive subcutaneous edema.

Gross lesions in the upper respiratory tract are the most obvious and these include necrotic rhinitis, conjunctivitis, laryngitis, and tracheitis. The lungs show congestion, edema, and some hemorrhages. Hemorrhages may be present under the endocardium and excess fluid is often present in the pericardial sac. In pigs, there are additional lesions of visceral involvement. Slight splenomegaly, meningitis, and excess pericardial fluid are observed, and there may be small necrotic foci in the spleen and liver. In sows, there may be a necrotizing placentitis and endometritis. Foci of hepatic, splenic, or pulmonary necrosis may be seen in aborted fetuses.

Histologically, in all species, there is severe and extensive neuronal damage in the spinal cord, paravertebral ganglia, and brain. Perivascular cuffing and focal necrosis are present in the gray matter, particularly in the cerebellar cortex. Intranuclear inclusion bodies occur infrequently in the degenerating neurons and astroglial cells, particularly in cerebral cortex in the pig. These inclusions are of considerable importance in differential diagnosis. Necrotizing lesions with

inclusion-body formation in the upper respiratory tract and lungs is strongly suggestive of porcine pseudorabies. Ultrastructural observations have been made that included syncytia, cellular debris and macrophages, and lymphocytes with vacuoles in their cytoplasm. Virus may be detected by direct fluorescent antibody examination or by growth in tissue culture. The tissues of the head and neck regions of nonimmune pigs yield virus most consistently and in the highest concentration after challenge. The immunoperoxidase test can be used to study the distribution of the virus in different tissues. Latent virus can be detected using a DNA hybridization dot blot assay. Whenever possible, whole carcasses and fetuses should be submitted for laboratory examination. The location of the optimal neural samples, including the paravertebral ganglia, has been described for sheep. The placental lesions in pregnant sows that have aborted from natural infection with pseudorabies consist of necrotizing placentitis and the presence of intranuclear inclusions. In an experimental infection of loops of intestine it was shown that there was necrosis of the follicles in the Peyer's patches and degeneration of the epithelial cells in the crypts and villi and degeneration of the cells in the myenteric plexuses. Intranuclear inclusion bodies were found 2 to 4 days after inoculation. The primary target of the wild PRV was the macrophages of the subepithelial area of the dome of the Peyer's patch.

Samples for Confirmation of Diagnosis

- Histology: half of midsagittally sectioned brain, spinal cord with paravertebral ganglia, gasserian ganglion, placenta, liver, lung, spleen, tonsil, and retropharyngeal lymph node (LM) should be collected. IHC has been used to confirm cases in countries where the disease is rare and other corroborating evidence is lacking. In situ hybridization has also been used Can also collect muscle samples for meat juice ELISAs.
- Virology: brain, spinal cord, liver, spleen, tonsil, retropharyngeal lymph node (FAT, ISO). CSF is not good for virus isolation. The best source is the trigeminal ganglion in the domestic pig and the sacral ganglia in feral pigs. Viral isolation takes about 2 to 5 days. There are several PCRs available[5] and also nested PCRs and RT-PCRs.[16,17]

DIFFERENTIAL DIAGNOSIS

The different clinical forms of pseudorabies in pigs and ruminants resemble several diseases.

Teschen disease occurs in similar forms in certain areas; the diagnosis is dependent on serology and pathology.

Rabies is rare in pigs and is usually accompanied by pruritus at the site of the bite.

Streptococcal meningitis is restricted to sucking pigs of 2–6 weeks of age, the lesions are usually obvious at necropsy, and the causative organism is readily cultured from the meninges. The response to treatment with penicillin is good and is of value as a diagnostic test.

Encephalopathy associated with hog cholera, African swine fever, salmonellosis, Glasser's disease, *Escherichia coli* septicemia and erysipelas are considerations, and are usually obvious at necropsy.

Bowel edema causes typical edema of the head and eyelids in weaner pigs as well as a rapid death.

Salt poisoning causes typical intermittent nervous signs, with a typical history of water deprivation.

Respiratory form of pseudorabies should be considered in any outbreak of respiratory disease that is poorly responsive to usually effective therapeutic measures.

Reproductive inefficiency associated with enterovirus (SMEDI) and parvovirus infections closely resembles that associated with pseudorabies and requires laboratory differentiation by virus isolation and serologic testing.

In cattle the local pruritus is distinctive, but the disease may be confused with the nervous form of acetonemia in which paresthesia may lead to excitement. The rapid recovery that ordinarily occurs in this form of acetonemia is an important diagnostic point. The furious form of rabies and acute lead poisoning cause signs of mania, but pruritus does not occur.

SMEDI, *stillbirth, mummification, embryonic death, and infertility.*

TREATMENT

There is no treatment.

CONTROL

The control of pseudorabies is difficult and currently unreliable because normal healthy pigs may be infected and shed the virus for up to several months. One of the most important future concerns is the infection in wild boar[18] and their illegal transportation across countries.[19]

An important principle in control and eradication of the disease is the reproduction ratio, R_0, which is defined as the average number of new infections caused by one typical infectious animal. When $R_0 > 1$, the infection can spread; when $R_0 < 1$, the infection will disappear. In eradication programs it is essential that R be less than 1 and the infection will die out in the herd.

Strategies Available

The methods of control or eradication include depopulation and repopulation, test and removal, segregation of progeny, and vaccination. The selection of a strategy for the control or elimination of the disease depends on the following: (1) source of the herd infection; (2) method of transmission of the virus; (3) survival of the virus in the environment; (4) sensitivity and specificity of the diagnostic test; (5) risk factors in the herd, which include type of operation, degree of herd isolation, prevalence of infection, value of the genetic material, level of management expertise, and availability of suitable virus-free replacement swine if depopulation and repopulation is chosen as a strategy.

The eradication of the disease from small herds was described in Hungary. In this country the shared use of boars, the pig density, and the infection in the surrounding area were the most significant influences on the spread and control of the disease.

Breeding stock producers favor eradication, farrow–finish producers that do not sell breeding stock or feeder pigs are generally more concerned with the reduction of losses from clinical PRV infection than with eradication. In the United States offsite all in/all out finishing was more frequent among the successful farms than the unsuccessful ones. The unsuccessful farms also had other infected herds within 3.2 km (2 miles) and often no cleaning or disinfection.

Economics of Control and Eradication

Depopulation–repopulation is the most expensive form of eradication, the segregation of progeny method the is next expensive, and the test and removal method is the most inexpensive per sow. A computerized decision-tree analysis and simulation modeling can evaluate the economics of control and eradication strategies. The optimal alternative is to test and remove seropositive animals if the initial prevalence is ~57%; otherwise vaccination of sows only is preferred. Vaccination may be recommended at lower prevalence rates as a conservative approach. Eradication by test and removal combined with the use of gene-deleted vaccines is advantageous at any prevalence rate of infection. Depopulation and repopulation is not the best option under any circumstances. Once formulated, a decision-tree analysis can be adapted to the prevailing economic or epidemiologic conditions.

Determination of Prevalence of Infection

In large herds, the virus must be eliminated from the growing–finishing pigs and the breeding herd. Large herds that are virus positive are infected in both groups; smaller herds are frequently infected in only the breeding herd. An initial step in eradication is to determine the prevalence of infection. Representative samples of finishing pigs older than 4 months, and of breeding sows, gilts, and boars are tested. On the basis of the test results and the risk factors in the herd, a

cost-effective plan can be devised for the individual herd.

Depopulation and Repopulation

When the prevalence of infection in the herd is over 50%, eradication can be achieved by depopulation and repopulation with virus-free breeding stock. However, depopulation is the most expensive method and is not compatible with the retention of valuable pedigree stock. The entire herd is depopulated over a period of months as the animals reach market weight. After removal of the animals the entire premises are cleaned and disinfected. Repopulation should be delayed at least 30 days after the final disinfection, and swine should originate from a pseudorabies-free qualified herd and be isolated on the premises and retested 30 days after introduction. All herd additions should be isolated and tested 30 days after introduction.

Test and Removal

The test and removal program is recommended when the prevalence of infection in the herd is below 50%. This method requires testing of the entire breeding herd and immediate removal of all seropositive animals; 30 days after removal of seropositive animals, the herd is retested, and if necessary at 30-day intervals, until the entire herd tests are negative. Following a second negative test, the testing regimen may be changed to test only 25% of the herd every 4 months. Seropositive animals are identified and culled. The test and removal method is superior to the vaccination system as a method of control. Valuable genetic material from breeding stock that is seropositive may be salvaged using embryo transfer techniques. Embryos may be transferred safely to susceptible recipient gilts from sows that have recovered from infection, but not from sows that are in the active stages of infection. The virus does not penetrate the outer covering of the embryo, but it can become attached to it so that it may physically transfer to the uterus of the recipient. This transfer of infection may occur if the donor sow is in the active phase of infection.

Offspring Segregation

The objective of this strategy is to raise a PRV-negative breeding herd to replace the infected herd. Once the herd is diagnosed as PRV infected, a regular schedule of vaccination is instituted. Gilts are vaccinated at first breeding, and both sows and gilts are vaccinated 2 to 4 weeks before farrowing to provide a high level of colostral immunity to their piglets. Offspring are removed at weaning and raised apart from the infected herd. At 4 months of age, and then again before breeding, the segregated replacements are tested for antibody. Because colostral immunity is no longer detectable by 4 months of age, any animals over 4 months of age that are seropositive are considered pseudorabies infected. As the gilts reach reproductive maturity, the old sow herd is replaced. Segregation between the infected sow herd and the clean gilt herd is maintained until all positive sows have been removed and the facilities disinfected. Groups of seronegative pigs are identified and combined into larger groups to establish a new herd. The original herd is gradually depopulated and the premises cleaned and disinfected. The new herd is then monitored on a regular basis.

Control Programs in Effect

PRV was first diagnosed in the North Island of New Zealand in 1976, an eradication program was started in 1989, and the virus was cleared from the North Island in 1997.

A pseudorabies control program was introduced in England in 1983 when the infection was spreading rapidly. New legislation imposed restrictions on the movement of pigs where clinical signs of the disease were present in the herd. The first part of the eradication scheme involved testing all of those herds previously known to have PRV. Within several months after the beginning of the eradication campaign, 417 herds had been slaughtered, involving 342,275 pigs, of which 72.5% were salvaged. Only 121 herds had been known to be previously infected, while the remaining 296 herds had been identified through trace backs and reports of new cases. By 1985 it was concluded that the disease was well controlled in England with only 10 to 14 infected herds remaining. Farmers were compensated for all animals slaughtered and also for consequential loss associated with the loss of stock. The cost of the eradication program was financed by a levy on all pigs normally marketed for slaughter in England. In 1995 England was free of Aujeszky's disease. Following the successful use of the gene-deletion vaccination and an eradication program the Netherlands and Germany are free of the disease. In Sweden the herds were declared free from 12 to 53 months after the start of the program. Now, in Northern Ireland, PRV is more widespread than it ever was in Britain before the eradication program. Because the infection rate is over 50%, an eradication program based on slaughter of infected herds would destroy the swine industry. Thus the control program in Northern Ireland is based on the use of vaccination, the culling of seropositive animals, and the gradual introduction of seronegative animals.

In the United States the national pseudorabies eradication program was implemented in 1989 as a joint State-Federal-Industry–sponsored program. Pilot projects were conducted in Iowa, Illinois, Pennsylvania, Wisconsin, and North Carolina from 1984 to 1987. In the pilot projects, 97.5% of 116 herds that were initially PRV positive were successfully cleared of infection. This indicated that eradication of PRV virus from herds of swine can be efficiently achieved and is most effective applied on an area basis. The introduction of the gene-deleted PRV vaccines in the program was the technical breakthrough needed to be able to offer the national eradication program, since it was now possible to distinguish between naturally infected and vaccinated animals. The program consisted of the following: stage I, preparation; stage II, control; stage III, mandatory herd clean-up; stage IV, surveillance; and stage V, free. As of 2004, commercial swine operations in all 50 states of the US were considered free of PRV; however, endemic infection exists in feral pigs in a number of states. Endemic PRV infection remains a concern for commercial herds.

When an outbreak of the disease occurs in a susceptible herd the mortality may be very high, and the first consideration is to prevent spread to uninfected sows and litters and pregnant sows from infected pigs. They should be attended by separate personnel, or adequate barriers to mechanical transmission of infection should be arranged. On affected premises, cattle should be separated from pigs, and dogs and cats should be kept from the area. The affected herd should be quarantined, and all pigs sold off the farm should be for slaughter only.

Vaccines and Vaccination

Vaccination is used to reduce clinical disease when outbreaks occur or when the disease is endemic in the herd. An effective immunity develops after natural infection or vaccination, and piglets from immune sows are protected from clinical disease during the nursing period by colostral immunity. However, the presence of circulating antibody does not prevent infection, the development of latency, and subsequent activation and excretion of the virus. However, vaccination reduces viral shedding after natural infection. On farms in which the disease is endemic or outbreaks have occurred, vaccination of the sows, and management procedures to reduce the spread of infection, have markedly reduced preweaning mortality and reproductive failures. Field studies in large numbers of herds in which the sows were vaccinated three times annually show that the reproduction ratio was below 0.66, which is significantly below,[1] and massive spread of the virus does not occur.

It is often virtually impossible to prevent the spread of infection in a susceptible herd and vaccination of all pigs at risk, especially pregnant sows, is recommended. The vaccine reduces losses in infected herds, limits the spread of infection, and decreases the incidence in endemic areas. With a properly controlled and monitored vaccination and culling program in a breeding herd, it is possible to control clinical disease and reduce the infection pressure. All breeding stock present during an outbreak are subsequently vaccinated regularly until they are all culled,

which removes the major sources of virulent virus. Following this phase, newly introduced gilts and boars are tested, and monitored regularly. This is considered to be less costly than the test and slaughter policy.

However, in vaccinated herds, the virus continues to circulate and an accurate epidemiologic analysis is not possible because titers caused by vaccination cannot be distinguished from those caused by natural infections.

Control of the diseases in many countries has always been based on compulsory intensive vaccination of the entire population.

Vaccines

Conventional modified live virus and inactivated virus vaccines have been available. Both vaccines will reduce the incidence rate and severity of clinical disease in an infected herd. They also reduce the field virus shedding and latency in the trigeminal ganglion after exposure to field virus. The vaccine efficiency is, however, markedly influenced by the modified live virus vaccine strain and the route of administration. The vaccine genotype plays a very important role in the effectiveness of the vaccine program. Recently needle-free transdermal vaccination using a modified live PRV vaccine has been described, preventing the loss of any needles in the carcass. Cell-mediated immunity in the form of cytotoxic T cells may play an important part in the effectiveness of the vaccine. The deficiencies of inactivated vaccines in producing virus-specific interferon-γ (IFN-γ) can be enhanced by the use of simultaneous administration of interleukin-12, which appears to upregulate Th1/Th2 expression.

Pregnant Sows

Vaccination of pregnant sows induces SN antibodies, which are transferred to the newborn piglets and provide protection against infection. Vaccination during pregnancy produces more protection against PRV for piglets than sow vaccination before mating. A better protection was observed in sows vaccinated with an attenuated virus than in sows vaccinated with inactivated virus. Piglets rely on colostral and milk antibodies for protection, and the vaccination of piglets born from vaccinated sows does not produce a significant serologic response until the piglets are about 12 weeks of age. Maternally derived antibodies may disturb or even block the development of active humoral responses.[20] Earlier vaccination of piglets from infected or vaccinated sows is ineffective because high levels of maternal antibodies interfere with a serologic response stimulated by the vaccine. Maternal immunity interferes with the development of active immunity from vaccination until at least 15 weeks of age, even when the colostral titers are low. Thus in a situation in which the majority of sows have been infected or vaccinated, vaccination of weaned pigs may not yield desirable results. Both inactivated virus and attenuated live virus vaccines provide similar results when piglets born from vaccinated sows are vaccinated before colostral immunity has waned.

Growing and Finishing Pigs

The optimal vaccination strategy for growing and finishing pigs in an eradication program is controversial. In eight persistently infected herds' vaccinations, both intranasally and intramuscularly, were made at 4 and 10 weeks of age. Only one vaccination is given to finishing pigs in endemic areas in Europe. However, this does not reduce the prevalence of infection in finishing pigs in herds with a high prevalence. Double vaccination of finishing pigs will reduce the spread of the virus, but extensive spread can still occur. The presence of maternal antibodies may interfere with the induction of antibodies, and double vaccination 4 weeks later may boost immunity. Mean daily weight gain was also improved by a second vaccination with a direct economic benefit.

Marker or Subunit Vaccines

A major development in vaccination against pseudorabies has been the introduction of genetically engineered live vaccine strains used to make marker or subunit vaccines. Vaccination with modified live gene-deleted vaccines is now an integral part of pseudorabies eradication programs worldwide. The most common gene deletions are for glycoproteins E (gE) or gI and G (gG) or gX, and gIII. A gD/gE-negative vaccine was described. In Europe, use of gE vaccines has become the standard. These vaccines, in conjunction with a companion diagnostic test, can distinguish between naturally infected and vaccinated animals. Colostrum can also be used to monitor antibodies against gI protein of the virus.

A study comparing intranasal and intramuscular vaccination showed that pigs given both vaccines (intranasally and intramuscularly) had a significantly better clinical and virologic protection after challenge than the single intranasal vaccination. The recombinant vaccines are able to circumvent the inhibition of active immunity that occurs when maternally derived antibody is still present. Animals vaccinated with a deleted vaccine are not able to mount an immune response against the protein whose gene has been deleted in the vaccine virus genome. In contrast, wild-type virus-infected animals produce antibodies against all the viral glycoproteins. Differentiating ELISAs, specific for the deleted marker protein, then allow discrimination between infected animals, which can be culled from the herd, and vaccinated animals. These vaccines reduce the severity of clinical disease and viral shedding. However, the presence of colostral antibodies in growing pigs may interfere with an immune response, which may result in increased virus excretion on challenge exposure. Repeated vaccination is needed to provide some protective immunity against challenge exposure to virulent virus.

These mutants have also been rendered thymidine kinase-deficient (TK–) mutants, and are avirulent and immunogenic. Pigs inoculated with these mutants are resistant to experimental challenge with the virulent virus, and the virulent virus cannot be recovered from the ganglia, which suggests that vaccination reduced colonization of the ganglia. The ideal vaccine strain should prevent clinical disease and mortality, should not be transmitted to nonimmunized animals, and should prevent colonization of the ganglia by a potential superinfecting virulent virus reducing the natural reservoir of the virus. The TK– mutant virus possesses these desirable characteristics. The high efficacy of recently constructed gI-negative deletion mutant vaccines of PRV virus provide a sound basis for implementing the "gI" approach to the future control of the disease.

Piglets born from sows vaccinated with deleted (gIII, TK) strains at 3 days and 9 and 11 weeks of age developed detectable antibodies that lasted up to 100 days of age when vaccinated. Maternal antibodies in piglets from sows vaccinated with gIII-deleted vaccine decay to undetectable levels at 7 weeks of age. The vaccination of piglets at 3 days of age with the same vaccine results in a priming effect, which protects the piglets against virulent virus challenge at 7 weeks of age. Thus effective protection could be provided by active immunization from birth through weaning, in the nursery, and into the growing and finishing stages of production. Piglet vaccination at 10 and 14 weeks was considered to be the optimal time for vaccination.[21]

Although genetically engineered live virus vaccines have been shown to be efficacious and safe, there is a possibility of spread between vaccinated and unvaccinated animals, of persistence in the field and of recombination between different vaccine strains, which can lead to enhanced virulence. New viral mutants lacking glycoproteins gD, gE, gG, and gI may form the basis for the development of new vaccines that do not recombine. A gB deletion vaccine has been described for intranasal use and has been shown to produce both local and serum antibodies. Recently a DNA vaccine was shown to give as good a response as gD plasmid vaccine, but the DNA vaccine had to be given intradermally. It can overcome maternally derived antibody, and the vaccine described in this case still gave protection against infectious PRV challenge at the end of the finishing period.

Even more radical is a vaccine with a granulocyte-macrophage colony stimulating factor.

Experimentally, immunized pigs can be latently infected with the wild-type virus without being detected by the gE-specific ELISA routinely used to discriminate between infected and vaccinated pigs. Thus gE seronegative pigs may still be infected and be a source of infection.

Remarkable progress has been made with the use of gI-deleted vaccines. Intensive regional vaccination of finishing pigs with a gI-deleted vaccine, along with companion diagnostic tests, reduced the seroprevalence in infected finishing herds from 81% to 19% in 2 years. Vaccination increases the virus dose needed for establishment of infection and decreases the level and duration of virus excretion after infection. In the control group, with routine disease control, no significant change in seroprevalence occurred. The consistent application of intensive vaccination of all breeding herds in a region, including those herds participating in a production chain, can also decrease the prevalence of infection in heavily infected areas. The intensive regional vaccination did not completely eliminate virus infections within these herds; the source of infection was not determined. It is suggested that the virus either circulated at a low level within herds, or its introduction or reactivation did not lead to an extensive spread of the virus. A voluntary vaccination program on individual farms was unsuccessful in reducing the prevalence of virus-infected breeding pigs. The importation of breeding stock from outside the area is associated with a higher prevalence of virus-infected pigs because of lack of vaccination. The introduction of infections can be reduced by purchasing virus-free animals and by increasing farm biosecurity procedures.

Vaccination of breeding herds three times annually to ensure a high level of immunization can lead to elimination of the disease when the reproduction ratio is less than one.

The method used for vaccination may influence the effect of the vaccine. Using glycoprotein vaccines, intramuscular vaccination in the neck, and six-point intradermal vaccination in the back provided the best protection; six-point intradermal injections resulted in a better vaccination than two-point injections. BW changes and viral excretion after challenge were compared with VN titers, antigen-specific IgG and IgA responses in serum, and virus-specific lymphoproliferative responses in peripheral blood during the immunization period.

An intensive eradication program in farrow–finish herds using a gI-deleted vaccine in breeding and growing–finishing pigs, and decreases of movement and mixing of growing–finishing pigs was successful in 3 years. The initial goal was to decrease viral spread in the growing–finishing pigs, which enabled production of seronegative replacement gilts. Increases in the number of sows culled, combined with an increase in the number of seronegative replacement gilts, resulted in a decrease in seroprevalence of sows. Bimonthly serologic monitoring indicated minimal spread of the virus in the growing–finishing pigs after 1 year. Eighteen months after the initiation of the program, the test and removal of seropositive sows commenced in all herds. All herds were released from quarantine within 3 years, indicating that eradication can be achieved by vaccination and management changes designed to minimize the spread of virus combined with test-and-removal procedures.

An attenuated gI-deleted–TK-deleted vaccine was used to eradicate the virus from a large farrow–finish herd in Sweden. At the start of the program, 86% of the breeding animals were seropositive. The breeding stock was vaccinated every 4 months and monitored serologically. Seropositive sows and boars were culled at an economic rate. The herd was declared gI negative 39 months after the start of the program. Monitoring the herd for another 4 years, until all vaccinated animals had been culled, revealed the herd free of the virus.

In New Zealand, progress toward eradication using a subunit vaccine is reported. Those farms that combined vaccination with good management techniques, intensive testing, and culling eradicated the wild virus infection within 2 years; those that made little or no progress has less than satisfactory standards of hygiene and did not practice an intensive testing and culling program.

Vaccination of both breeding stock and growing pigs is recommended. A combined vaccination–eradication program for the disease would generally comprise four phases:

1. A systematic and intensive vaccination campaign
2. Screening of pigs for gI antibodies
3. Economic culling of infected breeding pigs
4. Final ending of vaccination.

Piglets at 3 days of age can be vaccinated with one of these genetically engineered vaccines and be protected from experimental challenge at 5 weeks of age.

A recent study has shown that infection with PRRS virus does not inhibit the development of a vaccine-induced protection against PRV.

Vaccination of wild boar with an attenuated live vaccine has been shown to protect against infection.[22]

Vaccination of cattle with an inactivated vaccine is recommended where they are in close contact with swine and where a low level of exposure is likely.

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SPORADIC BOVINE ENCEPHALOMYELITIS (BUSS DISEASE AND TRANSMISSIBLE SEROSITIS)

Sporadic bovine encephalomyelitis (SBE) is associated with a chlamydia, and characterized by inflammation of vascular endothelium and mesenchymal tissue. There is secondary involvement of the nervous system, with nervous signs, in some cases.

ETIOLOGY

The disease is associated with specific strains of *Chlamydophila* (*Chlamydia*) *pecorum*.[1,2] It resists freezing but is highly susceptible to sodium hydroxide, cresol, and quaternary ammonium compounds in standard concentrations. The chlamydia can be passaged in guinea pigs and hamsters and adapted to grow in the yolk sac of developing chick embryos.

EPIDEMIOLOGY

Occurrence

The disease has been reported only from the United States, Europe, Japan, Israel, and Australia,[1] but a provisional diagnosis has been made in Canada and South Africa. In the United States it was most common in the midwestern and western States, but there have been no reports of its occurrence for the last 30 years.

Sporadic cases or outbreaks occur in individual herds. Although the disease has not reached serious economic proportions in the endemic infection, there is some serologic evidence that widespread subclinical infections occur.

Only cattle and buffalo are affected, and calves less than 6 months of age are most susceptible. Other domestic and experimental species appear to be resistant. There is no seasonal incidence and cases appear at any time of the year. A strong and apparently persistent immunity develops after an attack of the disease.

Prevalence of Infection

Morbidity and Case–Fatality Rates

The occurrence is sporadic, but outbreaks have occurred resulting in severe loss from both deaths of animals and loss of condition. Morbidity rates average 12.5% (5–50%) and are highest in calves (25%) and lowest in animals over a year old (5%). Mortality rates average about 31% and are higher in adults than in calves. In affected herds a stage of herd immunity is reached when only introduced animals and newborn calves are susceptible.

Method of Transmission

The method of spread is not known but is suspected to be fecal–oral.[1] Spread from farm to farm does not occur readily. On some farms only sporadic cases may occur, but on others one or two cases occur every year. In still other herds the disease occurs in outbreak form, with a number of animals becoming affected within a period of about 4 weeks. The epidemiology of SBE resembles in many ways that of malignant catarrhal fever in cattle. The organism can be isolated from many organs, including liver, spleen, and CNS, and from the blood, feces, urine, nasal discharges, and milk in the early stages of the disease. There is some evidence that the organism is eliminated in the feces for several weeks after infection.

PATHOGENESIS

The causative agent is not specifically neurotropic and attacks principally the mesenchymal tissues and the endothelial lining of the vascular system, with particular involvement of the serous membranes. Encephalomyelitis occurs secondarily to the vascular damage. Neurologic signs may be caused by infection with specific strains; *C. pecorum* genotype ST 23 has been associated with SBE cases from Australia, England, and the United States,[1] whereas other strains have been isolated from cattle with pneumonia and polyarthritis[2] and calves with poor weight gain.[3]

CLINICAL FINDINGS

Affected calves are depressed and inactive, but the appetite may be unaffected for several days. Nasal discharge and salivation with drooling are frequently observed. A **fever is common** (40.5°C-41.5°C, 105°F-107°F), and remains high for the course of the disease. Dyspnea, coughing, a mild catarrhal nasal discharge, and diarrhea may occur. During the ensuing 2 weeks, difficulty in walking and lack of desire to stand may appear. Stiffness with knuckling at the fetlocks is evident at first, followed by staggering, circling, and falling. Opisthotonus may occur but there is no excitement or head-pressing. The course of the disease varies between 3 days and 3 weeks. Animals that recover show marked loss of condition and are slow to regain the lost weight.

CLINICAL PATHOLOGY

Hematology

In experimental cases, leukopenia occurs in the acute clinical stage. There is a relative lymphocytosis and depression of polymorphonuclear cells.

Detection of Agent

The causative agent can be isolated from the blood in the early clinical phase, and can be used for transmission experiments in calves and guinea pigs, and for culture in eggs. Elementary bodies are present in the guinea pig tissues and yolk-sac preparations.

Serology

Serologic methods, including a complement fixation test for the detection of circulating antibody, are available although there is difficulty in differentiating antibodies to the chlamydia from those to the typical psittacosis virus.

NECROPSY FINDINGS

A fibrinous peritonitis, pleurisy, and pericarditis, accompanied by congestion and petechiation, are characteristic. In the early stages, thin serous fluid is present in the cavities, but in the later stages this has progressed to a thin fibrinous net covering the affected organs, or even to flattened plaques or irregularly shaped masses of fibrin lying free in the cavity. Histologically, there is fibrinous serositis involving the serosa of the peritoneal, pleural, and pericardial cavities. A diffuse encephalomyelitis involving particularly the medulla and cerebellum, and a meningitis in the same area, are also present. Minute elementary bodies are present in infected tissues and in very small numbers in exudate. The necropsy findings are diagnostic for SBE, and confirmation can be obtained by the complement fixation test or SN tests.

DIFFERENTIAL DIAGNOSIS

Clinically, the disease resembles other encephalitides of cattle. The epidemiology and pathogenesis resembles malignant catarrhal fever in cattle, but the mortality rate is much lower, there are no ocular or mucosal lesions, and the serositis of SBE does not occur in bovine malignant catarrh. A viral encephalomyelitis of calves (Kunjin virus) has been identified, but has not been associated with clinical signs of disease of the nervous system. An encephalomyocarditis virus, a primary infection of rodents that also occurs in primates and causes myocarditis in pigs, has been transmitted experimentally to calves but without causing significant signs of disease.

Listeriosis is usually sporadic and is accompanied by more localizing signs, especially facial paralysis and circling.

Rabies may present a very similar clinical picture, but the initial febrile reaction and the characteristic necropsy findings as well as the epizootiologic history of SBE should enable a diagnosis to be made.

Lead poisoning can be differentiated by the absence of fever, the more severe signs of motor irritation, and the shorter course of the disease. Because of the respiratory tract involvement, SBE may be easily confused with pneumonic pasteurellosis, especially if outbreaks occur, but in the latter disease nervous signs are unusual and the response to treatment is good.

SBE, *sporadic bovine encephalomyelitis.*

TREATMENT

Broad-spectrum antimicrobials control the agent in vitro. However, clinical results with chlortetracycline and oxytetracycline have been irregular, but may be effective if used in the early stages of the disease.

CONTROL

Control measures are difficult to prescribe because of lack of knowledge of the method of transmission. It is advisable to isolate affected animals. No vaccine is available.

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BORDER DISEASE (HAIRY SHAKER DISEASE OF LAMBS, HAIRY SHAKERS, HYPOMYELINOGENESIS CONGENITA)

SYNOPSIS

Etiology Pestivirus strains in the border disease and bovine virus diarrhea genotypes.

Epidemiology Congenital disease transmitted by persistently infected sheep, rarely cattle.

Clinical findings Abortions, stillbirths, barren ewes, and the birth of small weak lambs, some of which have an abnormally hairy birth coat, gross tremor of skeletal muscles, inferior growth, and a variable degree of skeletal deformity.

Clinical pathology None specific.

Lesions Hypomyelination in brain and spinal cord of lamb.

Diagnostic confirmation Detection of virus and/or demonstration of serologic response.

Treatment Supportive.

Control Avoid infection of pregnant sheep. Identify and cull persistently infected animals.

ETIOLOGY

The causal agent, border disease virus (BDV), is a pestivirus within the family Flaviviridae. Four members of the pestivirus genus have been identified; bovine virus diarrhea virus

(BVDV) types 1 and 2, classical swine fever virus, and BDV. Isolates from border disease predominantly fall within the BDV genotype, but sheep and goat isolates also fall in the BVDV genotypes. Pestiviruses consist of a single strand of RNA and were originally named after the host from which they were isolated. However, their interspecies transmissibility means an increasing reliance on phylogenetic studies based on sequences generated from relatively well conserved regions of the viral genome, such as the 5′ untranscribed region. On this basis BDV can be phylogenetically segregated into at least seven clusters, subtypes BDV-1 to BDV-7.[1]

Strains of BDV have differing pathogenicity, and variations in pathogenicity also result from interactions between the virus and different host genotypes, specifically between different breeds of sheep. Persistent infections in sheep are associated with noncytopathic strains of virus. An isolate of BDV, now designated as BDV-5, caused a leukopenic enterocolitis in sheep and growing lambs in the Aveyron region of France (Aveyron disease).[2] The disease caused high mortality in sheep in this region in 1984 but has not occurred since then.

EPIDEMIOLOGY

Occurrence

Border disease was originally described in the border country between England and Wales. It has subsequently been reported from most of the major sheep-producing countries and probably occurs in all of them. The disease occurs primarily in sheep, and less often in goats and free-living ruminants, such as chamois.[3] The prevalence of infection is much higher than the incidence of clinical disease because the latter only occurs when there is infection during pregnancy. BDV-1 has been detected in sheep from Australia, New Zealand, UK, and United States; BDV-2 from ruminants in Germany; BDV-3 in Switzerland and Austria; BDV-4 in Spain; BDV-5 and BDV-6 in France; and BDV-7 in Turkey.[1]

Studies on seroprevalence suggest that pestivirus infections in sheep and goats are less common than in cattle, but there are considerable differences in seroprevalence between different geographic areas and flocks. Flock seroprevalence in different regions or countries generally falls within the range of 5% to 50%. The prevalence of seropositive females within positive flocks is influenced by age, with a lower seroprevalence in sheep 4 to 8 months of age than in older sheep. Seroprevalence is higher in flocks with persistently infected sheep, but there can still be a significant proportion of seronegative sheep present in a flock containing persistently infected sheep.

Source of Infection

Infection can be introduced into a flock with the purchase of persistently infected replacement sheep. Persistently infected sheep excrete virus in nasal secretions, saliva, urine, and feces, and provide the major source of infection. A proportion of persistently infected sheep may survive to adulthood and may breed successfully to produce further persistently infected sheep. However, the breeding efficiency of persistently infected sheep is poor, and the probability of establishing lines of persistently infected sheep appears less than with the equivalent infection in cattle.

Virus is also present in the placenta and fetal fluids at the birth of persistently infected lambs and in the products of abortion resulting from infection with the virus in early pregnancy. In flocks where there is a long lambing period it is possible that this could provide a source for clinical disease in late-lambing ewes. Field observations suggest that transmission during the lambing period is limited.

Calves persistently infected with BVDV can infect sheep, and in countries where pregnant sheep and cattle are housed in close proximity during the winter this can be an important source of infection for outbreaks of border disease. In some countries this appears to be the major source, and studies in both Northern Ireland and the Republic of Ireland suggest that cattle are the primary source of infection for sheep in those countries. There is also evidence that bovine strains are important in goat infections. In contrast BDV is the predominant ovine pestivirus in Great Britain and New Zealand.

Free-living deer are also a potential source of infection. Outbreaks of disease have also occurred after vaccinating pregnant goats with an Orf vaccine contaminated with a pestivirus.

Transmission

Natural transmission is by sheep-to-sheep contact, but successful experimental transmission has followed both oral and conjunctival challenge.

The spread of infection within a susceptible flock is facilitated by factors such as close contact at mating time or mustering and aggregating sheep for any purpose. There is an increased risk for explosive outbreaks of border disease where animals are housed in early pregnancy.

Host Risk Factors

Border disease may occur as an outbreak or as a sporadic disease. When infection is introduced into a susceptible flock in early pregnancy, an outbreak with infertility, abortion, and congenital disease in lambs from all ages of ewes is likely. Subsequently, older sheep in the flock will have acquired immunity and disease occurs only in introduced sheep and maiden ewes. Persistently infected ewes have reduced fertility but will give birth to congenitally affected lambs throughout their breeding life. The disproportional occurrence of outbreaks of clinical disease in certain breeds suggests that they may have higher rates of persistently infected individuals.

Experimental Reproduction

Border disease is readily reproduced by the experimental oral, conjunctival, and parenteral infection of pregnant ewes before 80 days' gestation. Experimental disease can be produced with both BDV and BVDV strains.

The following have been produced experimentally, although there are strain differences in clinical and pathologic manifestations:

- Placentitis
- Abortions
- Mummified fetuses
- Congenital malformations, including hydrocephalus, porencephaly, cerebellar hypoplasia and dysplasia, and arthrogryposis
- Fetal growth retardation
- Hypomyelinogenesis
- Birth of weak lambs with nervous disorders
- A hairy birth coat

Experimental infections of pregnant cows with BDV results in similar defects with placentitis, mummification, and abortion of fetuses; intrauterine growth retardation with abnormal osteogenesis; and hypomyelinogenesis.

The disease has also been produced experimentally in goat kids by inoculation of pregnant goats but there are no abnormalities of hair coat, and embryonic mortality and abortion are more common than in the experimental disease in ewes.

Economic Importance

The effect of infection varies with the immune status of the flock and whether infection occurs during pregnancy. In fully susceptible flocks, abortion and neonatal lamb loss resulting from infection can be 25% to 75% of the expected lamb crop depending on the strain of the virus. An assessment of the economic losses caused by infertility, abortion, neonatal losses, and low carcass weight indicate that an outbreak of border disease can result in a potential reduction of income in excess of 20%.

Where sheep and cattle are comingled, the presence of BDV in sheep could also jeopardize efforts to control and eradicate pestivirus (BVDV) from cattle herds. Persistently infected sheep readily transmit BDV to seronegative calves; thus the antigenic similarity between the two viruses will complicate attempts to demonstrate freedom from BVD in cattle by serology.[4]

PATHOGENESIS

Nonpregnant Sheep

In adolescent and adult nonpregnant sheep, infection and viremia are subclinical. The intramuscular inoculation of immunocompetent lambs with BDV results in a mild

transient disease and a subsequent reduction in growth rate, but no gross or microscopic lesions.

Pregnant Sheep

When BDV infects susceptible pregnant ewes the virus infects the placenta to produce an acute necrotizing placentitis and it subsequently invades the fetus. This may result in early embryonic death, abortion and stillbirth, the birth of lambs with malformations and/or neurologic abnormalities, the birth of small weak lambs that are immunosuppressed, or the birth of lambs with no clinical abnormality. The ultimate outcome of the infection depends on the age of the fetus, the properties of the strain of the virus, the dose of the virus, the genotype of the host, and the ability of the fetus to respond to the virus. Immune competence to the virus in the fetus develops between approximately 61 and 80 days' gestation; thus fetal age at the time of infection determines the outcome of infection.

Infection in Early Pregnancy

Fetal death occurs when there is infection of the fetus with virulent strains before the development of immune competence and uncontrolled viral replication. Prenatal death is more likely to follow infections in early pregnancy, but is recorded with infections from 45 to 72 days' gestation.

Persistent infections occur in lambs that survive infection in early pregnancy before the development of immune competence and result from maternal infections between 21 and 72 days' gestation but never later. The virus is present in all organs, and lambs born persistently infected will remain so for their lifetime, with few exceptions; persistent infections have been recorded to at least 5 years of age.

Most persistently infected sheep are unable to produce a specific antibody to BDV, but some show intermittent seropositivity with low antibody levels or occasionally undergo frank seroconversion. The humoral response to other pathogens and antigens is normal. However, cell-mediated immunity is compromised, with change in T-cell populations and a deficiency in lymphocyte function. Persistently infected lambs are more susceptible to intercurrent disease and commonly die before reaching maturity.

Hypomyelinogenesis occurs in persistently infected lambs and resolves spontaneously in lambs that survive to the age of 6 months. Most of these lambs exhibit neurologic dysfunction at birth, varying from a continuous light tremor to tonic-clonic contraction of the skeletal muscles involving the whole body and head (shakers).

A deficiency of the thyroid T_3 and T_4 hormones has been detected in lambs affected with border disease and may be the basic cause of the lack of myelination. The enzyme 2,3-cyclic nucleotide-3-phosphodiesterase is associated with normal myelination and depends on normal amounts of thyroid hormone. The deficiency in thyroid hormones may also result in the reduced rate of weight gain that occurs in infected lambs. Other studies suggest a direct infection of oligodendroglia with the virus as the cause of the defective myelination.

Fleece abnormality also occurs in persistently infected lambs and results from an enlargement of the primary hair follicles and a concurrent reduction in the number of secondary follicles. The resulting hairiness is caused by the presence of large medullated primary fibers. BDV appears to have no effect on the skin and birth coat of coarse-fleeced breeds of sheep or on goats.

Intrauterine growth retardation is a common feature of infection with BDV and is initiated shortly after infection. Deformities of the skeleton include abnormally shortened long bones and a reduction in crown–rump length and the long axis of the skull, which results in lambs appearing more compact and short-legged than normal (goat lambs). In the long bones there is evidence of growth arrest lines and disturbed osteogenesis and ossification.

Some persistently infected lambs do not have nervous signs or abnormalities of the fleece and are phenotypically normal. This limits the value of identification of infected lambs based on the presence of clinical abnormality at birth.

In Midpregnancy

When fetal infection occurs during the period of development of the ability to mount an immune response (between approximately 61 and 80 days' gestation), the effect is variable. Some fetuses infected at this stage respond with a severe inflammatory process in the CNS with nodular periarteritis, necrosis, and inflammation of the germinal layers of the brain. Resultant lesions are hydranencephaly, cerebellar dysplasia, and multifocal retinal atrophy; such lambs exhibit behavioral abnormalities and more severe neurologic disease than shaker lambs.

Infection in Late Pregnancy

Infection of the fetus after 80 days' gestation is likely to be controlled or eliminated by a fetal immune response. These lambs are born without clinical disease, and are virus negative, but have precolostral circulating antibody.

Goats

In goats, fetal death is the major outcome of infection of the pregnant doe with both BDV and BVDV, and infections before 60 days' gestation almost invariably result in reproductive failure. Persistently infected shaker kids and clinically normal kids are born with infections around 60 days' gestation but are a less common manifestation of the disease than occurs in sheep. The caprine fetus develops immune competence against pestiviruses between 80 and 100 days' gestation.

Enteric Disease

Experimental inoculation of a homologous strain of the BDV into persistently infected but clinically recovered lambs results in a severe clinical syndrome. This is characterized by persistent diarrhea and respiratory distress associated with an inflammatory lymphoproliferative response in the CNS, intestines, lungs, heart, and kidney. A similar syndrome is seen in some persistently infected sheep that survive early life and reach weaning. This syndrome resembles certain aspects of mucosal disease in cattle, in which it is postulated that superinfection of persistently viremic immunotolerant cattle with a homologous strain of BVDV results in fatal mucosal disease. In such animals a specific and dynamic equilibrium exists between an attenuated form of the virus and the immunotolerant host. Disturbance of this equilibrium either by injection of the homologous strain of BDV, or some other factor, results in fatal disease.

CLINICAL FINDINGS

The most obvious and characteristic features of border disease are evident at birth and relate to conformation and growth, fleece type, and neurologic dysfunction. An increased proportion of barren ewes will also be apparent in severe outbreaks.

Conformation

Affected lambs may have a lower birth weight than uninfected lambs, a decreased crown–rump length, and a shorter tibia/radius length so that they have a boxy appearance. The head has a shortened longitudinal axis and the cranium may be slightly domed (goat, lambs).

Fleece

The fleece, when dry, appears hairy and rough because of long hairs rising above the fleece to form a halo, especially over the nape, back, flanks, and rump. This feature is most evident in medium-wool and fine-wool breeds and is not observed in the coarse kempy-fleeced breeds, such as the Scottish Blackface. The halo kemp fibers are shed with time and are most evident in the first 3 weeks of life. Some lambs have abnormal pigmentation occurring as patches of pigmented fleece or hair, or a totally pigmented fleece. This can occur in white-faced sheep.

Neurologic Dysfunction

Neurologic dysfunction is manifest, with rhythmic tremors of the muscles of the pelvis and upper parts of the hindlimbs, or of the whole body, resulting in a characteristic jerking movement, and of the head and neck with rhythmic bobbing of the head (shaker lambs). In some less severe cases, only fine

tremors of the ears and tail are evident. Tremors are most apparent during movement, and are absent while the lamb is sleeping. The tremors usually decline in severity as the lamb matures and may seem to disappear unless the animal is stressed. More severely affected lambs have difficulty in rising, and if able to stand with assistance exhibit an erratic gait especially of the hindquarters. Paralysis does not occur. Affected lambs are often unable to nurse the ewe because they cannot hold onto the teat. They appear languid and lie around listlessly. They do not suck as they should and bloat continuously, and the ewes' udders become engorged with milk.

Behavioral and visual defects with circling, head-pressing, nystagmus, and gross incoordination are seen in lambs with the type of infection producing hydranencephaly and cerebellar dysplasia. These lambs are of lighter birth weight but have normal birth coats.

Growth Rate

Growth rate is reduced, affected lambs are unthrifty, and the majority will die before or at weaning time from parasitism, pneumonia, a mucosal disease-like syndrome, or nephritis. With good nursing care, they can be reared, but deaths may occur at any age. Puberty may be delayed and, in males, the testes are flabby and may not develop normally. A study of lambs in a Spanish feedlot found that BDV-positive lambs (by RT-PCR or ELISA) were 12% (3.3 kg) lighter after 41 days of lot feeding because of significantly lower average daily gain, 260 g per head per day compared with 320 g per head per day in BDV-negative lambs.[5] BDV-positive lambs also had double the chance of having diarrhea or respiratory signs.

Reproductive Performance

Impaired reproductive performance of the flock occurs from low fertility, abortion, and poor viability of lambs. Abortions usually are not noticed until lambing when it is evidenced by an unexpected increase in barren ewes. In goats, where there is often closer observation, the aborted fetuses may be reasonably well developed, small and underdeveloped, or autolyzed and unrecognizable as a fetus in expelled fetal fluid.

CLINICAL PATHOLOGY

There are no consistent changes in hematology or blood chemistry. Persistently infected lambs have changes in lymphocyte subpopulations, with a reduction in T lymphocytes and an altered CD8:CD4 ratio.

Virus can be detected in blood and tissues by virus isolation, antigen ELISAs, and RT-PCR techniques (both conventional and real time). These are specialist techniques, but an RT-PCR ELISA may be a cost-effective and sensitive alternative for nonspecialist laboratories.[6] Antibody can be detected by antibody ELISAs or SN tests, and a combination of serology and virus isolation is usually used in the diagnosis of border disease.

Detection of Persistently Infected Sheep

For diagnosis of border disease in newborn lambs, precolostral blood samples should be taken from both clinically normal and affected lambs. Persistently infected sheep are seronegative and BDV can be isolated from leukocytes in the blood buffy coat. Lambs infected late in gestation will be seropositive but virus negative. Persistently infected lambs that have received colostrum from their dam will be seropositive until they lose maternal passive immunity.

Persistently infected adolescent and adult sheep in a flock can be identified by the detection of virus in blood; however, this is expensive in large flocks and an alternative is to test all sheep for antibody and then culture the buffy coat of seronegative sheep. Antigenic differences between laboratory strains and field virus can result in false-negative serology, and serologic studies are best done with the homologous virus.

Abortion

Serologic tests are of limited value as an aid to the diagnosis of abortion associated with BDV infection. The infection of the ewe that results in abortion occurs several weeks before clinical disease is apparent, and unless prospective samples can be taken there is little chance of a rise in antibody titers in paired samples. Seropositivity in ewes indicates that the flock has been exposed to pestivirus but does not incriminate it in a disease process. Seronegativity indicates that BDV is not the cause of the abortion, with the exception that aborting ewes, who themselves are persistently infected, will have no antibody titer.

NECROPSY FINDINGS

Gross findings may be normal, or may include an abnormal wool coat and a reduction in the size of the brain and spinal cord. Arthrogryposis, hydranencephaly, porencephaly, and cerebellar dysplasia may also be present. Histologically, there is a deficiency of stainable central myelin, with neurochemical and histochemical evidence of demyelination or myelin dysmorphogenesis. In most sheep the myelin defect resolves substantially during the first few months of life. The brain, which has been very small, returns to normal weight, and chemical composition and degree of myelination. The histologic lesions of the skin consist of primary follicle enlargement, increased primary fiber size, and an increased number of medullated primary fibers.

Virus can be demonstrated by immunofluorescent staining of cryostat sections of tissues from affected lambs or by IHC staining of formalin-fixed material. Preferred tissues for such tests include brain, thyroid gland, and skin. Virus titers reach high levels in the placentomes, so caruncles or cotyledons should be cultured for virus. Isolates are noncytopathic and the presence of viral antigens must be demonstrated by direct or indirect immunofluorescence or immune peroxidase techniques.

Because of the closely related character of this pestivirus and BVDV, diagnostic tests to confirm infection parallel those for BVDV. Fetal serology can be useful for confirming exposure in abortions and stillbirths. PCR and ELISA techniques may be substituted for virus isolation if available.

In the brain of naturally infected cases, viral antigens and RNA are found in the neuropil, glial, and neuronal cells, especially in periventricular areas, cerebellum, and brainstem.[7] Cell death occurs in both BDV-infected and adjacent cells by the activation of pathways that cause apoptosis, which are associated with the increased expression of nitric oxide synthases.[8,9]

Samples for Confirmation of Diagnosis

- **Histology:** formalin-fixed skin, spinal cord, half of midsagittally sectioned brain, skin, thyroid, distal ileum, colon, cecum, thymus, spleen, liver, heart, kidney (LM, IHC)
- **Serology:** heart blood serum/thoracic fluid (virus neutralization)
- **Virology:** placenta/caruncle, thymus, lymph node, spleen, thyroid, brain, ileum (ISO, FAT, ELISA, PCR).

DIFFERENTIAL DIAGNOSIS

Congenital disease
- Swayback (copper deficiency)
- Caprine encephalomyelitis

Abortion
- Enzootic abortion
- Listeriosis
- Toxoplasmosis
- Leptospirosis
- Rift Valley fever
- Akabane disease

TREATMENT

There is no specific treatment for border disease. With care and nursing, many affected lambs will survive the immediate neonatal period, but they grow poorly, are very susceptible to intercurrent disease during the growing period, and it is generally not economic to attempt to raise these lambs.

CONTROL

The principles are to attempt to engender flock immunity and to avoid exposing sheep to infection in early pregnancy. Persistently infected sheep are a continuous source of infection and those that survive to breeding age can perpetuate the disease. They should be identified and culled.

The problem is with their identification, because some persistently infected lambs show no clinical or phenotypic abnormality. Lambs that are clinically affected at birth should be permanently identified because the tremor and fleece abnormality disappear at 1 to 2 months of age and the lambs may no longer be recognizable as infected. Persistently infected animals can be identified by serologic screening of the ewe lambs intended for replacement stock at 6 months of age (after maternal passive immunity has waned), followed by virus isolation in seronegative animals, but this is expensive and only practical in small flocks. An alternative is to keep no replacement ewes from an affected lamb crop.

Persistently infected sheep can be run with the flock when it is not pregnant, particularly with the replacement ewes, in an attempt to produce infection and immunity before pregnancy. They should be removed before breeding. Although this can result in "natural vaccination," the rates of infection and seroconversion in replacement females can be low. In theory, cattle BVDV vaccines could be used to produce immunity but their efficacy would depend on a significant relatedness to the BDV under consideration.

In most flocks a serious outbreak of the disease is followed by minor disease in subsequent years, with the flock developing immunity in the initial outbreak.

In flocks that are free of infection, replacement ewes and rams should be screened for infection before purchase or quarantined after arrival on the farm. Newly introduced sheep should be kept separate from the main flock until after lambing. Ideally, cattle should not be pastured or housed with pregnant sheep.

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VISNA

SYNOPSIS

Etiology Neurovirulent strains of maedi-visna virus, a lentivirus.

Epidemiology Occurs in association with maedi but endemic visna only recorded in Iceland.

Clinical findings Afebrile disease with insidious onset. Progressive ataxia and wasting, long clinical course.

Clinical pathology Pleocytosis and elevated protein, virus, virus proteins, and antivirus antibody in cerebrospinal fluid.

Lesions Chronic demyelinating encephalomyelitis.

Diagnostic confirmation Histology, demonstration of virus, PCR.

Treatment None.

Control As for ovine progressive pneumonia.

ETIOLOGY

Visna is the neurologic manifestation of maedi-visna disease caused by infection with Maedi-Visna Virus (MVV). This virus is a single-stranded RNA, nononcogenic lentivirus within the retrovirus family. There are neurovirulent and nonneurovirulent strains of MVV, and neurovirulence is enhanced by intracerebral passage of virus. There is a high degree of relatedness between MVV, the ovine lentivirus associated with ovine progressive pneumonia (OPP), and the Caprine Arthritis Encephalitis (CAE) virus. These ovine and caprine lentiviruses share nucleotide homology and serologic properties and are now regarded as a viral continuum and referred to as small ruminant lentiviruses (SRLV).[1]

Visna usually occurs in conjunction with maedi lesions in the lungs, with up to 18% of sheep affected by maedi having histologic lesions of visna in the brain.

EPIDEMIOLOGY

Occurrence

Visna is a disease of sheep and rarely of goats. It was originally a significant cause of death in the epizootic of maedi-visna that occurred in Iceland from 1933 to 1965. It always occurred in association with maedi, but was sporadic and generally less important than the pulmonary manifestation of the infection. The exception was in some flocks in which it was the major manifestation of the maedi-visna disease complex, but visna not been seen in Iceland since 1951 and maedi-visna has since been eradicated from that country.

Despite the widespread occurrence of maedi-visna or OPP in many countries, visna is now an uncommon disease, and a high prevalence of neurologic disease has seldom been recorded in countries other than Iceland. The reason for this is not known but might be from an increased susceptibility of the Icelandic breed of sheep to the neurologic form of the disease, or to differences in the neurovirulence of different strains of the virus. In Britain, MVV was first detected in the late 1970s, and the initial clinical expression was largely maedi (dyspnea), but occasionally with coexistent visna.

Experimental Transmission

Sheep experimentally infected by intracerebral inoculation spread MVV to commingled sheep. The incubation period and the course of the disease are both protracted, with clinical signs not appearing until 2 years after experimental inoculation.

PATHOGENESIS

The virus infects cells of the monocyte–macrophage lineage and replicates its RNA genome via a DNA intermediate provirus, which is integrated into the chromosomal DNA of the host cell. Replication is limited and does not proceed beyond the synthesis of provirus in most cells. Persistent production of viral antigen results in lymphocytic hyperplasia.

There are two basic lesions, an inflammatory lesion that is not related to the occurrence of nervous signs, and a focal demyelination in the brain and spinal cord, the occurrence of which is related to the appearance of paresis. Experimental immunosuppression reduces the severity of lesions by suppressing the cellular proliferative response without suppressing the growth of the virus, whereas postinfection immunization enhances the severity of experimental visna. Viral nucleic acid and proteins are present in oligodendrocytes, and demyelination is thought to be a direct effect of the virus on these cells as well as a sequel to the inflammatory response they provoke.

CLINICAL FINDINGS

The disease has an insidious onset, and the early clinical signs include lagging behind the flock because of ataxia and body wasting. The body wasting and the hindlimb ataxia are progressive. Affected animals show hypermetria and may stumble or fall as they traverse uneven ground or when making sudden turns. There is no fever, and a normal appetite and consciousness are retained. Additional signs include severe tremor of the facial muscles and knuckling of the distal limbs so that the animal stands on the flexed tarsi. Some animals may show a head tilt, aimless wandering, circling, and blindness.[2]

The clinical picture is not unlike that of scrapie without the pruritus. During the course of the disease, periods of relative normality may occur. Affected animals may show clinical signs for several months before final paralysis necessitates slaughter. The disease is always fatal, and the clinical syndrome in goats is the same as for sheep.

CLINICAL PATHOLOGY

There are an increased number of mononuclear cells in the CSF, an elevated protein, and positive Pandy test. The pleocytosis is variable during the course of the disease. Virus, virus antigen, and antibody are also demonstrable in CSF. Serologic tests are detailed under the section on ovine progressive pneumonia in chapter 12.

NECROPSY FINDINGS

Muscle wasting and an interstitial pneumonia may be visible but there are no gross changes in the CNS. The characteristic histologic lesion is patchy, demyelinating encephalomyelitis. The inflammatory infiltrate is predominantly composed of lymphocytes and macrophages. Demyelination occurs in the white matter of the cerebrum and cerebellum, and in the spinal cord. The histologic character of the lung is typical of ovine lentivirus-associated pneumonia. Isolation of the virus is difficult. Typical neural lesions and a positive serologic titer usually suffice for confirmation of the diagnosis. IHC tests and PCR-based assays have been successfully used to confirm this lentiviral infection in lung, mammary gland, and even third eyelid, but the use of these tests to confirm of the infection in CNS tissues is not well documented.

Samples for Confirmation of Diagnosis

- **Histology:** fixed spinal cord, half of midsagittally sectioned brain, lung, mammary gland, joint synovium (IHC, LM)
- **Serology:** serum (Agar gel immunodiffusion test, ELISA)
- **Virology:** chilled brain, spinal cord, lung, mammary gland (PCR, ISO).

DIFFERENTIAL DIAGNOSIS

Visna is a sporadic disease of mature sheep with an insidious onset of muscle wasting, progressive ataxia, and a long clinical course. These characteristics differentiate it from other diseases of sheep manifest with ataxia.

Differentials include

- Scrapie
- Delayed organophosphate toxicity
- Cerebrospinal nematodiasis
- Segmental axonopathy (Murrurrundi disease)

TREATMENT AND CONTROL

There is no treatment for visna. It usually occurs in conjunction with signs of maedi and is a comparatively rare disease by itself. Control procedures are as for those suggested for OPP/maedi. It is possible to greatly reduce the prevalence, and even eradicate the disease, by either (1) testing all sheep with an ELISA and removing seropositive sheep from the flock, or (2) by removal of lambs at birth and rearing them in isolation from other sheep. Testing all sheep at shorter intervals (3–6 months) with a combination of serology and PCR tests can reduce the prevalence more rapidly but is more costly.

Many jurisdictions have developed accreditation programs for flocks to establish that they have a low risk of infection with MVV. Once flocks are seronegative they are subjected to testing at various intervals, typically 1 to 3 years depending on an assessment of the biosecurity risk and the presence of untested sheep on the same farm holding.

There is currently no effective vaccine against MVV, and in some cases candidate vaccines have enhanced viremia and/or the immune-mediated pathology of the disease.[3] The difficulty in developing effective vaccines is common among the lentiviruses, with various approaches including attenuated vaccines, vector vaccines, and proviral DNA vaccines having little success.

Marker-assisted genetic selection, to identify those sheep less susceptible to infection with MVV, has the potential to supplement existing control measures. For example, in a trial involving 187 lambs, the probability of infection following natural exposure to OPP virus (a related virus that is part of the SRLV continuum) was 3.6 times greater in crossbred lambs with susceptible or heterozygous diplotype to ovine transmembrane protein gene 154 (TEM154 diplotype "1 3" or "3 3") compared with lambs with diplotype "1 1."[4] This is an active research area and it is expected that additional markers will be identified with future investigations.

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CAPRINE ARTHRITIS ENCEPHALITIS

SYNOPSIS

Etiology Retrovirus (a small ruminant lentivirus).

Epidemiology Persistent infection with perinatal and horizontal spread. Management of herd influences extent of seropositivity.

Clinical findings This disease of goats is characterized by arthritis, especially of the carpal joints (big knee), in mature goats, and acute leukoencephalomyelitis in young goats. Indurative mastitis, and less commonly chronic pneumonia and chronic encephalomyelitis, occur in older goats.

Clinical pathology Increased mononuclear cell count in cerebrospinal fluid. Lower or inverted CD4:CD8 ratio in peripheral blood.

Lesions Chronic polysynovitis, degenerative joint disease in adults. Nonsuppurative demyelinating encephalomyelitis. Interstitial pneumonia.

Diagnostic confirmation Microscopic lesions and agar gel immunodiffusion test.

Treatment None.

Control Segregation of the newborn from seropositive animals, and feeding of virus-free colostrum and milk. Prevention of horizontal transmission. Regular testing with segregation or culling.

ETIOLOGY

Caprine arthritis encephalitis (CAE), maedi-visna, and Ovine Progressive Pneumonia (OPP) viruses are single-stranded RNA, nononcogenic lentiviruses within the retrovirus family. They have a tropism for monocytes, macrophages, and dendritic cells, but not T lymphocytes. This is an important determinant of their pathogenesis because they induce a persistent infection that can cause lymphoproliferative changes in the lung, mammary tissues, brain, and joints. There is a high degree of relatedness between these lentiviruses, with shared nucleotide homology and serologic properties. Consequently, CAE, maedi-visna, and OPP viruses are now regarded as a viral continuum known as SRLV.[1]

There are genetically distinct isolates of CAE virus and they may differ in virulence. Because of the nature of the virus, recombination during replication, hence antigenic drift, is common and may facilitate persistence of the virus in the host and the development of disease. Based on analysis of *gag* and *pol* genomic regions, SRLVs have been placed into five clusters (A to E), with A and B further divided into at least 13 and 3 subtypes, respectively. Some of these are geographically restricted, such as cluster C in Norway, whereas others appear more dispersed, probably reflecting the active trading of animals. In Canada, molecular analysis of goat and sheep isolates of SRLV from herds or flocks with only sheep or goats reveals a relatively simple arrangement, with goats infected with B1 subtype and sheep with A2 subtype, respectively. However, on farms with both goats and sheep, there is evidence of crossover between sheep and goats, and vice versa, and mixed infections in both species.[2] Consequently, mixed flocks of goats and sheep may represent an active source for the evolution of these viruses, with a CAE-like virus responsible for severe outbreaks of arthritis in sheep in Spain and mixed infections confirmed in many European countries and North America.[2-4]

EPIDEMIOLOGY

Geographic Occurrence

There is serologic evidence of infection in most areas of the world, including Europe,

the UK, North America, Africa, Arabia, Australia, New Zealand, and South America. Although there is sampling bias, one study found marked differences in prevalence between countries, with a lower prevalence in developing countries that did not import dairy-type goats from North America or Europe. This may also reflect the absence of management factors that have a high risk of propagating infection in some countries, such as the pooling of colostrum. Other countries, such as New Zealand, have a low prevalence with the occurrence of CAE mainly in exotic importations.

There may also be variation in seroprevalence within countries. For example, in the United States, the prevalence of infection in goats in the western and middle parts of the country is approximately 50% of all goats tested, which is about twice that in the eastern and Rocky Mountain areas. Herd seroprevalence is greater than 60% in all regions. The seroprevalence within herds shows clustering, with most herds falling into either high or low seroprevalence groups. There are area differences in age prevalence of seropositivity, with some surveys showing no difference and others showing an increasing prevalence with increasing age.

Clinical disease is much less common than infection, and the annual incidence of disease in heavily infected flocks is usually low and approximates 10%.

Host Risk Factors

Breeds

All breeds are susceptible to infection but several studies have recorded apparent differences in breed susceptibility, which may reflect differences in management practices such as feeding practices of colostrum and milk, or genetic differences in susceptibility. There is often a higher prevalence of seropositive goats in family-owned farms compared with institutional herds, which might reflect a greater movement of goats or comingling with other herds among the former.

Housed Rocky Mountain goats (*Oreamnos americanus*) have developed clinical disease attributed to infection with CAE virus, including interstitial pneumonia and synovial changes. Three of four affected goats had been fed raw goat milk from a source later found to have CAE virus.[5]

Age

There is no age difference in susceptibility to experimental infection. Some herds show similar seroprevalence across age groups, whereas others show an increasing seroprevalence with increasing age. These differences probably reflect differences in management between herds and differences in the relative importance of the mechanisms of transmission between herds. Increasing prevalence with age reflects management systems that increase the risk of acquiring infection from horizontal transmission. Leukoencephalomyelitis occurs predominantly in young kids and arthritis in older goats.

Method of Transmission

More than 75% of kids born to infected dams may acquire infection, which can be potentially transmitted to them by several routes. Infection can also occur in older goats.

Colostrum and Milk

Observation of the natural disease and experimental studies indicate that the primary mode of transmission is through the colostrum and milk. The presence of antibody in colostrum does not prevent infection. The virus can be isolated both from the cells in the milk and from cell-free milk from infected dams. Kids born of noninfected dams, but fed colostrum and/or milk from infected dams, can become infected. A single feeding of infected milk can be sufficient to infect a kid. Conversely, the risk of infection is much lower in kids that are removed from the doe immediately after birth and reared on pasteurized milk, and many can be reared free from infection.

Other Perinatal Transmission

Intrauterine infection can occur, but appears to be infrequent and not of major significance in the control of the disease. The disease can be transmitted by contact both during and following the perinatal period, and perinatal transmission is most important in the epidemiology of the disease. Perinatal transmission can result from contact with vaginal secretions, blood, saliva, or respiratory secretions, with the relative importance of these not clearly known.

Contact Transmission

Horizontal transmission occurs at all ages, and older goats can be infected by oral challenge with virus. Contact transmission will result in the spread of the disease when an infected animal is introduced into an infection-free herd and has been one cause of spread in countries in which the infection has been introduced with imported animals.

Prolonged comingling of uninfected with infected animals is likely to promote horizontal transmission.

Other Routes

Milk contains virus-free and virus-infected cells and shared milking facilities increase the risk of cross-infection. This possibly results from the transfer of infected cells in milk during the milking process. Both iatrogenic and venereal transmissions are possible but are probably of limited significance.

Experimental Reproduction

Arthritis and mastitis have been reproduced by oral, intravenous, and intraarticular challenge with CAE virus, although pneumonia is often not a feature of the experimental disease. Leukoencephalomyelitis in young lambs can be reproduced by intracerebral challenge, but this form of the disease has not been reproduced by more natural challenge routes. Strains of the virus can be neuroadapted by passage and show increased neurovirulence but not neuroinvasiveness, suggesting that these are separate characteristics.

The relatedness between caprine and the ovine lentiviruses was first evident with experimental infections, with the CAE-type virus transferred to lambs by feeding them infected colostrum. This experimental infection was followed by viremia and seroconversion, but some strains of the virus produced no clinical or histopathologic evidence of disease. Goat kids have been similarly infected with the maedi virus. The arthritic form of the disease has been produced experimentally in cesarean-derived kids injected with virus isolated from the joints of infected goats.

Economic Importance

There is a high prevalence of infection in many countries, and several have opted for national or breed-associated control programs. There is a higher cull rate in infected herds, with as many as 5% to 10% of goats culled each year for arthritis, and affected animals cannot be entered for show. Seropositive herds have a higher incidence of disease.

There are conflicting reports on the effect of infection on productivity in goat herds, but seropositive goats can have significantly lower milk production (around 10%), a reduced length of lactation, lower 300-day yields of milk, and impaired reproductive performance compared with seronegative goats.

PATHOGENESIS

Animals infected at birth remain persistently infected for life, although only a proportion, typically from 10% to 30%, will develop clinical disease. The virus persistently infects some cells of the monocyte–macrophage type, and the expression and shedding of virus occurs as infected monocytes mature to macrophages.[1] Disease is associated with the host's immune response to the expressed virus. The development of neutralizing antibody does not arrest viral replication because of ongoing expression of antigenic variants of the virus with differing type-specific neutralization epitopes. However, the immune complexes are thought to be the basis for the chronic inflammatory changes in tissues. Goats vaccinated with CAE virus develop more severe clinical disease following challenge compared with nonvaccinated controls. The lesions are lymphoproliferative and followed by a multisystem disease syndrome. This primarily involves synovial-lined connective tissue, causing chronic arthritis, in the udder, causing swelling and hardening of

the glands (with or without mastitis), and in the lungs causing a chronic interstitial pneumonia.

A retrovirus infection, detected by electron microscopy and the presence of RT activity, is suspected as the cause of an immunodeficiency syndrome in llamas characterized by failure to thrive, anemia, leukopenia, and recurrent infection, but this has not been reported since 1992.

CLINICAL FINDINGS

Joints

Arthritis occurs predominantly in adult goats and is a chronic hyperplastic synovitis, which is usually noticeable only in the carpal joints. This gives rise to the lay term of big knee, although tarsal joints may also be affected. The onset may be insidious or sudden, and unilateral or bilateral. Goats may be lame in the affected leg, but this is usually not severe. Affected goats may live a normal life span but some gradually lose weight, develop poor hair coats, and eventually remain recumbent most of the time and develop decubitus ulcers. Dilatation of the atlantal and supraspinous bursae occurs in some cases. The course of the disease may last several months. The arthritis may be accompanied by enlargement and hardening of the udder and by interstitial pneumonia, although this may be clinically inapparent. There can be herd and area differences in the clinical expression of the disease. For example, in some outbreaks in Australia pneumonia, rather than arthritis, has been the predominant clinical sign.

Radiographically, there are soft tissue swellings in the early stages and calcification of periarticular tissues and osteophyte production in the later stages. Quantitative joint scintigraphy provides an accurate noninvasive method for assessing the severity of the arthritis in a live animal.

Brain

Leukoencephalitis occurs primarily in 1- to 5-month-old kids. The syndrome is characterized by unilateral or bilateral posterior paresis and ataxia. In the early stages, the gait is short and choppy, followed by weakness and eventually recumbency. In animals that can still stand, there may be a marked lack of proprioception in the hindlimbs (Fig. 14-4). Brain involvement is manifested by head tilt, torticollis, and circling. Affected kids are bright and alert and drink normally. Kids with unilateral posterior paresis usually progress to bilateral posterior paresis in 5 to 10 days. The paresis usually extends to involve the forelimbs, so that tetraparesis follows, and most kids are euthanized. The interstitial pneumonia that often accompanies the nervous form of the disease is usually not severe and not clinically obvious.

Udder

Indurative mastitis, or hard bag, is often initially detected a few days after kidding. The udder is firm and hard but no milk can be expressed. There is no systemic illness and no bacterial mastitis. Recovery is never complete but there may be some gradual improvement.

CLINICAL PATHOLOGY

The synovial fluid from affected joints is usually brown to red-tinged, and the cell count is increased up to 20,000 µL with 90% mononuclear cells. The CSF may contain an increased mononuclear cell count. There is a reduction in monocytes in peripheral blood, a decrease in the number of CD4+ lymphocytes, and a lower or inverted CD4:CD8 ratio.

Serologic Testing

For the live animal, there are a number of test systems available whose sensitivity and specificity varies. The agar gel immunodiffusion test (AGID) and a variety of commercial ELISA tests are the most widely used, and the latter usually has a higher sensitivity and specificity. Differences in the performance of the ELISA tests may be related to the peptides they use and the types of SRLV present.[6] Maternal antibody is lost by approximately 3 months of age, hence a seropositive test in a goat older than 6 months is considered evidence of infection. Most animals have a persistent antibody response and remain seropositive for life, although some infected goats may become seronegative over time.

A negative test does not rule out the possibility of infection because there may be a considerable delay between infection and the production of detectable antibody. It is possible that in some infected goats there is insufficient virus expression to lead to an antibody response.

A competitive-inhibition ELISA, which detects antibody to the surface envelop of the virus, has very high sensitivity and specificity and may be more useful in determining the status of individual animals, such as before the movement of goats. Other tests with potentially greater sensitivity and/or specificity are described, but are not generally available. For example, serum adenosine deaminase activity is used as a biochemical marker of HIV infection in humans, and is elevated in goats infected with CAE, but is not a routinely available veterinary test.[7]

Other Tests

A more cost-effective way of monitoring CAE in dairy goats may be testing the bulk tank milk. In Norwegian dairy flocks, an ELISA for testing bulk tank milk detected a within-herd prevalence of CAE of at least 2%, with a sensitivity of 73% and specificity of 87%.[8] Identification of the presence of CAE is usually provided by isolation of the virus from tissue explants into tissue culture. PCR can be used to detect the presence of viral antigen or proviral DNA. Most primers for diagnostic purposes are selected to detect the broadest possible range of SRLV strains, whereas those selected for research purposes may take a type-specific approach.[2] A rapid detection assay based on LAMP has been developed for detecting CAEV proviral DNA in whole blood and whole-blood samples and separated mononuclear cells.[9] This assay can be performed in less well-equipped laboratories as well as in the field.

Fig. 14-4 A 3-month-old Toggenburg kid with advanced progressive neurologic signs caused by infection with caprine arthritis encephalitis virus. The goat has normal mentation but is exhibits asymmetric weakness (hindlimbs worse than forelimbs) and proprioceptive abnormalities.

NECROPSY FINDINGS

In the arthritic form of CAE, there is emaciation and chronic polysynovitis, with degenerative joint disease affecting most of the joints of animals submitted for necropsy. Periarticular tissues are thickened and firm and there is hyperplasia of the synovium. The local lymph nodes are grossly enlarged and a diffuse interstitial pneumonia is usually present. Mammary glands are frequently involved, although gross changes are restricted to induration and increased texture. Microscopically, lymphoplasmacytic infiltrates of the interstitial tissues of mammary gland, lung, and synovium are characteristic. In the neural form the diagnostic lesions are in the nervous system and involve the white matter, especially of the cervical spinal cord and sometimes the cerebellum and the brainstem. The lesion is a bilateral, nonsuppurative demyelinating encephalomyelitis. The infiltrating mononuclear leukocytes tend to be more numerous in the periventricular and subpial areas. There is usually also a mild, diffuse, interstitial pneumonia in this form of the disease. In some cases, a severe lymphoplasmacytic interstitial pneumonia with extensive hyperplasia of type II pneumocytes can occur in the absence of neurologic disease.

Culture of the virus is difficult but can be attempted. A variety of nucleic acid recognition tests, including in situ hybridization, PCR, and IHC, have been developed. For most cases, confirmation of the diagnosis is based on the characteristic microscopic lesions, preferably supported by antemortem serology.

Samples for Confirmation of Diagnosis

- **Histology:** formalin-fixed lung, bronchial lymph node, mammary gland, synovial membranes, half of midsagittally sectioned brain, spinal cord (LM, IHC)
- **Serology:** blood (ELISA, AGID, PCR)
- **Virology:** lung, synovial membrane, mammary gland, hindbrain (PCR, virus isolation).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the arthritic form of the disease includes the other infectious arthritides, such as those associated with mycoplasma and chlamydia.

Leukoencephalitis must be differentiated from:

- Swayback caused by copper deficiency
- Spinal abscess
- Cerebrospinal nematodiasis
- Listeriosis
- Polioencephalomalacia

TREATMENT

There is no treatment likely to be of value for any form of CAE.

CONTROL

A measure of control can be achieved by testing the herd every 6 months, and segregating or culling of seropositive animals. More complete control is dependent on preventing/minimizing perinatal transmission of infection to the kid, particularly colostrum and milk transmission, coupled with identifying infected animals and maintaining them physically separated from the noninfected animals or culling them from the herd.

Because of the evidence of transmission of SRLV between sheep and goats, the presence of each species needs to be considered when developing control programs for CAE of goats or OPP of sheep.

Prevention of Perinatal Transmission

Early recommendations for control concentrated on reducing transmission via milk and colostrum, but it is now recognized that this must be coupled with segregation. Newborn kids should be removed from the dam immediately at birth. There should be no contact with the dam, and fetal fluids and debris should be rinsed off the coat. Heat-treated goat colostrum or cow colostrum should be fed, followed by pasteurized milk or a commercial milk replacer. The kid should be segregated from the doe and other infected animals. In herds that feed pasteurized colostrum and milk there is a significant difference in subsequent seroconversions between those that segregate the kids at birth and for rearing and those that do not.

Test and Segregate/Cull

Animals over 3 months of age should be tested by ELISA or AGID every 6 months, and seropositive animals segregated or (preferably) culled from the herd. The interval between infection and seroconversion varies between goats, and the optimal interval for testing has not been determined. More frequent testing may be needed for large herds with a high seroprevalence. Segregation of seropositive and seronegative goats is essential because horizontal spread in adult goats is important in maintaining and increasing infection rates in some herds, and even a brief contact time can allow transmission. Where culling is not practiced, seropositive goats should be milked after seronegative ones, and the use of common equipment, such as for ear-tagging, tattooing, and vaccinating, should be avoided.

Several countries have programs for herd accreditation of freedom from infection. The stringency of these schemes varies, and they may be governmental or breed society accreditation programs. Typically, they require that all adults in the herd test negative on two herd tests at a 6-month interval. There are also restrictions on the movement and purchase of animals, and periodic serologic surveillance. For example, a scheme in Norway has been quite successful, with only 5 of 406 flocks (1.2%) being reinfected over a 10-year period.[8]

Vaccination and Genetic Selection

There is currently no effective vaccine against the SRLVs, including CAE, maedi-visna, or OPP viruses, and in some cases candidate vaccines have enhanced viremia and/or the immune-mediated pathology of the disease.[1] The difficulty in developing effective vaccines is common among the lentiviruses, with various approaches, including attenuated vaccines, vector vaccines, and proviral DNA vaccines having little success. The reasons are obscure, but probably relate to the underlying dysfunction in T-cell–mediated immune responses.

However, marker-assisted genetic selection, to identify animals less susceptible to infection, has the potential to supplement existing control measures. For example, in a trial investigating the control of OPP in lambs, the probability of infection following natural exposure to OPP virus was 3.6 times greater in crossbred lambs with susceptible or heterozygous diplotype to ovine transmembrane protein gene 154 (TEM154 diplotype 1 3 or 3 3) compared with lambs with diplotype 1 1.[10] Similar studies have not yet been undertaken in goats, but this is an active research area and it is expected that additional markers for conditions caused by SRLV will be identified in future.

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OVINE ENCEPHALOMYELITIS (LOUPING-ILL)

SYNOPSIS

Etiology Louping-ill virus, flavivirus.

Epidemiology Disease of sheep (and red grouse), and occasionally other domestic

animals and man, transmitted by *Ixodes ricinus*. Occurs predominantly in lambs and yearling sheep in Great Britain and Europe in the spring, associated with tick rise.

Clinical findings Fever, neurologic dysfunction, muscle tremor, incoordination, bounding gait. Recovery or convulsions and death.

Lesions Nonsuppurative encephalitis.

Diagnostic confirmation Serology, demonstration of virus.

Control Vaccination, tick control.

ETIOLOGY

Louping-ill virus belongs to the genus *Flavivirus,* which is divided into eight groups, one of which is the tick-borne encephalitis group. Louping-ill is antigenically related to the tick-borne encephalitis viruses. The latter circulate in Europe and Asia and are a serious zoonotic disease for humans, but do not infect sheep.[1] Louping-ill virus occurs in Great Britain, Ireland and Norway, but similar disease occurs elsewhere and there is antigenic diversity between isolates from different geographic areas. Viruses that are closely related to louping-ill virus, and that cause very similar disease but in different regions of the world, include Russian spring-summer encephalitis, Turkish sheep encephalitis, Spanish sheep encephalitis, Spanish goat encephalitis,[2] and Greek goat encephalitis viruses. In sheep, concurrent infection with the agent of tick-borne fever *Ehrlichia* (*Cytoecetes*) *phagocytophila* enhances the pathogenicity of the virus.

EPIDEMIOLOGY

Occurrence

Geographic Occurrence

Louping-ill was originally considered to be restricted to the border counties of Scotland and England but is now recognized as also occurring in upland grazing areas of Scotland, in Ireland, southwest England, and in Norway; related viruses and diseases occur in Spain, Bulgaria, Greece, and Turkey. The distribution of the disease is regulated by the occurrence of the vector tick *Ixodes ricinus,* which requires suitable hosts and a ground layer microclimate of high humidity throughout the year. In these areas, louping-ill can be a common infection and may be a significant cause of loss.

Host Occurrence

Louping-ill virus can infect and produce disease in a wide variety of vertebrates including man, but predominantly sheep are affected because of their susceptibility and the fact that they are the main domestic animal species that graze the tick-infested areas. Nonruminant species, such as alpaca and horses, and wild ungulates such as chamois,[3] have also been infected.

Although sheep (and red grouse) are the only animals that commonly develop clinical disease, *I. ricinus* feeds on a number of different hosts and the adult tick requires a large mammalian host. As a consequence, seropositivity and occasional clinical disease occur in all other domestic species, especially goat kids, but also cattle, horses, alpaca,[4] pigs, and humans.

Traditionally, pigs have not been free-ranged on upland tick-infested areas, but they are susceptible to experimental infection by all routes.

Red deer (*Cervus elaphus*) and roe deer (*Capreolus capreolus*) are hosts for the tick in Scotland, and the elk (*Alces alces*) may be in Sweden. Infection in these species is usually subclinical; however, when these animals are subjected to the stress of captivity, clinical illness is more likely to occur. This may be important to commercial deer farmers.

Transmission

Tick Transmission

The reservoir for the disease and the major vector is the three host tick *I. ricinus,* which requires a single blood meal at each stage of development. Changes in the distribution of the tick are probably introducing this and other tick-borne disease into previously unaffected areas. The tick feeds for approximately 3 weeks every year and completes its life cycle in 3 years. The larval and nymphal stages will feed on any vertebrate, but the adult female will engorge and mate only on larger mammals. The tick becomes infected by feeding on a viremic host and the virus translocates to the salivary gland of the subsequent stage to provide a source of infection at feeding in the following year. Transstadial transmission of the virus occurs, but transovarial transmission does not; thus only the nymph and adult ticks are capable of transmitting the disease. The tick is seasonally active at temperatures between 7°C and 18°C. Most ticks feed in the spring, with peak activity dependent on the latitude and elevation of the pasture, but generally occurring in April and May. In some areas there is a second period of activity of a separate population of *I. ricinus* in the autumn during August and September. Although infected ticks can transmit the infection to a large number of vertebrate hosts, only sheep, red grouse (*Lagopus scoticus*), and possibly horses, attain a viremia sufficient to infect other ticks and act as maintenance hosts. Grouse amplify the virus, deer amplify the vector, and hares (*Lepus timidus*) amplify both. Infection in red grouse is accompanied by a high mortality, and the louping-ill virus is essentially maintained in an area by a sheep–tick cycle and hare tick cycle.

Nontick Transmission

Although the major method of spread is by the bites of infected ticks, spread by droplet infection is of importance in man, and the infection can be transmitted in animals by hypodermic needle contamination and other methods. The virus is not very resistant to environmental influences and is readily destroyed by disinfectants. Pigs fed the carcasses of sheep that had died of louping-ill become infected with the louping-ill virus. The virus is excreted in the milk of experimentally infected female goats, and infects sucking kids to produce an acute disease. Virus is also excreted in the milk of ewes during the acute stages of infection but, paradoxically, does not result in the transmission of the infection to lambs. Grouse can be infected by eating infected ticks, and this is considered a major mechanism of infection for grouse.

Host and Environmental Risk Factors

The epidemiology of disease is dictated by the biology of the tick and so disease is seasonal, occurring during spring when the ticks are active. The prevalence of infection, as measured by seropositivity, is high in areas where the disease is enzootic. In these areas, the annual incidence of disease varies but there are cases every year and they occur predominantly in yearlings and in lambs. In enzootic areas, the majority of adult sheep have been infected and are immune. Colostral immunity from these ewes will protect their lambs for approximately 3 months, and these lambs are resistant to infection during the spring rise of the ticks. Ewe lambs that are retained in the flock are susceptible to infection at the second exposure the following spring. In the UK there are concerns that the density and range of ticks is increasing because of changes in climate and land management; thus the distribution of tick-borne disease is also changing.[5]

The proportion of infected animals that develop clinical disease in any year is estimated to vary from 5% to 60% and is influenced by the intensity of the tick vector; the immune status of the flock; the age at infection; nutritional status; and factors such as cold stress, herding, and transport, and the occurrence of intercurrent disease. Naive animals introduced to an enzootic area are at high risk for infection and clinical disease.

Intercurrent infection with *E.* (*Cytoecetes*) *phagocytophila* and *Toxoplasma gondii* have been shown to increase the severity of experimental tick-borne fever in young lambs, but the relevance of this association to naturally occurring disease is uncertain. It would appear that concurrent infection with louping-ill and tick-borne fever is unlikely to occur in the field in young lambs because colostral immunity will protect against infection with the louping-ill virus, whereas colostral immunity is not protective against tick-borne fever. Similarly, the superinfection of *Rhizomucor pusillus* on this concurrent infection has been observed in experimental conditions, but is not a

commonly recorded observation in natural disease.

Zoonotic Implications

Louping-ill is a zoonosis. The major risk for veterinarians is with the postmortem examination and handling of tissues from infected animals. Laboratory workers, and shepherds and abattoir persons who handle infected sheep, are also at risk. The occurrence of virus in the milk of goats and sheep is a risk for human disease where raw milk is consumed.

PATHOGENESIS

After tick-borne infection, the virus proliferates in the regional lymph node to produce a viremia that peaks at 2 to 4 days and declines with the development of circulating antibody before the development of clinical disease. Invasion of the CNS occurs in the early viremic stage in most if not all infected animals, but in most the resultant lesions are small and isolated and there is no clinical neurologic disease. The occurrence of clinical disease is associated with the replication of the virus in the brain, severe inflammation throughout the CNS, and necrosis of brainstem and ventral horn neurons. The reason for more severe disease in some animals appears to be related to the rapidity and extent of the immune response. Animals that survive exposure to louping-ill virus have an earlier immune response to the infection and have high concentrations of antibody in the CSF.

In experimental studies, there is a more severe and prolonged viremia and a higher mortality from louping-ill when there is concurrent infection with tick-borne fever. Sheep with tick-borne fever have severe neutropenia, lymphocytopenia, defective cellular and humoral immunologic responses, and high mortality associated with concurrent infection with this agent is thought to be from enhanced viral replication of the louping-ill virus. The dual infection in experimental sheep also facilitates fungal invasion and a systemic mycotic infection with *R. pusillus*.

CLINICAL FINDINGS

In most sheep, infection is inapparent. There is an incubation period of 2 to 4 days followed by a sudden onset of high fever (up to 41.5°C, 107°F) for 2 to 3 days followed by a return to normal. In animals that develop neurologic disease, there is a second febrile phase during which nervous signs appear. Affected animals stand apart, often with the head held high and with twitching of the lips and nostrils. There is marked tremor of muscle groups and rigidity of the musculature, particularly in the neck and limbs. This is manifested by jerky, stiff movements and a bounding gait, which gives rise to the name louping-ill. Incoordination is most marked in the hindlimbs. The sheep walks into objects and may stand with the head pressed against them. Hypersensitivity to noise and touch may be apparent. Some animals will recover over the following days, although there may be residual torticollis and posterior paresis. In others, the increased muscle tone is succeeded by recumbency, convulsions, and paralysis, and death occurs as early as 1 to 2 days later. Young lambs may die suddenly with no specific nervous signs.

The clinical picture in cattle is very similar to that observed in sheep, with hyperesthesia, blinking of the eyelids, and rolling of the eyes, although convulsions are more likely to occur in cattle, and in the occasional animals that recover from the encephalitis there is usually persistent signs of impairment of the CNS.

Horses also show a similar clinical picture to sheep, with some showing a rapidly progressing nervous disease with a course of approximately 2 days and others a transient disorder of locomotion with recovery in 10 to 12 days.

The infection is usually subclinical in adult goats but the virus is excreted in the milk and kids may develop severe acute infections. In humans an influenza-like disease followed by meningoencephalitis occurs after an incubation period of 6 to 18 days. Although recovery is common, the disease can be fatal and residual nervous deficiencies can occur.

CLINICAL PATHOLOGY

The initial viremia that occurs with infection declines with the emergence of serum antibody and virus is no longer present in the blood at the onset of clinical signs. Hemagglutination inhibition (HI), complement-fixing, and neutralizing antibodies can be detected in the serum of recovered animals. HI and complement-fixing antibodies are relatively transient, but neutralizing antibodies persist. HI IgM antibody develops early in the disease and can be used as an aid to diagnosis in animals with clinical disease. Analysis of CSF is usually not considered because of the zoonotic risk.

Molecular tests, including conventional and real-time RT-PCR, can target specific viruses in this tick-borne encephalitis virus group, and a pan-flavirvirus test has been developed.[6]

NECROPSY FINDINGS

No gross changes are observed. Histologically, there are perivascular accumulations of cells in the meninges, brain, and spinal cord, with neuronal damage most evident in cerebellar Purkinje cells and, to a lesser extent, in the cerebral cortex. Louping-ill virus can be demonstrated in formalin-fixed tissues by the avidin-biotin–complex immunoperoxidase technique.

Samples for Confirmation of Diagnosis

- **Virology:** chilled brain, halved midsagitally (VI, RT-PCR)
- **Histology:** fixed brain, other half (LM, IHC)
- **Molecular:** CNS tissue, blood, ticks (conventional and real-time RT-PCR)

DIFFERENTIAL DIAGNOSIS

The disease is restricted to areas in which the vector tick occurs.

- In lambs, the disease has clinical similarities with delayed swayback, spinal abscess, and some cases of tick pyemia. Spinal abscess occurs shortly following a management procedure such as docking or castration or with tick pyemia; it has a longer clinical course, is commonly present at C7-T2, and can be established by radiographic examination. Tick pyemia can also occur in flocks that have louping-ill, and the determination of the contribution of each disease to flock mortality relies on clinical, epidemiologic, and postmortem examination.
- In yearlings, the disease has similarities to spinal ataxia caused by trauma, to gid (*Coenurus cerebralis*), and to the early stages of polioencephalomalacia.
- In adults, the disease in sheep resembles some stages of acute neurologic diseases, including scrapie, tetanus, hypocalcemia, hypomagnesemia, pregnancy toxemia, and listeriosis.

TREATMENT

An antiserum has been used and is protective if given within 48 hours of exposure, but is of no value once the febrile reaction has begun. However, it is not commercially available. Animals with clinical disease should be sedated if necessary during the acute course of the disease and kept in a secluded and dark area with general supportive care.

CONTROL

The prevention of louping-ill requires either the prevention of exposure of sheep to tick-infested pastures or the immunization of animals before exposure. Immunization has been the traditional approach.

Historically, a formalinized tissue vaccine derived from brain, spinal cord, and spleen was used and provided excellent immunity in enzootic areas. The vaccine was not without risk for persons manufacturing it and at one stage led to an outbreak of scrapie where the vaccine was prepared from sheep incubating the disease. Currently, vaccination is with a formalin-killed tissue culture–derived vaccine administered in an oil adjuvant. A single dose of this vaccine will give protection for at least 1 year and possibly up to 2 years. The vaccine is used in the autumn, or in the early spring 1 month before the anticipated tick rise, in all ewe lambs that will be held for flock replacements. Vaccination of pregnant ewes twice in late pregnancy is recommended to ensure adequate passive immunity to the lambs via

the colostrum. A recombinant vaccine has also been shown to offer protection against infection.

The limited geographic occurrence of this disease and commercial economics has, and may, restrict the availability of vaccines. Consequently tick control, or the elimination of infection from pastures, may be required in the future. The intensity of tick infestation of pastures can be reduced by influencing the microclimate that they require for survival. In some areas this can be achieved by ditching and drainage of the pastures. The control of the causative tick using acaricides provides some protection against disease.

Epidemiologic, modeling, and experimental studies indicate that sheep, red grouse, and hares are the only maintenance hosts for the virus and this, coupled with the fact that there is no transovarial transmission of the virus in the tick, offers a potential method for eradication of the infection from an area. However, this approach (the elimination of wildlife hosts) is increasingly unacceptable in relationship to game and wildlife conservation, may have unintended consequences and is probably of dubious benefit–cost in relationship to alternate methods of control.[7]

FURTHER READING

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WEST NILE, KUNJIN, AND MURRAY VALLEY ENCEPHALITIS

SYNOPSIS

Etiology Flavivirus including West Nile virus (lineages 1 and 2) including Kunjin virus, and Murray Valley encephalitis virus. Closely related to Japanese encephalitis virus.

Epidemiology Maintained in a bird–mosquito cycle. Mammals are incidentally infected. Enzootic in Africa, North America, Pakistan, southern Europe, and Australia. Epizootics. Affects a wide variety of species with a major impact on humans and horses.

Clinical signs Weakness, incoordination, altered mentation, muscle fasciculations, recumbency.

Clinical pathology MAC-ELISA for diagnosis.

Lesions Polioencephalomyelitis.

Diagnostic confirmation MAC-ELISA, PCR, clinical signs, lesions.

Treatment None specific. Supportive care.

Control Vaccination. Mosquito control.

MAC-ELISA, *M antibody-capture enzyme-linked immunosorbent assay.*

ETIOLOGY

Encephalitis in horses, humans, and other species is associated with West Nile virus, an arthropod-borne flavivirus in the Japanese encephalitis virus group. Other viruses in the group include Japanese encephalitis virus (Japan and Southeast Asia), St. Louis encephalitis virus (United States), Kunjin virus (now considered a subtype of West Nile virus, Australia),[1,2] Murray Valley encephalitis virus (Australia),[3-5] and Rocio virus (Brazil). Murray Valley virus causing encephalomyelitis in horses in southeastern Australia is endemic to northern Australia.[4] Viruses causing, or suspected of causing encephalomyelitis in equids, are listed in Table 14-11.[6]

The virus was first isolated in 1937 from a human with fever in Uganda. There are at least two lineages of the virus, with one lineage (Lineage 1) isolated from animals in central and North Africa, Europe, Israel, and

Table 14-11 Viruses causing encephalomyelitis in horses. reproduced with permission.[6]

Virus species	Geographic location	Reservoir species	Equine syndrome
Alphavirus			
Eastern equine encephalitis virus	North/South/Central America, Caribbean	Birds, rodents, snakes	Encephalomyelitis
Western equine encephalitis virus	North/South America	Birds, rodents, snakes	Encephalomyelitis
Venezuelan equine encephalitis virus	Central/South America, Caribbean	Cotton rat	Encephalomyelitis
Ross River virus	Australia, Papua New Guinea	Marsupial and placental mammals	Systemic: hemolymphatic Neurologic ataxia
Semliki Forest virus	East and West Africa	Unknown	Encephalomyelitis
Flavivirus			
Japanese encephalitis	Asia, India, Russia, Western Pacific	Birds, swine	Encephalomyelitis
Murray Valley	Australia, Papua New Guinea	Birds, horses, cattle, marsupials, and foxes	Encephalomyelitis
Kunkin virus	Australia	Water birds: herons and ibis	Encephalomyelitis
St. Louis encephalitis	North, Central and South America	Birds	Serologic only recorded
Usutu	Europe, Africa	Birds	Serologic only recorded
West Nile	Africa, Middle East, Europe, North, Central and South America, Australia	Passerine birds (crows, sparrows, robins)	Encephalomyelitis
Louping-ill	Iberian Peninsula, UK	Sheep, grouse	Encephalomyelitis
Powassan	North American, Russia	Lagomorphs, rodents, mice, skunks, dogs, birds	Encephalomyelitis
Tick-borne encephalitis	Asia, Europe, Finland, Russia	Small rodents	Encephalomyelitis
Bunyavirus			
California serogroup: California encephalitis, Jamestown Canyon, La Crosse, Snowshoe hare	North America (United States and Canada), parts of eastern Asia	Rodents and lagomorphs	Encephalomyelitis

North America, whereas the other (Lineage 2) is enzootic in central and southern Africa with outbreaks of disease in humans in central Europe, Greece, and Russia.[6-10] The recent outbreak in North America was associated with a Lineage 1 (Clade a) virus of African origin almost identical to that isolated from diseased geese in Israel, and which subsequently acquired a mutation that enhanced its capacity to reproduce in mosquitos and its virulence in corvid birds and other species.[11] Viruses of both lineages can circulate at the same time in the same geographic region. Virus of either lineage can cause disease, although that of Lineage 1 appears to be associated with more severe disease in horses and other species. Kunjin virus, a West Nile virus (Lineage 1, Clade b), causes encephalomyelitis in horses in Australia.[12,13] An outbreak in Australia in 2011 was associated with unusually wet weather (see later) and emergence of a strain of West Nile virus (WNVNSW2011) that had at least two amino acid changes associated with increased virulence of WNVNY99 (the strain associated with the epidemic in North America in 1999).[12] The WNV(KUN) NSW2011 strain also had adaptations that increased the amount of virus in material (saliva) regurgitated by mosquitos, which could have increased the rate of vector transmission of the virus.[14] The WNVNSW2011 strain did not have all the virulence attributes of the WNVNY99 strain.[15]

Murray Valley encephalitis virus causes encephalomyelitis in horses in Australia.[3]

The West Nile virus causes disease in humans, horses, birds (including geese, raptors, and corvids), sheep, alpaca, and dogs. Experimental inoculation of little ravens (*Corvus mellori*) with WNVKUN resulted in infection and viremia but not clinical disease.[13]

EPIDEMIOLOGY

Distribution

West Nile encephalitis virus is enzootic to Africa and sporadic outbreaks of the disease occurred in the 1960s in Africa, the Middle East, and southern Europe. Recently outbreaks affecting horses and other animals have occurred in southern France, Tuscany, Israel, and other parts of southern Europe. There is serologic evidence of common and widespread infection of equids with West Nile virus in Pakistan and Tunisia.[16,17]

The virus was introduced into New York City in North America in 1999 and subsequently spread widely across the continent, including Canada, Mexico, and the Caribbean, reaching the west coast by 2004. The virus caused widespread deaths of wild birds and disease and death in humans, horses, and other species in North America during this period.

Introduction of the infection to North America was associated with an epizootic of disease that over several years moved across the continent. During the initial years of the epizootic there were large numbers of cases in horses (15,000) and humans (4,000) and death of at least 16,500 birds. As the front of the epizootic moved across the country, the infection became enzootic and the number of cases in horses in these regions decreased markedly over those in the first year.

Infection by Kunjin virus (a strain of West Nile virus) rarely causes disease of horses in areas in which it is endemic (northern Australia) but was associated with an outbreak of neurologic disease in horses in southeastern Australia after a decade-long drought broke with record rains resulting in sixfold increases in vector density.[1,12] The outbreak did not extend into the subsequent year.[12] There is serologic evidence of infection by flaviviruses (including Kunjin and/or Murray Valley encephalitis virus in 15%–18% of horses in southeast Queensland, where infection is presumed to be endemic and clinical disease is rare.[18]

Viral Ecology

The virus is maintained by a cycling between amplifying hosts, usually birds, and insect vectors. Large mammals, including horses and humans, are incidentally infected and are not important in propagation of the virus. Amplifying hosts are those in which the viremia is of a sufficient magnitude and duration (1–5 days) to provide the opportunity to infect feeding mosquitoes. Mammals, and in particular horses, are generally not amplifying hosts because of the low level of viremia.

The virus is spread by the feeding of ornithophilic mosquitoes, usually of the genus *Culex* with mosquitos of the *C. pipiens* group being effective vectors.[19,20] The principal vectors for West Nile virus include Africa, *C. univittatus*; Europe, *C. pipiens, C. modestus,* and *Coquillettidia richiardii*; Asia, *C. quinquefasciatus, C. tritaeniorhynchus,* and *C. vishnui*; United States, *C. pipiens* complex including *C. pipiens* and *C. restuans* in the northeastern and north central United States, *C. tarsalis* in the Great Plains and western United States; and *C. nigripalpus* and *C. quinquefasciatus* in southeastern United States.[21] *C. annulirostris* and a variety of other native and introduced species of mosquitos are actual or potential vectors of West Nile virus in Australia.[21]

Infected mosquitoes carry the virus in salivary glands and infect avian hosts during feeding. The virus then multiplies in the avian host causing a viremia that may last for up to 5 days. Mosquitoes feeding on the avian host during the viremic phase are then infected by the virus. This pattern of infection of amplifying hosts and mosquitoes is repeated such that the infection cycles in these populations. Increases in mosquito number, such as occur at the end of the summer, and enhanced viral replication in mosquitoes at higher ambient temperatures, increase the likelihood that avian hosts, or incidental hosts, will become infected. This results in an increase in the incidence of disease in late summer and early autumn.

The principal avian host and vector species vary markedly between geographic regions. In North America the house sparrow (*Passer domesticus*) is the principal amplifying host and *C. pipiens* is the principal vector. *C. pipiens,* and other mosquito vectors, feed almost exclusively on passerine and columbiform birds early in the season, but later in the summer in temperate regions switch to feeding on mammalian hosts. This change in feeding behavior is associated with increased frequency of infection and disease in mammals, including horses and humans, in the late summer.

The virus cycles between the avian host and insect vectors year round in tropical regions. However, in temperate regions in which mosquitoes do not survive during the winter the mechanism by which the virus survives over winter is unknown.

The primary vector involved in Murray Valley encephalitis virus transmission is the mosquito *C. annulirostris.*[1,3] Wading birds, particularly the rufous night heron (*Nycticorax caledonicus*) appear to be the principal natural reservoirs of Murray Valley encephalitis virus and West Nile virus in Australia.[1]

Transmission

Transmission is only by the bite of infected insect vectors. There is no evidence of horizontal spread of infection among horses. The disease can be spread in humans by transfusion of blood or transplantation of organs obtained from an infected person.

Animal Risk Factors

The disease occurs in parts of the world as epidemics, apparently associated with sporadic introduction of the virus into nonendemic regions, such as the Mediterranean littoral and parts of central Europe.[22] Introduction of the virus to these regions occurs infrequently enough that horses have no active immunity and are susceptible to infection and disease. Horses immune through either natural infection or vaccination are resistant to the disease. The effect of immunity was evidenced in North America by the marked decrease in morbidity and mortality among horses after the epizootic waned and the disease became enzootic. The decrease in morbidity was attributed to both natural and vaccinal immunity. Interestingly, although the number of cases in horses decreased rapidly, there was not a similar decrease in the number of human cases, perhaps because of the lack of a vaccine for use in humans.

Horses of all ages appear to be equally susceptible to infection. Disease is reported in horses aged from 5 months to >20 years. There does not appear to be any predilection based on breed or sex. Polymorphism in horse genome is associated with

susceptibility to disease, including a haplotype associated with the promoter region of the OAS1 gene.[23]

Morbidity and Case Fatality

The incidence of the disease during an epizootic can be as high as 74 cases per 1000 horses at risk. The case–fatality rate for West Nile virus encephalomyelitis in horses in North America treated in the field is 22% to 44%, whereas it is 30% to 43% of horses in referral centers.[24] The case–fatality rate for West Nile virus (Kunjin) and Murray Valley encephalitis virus infected horses in Australia with signs of disease is 5% to 20%.[1]

Zoonotic Implications

Infection of humans by West Nile virus or Murray Valley encephalitis virus can result in fatal encephalitis, although less severe disease or inapparent infection is more common.[7,12,25] The virus has zoonotic potential and tissues from potentially infected animals and virus cultures should be handled in containment level 3 facilities, particularly material from potentially infected birds.

PATHOGENESIS

Horses are infected by the bite of infected mosquitoes. Feeding by as few as seven infected mosquitoes is sufficient to cause infection in seronegative horses. Viremia, which persists for less than 2 days, occurs 2 to 5 days after feeding by infected mosquitoes. West Nile encephalitis occurs in only a small proportion of infected horses. The virus localizes in cells in the CNS where it induces a severe polioencephalomyelitis with the most severe lesions being in the spinal cord. Lesions are often evident in the ventral horn of the spinal cord, which is consistent with clinical signs of weakness.

CLINICAL FINDINGS

The incubation period of Wes Nile virus after natural infection is estimated to be 8 to 15 days. Fever occurs early in the disease but is uncommon at the time that signs of neurologic disease become evident. Affected horses are often somnolent, listless, or depressed, although hyperexcitability has been reported. The signs of neurologic disease, including muscle fasciculation, weakness, and incoordination, develop within a period of hours and can progress over several days. Muscle fasciculations are common in the head and neck, but can occur in any muscle group. Weakness is most pronounced in limb and neck muscles and severely affected horses are recumbent with flaccid paralysis. Signs of neurologic disease are usually, but not reliably, bilaterally symmetric. Altered mentation, blindness, and cranial nerve abnormalities, if they occur, usually become evident after signs of spinal cord disease are apparent.

Weakness with or without ataxia is present in almost all affected horses, whereas altered mentation is detected in approximately 66% of horses. Cranial nerve abnormalities are evident in approximately 40% of horses, whereas apparent blindness or lack of menace reflex occurs in 3% to 7% of horses.

Median recovery time for horses treated in the field is 7 days, with a range of 1 to 21 days.

The prognosis depends on the severity of clinical signs. Horses that become recumbent and unable to rise are approximately 50 times more likely to die than are horses that remain able to stand while affected by the disease. Most horses that survive the initial disease do not have signs of neurologic dysfunction 6 months later.

Murray Valley encephalitis in horses causes signs consistent with encephalitis including fever, depressed mentation, abnormalities in cranial nerves including paralysis of the facial muscles, ataxia, and recumbency.[3,5] The clinical course can be prolonged.

Other Species

Disease associated with West Nile virus is documented in small numbers of other species, including squirrels, chipmunks, bats, dogs, cats, reindeer, sheep, alpaca, alligators, and a harbor seal during intense periods of local viral activity. West Nile virus infection in dogs is usually subclinical.[26] The disease in camelids is characterized by acute recumbency and altered mentation.

CLINICAL PATHOLOGY

Affected horses are often mildly lymphopenic, and hyperbilirubinemic (likely from anorexia), and occasionally azotemic. These changes are not diagnostic of West Nile or Murray Valley encephalitis.

CSF is abnormal in approximately 70% of horses with signs of neurologic disease. Abnormalities include mononuclear pleocytosis and elevated total protein concentration.[6]

Serologic Tests

Antibody can be identified in equine serum by IgM capture ELISA (IgM capture ELISA, M antibody-capture ELISA [MAC-ELISA]), HI, IgG ELISA, or plaque reduction neutralization (PRN).[27,28] Equine West Nile-specific IgM antibodies are usually first detectable 7–10 days after infection and persist for 1 to 2 months. Because the incubation period of the disease after infection by bite of infected mosquitoes is at least 8 days, West Nile-specific IgM is usually present at the time of development of clinical signs of the disease. MAC-ELISA is therefore a useful test in the diagnosis of the disease.

West Nile virus neutralizing antibodies are detectable in equine serum by 2 weeks postinfection and can persist for more than 1 year. In some serologic assays, antibody cross-reactions with related flaviviruses (St. Louis encephalitis virus or Japanese encephalitis virus), can be encountered. The PRN test is the most specific among West Nile serologic tests and all affected horses have titers ≥1:100 4 to 6 weeks after recovering from the disease, and 90% of horses maintain this titer 5 to 7 months after recovery.

Detection by MAC-ELISA of West Nile-specific IgM in serum at dilutions greater than 1:400, in the presence of appropriate clinical signs, is considered diagnostic of West Nile virus. Similarly, a fourfold increase in PRN titer in serum collected during the acute and convalescent stages of the disease, in the absence of vaccination and in the presence of appropriate clinical signs, is considered diagnostic.

Identification of West Nile Virus

The virus can be grown in cell culture, and viral nucleic acid can be demonstrated in tissues of infected animals by RT-PCR.[29,30] Note that infected horses have much lower concentrations of virus than do infected birds, and failure to demonstrate viral antigen in infected horses is not uncommon, especially if less sensitive techniques, such as IHC, are used.

NECROPSY FINDINGS

Gross lesions are infrequently seen. When present they consist of multifocal areas of congestion and hemorrhage within the medulla oblongata, midbrain, and spinal cord. Histopathologic changes include a nonsuppurative poliomeningoencephalomyelitis with multifocal glial nodules and neuronophagia. The inflammatory changes and viral distribution are concentrated in the rhombencephalon and spinal cord, with comparatively little damage to the cerebrum. One IHC study of naturally infected horses concluded that examination of the spinal cord is required to accurately identify West Nile virus infection. Another report, in which RT-PCR was used, concluded that high-quality samples of medulla were sufficient to detect the presence of the virus. Postmortem confirmation of the diagnosis through virus isolation is possible, but the sensitivity is generally inferior to molecular biology-based techniques. RT-PCR is generally superior to IHC. The processing of tissue from multiple CNS sites is recommended to increase the chances of finding a virus-rich focus. High concentrations of West Nile virus are not found in non-CNS tissues of infected equids, in contrast to the distribution of the virus in many other species.

Samples for Confirmation of Diagnosis

- **Virology:** minimum sample is half of sagittally sectioned hindbrain (must include medulla). Ideally a segment of thoracolumbar spinal cord as well. Submit samples chilled (VI, RT-PCR)
- **Histology:** same samples, fixed in formalin (LM, IHC, RT-PCR).

Note the zoonotic potential of this disease when collecting and submitting specimens. Some authorities recommend using containment level 3 precautions when handling potentially infected tissues, such as that from birds.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses for West Nile encephalitis include (Table 14-11) the following:

- Eastern and Western encephalitis
- Venezuelan equine encephalitis
- Equine herpesvirus-1 myeloencephalopathy
- Hendra virus infection
- Rabies
- Botulism
- Hepatic encephalopathy
- Borna disease
- Equine protozoal myeloencephalitis
- Leukoencephalomalacia
- Lower motor neuron disease

TREATMENT

There is no specific treatment for West Nile encephalitis, although administration of IFN or hyperimmune globulin has been advocated. Affected horses are often administered nonsteroidal antiinflammatory drugs such as flunixin meglumine, dimethyl sulfoxide, or corticosteroids in an attempt to reduce inflammation in neural tissue. Administration of corticosteroids minimally but statistically significantly increases the likelihood of survival, but this practice is controversial. Treatment is based on supportive care and prevention of complications of neurologic disease and includes assistance to stand, including use of a sling support, administration of antimicrobials, and maintenance of hydration and nutrition.

CONTROL

Control of disease associated with West Nile virus and other flaviviruses is achieved by vaccination and minimization of exposure. It is important to recognize that factors affecting vector density, as happened in Australia in 2011, introduction of new vectors, or emergence of virus strains with higher virulence can affect incidence of the disease and require revision of existing control measures.[12,25,31] Elimination of the virus is not practical given that it cycles through avian and insect vectors and that the horse is incidentally infected.

Vaccination is effective in preventing development of disease, and reduces the likelihood of death in horses with West Nile encephalitis by approximately two to three times.[32-34] Vaccination is an important aspect of controlling the disease. There is no evidence that administration of the inactivated virus vaccine increases the risk of fetal loss in mares. Vaccination prevents viremia in most horses following exposure to West Nile virus-infected mosquitoes. Vaccination induces an IgG, but not an IgM, response in horses providing a means of identifying recently naturally infected horses from those with vaccine-induced serologic results.[32]

Both inactivated virus vaccine and a live canarypox-vectored recombinant vaccine are available in North America.[6] The inactivated virus vaccine should be administered in two doses at an interval of 3 to 6 weeks in early summer in the first instance, and then again once to twice yearly before the season of peak disease incidence. Foals from unvaccinated mares should be administered the vaccine beginning at 2 to 3 months of age, and foals of vaccinated mares should be administered the vaccine beginning at 7 to 8 months of age. Vaccination of foals that acquired passive immunity from the dam can be effective at inducing active immunity when the first dose of vaccine is administered at 3 months of age.[35]

Administration of the recommended two doses of inactivated virus vaccine fails to induce an adequate plaque reduction titer in approximately 14% of horses 4 to 6 weeks after vaccination and in 30% of horses 5 to 7 months after vaccination. This effect was especially evident in horses >10 years of age. These results indicate that some horses will not develop protective immunity against West Nile virus despite administration of vaccine in the recommended dose and interval.

Minimization of exposure of horses to the virus includes reducing the population density of mosquitoes and protecting horses from being bitten. Reducing the population of mosquitoes includes widespread spraying with insecticides and elimination of mosquito breeding sites. Widespread spraying in cities is used when the disease is a risk for humans but is not practical for controlling mosquitoes in rural areas. Environmental concerns make this approach to control unacceptable in many regions.

Removal of larval habitat by draining standing water is recommended for control of West Nile virus, although the efficacy of this approach has not been demonstrated. Standing water includes not just dams and ponds but also poorly maintained outdoor swimming pools, bird baths, discarded vehicle tires, and other receptacles that could hold water. Use of larvicidal compounds in standing water is recommended by some authorities.

Minimizing the frequency with which horses are bitten by mosquitoes has the potential to reduce the risk of contracting the disease. However, specific recommendations are not available. Housing during periods of peak mosquito activity, especially at dawn and dusk, might reduce the risk of disease.

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JAPANESE ENCEPHALITIS

Japanese encephalitis is a neurologic disease of humans, horses, and cattle caused by Japanese encephalitis virus. The disease is an important zoonosis in Asia, arising as a result of virus infection of amplifying hosts (pigs) transmitted by mosquitos from the avian wildlife reservoir. Horses, cattle, and humans are not important in the propagation of the disease because of the low levels of viremia in these species. There is an effective vaccine.

ETIOLOGY

Japanese encephalitis flavivirus (JEV), a member of the Flaviviridae family (which also includes Murray Valley encephalitis virus, Kunjin virus, and West Nile virus), all of which cause disease in humans, horses, and other mammals, and Usutu virus, which causes disease only in birds.[1-3] JEV, an enveloped virus of about 50 nm in diameter, has a nonsegmented, single-stranded, positive-sense RNA genome of about 11 kb in length.[3] The genome has one long open reading frame (ORF) that encodes a single poly-

protein is cleaved cotranslationally and posttranslationally into three structural proteins and seven nonstructural proteins. The three structural proteins are the capsid (C), precursor to membrane (prM), and envelope (E) proteins.[3] Based on the nucleotide sequence of genomic RNA, JEV is classified into five major genotypes.[4-9] Genotype 1 occurs in the People's Republic of China, Vietnam, South Korea, Northern Thailand, Cambodia, Japan, Australia, India, and Chinese Taipei; Genotype 2 occurs in Southern Thailand, Malaysia, Indonesia, Northern Australia, and Papua New Guinea; Genotype 3 is present in Indonesia, Malaysia, Nepal, Sri Lanka, India, Indochinese Peninsula, Philippines, Chinese Taipei, South Korea, People's Republic of China, Vietnam, and Japan; Genotype 4 was isolated only during 1980 and 1981 in Indonesia; and Genotype 5 occurs Malaysia, Tibet (China), and South Korea (Fig. 14-5).[2,4,5,9] JEV RNA has been detected in dead birds and a *C. pipiens* mosquitos in Italy.[10]

The virus cycles between avian and mammalian amplifying hosts and the mosquitoes (Fig. 14-6).[2] The natural maintenance reservoir for JEV are birds of the family Ardeidae (herons and egrets), which do not demonstrate clinical disease but do have high levels of viremias. The pig is the principal mammalian amplifying host among domestic animals. Horses, cattle, sheep, goats, dogs, cats, and humans become infected but likely play only a minor role in the spread of the virus because of the low level of viremia in these species. There are a number of species of mosquito important in the biology of the virus:[11,12] *C. tritaeniorhynchus* is the primary vector, whereas *C. gelidus, C. fuscocephala*, and *C. annulirostris* are considered as secondary/regional vectors. The virus has been detected in *Anopheles peditaeniatus Leicester, A. barbirostris* (*van der Walp*), and *A. subpictus* in India.

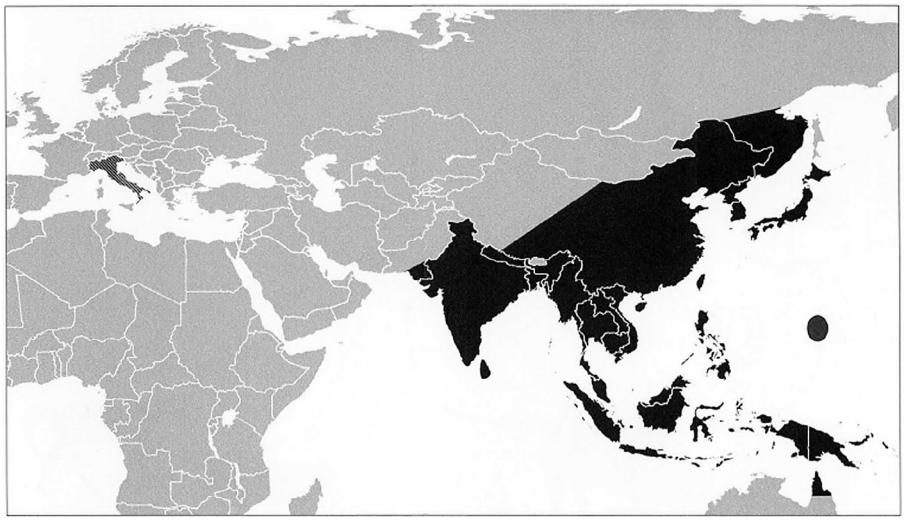

Fig. 14-5 Distribution of Japanese Encephalitis Virus as of 2015. Viral genome has been detected in dead birds and mosquitos in Italy, but the virus has not been isolated nor disease consistent with Japanese encephalitis detected in that country. (reproduced with the permission of the World Organisation for Animal Health (OIE, www.oie.int). Fig. 2 of Morita K., et al., Japanese encephalitis. *In* New developments in major vector-borne diseases. Part II: Important diseases for veterinarians (S. Zientara, D. Verwoerd & P.-P. Pastoret…, eds). *Rev. Sci. Tech. Off. Int. Epiz.*, 34 (2), page 443. doi: 10.20506/rst.34.2.2370.)

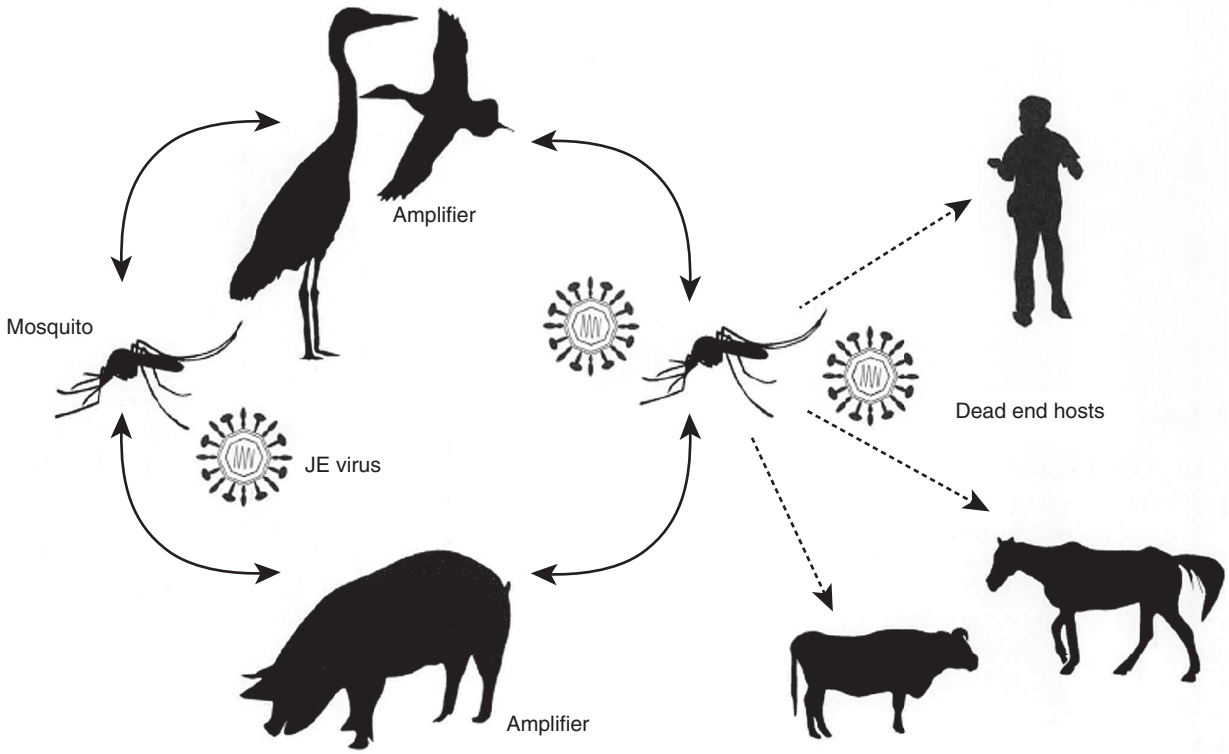

Fig. 14-6 Transmission cycle of Japanese encephalitis virus between amplifiers (pigs and wild birds) and mosquito vectors (especially *Culex tritaeniorhynchus*), including the infection of dead-end hosts (humans, horses, cattle). (reproduced with the permission of the World Organisation for Animal Health (OIE, www.oie.int). Fig. 3 of Morita K., et al., Japanese encephalitis. *In* New developments in major vector-borne diseases. Part II: Important diseases for veterinarians (S. Zientara, D. Verwoerd & P.-P. Pastoret…, eds). *Rev. Sci. Tech. Off. Int. Epiz.*, 34 (2), page 444. doi: 10.20506/rst.34.2.2370.)

Aedes koreicus, a potential vector of JEV, is reported for the first time in northern Italy/Switzerland (it has been reported in Belgium and parts of central Europe), continuing a pattern of climate change-induced incursions of insect vectors of important viral diseases into Europe.[13] *Ochlerotatus detritus* (syn. *Aedes detritus*), a temperate zone (British) mosquito can be infected by JEV in laboratory settings and might be a competent vector in the field, although this remains to be established.[11]

The virus is destroyed by heating for 30 minutes above 56°C and the thermal inactivation point (TIP) is 40°C. It is inactivated in acid environment of pH 1 to 3 but stable in alkaline environment of pH 7 to 9. The virus is very labile, is sensitive to ultraviolet light and gamma irradiation, and does not survive well in the environment.

EPIDEMIOLOGY

The disease in humans, horses, pigs, or cattle occurs **throughout the Orient and Southeast Asia** and has extended into Papua New Guinea, the Torres Strait, and northern Australia. Outbreaks of disease occurred in the Torres Strait in 1995, and disease in humans has occurred rarely in northern Australia. Outbreaks of disease have not occurred in Australia, despite large populations of wild pigs, wading birds, and mosquitoes probably because the mosquitoes prefer to feed on marsupials, which are poor hosts for JEV.

Sporadic clinical cases of JEV in horses have been reported in various countries including Japan, Hong Kong, Taiwan, and India.[4,14,15] Horse deaths are now uncommon in Japan with few to none reported in several decades,[2,15] because of vaccination of most horses, but 15% to 70% of race horses have antibodies to JEV that are not induced by vaccination. Antibodies against JEV were detected in 67 of 637 (10.5%) horses in India screened between 2006 and 2010.[14] Seroepidemiologic surveys of cattle in Japan reveal that about 68% of animals are positive. Disease in horses and humans occurs in China. The prevalence of the disease is related to the population of pigs, the main amplifying host; the mosquito vector; and susceptible human and equine hosts. Japanese encephalitis virus HI seroprevalence was 74.7% (95% CI = 71.5%–77.9%), JEV IgM seroprevalence was 2.3% (95% CI = 1.2%–3.2%) in pigs at slaughter in Laos, with greater prevalence during the monsoonal season.[16] Factors affecting the number of mosquitoes include availability of suitable habitat, such as a rice field in which survival of mosquito larvae is enhanced by application of nitrogenous fertilizers and the presence of phytoplankton, which provide food and shelter for the larvae.

CLINICAL SIGNS

The **clinical manifestations** of the disease in horses vary widely in severity.[15] Mild cases show fever up to 39.5°C (103°F), anorexia, sluggish movements, and sometimes jaundice for 2 to 3 days only. A more severe form of the disease includes lethargy with variable febrile periods (as high as 41°C), with a pronounced stupor, bruxism and chewing motions, difficulty in swallowing, petechiation of mucosa, incoordination, neck rigidity, apparent impaired vision, paresis, and paralysis. Recovery usually occurs within about a week. More severe cases show pronounced lethargy, mild fever, and somnolence. Jaundice and petechiation of the nasal mucosa are usual. There is dysphagia, incoordination, staggering, and falling. There is also a hyperexcitable form of the disease characterized by high fevers (41°C or higher), profuse sweating and muscle tremors, aimless wandering, behavioral changes manifested by aggression, loss of vision, collapse, coma, and death. This severe type of the disease is uncommon, representing only about 5% of the total cases, but is more likely to terminate fatally. In most cases complete recovery follows an illness lasting from 4 to 9 days. The disease occurs in foals and can manifest as encephalitis.[14]

Infection of **cattle, sheep, and goats** is usually clinically inapparent and of little overall significance, although rare cases of clinical disease occur in these species.[2,17,18] Widespread losses, however, have been reported in **swine**, particularly in Japan. The disease occurs as a nonsuppurative encephalitis in pigs under 6 months of age. Sows abort or produce dead pigs at term, and the disease has economic importance because of these losses.

CLINICAL PATHOLOGY

A variety of tests are available to detect antibodies to JEV or viral RNA. A latex agglutination test provides accurate detection of antibodies in the field. However, definitive diagnosis of Japanese viral encephalitis should not be based exclusively on serology because infection with antigenically related viruses including Murray Valley encephalitis virus, Kunjin virus, and West Nile virus can cause false-positive (from the perspective of JEV) results. Isolation of this flavivirus is difficult, and bioassay techniques are comparatively slow. As a result, detection via PCR is likely to be increasingly utilized. Tests to detect viral RNA in mammalian tissues or mosquitos are available.[19-23]

NECROPSY FINDINGS

There are no characteristic gross changes. As is typical of most viral encephalitides, microscopic changes include a nonsuppurative encephalomyelitis, focal gliosis, neuronal necrosis, and neuronophagia. Lesions in piglets following experimental infection are glial cell aggregates and perivascular cuffing throughout the olfactory tract and pyriform cortex. JEV antigens were detected in the cytoplasm and neuronal processes of small nerve cells in the granule cell layer of the olfactory bulb, in the neuronal processes of the olfactory tract, and in the cytoplasm of neurons in the pyriform cortex.[24]

IHC can be used to demonstrate this virus in formalin-fixed, paraffin-embedded sections.

ZOONOSIS[25,26]

Japanese encephalitis virus is endemic in 24 countries in the WHO Southeast Asia and Western Pacific regions with more than 3 billion people at risk of infection. Japanese encephalitis is the main cause of viral encephalitis in people in many countries of Asia occurring in almost 68,000 clinical cases yearly. Children are at greatest risk, with adults in endemic areas having protective immunity as a consequence of childhood infection. Most JEV infections are mild (fever and headache) or without apparent symptoms, but approximately 1 in 250 infections results in severe disease characterized by rapid onset of high fever, headache, neck stiffness, disorientation, coma, seizures, spastic paralysis, and death.[25] Although symptomatic JEV is rare, the case–fatality rate among those with encephalitis can be as high as 30%. Permanent neurologic or psychiatric sequelae occur in 30% to 50% of people with clinical encephalitis. There is no effective, specific treatment and care of affected people includes symptomatic treatment. Safe and effective vaccines are available to prevent JEV in people and consequently the WHO recommends JEV vaccination in all regions in which the disease is a recognized public health problem.[25]

Samples for Confirmation of Diagnosis

- **Virology:** 5 mL chilled CSF fluid, chilled brain (split along midline) (ISO, BIOASSAY, PCR)
- **Histology:** fixed samples of the other half of brain, lung, spleen, liver, heart (LM, IHC)

Note the zoonotic potential of this organism when handling carcass and submitting specimens.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis in horses include[27] other equine viral encephalitides (Eastern, Western, Venezuelan, Murray Valley, West Nile), African horse sickness, Borna disease, EHV infection, equine infectious anemia, acute babesiosis, hepatic encephalopathy, rabies, tetanus, botulism, cerebral nematodiasis or protozoodiasis, or leukoencephalomalacia (*F. moniliforme*).

Differential diagnoses for pigs include[27] Menangle virus infection, porcine parvovirus infection, classical swine fever, porcine reproductive and respiratory syndrome, Aujeszky's disease (pseudorabies), La Piedad Michoacan paramyxovirus (blue eye paramyxovirus), hemagglutinating encephalomyelitis, encephalomyocarditis virus,

porcine brucellosis, Teschen/Talfan, water deprivation/excess salt, and any other causative agent of stillbirth, mummification, embryonic death, and infertility (SMEDI) or encephalitis in newborns.

TREATMENT AND CONTROL

There is no specific treatment for the disease.

Control is by vaccination. Formalinized **vaccines** afford excellent protection in pigs and horses. A delta inulin-adjuvanted, inactivated cell culture-derived JEV vaccine was safe and well tolerated and induced a strong JEV-neutralizing antibody response in all foals and pregnant mares. The neutralizing activity was passively transferred to their foals via colostrum. Foals that acquired passive immunity to JEV via maternal antibodies had evidence of maternal antibody interference to subsequent vaccination at ~35 days, but not at 1 year of age.[28]

The virus is inactivated by organic and lipid solvents, common detergents, iodine, phenol iodophors of 70% ethanol, 2% glutaraldehyde, 3% to 8% formaldehyde, and 1% sodium hypochlorite.[27]

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EASTERN AND WESTERN EQUINE ENCEPHALOMYELITIS

SYNOPSIS

Etiology Eastern encephalitis and Western encephalitis viruses.

Epidemiology Disease limited to the Americas. Arthropod, usually mosquito-borne virus. Mammals, including horses, are accidental hosts. Horse is dead-end host for EEE and WEE. Case–fatality rate 5%–70%. WEE and EEE occur as sporadic cases and as outbreaks. Both diseases affect humans.

Clinical signs Fever, muscle fasciculation, severe depression, head-pressing, incoordination, recumbency, opisthotonus and paddling, and death.

Clinical pathology Leukopenia.

Lesions Nonsuppurative encephalomyelitis.

Diagnostic confirmation Virus isolation and identification. Identification of viral antigen by indirect immunofluorescence. Serologic confirmation of exposure, preferably demonstrating an increase in hemagglutination inhibition, virus neutralization, or complement fixation titer.

Treatment No specific treatment. Supportive care.

Control Vaccination with formalin-inactivated vaccines (EEE, WEE). Insect control.

EEE, *eastern equine encephalitis;* WEE, *western equine encephalitis.*

ETIOLOGY

Equine encephalomyelitis is associated with one of the two immunologically distinct arthropod-borne alphaviruses (family Togaviridae): **eastern equine encephalomyelitis** virus (EEE) and **western equine encephalomyelitis** virus (WEE).

- There is one EEE virus strain, but two antigenic variants: North American and South American.[1]
- WEE likely arose as a recombinant of EEE and Sindbis virus. There are strains of WEE from Argentina, Brazil, and South Dakota that differ antigenically, and there are four major lineages of WEE in California whose geographic distributions overlap.

All the viruses are extremely fragile and disappear from infected tissues within a few hours of death. Both EEE and WEE cause disease in humans.[2] **WEE** is the least virulent of these viruses in horses and humans and incidence of disease in humans appears to be declining.[3,4] Transmission cycles are depicted in Fig. 14-7.

EPIDEMIOLOGY

These encephalitis viruses cause disease in horses, humans, pigs, and various birds including ratites[5,6] and domestic pheasants.

Distribution

Equine eastern and western encephalomyelitis viruses are restricted to the Americas. The two viruses have distinct geographic ranges that may overlap: **EEE** is restricted to South America and North America typically east of the Mississippi River, whereas **WEE** is found west of the Mississippi River and predominantly in the western United States and Canada, although it also occurs in Florida and South America. There is recent evidence of extension of the range of EEE into northern Maine and Vermont and the emergence of the disease in Tennessee.[6-11]

Viral Ecology

Humans, horses, cattle, pigs, dogs, and ratites are accidental hosts of the virus. The EEE and WEE viruses are normally maintained in a host–vector relationship by cycling between mosquitoes, and some other hematophagous insects, and the definitive host. However, there are some important differences in the ecology of the different viruses.

Western Equine Encephalomyelitis

The definitive hosts of endemic WEE are wild birds, which are not clinically affected, and the vectors are the mosquitoes *C. tarsalis* (in the western United States) and *Culiseta melanura* (in the eastern and southern United States). Infected mosquitoes bite susceptible birds, usually nestlings or fledglings that then develop viremia. Mosquitoes are infected by feeding on viremic birds or by vertical transmission. Vertical transmission is likely an important overwintering mechanism in WEE, and possibly EEE.

Epidemics of WEE are uncommon, but sporadic individual cases are not. Epidemics of WEE are associated with factors that increase the number of infected mosquitoes or their feeding on susceptible (unvaccinated) horses. The disease in horses occurs in midsummer and fall, and is associated with a change in the feeding habits of *C. tarsalis.* Horses, and humans, are dead-end hosts because the viremia in these species is not sufficiently severe to allow infection of feeding **mosquitoes.**

Eastern Equine Encephalomyelitis

The primary **maintenance cycle of EEE virus** is transmission between passerine birds by the mosquito *C. melanura,* an inhabitant of drainage ditches and swamps. However, other mosquitoes, including *Aedes sollicitans* and *A. vexans,* can propagate the virus through infection of large shore birds. The Carolina chickadee and yellow-crowned night heron are the most common avian hosts in the southeastern United States. Virus is detected in *C. melanura* and *Anopheles quadrimaculatus* mosquitos in Florida in February, both of which feed on the black-crowned night heron (*Nycticorax nycticorax*), The yellow-crowned night heron (*Nyctanassa violacea*), anhinga (*Anhinga anhinga*), and great blue heron (*Ardea Herodias*), suggesting a means for the virus cycle to overwinter.[12] There is increasing evidence that snakes could be a reservoir for the virus, with high seroprevalence rates for antibody to EEE.[13,14] The reservoir of the virus during winter might involve the vertical

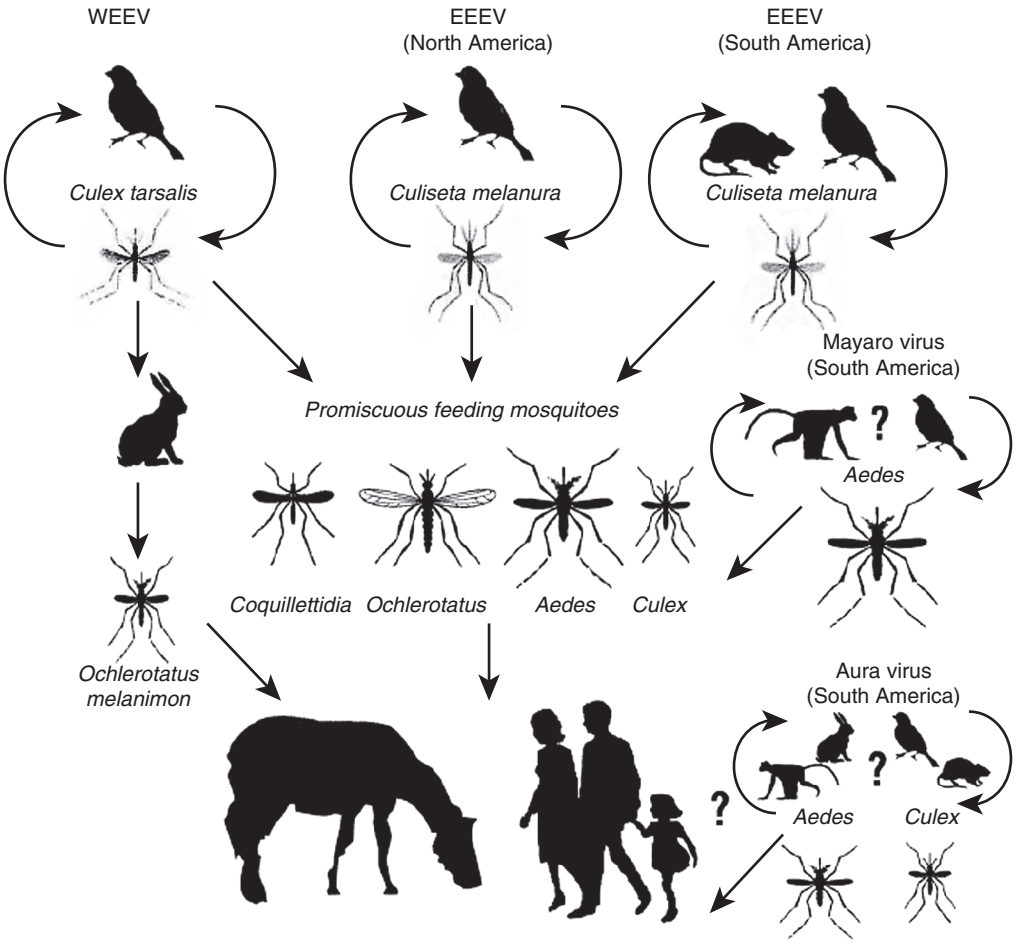

Fig. 14-7 Transmission cycles for infection with Western Equine Encephalitis Virus and Eastern Equine Encephalitis Virus in the Americas. (reproduced with the permission of the World Organisation for Animal Health (OIE, www.oie.int). Adapted from Fig. 1 of Arechiga-Ceballos N. & A. Aguilar-Setién, Alphaviral equine encephalomyelitis (Eastern, Western and Venezuelan). *In* New developments in major vector-borne diseases. Part II: Important diseases for veterinarians (S. Zientara, D. Verwoerd & P.-P. Pastoret..., eds). *Rev. Sci. Tech. Off. Int. Epiz.,* 34 (2), page 492. doi: 10.20506/rst.34.2.2374.)

transmission of infection to larvae that survive the winter.

The vertebrate host in South America has not been identified, but cotton rats and house sparrows both have the potential to be vectors.[15] The virus in North America likely has Florida as its overwintering site with subsequent seasonal spread into other states of the United States and into Eastern Canada.[1,12]

Horses are usually dead-end hosts, although viremia can be sufficiently severe in some horses to permit infection of mosquitoes.

Epidemics of EEE have occurred in the provinces of Ontario and Quebec; in virtually all the states of the United States east of the Mississippi River; in Arkansas, Minnesota, South Dakota, and Texas; in many of the Caribbean Islands; in Guatemala, Mexico, and Panama; and in Argentina, Brazil,[2,16] Columbia, Ecuador, Guyana, Peru, Suriname, and Venezuela. EEE continues to cause significant death losses annually in horses in Florida, primarily in unvaccinated horses. It is suggested that the incidence of clinical disease caused by EEE in Florida is much higher than reported, and there is a need to increase public awareness about the importance of vaccination, particularly in foals. **Unexpected epizootics** occur in inland states of the United States, and frequently the source of the infection is undetermined, although **meteorologic factors** that allow rapid movement of infected mosquitoes may be important.[5] For instance, in 1972, outbreaks of EEE occurred in Quebec, Canada, and in Connecticut, which originated with mosquitoes carried on surface winds from Connecticut to Quebec, a distance of 400 km, in 14 to 16 hours at a speed of 25 to 30 km/h and a temperature of 15°C. There may be a continual cycle of EEE virus in mosquitoes and birds in the southeastern United States, from where the virus could be distributed by infected mosquitoes on the wind along the Gulf and Atlantic Coasts and up the Mississippi Valley.

There is an increased likelihood of detecting the virus in mosquitos near wooded areas in Florida, an observation that is consistent with the patchy occurrence of the disease in that state.[17] An outbreak of EEE in equids, a llama, and pheasants in Maine was associated with unusually high numbers of *C. melanura* that year.[8]

Animal Risk Factors

Recovered horses are resistant to infection for at least 2 years, and vaccination confers immunity of variable duration (see under the section Control). **Unvaccinated horses** are at increased risk of disease; the risk of a vaccinated horse contracting EEE is only 0.14 that of an unvaccinated horse. The disease is more severe, and case fatality is higher, in unvaccinated horses than in vaccinated horses. The case fatality in young foals from nonimmune mares, which are infected with WEE, is always high, often as high as 100%.

Housing and **exposure to mosquitoes** are important risk factors for EEE, and presumably WEE. During an outbreak in 1831, only horses kept at pasture were affected. The use of **insect repellants** reduces the odds of

a horse being infected with EEE to 0.04 that of an unprotected horse. Similarly, keeping horses at pasture near woods increases the risk of disease by almost four times, and the presence of **swamp land** increases the risk by over two times. Horses kept in areas with **high precipitation** have an increased risk of the disease, presumably because of the density of mosquitoes in these areas.

Morbidity and Case Fatality

Morbidity varies widely depending on seasonal conditions and the prevalence of insect vectors; cases may occur sporadically or in the form of severe outbreaks affecting 20% or more of a group. The prevalence of infections, as judged by serologic examination, is much higher than the clinical morbidity with ~9% of horses in Quebec serologically positive for EEE but with a much lower rate of occurrence of clinical disease.[18] The **case–fatality rate** differs with the strain of the virus; in infection with the WEE virus it is usually 20% to 30% and with the EEE it is usually between 40% and 80% and may be as high as 90%.

Zoonotic Implications

The **susceptibility of humans** to the causative virus gives the disease great public health importance. Humans can become infected with the EEE and the WEE virus.[2]

PATHOGENESIS

Inapparent infection is the mildest form of the disease and may be characterized by only a transient fever. A more severe form of the disease is manifested by tachycardia, depression, anorexia, occasional diarrhea, and fever.

A transitory **viremia** occurs at the height of the fever. Penetration of the virus into the **brain** does not occur in all cases, and the infection does not produce signs, other than fever, unless involvement of the CNS occurs. The lesions produced in nervous tissue are typical of a viral infection and are localized particularly in the **gray matter of the cerebral cortex, thalamus, and hypothalamus**, with minor involvement of the medulla and spinal cord. It is this distribution of lesions that is responsible for the characteristic signs of mental derangement, followed at a later stage by paralysis. The early apparent blindness and failure to eat or drink appear to be cortical in origin. True blindness and pharyngeal paralysis occur only in the late stages.

CLINICAL FINDINGS

The diseases associated with EEE and WEE viruses are **clinically indistinguishable**. The **incubation period** for EEE is 1 to 3 days and is 2 to 9 days for WEE. Uncomplicated disease usually lasts about 1 week. In the initial viremic stage there is fever, which may be accompanied by anorexia and depression, but the reaction is usually so mild that it goes unobserved. In the experimental disease, the temperature may reach 41°C (106°F) persisting for only 24 to 48 hours, with signs of neurologic dysfunction appearing at the peak of the fever. Animals that have signs of neurologic disease for more than 24 hours are often not pyrexic.

Initial signs of neurologic disease include hypersensitivity to sound and touch, and in some cases transient periods of excitement and restlessness, with apparent blindness. Horses can have a period of anorexia and colic before onset of signs of neurologic disease. Affected horses may walk blindly into objects or walk in circles and in severe cases can mimic signs of horses with catastrophic intestinal disease. Involuntary muscle movements occur, especially tremor of shoulder and facial muscles and erection of the penis. A stage of severely depressed mentation follows. Affected horses stand with the head hung low; they appear to be asleep and may have a half-chewed mouthful of feed hanging from the lips. At this stage the horse may eat and drink if food is placed in its mouth. The pupillary light reflex is still present. The animal can be aroused, but soon relapses into a state of somnolence.

A stage of **paralysis** follows. There is inability to hold up the head, and it is often rested on a solid support. The lower lip is pendulous and the tongue protrudes from the mouth. Unnatural postures are adopted, with the horse often standing with the weight balanced on the forelegs or with the legs crossed. Head-pressing or leaning back on a halter are often seen. On walking, there is obvious incoordination, particularly in the hindlegs, and circling is common. Defecation and urination are suppressed, and the horse is unable to swallow. Complete paralysis is the terminal stage. The horse goes down, is unable to rise, and usually dies within 2 to 4 days from the first signs of illness. A proportion of affected horses do not develop paralysis and survive, but have persistent neurologic deficits.

Pigs

EEE causes an encephalitis and myocarditis of piglets less than 2 weeks of age. The disease is characterized by incoordination, seizures, vomition, weight loss, and paddling. Recovered piglets can have retarded growth.

Ratites and Pheasants

The disease in emus is characterized by vomiting, bloody diarrhea, and depression with absent to minimal signs of neurologic disease.[5] Pheasants display signs of neurologic disease and aberrant behavior such as excessive aggressive pecking and mortality rates of 30%.[8] Wild turkeys are rarely clinically infected, although they can become infected.[8]

CLINICAL PATHOLOGY

There are no characteristic hematologic or biochemical abnormalities. The absence of biochemical indication of liver disease (hyperbilirubinemia, increased activity in serum of liver-specific enzymes such as sorbitol dehydrogenase or γ-glutamyl transferase, absence of hyperammonemia) rules out hepatic encephalopathy.

Diagnostic confirmation is achieved by one or more of the following:

- Isolation of virus from an affected animal
- Detection of viral antigen or nucleic acid in an animal with appropriate clinical signs
- Seroconversion or an increase in serum titer of sick or recovered animal

Virus isolation provides definitive proof of infection. However, viremia may have resolved by the time nervous signs have developed, and it can be advantageous to sample febrile animals instead of animals showing more advanced signs of the disease. Virus can be cultured in intracranially inoculated suckling mice, weanling mice, guinea pigs, cell culture, newly hatched chicks, or embryonated eggs. Viral genome can be detected, and isolates can be identified, by quantitative RT-PCR,[19-21] or by complement fixation, HI, virus neutralization, immunofluorescent assay (IFA), and antigen capture ELISA.

Acute and convalescent sera taken 10 to 14 days apart for the presence of neutralizing, hemagglutination-inhibiting, or complement-fixing antibodies in the serum of affected or in-contact horses, is of value in detecting the presence of the virus in the group or in the area. A fourfold increase in complement-fixing antibodies is considered positive.

Demonstration of viral nucleic acid in tissue, blood, or insects by PCR test may be a useful indicator of the presence of the virus. There may be sufficient viral antigen to be detected by ELISA in clinical material, and this may provide a useful test in the early stages of an epidemic.

The presence of a high HI, complement fixation and neutralizing antibody in a **single serum sample** obtained from a horse during the acute phase of illness associated with the WEE virus can be used as presumptive evidence of infection with this virus. However, antibodies against the WEE virus can persist for years, are produced after vaccination with WEE or WEE/EEE bivalent vaccines, and in foals might be caused by colostral immunity. Therefore a single serum sample cannot be used to make a confirmed diagnosis of WEE using the HI, complement fixation or neutralization tests. Horses infected experimentally or naturally with either the WEE or the EEE virus do not produce detectable HI or neutralizing antibody for 5 to 10 days after infection.

Circulating antibody appears on or near the day of onset of clinical illness. Infection with the WEE virus results in the production of serum IgM specific to WEE, and the ELISA test is a rapid, sensitive, and specific

test for IgM against WEE and EEE viruses. Additionally, the ratio of titers of EEE and WEE can be useful in detecting infection by EEE; ratios of >8:1 are highly suggestive of EEE infection.

NECROPSY FINDINGS

The brain meninges may appear congested, but there are generally no gross changes. Histologic examination of the brain reveals perivascular accumulations of leukocytes and damage to neurons. The gray matter of the forebrain and midbrain are the most severely affected areas. Lesions associated with EEE antigen are also present in myocardium, stomach, intestine, urinary bladder, and spleen.

Cell culture and transmission experiments using brain tissue as an inoculum are the traditional means of confirming a diagnosis and require that the brain be removed within an hour of death. Transmission is by intracerebral inoculation of brain tissue into sucking mice or duck embryo tissue culture. Fluorescent antibody tests have been developed to detect EEE virus in brain tissue. A PCR-based diagnostic test is available for EEE virus. Lesions similar to those seen in horses have also been described in a beef cow infected with EEE. **The disease in piglets** is characterized by disseminated perivascular cuffing, gliosis, focal necrosis of the cerebral cortex, and multifocal myocardial necrosis.

Samples for Postmortem Confirmation of Diagnosis

- Half of midsagittally sectioned brain and liver and spleen should be submitted for fluorescent antibody and PCR testing, virus isolation and bioassay.
- Half of midsagittally sectioned brain, fixed in formalin, should be submitted for light microscopic examination.

Note the zoonotic potential of these organisms when handling the carcass and submitting specimens.

DIFFERENTIAL DIAGNOSIS

Clinically, the disease has very great similarity to the other viral encephalomyelitides, from which it can often be discriminated by the geographic location of the horse, and to the hepatic encephalopathies and a number of other diseases (see later and in Table 14-12).

West Nile encephalitis is predominantly a myelitis with later development of signs of neurologic disease, whereas EEE and WEE have predominant signs of encephalopathy.

- Rabies.
- Borna disease (occurs in Europe).
- Japanese encephalitis (occurs in Asia).
- Various other viral infections that are geographically restricted.
- Hepatic encephalopathy, such as that associated with poisoning by *Crotalaria, Senecio,* and *Amsinckia* spp.; acute serum hepatitis or hepatopathy.
- Botulism causes weakness evident as muscle fasciculation, recumbency, and dysphagia, but does not cause cerebral signs (irritation, behavioral abnormalities).
- Yellow star thistle poisoning (*Centaurea solstitialis,* and poisoning by fumonisins (*Fusarium moniliforme*) can produce similar clinical signs to that of the encephalitides, with the exception of fever.

TREATMENT

There is no definitive or specific treatment. Supportive treatment may be given with the intention to prevent self-inflicted injury and maintain hydration and nutritional status.

CONTROL

Control of viral encephalomyelitis of horses is based on the following:

- Accurate clinical and laboratory diagnosis of the disease in horses
- Use of sentinel animals to monitor the presence of the virus in the region
- Quarantine of infected horses to stop movement of virus donors
- Insect abatement when deemed necessary
- Vaccination of all horses.

Vaccination

Vaccination of horses is important for the control of EEE and VEE.[3,22] Formalin-inactivated EEE and WEE virus vaccines are available (see Table 14-14 in Venezuelan Equine Encephalitis) and are effective, although over 50% of horses with EEE had been vaccinated within the previous year. This apparent poor protection can be explained by many horses not developing a detectable change in antibody titer after vaccination with a bivalent vaccine and rapid decreases in antibody titer from a peak value achieved 2 to 4 weeks after vaccination. Vaccines are available as univalent or bivalent preparations and in combination with other antigens (for instance, tetanus toxoid). Horses should be vaccinated well in advance of the anticipated encephalomyelitis season in a given area. Vaccination against both strains of the virus is advisable in areas where the strain has not been identified or where both strains exist. The currently recommended vaccination schedule consists of two doses of the vaccine initially, 10 days apart, followed by annual revaccination using two or three doses.[22] **Annual revaccination** is currently recommended because the duration of effective immunity beyond 1 year is not known. It is probable that the initial two-dose vaccination lasts for up to 3 to 4 years. The emphasis in a vaccination program should be on the young horses.

Colostral antibody can be detected in the blood of foals from vaccinated dams for up to 6 to 7 months, after which time it declines rapidly. Foals from vaccinated dams should be vaccinated at 6 to 8 months of age and revaccinated at 1 year of age. Foals from unvaccinated dams may be vaccinated at 2 to 3 months of age and again at 1 year of age. Colostral antibodies in the foal will prevent the development of autogenous antibodies, and foals vaccinated when less than 6 months should be revaccinated when they are 1 year old or, in high-risk areas. Foals from vaccinated mares should be vaccinated at 3, 4, and 6 months of age.

Experimental DNA vaccines hold promise for the prevention of WEE.

Protection From Insects

Housing of horses indoors at night, especially in fly-proofed stables, and the use of insect repellents may restrain the spread of the virus. Use of insect repellents decreases the risk of EEE in horses to 0.04 that of unprotected horses.

Widespread spraying of insecticides to reduce the population of the vector insects has been used in the control of VEE; however, such measures are not practical for preventing sporadic cases of EEE or WEE, and the environmental impact of widespread insecticide use should be considered.

Complete eradication of the virus appears to be impossible because of the enzootic nature of the ecology of the virus. The horse is an accidental host for EEE and WEE virus making elimination of the virus impossible with methods currently available.

Zoonotic Aspects of Control

Control of the disease in humans in areas where the disease may occur is dependent on insect control, and a monitoring and surveillance early warning system is necessary to decide whether or not to take control measures. In areas where WEE occurs, clinical cases of the disease in unvaccinated horses usually precede the occurrence of the disease in humans. The establishment of a reporting system in which practicing veterinarians report all clinical cases of the disease in horses will also assist in predicting potential epidemics of WEE virus infection in the human population. Serologic surveys of wildlife may also serve as good indicators of the geographic distribution and seasonality of circulation of these viruses and provide an early warning system before the detection of human cases.

FURTHER READING

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VENEZUELAN EQUINE ENCEPHALOMYELITIS

SYNOPSIS

Etiology Venezuelan encephalitis virus (types IAB, IC, and, to a lesser extent, IE), an alphavirus.

Epidemiology Disease limited to the Americas. Arthropod-borne, usually mosquito-borne, virus. VEE occurs as epidemics associated with mutation of virus and associated movement from enzootic to epizootic cycles. Virus cycles between sylvatic rodents (and probably not birds) and mosquitos in enzootic areas. Equids and humans are amplifying hosts important in propagation of VEE in epizootics. Care–fatality rate 5%–70% for equids.

Clinical findings Fever, muscle fasciculation, severe depression, head-pressing, incoordination, recumbency, opisthotonus and paddling, and death.

Clinical pathology Leukopenia.

Lesions Nonsuppurative encephalomyelitis.

Diagnostic confirmation Virus isolation and identification. RT-PCR provides more rapid identification of virus. Identification of viral antigen by indirect immunofluorescence. Serologic confirmation of exposure, preferably demonstrating an increase in hemagglutination inhibition, virus neutralization, or complement fixation titer.

Treatment No specific treatment. Supportive care.

Control Vaccination with formalin-inactivated or modified live virus is effective. Vaccines being developed with newer technologies. Insect control.

RT-PCR, *reverse transcriptase-polymerase chain reaction.*

ETIOLOGY

Venezuelan equine encephalomyelitis (VEE) is associated with an arthropod-borne alphavirus (family Togaviridae) VEE. The VEE complex has one virus, VEE, with six antigenically related subtypes: I, VEE; II, Everglades; III, Mucambo; IV, Pixuna; V, Cabassou; and VI, AG80-663. Within subtype I are at least five variants (IAB, IC, ID, IE, and IF). Epidemic (pathogenic) VEE in horses is associated with variants IAB (originally identified as distinct variants, A and B are now considered the same variant) IC, and IE; all other subtypes of I (D-F), and other variants of VEE virus (II-VI), are usually nonpathogenic for horses and are found in sylvatic or enzootic, nonequine cycles, although they can cause disease in humans.[1] The pathogenic variant, IAB, has been detected in cryptic circulation up to 8 years after an epizootic.[2] The infection cycles between rodents and mosquitos as an enzootic cycle not associated with disease in equids or humans (Fig. 14-8). Birds might be involved in this enzootic cycling. Disease occurs when pathogenic variants of the virus become established and cycle between humans or horses, both of which have high levels of viremia, and mosquitos.[1,3]

Outbreaks of disease in horses and humans occur infrequently, but can affect large numbers of equids and humans when they do occur. Outbreaks were documented in Mexico in 1993 and 1996, and in Venezuela and Columbia in the autumn of 1995. The Columbian outbreak affected 90,000 people and killed an estimated 4000 horses. The strain involved in the Columbian outbreak was IC, whereas that involved in the Mexican outbreaks was a variant of the usually nonpathogenic IE. The outbreak in Mexico was associated with a variant of VEE that did not cause viremia in horses, although it was capable of causing neurologic disease in this species, and it might have been this attribute that abbreviated the course of the epidemic. There is evidence of continuing enzootic circulation of VEE IE in southern Mexico.[4,5]

The virus is extremely fragile and disappears from infected tissues within a few hours of death.

EPIDEMIOLOGY

Venezuelan equine encephalitis virus infects a range of species including rodents, humans, equids, cattle and dogs.[5] It causes disease in humans and equids.

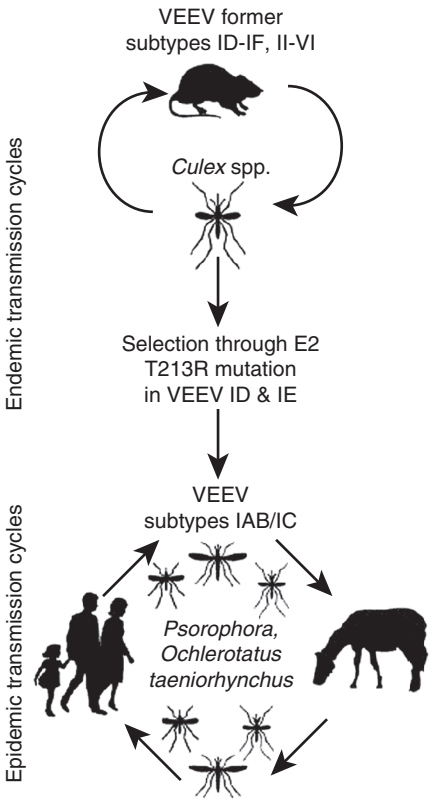

Fig. 14-8 Epidemiology of Venezuelan Equine Encephalitis virus in enzootic (endemic) and epizootic (epidemic) cycles. Note the need for mutation of the virus for development and establishment of epizootics. (reproduced with the permission of the World Organisation for Animal Health (OIE, www.oie.int). Adapted from Fig. 1 of Arechiga-Ceballos N. & A. Aguilar-Setién, Alphaviral equine encephalomyelitis (Eastern, Western and Venezuelan). *In* New developments in major vector-borne diseases. Part II: Important diseases for veterinarians (S. Zientara, D. Verwoerd & P.-P. Pastoret…, eds). *Rev. Sci. Tech. Off. Int. Epiz.,* 34 (2), page 492. doi: 10.20506/rst.34.2.2374.)

Distribution

Pathogenic or epizootic VEE is found in northern South America, Central America, Mexico and, rarely, in the southern United States. The epizootic variants are currently exotic to the United States. Enzootic VEE strains have been identified in the Florida Everglades (subtype II), Mexico (variant IE), Central American countries (variant IE), Panama (variants ID and IE), Venezuela (variant ID), Colombia (variant ID), Peru (variants ID, IIIC, and IIID), French Guiana (variant IIIB and subtype V), Ecuador (variant ID), Suriname (variant IIIA), Trinidad (variant IIIA), Brazil (variants IF and IIIA and subtype IV), and Argentina (subtype VI). In an atypical ecologic niche, variant IIIB has been isolated in the United States (Colorado and South Dakota) in an unusual association with birds.[3]

Viral Ecology

VEE exists as both nonpathogenic and pathogenic strains. **Nonpathogenic VEE viruses** persist in sylvatic cycles in northern South America, Central America, and parts of the southern United States, and are important because they are the source of the epizootic strains of the virus that emerge at infrequent intervals. The enzootic strains also confound the diagnosis of VEE because of the extensive serologic cross-reactivity among endemic and epidemic VEE viruses. However, recent advances in diagnostic techniques may have solved this diagnostic problem. The nonpathogenic viruses are maintained in rodents associated with swamps, and transmitted by mosquitoes of the genus *Culex,* and perhaps other hematophagous insects. Humans, horses, cattle, pigs, dogs, and ratites are accidental hosts of the virus. **Epidemics of VEE** occur irregularly, the latest being in northern Columbia in 1995, and Mexico in 1993 and 1996. The source of virus during outbreaks is infected horses. **Horses** develop a profound viremia and are **amplifying hosts** that aid in the spread of the epizootic; other domestic species, including cattle, pigs, and goats, are not considered to be amplifiers of the virus. During epizootics, all species of mosquitoes that feed on horses, including *Aedes, Psorophora,* and *Deinocerites* species, are thought to be capable of spreading the infection, although *O. taeniorhynchus* is thought to be the principal vector responsible for transmission of VEE virus during outbreaks, whereas *Culex* (*Melanoconion*) species mosquitoes transmit enzootic strains of VEE virus.[6] Epizootics end as the population of susceptible horses decreases below a critical level, either by death or vaccination. The **reservoir of the virus between outbreaks**, which may be up to 19 years, was unknown until it was demonstrated that epidemic VEE type IAB virus arises by **mutation of endemic strains** (types ID-F and II-VI), or that type IE (enzootic) mutates into an epizootic form serologically very similar to IE. This mutation of the endemic virus into the epidemic form has occurred on at least three occasions associated with epidemics of VEE. It is likely that pathogenic strains of VEE will continue to emerge in areas where the nonpathogenic strains of the virus are endemic.

Animal Risk Factors

Recovered horses are resistant to infection for at least 2 years, and vaccination confers immunity of variable duration (see under the section Control). **Housing** and **exposure to mosquitoes** are important risk factors for EEE, and presumably VEE.

Morbidity varies widely depending on seasonal conditions and the prevalence of insect vectors; cases may occur sporadically or in the form of severe outbreaks affecting 20% or more of a group. The prevalence of infections, as judged by serologic examination, is much higher than the clinical morbidity; for example, up to 72% of horses examined in the Gulf region of Mexico had antibodies to VEE virus (variant IE).[5] Only 0.8% of horses in Trinidad have serologic evidence of infection.[7]

The **case–fatality rate** is usually 40% to 80% and may be as high as 90% with VEE.

Zoonotic Implications

The **susceptibility of humans** to the causative virus gives the disease great public health importance. Humans can become infected with sylvatic and epizootic VEE subtypes. A recent outbreak of VEE in Columbia caused 75,000 human cases, 300 fatalities, and killed approximately 4000 horses. **Human infections** generally follow equine infections by approximately 2 weeks. The infection in humans is usually a mild, influenza-like illness in which recovery occurs spontaneously. When clinical encephalitis does occur, it is usually in very young or older people. Occurrence of the disease in humans can be limited by the use of a vaccine in horses, thus limiting the occurrence of the disease in horses in the area. There is a strong relationship between the **mosquito population** and the incidence of the disease in horses and in humans. The occurrence of the disease in humans may be predicted by an unusually high activity of virus in mosquitoes. There are usually, but not always, widespread mortalities in horses before the disease occurs in humans. VEE infections, and disease, of epizootic or enzootic virus have occurred among **laboratory workers** as a result of aerosol infections from laboratory accidents, from handling of infected laboratory animals, or inhalation of cage debris of infected laboratory animals.[3] Human VEE virus infections have originated by aerosol transmission from the cage debris of infected laboratory rodents and from laboratory accidents. Those who handle infectious VEE viruses or their antigens prepared from infected tissues or cell cultures should be vaccinated and shown to have demonstrable immunity in the form of a VEE virus-specific neutralizing antibody.

All procedures producing aerosols from VEE virus materials should be conducted in biosafety cabinets at containment level 3.[3]

VEEV viruses are highly infectious via the aerosol route for humans and has been developed as a biologic weapon in the United States and in the former Soviet Union.[6]

The TC83 live attenuated VEE virus vaccine may be **teratogenic** in humans.

PATHOGENESIS

Inapparent infection is the mildest form of the disease and may be characterized by only a transient fever. A more severe form of the disease is manifested by tachycardia, depression, anorexia, occasional diarrhea, and fever.

Viremia persists throughout the course of the disease in VEE, and the blood provides a source of infection for biting insects. Transplacental transmission of the VEE virus can occur in pregnant mares infected near term. The virus is present in saliva and nasal discharge, and this material can be used to transmit the disease experimentally by intranasal instillation.

Penetration of the virus into the **brain** does not occur in all cases and the infection does not produce signs, other than fever, unless involvement of the CNS occurs. The lesions produced in nervous tissue are typical of a viral infection and are localized particularly in the **gray matter of the cerebral cortex, thalamus, and hypothalamus**, with minor involvement of the medulla and spinal cord. It is this distribution of lesions that is responsible for the characteristic signs of mental derangement, followed at a later stage by paralysis. The early apparent blindness and failure to eat or drink appear to be cortical in origin. True blindness and pharyngeal paralysis occur only in the late stages.

CLINICAL FINDINGS

The diseases associated with the different viruses are **clinically indistinguishable**. The **incubation period** for VEE is 1 to 6 days. Uncomplicated disease usually lasts about 1 week. In the initial viremic stage there is fever, which may be accompanied by anorexia and depression, but the reaction is usually so mild that it goes unobserved. In the experimental disease, the temperature may reach 41°C (106°F) persisting for only 24 to 48 hours, with nervous signs appearing at the peak of the fever. Animals that have shown nervous signs for more than 24 hours may then have a temperature within the normal range.

Early nervous signs include hypersensitivity to sound and touch, and in some cases transient periods of excitement and restlessness, with apparent blindness. Affected horses may walk blindly into objects or walk in circles. **Involuntary muscle movements** occur, especially tremor of shoulder and facial muscles and erection of the penis. A stage of **severe mental depression** follows. Affected horses stand with the head hung low; they appear to be asleep and may have a half-chewed mouthful of feed hanging from the lips. At this stage the horse may eat and drink if food is placed in its mouth. The pupillary light reflex is still present. The animal can be aroused, but soon relapses into a state of somnolence.

A stage of **paralysis** follows. There is inability to hold up the head, and it is often rested on a solid support. The lower lip is pendulous and the tongue may hang out. Unnatural postures are adopted, with the horse often standing with the weight balanced on the forelegs or with the legs crossed. **Head-pressing** or leaning back on a halter are often seen. On walking, there is obvious incoordination, particularly in the hindlegs,

and circling is common. Defecation and urination are suppressed, and the horse is unable to swallow. Complete paralysis is the terminal stage. The horse goes down, is unable to rise, and usually dies within 2 to 4 days from the first signs of illness. A proportion of affected horses do not develop paralysis and survive but have persistent neurologic deficits.

In the experimental infection of horses with the endemic strain of the **VEE virus**, a fever and mild leukopenia occurs. Following infection with the epidemic strain of the virus, a high fever and severe leukopenia are common, and a high level of neutralizing antibodies develop about 5 to 6 days after infection. Clinical findings include profound depression, accompanied by flaccidity of lips, partially closed eyelids, and drooped ears; some horses chew continuously and froth at the mouth. In the terminal stages, there is recumbency and nystagmus.

CLINICAL PATHOLOGY

There are no characteristic **hematologic or biochemical abnormalities**. The **absence of biochemical indication of liver disease** (hyperbilirubinemia, increased activity in serum of liver-specific enzymes such as sorbitol dehydrogenase and γ-glutamyl transferase, absence of hyperammonemia) rules out hepatic encephalopathy.

Diagnostic confirmation is achieved by one or more of the following:

- Isolation of virus from an affected animal
- Detection of viral antigen or nucleic acid in an animal with appropriate clinical signs
- Seroconversion or an increase in serum titer of sick or recovered animal.

Virus isolation provides definitive proof of infection. However, viremia may have resolved by the time nervous signs have developed, and it may be advantageous to sample febrile animals instead of animals showing more advanced signs of the disease. Virus can be cultured in intracranially inoculated suckling mice, weanling mice, guinea pigs, cell culture, newly hatched chicks, or embryonated eggs. Virus isolates can be identified by complement fixation, HI, virus neutralization, PCR, IFA, and antigen capture ELISA. A recently developed indirect fluorescent test using monoclonal antibodies enables the differentiation of endemic from epidemic strains of VEE. Interpretation of the results of serologic tests of horses in an area where endemic, nonpathogenic VEE virus exists is difficult because of the cross-reaction between endemic and epidemic strains of the virus. Therefore in areas where there is endemic, nonpathogenic VEE, demonstration of the presence of antibodies should not be considered persuasive evidence of the presence of the disease.

Acute and convalescent sera taken 10 to 14 days apart for the presence of neutralizing, hemagglutination-inhibiting, or complement-fixing antibodies in the serum of affected or in-contact horses, is of value in detecting the presence of the virus in the group or in the area. A fourfold increase in complement-fixing antibodies is considered positive.

Demonstration of viral nucleic acid in tissue, blood, or insects by PCR test is a useful indicator of the presence of the virus.[8] Use of modern bioinformatic techniques can enable viral genotyping, facilitating diagnosis and forensic and epidemiologic investigations.[9] There can be sufficient viral antigen to be detected by ELISA in clinical material, and this may provide a useful test in the early stages of an epidemic.

NECROPSY FINDINGS

The brain meninges may appear congested, but there are generally no gross changes. Histologic examination of the brain reveals perivascular accumulations of leukocytes and damage to neurons. The gray matter of the forebrain and midbrain are the most severely affected areas. In some cases of VEE, liquefactive necrosis and hemorrhage are visible in the cerebral cortex. Cell culture and transmission experiments using brain tissue as an inoculum are the traditional means of confirming a diagnosis and require that the brain be removed within an hour of death. Transmission is by intracerebral inoculation of brain tissue into sucking mice or duck embryo tissue culture. Fluorescent antibody tests have been developed to detect VEE virus and EEE virus in brain tissue.

Samples for Postmortem Confirmation of Diagnosis

- Half of midsagittally sectioned brain and liver and spleen should be submitted for fluorescent antibody and PCR testing, virus isolation and bioassay.
- Half of midsagittally sectioned brain, fixed in formalin, should be submitted for light microscopic examination.

Note the zoonotic potential of these organisms when handling the carcass and submitting specimens.

DIFFERENTIAL DIAGNOSIS

Clinically, the disease has very great similarity to the other viral encephalomyelitides, from which it can often be discriminated by the geographic location of the horse, and to the hepatic encephalopathies and a number of other diseases (see next).

- Rabies.
- West Nile virus encephalomyelitis.
- Hendra disease (occurs in Australia).
- Borna disease (occurs in Europe).
- Japanese encephalitis (occurs in Asia).
- Various other viral infections that are geographically restricted.
- Hepatic encephalopathy, such as that associated with poisoning by *Crotalaria, Senecio,* and *Amsinckia* spp.; acute serum hepatitis or hepatopathy.
- Botulism causes weakness that is evident as muscle fasciculation, recumbency, and dysphagia, but does not cause cerebral signs (irritation, behavioral abnormalities).
- Yellow star thistle poisoning (*Centaurea solstitialis*) and poisoning by fumonisins can produce similar clinical signs to that of the encephalitides, with the exception of fever.

TREATMENT

There is no definitive or specific treatment. Supportive treatment may be given with the intention to prevent self-inflicted injury and maintain hydration and nutritional status.

CONTROL

Control of VEE of horses is based on the following:

- Accurate clinical and laboratory diagnosis of the disease in horses
- Use of sentinel animals to monitor the presence of the virus in the region
- Quarantine of infected horses to stop movement of virus donors
- Insect abatement when deemed necessary
- Vaccination of all horses

Vaccination

Vaccination of horses is important not only because it minimizes the risk of disease in vaccinated horses but also because it prevents viremia, subsequent infection of feeding mosquitoes, and propagation spread of VEE. There are a number of commercial vaccines available (Table 14-12).

One of the most important aspects of the control of VEE is the vaccination of the horse population to minimize the number of horses that are viremic and serve as amplifying hosts. A **tissue culture-attenuated virus vaccine, TC83**, is available for immunization of horses against VEE. The vaccine is considered to be safe and efficacious. Concerns about reversion to virulence and safety have prompted the development of DNA and chimeric vaccines, of which a number of experimental vaccines are reported.[10-15] The World Organization for Animal Health specifies vaccination by the TC83 attenuated virus vaccine or a formalin-killed virus vaccine.[3]

A **highly effective immunity** is produced within a few days following vaccination, and serum-neutralizing antibodies persist for 20 to 30 months. The vaccine causes a mild fever, leukopenia, and a viremia and, because of conflicting reports about its capacity to cause abortion, should not be used in pregnant mares. Antibodies to the heterologous alphaviruses, WEE and EEE, existing at the time of TC83 vaccination, may suppress the VEE antibody response to the vaccine.

Table 14-12 Commercial vaccines against alphaviral equine encephalomyelitis available for equines

Name*	Uses	Administration**
Equiloid Innovator: Encephalomyelitis vaccine-tetanus toxoid	For the vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis caused by Eastern and Western viruses, and tetanus	Inject one 1-mL dose intramuscularly using aseptic technique Administer a second 1-mL dose 3–4 weeks after the first dose
Fluvac Innovator 4 Encephalomyelitis-influenza vaccine-tetanus toxoid	For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis caused by Eastern and Western viruses, equine influenza from type A2 viruses, and tetanus	Inject one 1-mL dose intramuscularly using aseptic technique Administer a second 1-mL dose 3–4 weeks after the first dose
Fluvac Innovator 5 Encephalomyelitis-rhinopneumonitis-influenza vaccine-tetanus toxoid	For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis caused by Eastern and Western viruses, equine rhinopneumonitis caused by type 1 and 4 herpesviruses, equine influenza caused by type A2 viruses, and tetanus	Inject one 1-mL dose intramuscularly using aseptic technique Administer a second 1-mL dose 3–4 weeks after the first dose
Fluvac Innovator 6 Encephalomyelitis-rhinopneumonitis-influenza vaccine-tetanus toxoid	For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis caused by Eastern, Western, and Venezuelan viruses, equine rhinopneumonitis caused by type 1 and 4 herpesviruses, equine influenza caused by type A2 viruses, and tetanus	Inject one 1-mL dose intramuscularly using aseptic technique Administer a second 1-mL dose 3–4 weeks after the first dose
Fluvac Innovator Triple-E FT Encephalomyelitis-influenza vaccine-tetanus toxoid	For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis caused by Eastern, Western, and Venezuelan viruses, equine influenza caused by type A2 viruses, and tetanus	Inject one 1 mL dose intramuscularly using aseptic technique Administer a second 1-mL dose 3–4 weeks after the first dose
Triple-E T Innovator Encephalomyelitis vaccine-tetanus toxoid	For intramuscular vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis caused by Eastern, Western, and Venezuelan viruses, and tetanus	Inject one 1-mL dose intramuscularly using aseptic technique Administer a second 1-mL dose 3–4 weeks after the first dose
WEST Nile Innovator + EW Encephalomyelitis-West Nile virus vaccine	For vaccination of healthy horses as an aid in the prevention of viremia caused by West Nile virus, and as an aid in the prevention of equine encephalomyelitis caused by Eastern and Western viruses	Inject one 1-mL dose intramuscularly using aseptic technique Administer a second 1-mL dose 3–4 weeks after the first dose
West Nile Innovator + EWT Encephalomyelitis-West Nile virus-tetanus toxoid	For vaccination of healthy horses as an aid in the prevention of viremia caused by West Nile virus, and as an aid in the prevention of equine encephalomyelitis caused by Eastern and Western viruses and tetanus	Inject one 1-mL dose intramuscularly using aseptic technique Administer a second 1-mL dose 3–4 weeks after the first dose
West Nile-Innovator + VEWT Encephalomyelitis-West Nile virus-tetanus toxoid	For vaccination of healthy horses as an aid in the prevention of viremia caused by West Nile virus, and as an aid in the prevention of equine encephalomyelitis caused by Eastern, Western, and Venezuelan viruses and tetanus	Inject one 1-mL dose intramuscularly using aseptic technique Administer a second 1-mL dose 3–4 weeks after the first dose

**Commercial name and vaccine components*
***Recommended vaccination protocol*

However, the response to the vaccine is adequate to provide protection against VEE, and the interference is not considered significant. There is inconclusive evidence that WEE and EEE antibodies protect horses against infection with virulent VEE virus, or conversely that VEE antibodies protect against infection with WEE and EEE viruses. Simultaneous vaccination using formalin-inactivated EEE, WEE, and VEE (the TC83 strain of VEE) is effective and recommended in areas where all three viruses may be present.

Protection From Insects

Housing of horses indoors at night, especially in fly-proofed stables, and the use of **insect repellents** might restrain the spread of the virus.

Widespread spraying of insecticides to reduce the population of the vector insects has been used in the control of VEE in humans, along with vaccination of horses. **Complete eradication** of the virus appears to be impossible because of the enzootic nature of the ecology of the virus: epidemic VEE arising by chance mutation of endemic strains of VEE, makes elimination of the virus impossible with methods currently available.

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EQUID HERPESVIRUS-1 MYELOENCEPHALOPATHY, ABORTION, AND NEONATAL SEPTICEMIA

SYNOPSIS

Etiology EHV-1 causes respiratory disease of adults, abortion, neonatal septicemia, and myeloencephalopathy. Infection by specific variants of the virus increases the likelihood of the clinically important manifestations of infection—myeloencephalopathy and/or abortion.

Epidemiology Transmission between horses and by mediate contagion. Lifelong latency of infection with periodic reactivation of virus shedding. Respiratory disease, abortion, and myeloencephalopathy occur prominently as outbreaks, but can affect sole animals.

Clinical signs Upper respiratory disease, abortion, neonatal septicemia, and neurologic disease with incontinence, ataxia, and recumbency.

Clinical pathology No pathogenic changes in hemogram or serum biochemistry profile. Detection of viral DNA and variant genotyping by RT-PCR in nasal swabs or white blood cells, seroconversion or increase in titer using an ELISA able to differentiate between EHV-1 and EHV-4.

Diagnostic confirmation Virus isolation from, or polymerase chain reaction test on, blood, nasopharyngeal swabs or tissue. Seroconversion or increase in titer.

Treatment There is no specific treatment, although acyclovir, an antiviral agent, has been administered. Symptomatic treatment of neurologic signs in horses with myeloencephalopathy.

Control Infection is ubiquitous. Management including quarantine, maintaining mares in small bands, and education of staff about importance of control measures to prevent outbreaks of abortion or myeloencephalopathy. Vaccination for prevention of abortion. Quarantine. Hygiene.

EHV-1, *equid herphesvirus-1;* RT-PCR, *reverse transcriptase-polymerase chain reaction.*

Herpesviruses infecting equids (such as horses, donkeys, mules, and zebra) are all viruses with a linear, double-stranded DNA genome in the order Herpesvirales, family Herpesviridae.[1] Equid herpesviruses (EHV)-1, 3, 4, 8 (syn. asinine herpesvirus-3), and 9 (a virus infecting gazelle) are Alphaherpesvirinae (alphaherpesviruses) in the genus *Varicellovirus.* EHV-6 (syn. asinine herpesvirus-1) is tentatively assigned to this genus. EHV-2, 5, and 7 (syn. asinine herpesvirus-2) are Gammaherpesvirinae (gammaherpesviruses).[1] There is also a zebra gammaherpesvirus, which appears to be associated with disease in nonequids housed in proximity to zebras (see later).[2,3]

Five herpesviruses have been associated with various diseases of horses and foals (EHV-1 to 5). Common names are "equine abortion virus" for EHV-1, "cytomegalovirus" for EHV-2, "equine coital exanthema virus" for EHV-3, and "rhinopneumonitis virus" for EHV-4 (although this term is sometimes used, confusingly, for EHV-1). Related herpesviruses (asinine herpesvirus-1 to 6, some of which have been recently classified or identified as EHVs[1]) infect, and some cause disease in, donkeys, mules, or horses.[4-7] Some asinine herpesviruses cause a fatal interstitial pneumonia or neurologic disease in donkeys.[8]

Infection by EHV-1, EHV-4, or both is common, if not ubiquitous, in equids worldwide with most animals infected while juveniles and latent virus in trigeminal ganglia[9] and other tissues maintaining that infection. EHV-4 causes respiratory disease and, rarely, abortion. EHV-1 causes respiratory disease but also causes individual cases or outbreaks of myeloencephalopathy, abortion, and neonatal septicemia. Certain variants of EHV-1, detectable by examination of viral genome, are associated with increased risk of myeloencephalopathy, abortion, or both.

A partial list of disease syndromes attributed to EHV and asinine herpesvirus infection and the viruses associated with them include the following:

- **Upper respiratory tract disease** of adult horses, weanlings, and older foals is caused principally by EHV-4, although disease attributable to EHV-1 occurs. EHV-2 causes respiratory disease, including pneumonia, of foals, and rarely upper respiratory disease of adults.
- **Abortion** in horses is almost always associated with EHV-1, although rare sporadic cases are associated with EHV-4. EHV-7 (syn. asinine herpesvirus-2, a gammaherpesvirus) was associated with abortion in a donkey.[4]
- **Perinatal disease** of foals, including birth of sick and weak foals and development of viral septicemia within 48 hours of birth, is associated with EHV-1.
- **EHV-1 myeloencephalopathy** (EHM) is associated with EHV-1 and rarely, if ever, with EHV-4. In donkeys it has been associated with an asinine gammaherpesvirus.[8]
- **Coital exanthema** is associated with EHV-3, and genital disease is an unusual manifestation of EHV-1 infection.
- **Equine multinodular pulmonary fibrosis** in horses is associated with infection by EHV-5.[10,11]
- **Lymphoma** in horses is tentatively associated with infection by EHV-5.[12,13]
- **Chorioretinitis** is associated with EHV-1 infection.[14]
- **Dermatitis** (erythema multiforme) is associated with EHV-5 infection in horses.[15]
- **Neurologic disease or abortion** in gazelle, onagers, and polar bears is caused by EHV-9 or EHV-1 originating from zebra.[2,3,16,17]

The following discussion focuses on myeloencephalopathy, abortion, and neonatal septicemia in equids associated with infection by EHV-1. Respiratory disease caused by EHV-4 and EHV-1 is discussed elsewhere in this text as are other manifestations of EHV infection.

ETIOLOGY

EHV-1 is an alphaherpesvirus, a DNA virus with 76 ORFs. EHV-1 and EHV-4 are closely related and have extensive antigenic cross-reactivity but are genetically and biologically distinct viruses with different disease profiles.[18,19] Phylogenetic mapping ("trees") and genetic fingerprinting for EHV-1 are not available, as they are for many other viruses (see the section on Equine Influenza in Chapter 12 as an example), and are needed to investigate links between outbreaks and associations with virulence.

Although EHV-1 virus is genetically stable, with limited genetic divergence and differences in strains of less than 0.1%, genetic variants of EHV-1 exist and some have differing biologic characteristics.[20] Analysis of ORF 68 reveals at least 19 distinct DNA sequences allowing identification of 6 major strain groups of EHV-1.[20] Importantly, a single nucleotide polymorphism (SNP) (A-G) at position 2254 in the DNA polymerase gene (DNA_{pol}, ORF 30) that results in substitution of asparagine (N) by aspartic acid (D) at position 752 in the DNA polymerase protein is not limited to any one strain. Variants of the virus are therefore classified as N752 or D752, irrespective of the particular strain.[20] This suggests that the D752/N752 mutation has occurred multiple times.[21] The original isolation of EHV-1 in 1941 was of the D752 phenotype.[21]

The D752 variant is isolated more frequently than is N752 from horses with myeloencephalopathy and, increasingly, abortion.[22-27] Infection with the D752 variant increases the risk of myeloencephalopathy by 160× compared with that of infection with N752.[28] These data are based on retrospectively collected data that were not randomly collected, and this relative risk estimate could change markedly, although the association between increased risk of EHM and infection by D752 is well accepted.[18,19,21,23,24,29] However, horses can develop EHM when infected by the N752 variant in approximately 25% of cases (noting the uncertainty around this estimate).[28]

The N752 variant is the one most commonly reported as infecting asymptomatic horses.[28,30] Although estimates are potentially biased by the sampling method used in various epidemiologic studies, the D752 variant was identified in 3%, 10.8%–19.4%, 7.4%, 24%, and 10.6% of horses positive for EHV-1 sampled in Japan, the United States, Argentina, France, and Germany, respectively.[31] Horses can be infected by both variants of the disease simultaneously, and each variant can cause disease (D752 variant causing neurologic disease in the dam and N752 causing abortion).[32] Both D752 and N752 variants were both isolated from trigeminal ganglia of 12 of 153 horses

examined postmortem for reasons other than EHV-associated disease, indicating that symptomatic dual infection is common. One or the other variant, but not both, were isolated from a further 9/153 horses.[9] Similarly, of 70 Thoroughbred racehorses examined postmortem because of death secondary to catastrophic musculoskeletal injuries, 2 carried only a latent neurotropic strain of EHV-1, 6 carried a nonneurotropic genotype of EHV-1, and 10 were dually infected with neurotropic and nonneurotropic EHV-1.[33] Among 132 mares from central Kentucky sampled postmortem, latent EHV-1 DNA was detected in the submandibular lymph node tissues of 71 (54%). Thirteen (18%) of the 71 latently infected horses were infected with the D752 variant, of which 11 were also infected with the N752 variant.[30] The remainder were infected with only the N752 variant.

The D752 variant of EHV-1 differs from the N_{752} variant in that it causes higher levels of white blood cell–associated viremia (up to 10-fold), infects CD4+ and CD8+ cells to a greater extent but CD14 + and B cells to a lesser extent, and is less sensitive to aphidicolin, a drug targeting the viral polymerase.[34] The D752 variant is also more virulent in experimentally infected horses, with those infected with the D752 variant having higher rectal temperatures, a longer period of pyrexia after infection (3 days versus 1 day), and greater severity of nasal discharge, but no difference in nasal shedding of virus. Horses experimentally infected with D752 variant developed EHM, whereas those infected with the N752 variant did not, although uniform development of EHM in horses or ponies experimentally infected with D752 variant is not present in other studies of the disease.[34] The D752 variant infects submucosal immune cells in respiratory explants to a greater extent than does the N752 variant.[35] CSF from horses infected by D752 was abnormal, whereas that from horses infected with N752 was not abnormal.[34]

It is unclear whether viral load is associated with the outcome of clinical disease, although one study of a small number of horses (seven) treated at a referral institution, identified viral loads in nasal fluid and blood that were 1000× and 100× greater in nonsurviving horses with EHM. These findings require confirmation because of the small number of horses examined and in surviving (five) and nonsurviving groups (two).[36]

Both N752 and D752 variants can cause disease. Virulence is associated with presence of a functional gp2 protein, which is apparently responsible for viral egress from infected cells, and glycoprotein D and cell-surface glycosaminoglycans that are needed for efficient entry of EHV-1 into cells.

The most important clinical syndromes associated with EHV-1 infection are abortion, neonatal septicemia, and myeloencephalopathy. Genital disease is an unusual manifestation of EHV-1 infection. Infection with EHV-1 causes retinitis and fatal disease in camelids. It also causes disease in wild equids including zebras and neurologic disease in black bears (*Ursus americanus*), Thomson's gazelles (*Eudorcas thomsonii*), guinea pigs (*Cavia porcellus f. dom.)* Indian rhinoceros (*Rhinoceros unicornis*), and polar bears in zoologic parks in which these animals are in proximity to equids (such as zebra).[37-39] It is associated with abortions and stillbirths in guinea pigs.[37]

EPIDEMIOLOGY

Occurrence

Infection with EHV-1 is endemic in horse populations worldwide, and many adult horses have serologic evidence of infection. Serologic surveys, which provide an index of the extent of infection in the sampled population, performed before 1995 were hindered by the lack of an assay able to differentiate immune responses to EHV-1 from those to EHV-4. Furthermore, the advent of vaccines eliciting serum antibodies against EHV-1/4, and the inability of diagnostic tests to differentiate between antibodies induced by vaccination or natural infection, complicates assessment of the prevalence of serum antibodies to EHV-1/4. Seroprevalence of EHV-1–specific antibodies is 9% to 28% in adult Thoroughbred horses, 26% of Thoroughbred broodmares, 11% of Thoroughbred foals, and 46% to 68% of 1- and 2-year-old Thoroughbred race horses in Australia. Sixty-one percent of 82 normal horses and horses with upper respiratory tract disease had antibodies to EHV-1 in New Zealand. Of 70 Thoroughbred race horses examined postmortem, 18 (26%) and 58 (83%) horses were PCR positive for the gB gene of EHV-1 and EHV-4, respectively, in at least one of trigeminal ganglia, bronchial, or submandibular lymph nodes sampled. Twelve horses were dually infected with EHV-1 and EHV-4.[33]

The EHV-1 D752 variant has been detected in equids in North America, Europe (the Netherlands, France, Belgium, and Germany), Australia, New Zealand, and South America.[18,27,30-32,40-43] It likely occurs worldwide given that it is not a recent mutation, having been detected in samples collected in the 1940s.[21] EHM is rarely reported in the Southern Hemisphere with the first case described in New Zealand in 2013.[18]

Upper respiratory tract disease associated with EHV-1 infection has been suggested to occur as outbreaks, although this is not well documented. Signs of infectious upper respiratory disease affected 20% of Thoroughbred race horses at one race track in Canada over a 3-year period, and seroconversion to EHV-1 occurred in 5% to 18% of these horses, whereas the vast majority of horses seroconverted to influenza. However, all horses that seroconverted to EHV-1 also either seroconverted to influenza virus or had been recently vaccinated with a vaccine containing EHV-1. These results suggest that the stress of influenza disease may have triggered reactivation of latent EHV-1 infection in some horses, suggesting that EHV-1 did not have a primary role in the outbreak of respiratory disease. Similarly, in England, EHV-1 was not associated with clinical respiratory disease in Thoroughbred racehorses. EHV-1 was isolated from foals with purulent nasal discharge and respiratory disease concurrent with neurologic disease among the dams in Australia.

Abortion caused by EHV-1 occurs as both sporadic cases and as epizootics (abortion storms).[27,40,44] Approximately 3% of abortions in mares are attributable to EHV-1 infection, although the actual incidence probably varies widely among years and geographic regions. Outbreaks of EHV-1 abortion and birth of nonviable foals occurs sporadically on farms with sometimes catastrophic losses. Loss of foals through abortion or birth of nonviable foals can be as high as ~60% of pregnant mares on the farm.[27,40,44] Initial cases can, in the absence of appropriate control measures, rapidly spread the infection and prompt diagnosis, and implementation of control measures is important to limit the spread of infection.[27,29] Vaccination with killed EHV-1 vaccine during late gestation does not reliably prevent the disease, although conventional wisdom is to ensure that mares are well vaccinated (see the section Control).[27] EHV-4 rarely causes abortion in mares. Disease of neonates associated with EHV-1 occurs both sporadically and as outbreaks in which up to 25% of foals may be affected. Foals infected in utero usually die soon after birth, whereas those infected in the period after birth may have milder disease and a lower mortality rate (6%). One-third of viremic foals may not seroconvert, based on the complement fixation test.

Myeloencephalopathy occurs as sporadic cases but more often presents as an epizootic within a stable or barn or within a localized area. Morbidity rates in exposed horses range from 1% to 90%, mortality rates of 0.5% to 40%, and case–fatality rates of ~15%–75%.[25,32,41,43,45,46] The attack rate (number of horses with disease/number of horses infected) in outbreaks of the D752 variant is 22% to 50%.[20] Pregnant or nursing mares are suggested to be at greater risk of this disease, but outbreaks occur on premises, such as riding schools or race tracks, where there are no foals or pregnant mares.

Method of Transmission

EHV-1 is highly infectious, as evidenced by transmission of infection despite stringent biosecurity measures in referral hospitals, riding schools, and so on.[32,46,47] Transmission occurs by the inhalation of infected droplets

or by the ingestion of material contaminated by nasal discharges or aborted fetuses/placenta/fetal fluids. Viral loads in nasal fluids in horses with EHM or aborted fetuses and associated tissues and fluids can be very high.[36,48] Other routes of infection are not recognized, although EHV-1 binds in vitro to embryos, and binding persists after 10 cycles of washing, suggesting that embryo transfer has the potential to transmit infection.[49] This route of infection has not been demonstrated as being important, or indeed possible, in the spread of spontaneous disease. EHV-1 DNA, but not EHV-4, was detected in semen samples of 51 of 390 stallions, illustrating the potential for spread of the virus during mating or artificial insemination.[50]

The virus is efficiently transmitted to in-contact animals, and rapid spread of infection results from close contact of an infected animal with susceptible horses. Infection can be spread over short distances in the absence of physical contact or fomite transmission. This likely occurs by airborne spread of virus in droplets of aerosolized nasal secretions.

Infections always arise from other horses, either by direct contact or via fomites. Mediate infection from virus on fomites such as tack, veterinary equipment, vehicles, and housing occurs because the virus survives for 14 to 45 days outside the animal. The source of the virus is always one of the following:

- A horse or foal with active infection
- A fetus, fetal membranes, or reproductive tract secretions of a mare immediately after abortion or birth of a weak foal
- Virus shed by horses in which latent infection has reactivated.

Horses and foals are infectious during the active stage of disease and, because horses become **latently infected**, during subsequent periods of viral reactivation and shedding. Latent infection occurs by inclusion of virus in immune cells (CD8+ T cells) in trigeminal ganglia, submandibular lymph nodes, and likely other immunologically active tissues.[9,30,51] Latent infection by EHV-1 virus can be reactivated by administration of corticosteroids or other immunosuppressants but, at least in experimental situations, the resulting level of viremia is very low and in-contact susceptible horses were not infected.[51]

Virus is detectable in nasal fluids of approximately 70% of horses when they first exhibit clinical signs of EHM and for up to 9 days after development of it.[32,47] The duration of nasal shedding is not related to age, duration of fever, or severity of clinical signs.[32]

There is good circumstantial evidence, such as the occurrence of abortion, neonatal disease, or myeloencephalopathy in closed herds, to support a role for latency and reactivation in the genesis of the disease, although the importance of reversion from latency has been questioned. The duration of latency is unknown but is assumed to be lifelong. Latent EHV-1 virus is detectable in the trigeminal ganglion and CD5/CD8 lymphocytes. Reactivation of the virus might not result in clinical signs in the host animal, but there is shedding of virus in nasal secretions. Consequently, clinically normal animals harbor latent virus that can infect susceptible animals during periods of reactivation. This feature of the disease has obvious importance in the prevention, control, and management of outbreaks of disease.

Abortion storms are usually attributable to an index case with the following:

- A latently infected mare that sheds virus from the respiratory tract, but does not abort
- A mare that aborts an infected conceptus
- A mare that sheds virus from the respiratory tract, and then aborts

Mares usually, but not always, abort from EHV-1 infection only once in their lifetime. A likely scenario in abortion storms is the reactivation of latent virus in a resident horse with subsequent shedding of virus in nasal secretions or, if the mare aborts, fetal tissues and uterine fluids. Contamination of the environment or horse-to-horse contact spreads infection to susceptible cohorts (primary transmission). The infected cohorts then further spread the virus to other horses in that band of mares (secondary transmission), which then spread infection among other bands of mares and foals, paddocks or fields of horses, or farms (tertiary transmission).

Outbreaks of **myeloencephalopathy** likely occur through similar mechanisms. Most outbreaks are associated with an index case or introduction of a horse with signs of infectious respiratory disease, with subsequent development of new cases in horses that have either direct or indirect (aerosol or fomite) contact with the index case.[25,43,46,47] Horses with clinical signs of myeloencephalopathy excrete the virus in nasal fluids, often in high concentrations,[36] and for periods of time up to 14 days (nasal shedding of the virus has been demonstrated up to 9 days after the onset of clinical signs of EHM)[32] and can spread the disease, contrary to previous supposition. This has important implications for handling and care of affected horses, especially those severely affected horses that may be referred for intensive or specialized care. Extreme care should be exercised when accepting horses with EHM, or suspected EHM, to referral facilities or hospitals because these animals can cause nosocomial spread of infection and disease among hospitalized equids.[46,47] Furthermore, equids infected nosocomially can spread the infection when they return home.

Cycling of Infection

Studies on Thoroughbred stud farms in Australia have demonstrated the temporal sequence of events that contribute to spread of EHV-1 infection in that region and these studies likely have relevance to other regions of the globe. There is a cyclical pattern in which horses are infected at a young age and the source of infection is, depending on the age of the foal, either its dam or other foals. Foals are infected by EHV-1 and shedding virus in nasal secretions as young as 11 days of age, often without development of clinical signs but usually associated with mucopurulent nasal discharge. Peak incidences of cases of respiratory disease associated with EHV-1 are late during the foaling season before weaning, and again after weaning when foals from several groups are housed together. The source of infection in foals before weaning is mares and, as the number of foals in the herd increases over the course of the foaling season, other foals. Weanlings spread the disease among their herd during the period shortly after weaning when foals from more than one group are mixed. The incidence density of new cases among weanlings can be as high as 13 new cases per 1000 foal weeks. The disease associated with these outbreaks is mild and without long-term consequences to the foal or weanling. However, the presence of foals excreting large quantities of EHV-1 has the potential to increase the risk of viral abortion in late-term mares in contact with these foals. Furthermore, the presence of respiratory disease associated with EHV-1 and shedding of virus by foals is associated with development of myeloencephalopathy in mares.

Risk Factors

Risk factors for EHM include the following[21]:

- Presence of susceptible equids: based largely on age (>5 years) and immune status (there are no reports of horses affected twice by the disease, suggesting long-lasting immunity).
- Introduction of EHV-1: almost always associated with a horse shedding the virus, either as a result of new infection or recrudescence of latent infection.
- Presence of the D752 variant: although disease can occur associated with infection by N752.
- Season: there appears to be higher incidences of the disease in the Northern Hemisphere in autumn, winter, and spring.
- Pyrexia: horses that are pyrexic during an outbreak are more likely to develop EHM.
- Movement of new horses onto the property, or use of horses in riding schools.[32]
- Possible associations with sex (increased risk if female) or breed (pony), although these associations are not consistent in all or most studies and are of limited usefulness in controlling or managing the disease.[43,46,47]

Immunity

Immunity to EHV-1 is mediated by cytotoxic T cells, which explains the limited efficacy of inactivated virus vaccines that have minimal effect in stimulating cytotoxic T cells despite being capable of inducing a humoral immune response.[52] The presence of EHV-1 cytotoxic T-cell precursors correlates well with protection from experimental infection, and some of the EHV-1 antigens responsible for this resistance have been identified.[53-55] Mares usually only abort from EHV-1 infection once in their lifetime, and there are no reports of horses developing myeloencephalopathy more than once.

Lack of antibodies to EHV-1 was identified as a risk factor in an outbreak of EHM in a herd of mares with foals at foot. Mares with strong antibody responses to EHV-1 did not develop disease.

Economic Importance

Disease associated with EHV-1 is of considerable economic importance because of the loss of training time and opportunities to perform during convalescence and quarantine, the loss of pregnancies during abortion storms, and deaths caused by myeloencephalopathy and infection of neonates.

PATHOGENESIS

The three organ systems involved in clinical disease associated with EHV-1 infection are the respiratory tract, uterus and placenta, and CNS. The common final pathway for injury in each of these body systems is damage to vascular endothelium with subsequent necrosis, thrombosis, and ischemia.

Following EHV-1 exposure to the upper respiratory tract, virus can be detected in the soft palate and mainstem bronchus within 12 hours, and at all levels of the respiratory tract by 24 hours. The virus gains access to the body after binding to respiratory mucosal epithelium where it forms plaques that do not extend into submucosal tissues.[35] In the respiratory tract there is an initial phase after infection of nasal epithelium[56] in which there is rapid proliferation of the virus in the nasal, pharyngeal, and tonsillar mucosae, with subsequent penetration and infection of local blood vessels. This is followed by a systemic, viremic phase in which the virus is closely associated with blood lymphocytes (especially CD172a(+)),[56] from which it can be isolated. Infection induces increased production of IFN-γ by T lymphocytes.[54] Absence of viral antigens on the surface of EHV-1–infected peripheral blood mononuclear cells explains their ability to avoid complement-mediated lysis. This activity, combined with the immunosuppression that accompanies EHV-1 infection,[55,57-59] allows dissemination of the infection to the reproductive tract and CNS. Immunosuppression is mediated by production in EHV-1–infected cells of an "early protein" that interferes with peptide translocation by the transporter associated with antigen processing. Immunosuppression is evident as reduced in vitro proliferation of peripheral blood monocytes and downregulation of expression of major histocompatibility complex class I molecules on the surface of infected cells. It is from this point that the invasion of lungs, placenta, fetus, and nervous tissue occur. Movement of infected mononuclear cells into target tissues is associated with expression of adhesion molecules by endothelium in the gravid uterus and in leukocytes.

Viral infection of endothelium results in death of endothelial cells, inflammation, activation of clotting factors and platelets, increases in markers of fibrin degradation, and formation of blood clots in small vessels.[60-62] This thrombotic disease causes ischemia of neighboring tissues with subsequent necrosis and loss of function. Another theory is that deposition of antigen–antibody complexes in small vessels results in an Arthus reaction with subsequent ischemia, necrosis, and loss of function. However, recent demonstration that mares with no antibody titer to EHV-1 were at increased risk of developing myeloencephalopathy does not support a role for type III hypersensitivity in this disease. Regardless of the underlying mechanism, clinical signs are a result of vasculitis and necrosis of tissue in the CNS and reproductive tract. This is in contrast to neurologic disease associated with herpesvirus in other species, in which the nervous system disease is a direct result of infection of neural tissues.

Abortion is caused by damage to the placenta, endometrium, or fetus. Placental lesions include vasculitis, focal thrombosis, and infarction of the microcotyledons of the pregnant uterus. The fetus is infected and there are diagnostic lesions present in many aborted foals, including massive destruction of lymphocytes in the spleen and the thymus. In those abortions in which there is no lesion or evidence of virus infection in the foal, there may be extensive damage to the endometrium caused by an endothelial lesion and its attendant vasculitis, thrombosis, and secondary ischemia.

Foals that are infected in utero but survive to full term may be stillborn or weak and die soon after birth with pulmonary, hepatic, and cardiac lesions. EHV-1 infection in foals not infected before or at birth is usually a self-limiting, mild infection of the upper respiratory tract with an accompanying leukopenia and a transitory immune suppression, although uveitis and occasionally death occur in a small number of foals. Virus can be isolated from the nasal mucus and the buffy coat of the blood for some time after clinical signs have disappeared.

The pathogenesis of **myeloencephalopathy** in horses contrasts with herpesvirus encephalitis of other species in which there is viral infection of neuronal tissue. The myeloencephalopathy in horses is, as discussed earlier, the result of vasculitis, thrombosis, and subsequent ischemia of neural tissue. Impairment of blood flow results in hypoxia and dysfunction or death of adjacent neural tissue.

CLINICAL FINDINGS

EHV-1 infection manifests as several forms of disease on a farm such that nervous system involvement can occur in an outbreak in which abortion and respiratory disease also feature, although more commonly one form of the disease (myeloencephalopathy or abortion) occurs alone or with mild respiratory disease. Foals, stallions, and mares can be affected with one or the other form of the disease, although it is most commonly seen in adult horses. Onset of neurologic signs is usually, but not invariably, preceded by cases of respiratory disease, fever, limb edema, or abortion.

Myeloencephalopathy

Myeloencephalopathy initially occurs in an index case, which might or might not have had signs of infectious respiratory disease alone or with signs of neurologic disease. Signs of neurologic disease develop in other horses approximately 6 to 14 days after disease in the index case. Disease then develops in a number of horses over a short period of time (3–10 days). Outbreaks in a stable can evolve rapidly.[25,43,46,47]

Fever, without signs of respiratory disease, often precedes signs of neurologic disease by 24 to 72 hours. The onset of neurologic signs is usually rapid, with the signs stabilizing within 1 to 2 days. Fever is more common (odds ratio 20×, 95% CI 3.4–390) in horses that go on to develop EHM, but the presence of limb edema or severity of nasal discharge are not associated with the likelihood of developing EHM during an outbreak of the disease.[32,46] Thirteen percent of 61 horses with fever recorded during an outbreak of abortion and EHM developed signs of EHM.[25] Six of seven pregnant mares aborted.

Signs are variable but usually referable to spinal white matter involvement. Affected horses have variable degrees of ataxia and paresis manifest as stumbling, toe dragging, pivoting, and circumduction that is most severe in the hindlimbs. Signs are usually symmetric. There is often hypotonia of the tail and anus.

Fecal and urinary incontinence are common and affected horses often dribble urine, have urine scalding of the skin of the perineum and legs, and require manual evacuation of the rectum. The severity of signs can progress to hemiplegia or paraplegia manifesting as recumbency and the inability to rise. Less commonly, CN deficits, such as lingual or pharyngeal paresis, head tilt, nystagmus, or strabismus, are present. Affected horses are usually alert and maintain their appetite.

Severity of neurologic disease varies among horses within an outbreak, and the prognosis is related to the severity of disease. In general, horses that become recumbent have a poor prognosis for both short-term and long-term survival despite intensive nursing care.[43,46,47] However, less severely affected horses have a good prognosis for survival, with case–fatality rates as low as 2% to 3% in some outbreaks. Horses with mild signs of neurologic disease often recover completely and return to their previous level of performance, although some have persistent neurologic deficits after 1 year.

Abortion

Outbreaks of abortion might not be preceded by clinically apparent respiratory disease. The incidence of abortion is highest in the last third of pregnancy, particularly in the 8- to 10-month period but can occur as early as the fifth month. Abortion occurs without premonitory signs, and the placenta is usually not retained. Frequently there is no mammary development. Affected mares sometimes have prolapse of the uterus. Some foals are stillborn, whereas others are weak and die soon after birth.

Abortion storms are often long-lasting, with a period of 17 to 22 days separating the index case from cases caused by secondary transmission of the virus, suggesting an incubation period of 2 to 3 weeks. Experimental infections induce abortion 15 to 65 days after intranasal inoculation of the virus. Although most abortions then occur within 1 month of the first secondary cases, abortions on a farm can continue for many months.[27]

Neonatal Viremia and Septicemia

In utero EHV-1 infection causes abortion or the birth of infected foals, some of which are normal at birth, but become weak and die within 3 to 7 days of birth with signs of respiratory distress and septicemia. A less severe form of the disease, characterized by pyrexia, nasal discharge, and chorioretinitis, occurs in slightly older foals that are apparently infected after birth. Affected foals that survive sometimes do not have serum antibodies to EHV-1. Death may be associated with secondary bacterial infection with *E. coli* or *Actinobacillus equuli,* although EHV-1 infection alone is sufficient to cause death.

Respiratory Disease

The classical respiratory tract form of the disease (rhinopneumonitis) is virtually indistinguishable on the basis of clinical signs from the other upper respiratory tract diseases of horses and is identical to that associated with EHV-4.

CLINICAL PATHOLOGY

Results of hematologic and serum biochemical examinations are neither specific nor diagnostic. EHV-1 infection of adult horses results in leukopenia that is attributable to both neutropenia and T-cell lymphopenia, with B-cell lymphocytosis occurring during the recovery period. EHV-1 septicemia of foals is characterized by profound leukopenia, neutropenia with a left shift, and lymphopenia. An approach to achieving prompt antemortem diagnosis of EHM is suggested in Fig. 14-9.[63]

CSF of horses with EHV-1 encephalomyelopathy is characteristically xanthochromic and has an increased total protein concentration (>1 g/L) with a normal white cell count.[32,64] The interpretation of EHV-1 antibody in CSF is uncertain, although normal horses are not expected to have detectable antibodies to EHV-1 in the CSF.

Serologic tests are of critical importance in diagnosis and control of EHV infections. Many horses have serum antibodies to EHV-1 and EHV-4 as a result of previous infection or vaccination. Thus the demonstration of antibodies is not in itself sufficient to confirm a diagnosis of the disease. Complement-fixing antibody appears on the 10th to 12th day after experimental infection but persists for only a limited period. Demonstration of a threefold to fourfold increase in the serum concentration of specific complement-fixing antibodies in acute and convalescent serum samples provides persuasive evidence of recent infection. Complement-fixing antibodies persist for only a short time (several months) while VN

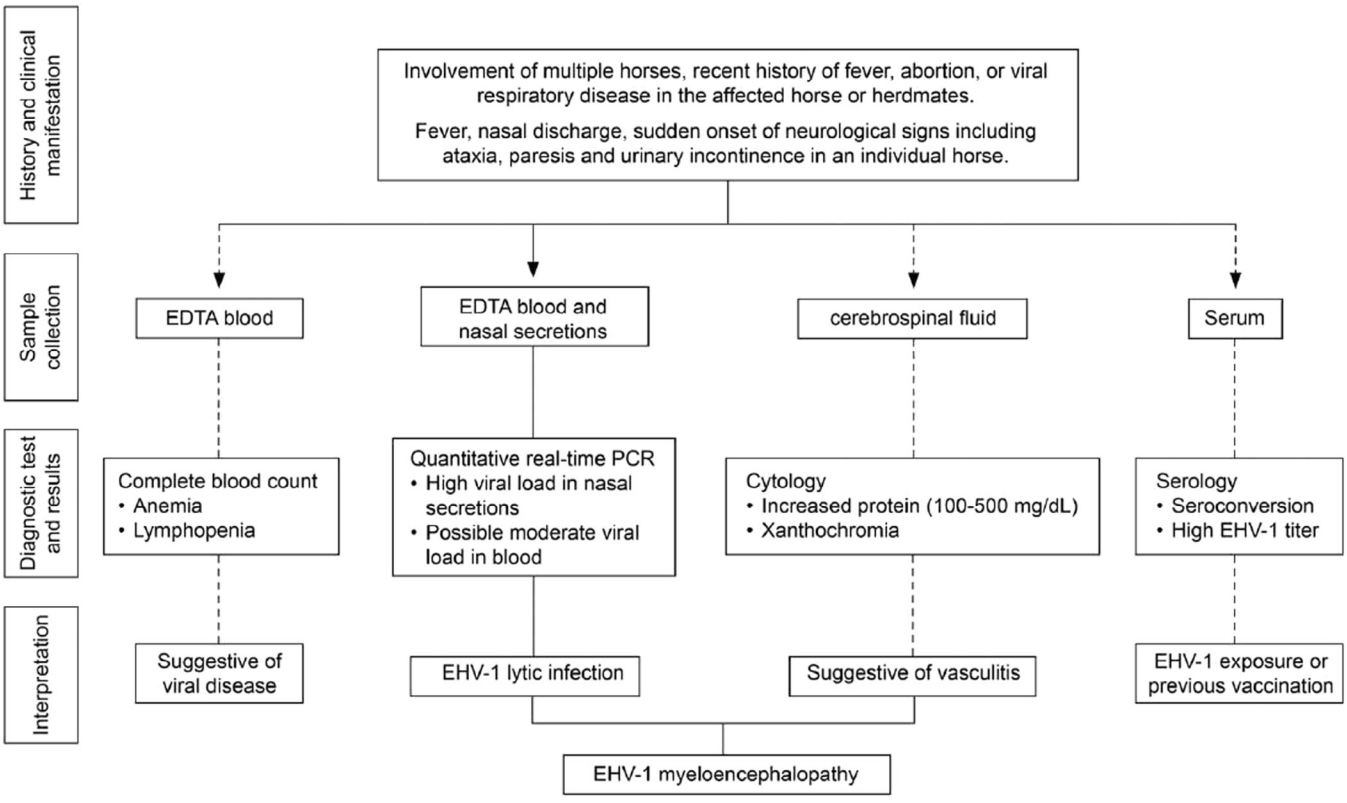

Fig. 14-9 Methodology for rapid antemortem diagnosis of equine herpesvirus-1 (EHV-1) myeloencephalopathy in horses with signs of nervous system disease. Solid lines represent a diagnostic pathway. *EDTA,* ethylenediaminetetraacetic acid. (Reproduced, with permission, from Pusterla N, Wilson WD, Madigan JE, Ferraro GL. Equine herpesvirus-1 myeloencephalopathy: a review of recent developments. *Vet J* 2009;180:279-289.)

antibodies persist for over a year, and testing for them is therefore a more reliable means of determining that previous infection with the virus has occurred. Until recently, serologic differentiation of antibodies to EHV-1 and EHV-4 was not possible. However, highly specific **ELISA** tests based on differences between EHV-1 and EHV-2 in the variable region of the C terminus of glycoprotein G, at least one of which is commercially available, have been developed that can differentiate between antibodies to EHV-1 and EHV-4 in horse serum. The ELISA is reported to be more sensitive, easier to perform, more rapid, and more reproducible than the virus neutralization test. Importantly, the ELISA test is able to differentiate between infections associated with EHV-1 and EHV-4.[65,66]

Identification of the virus in nasal swabs, or blood buffy coat, or tissue by culture or a PCR test provides confirmation of infection.[67-71] The use of seminested or multiplex PCR or qPCR, which avoids the risk of carryover contamination, provides rapid identification of EHV-1 viral genome in nasopharyngeal swabs, blood, and other tissues. The test is at least as sensitive as viral isolation in identifying presence of virus. Rapid identification of virus shedding using qPCR can facilitate monitoring and interventions to prevent spread of infection and additional examination or prophylactic treatment of infected horses.

Appropriate PCR testing can determine whether the EHV-1 is the D752 or N752 variant. This information can be important in epidemiologic investigations and might have implications for administration of antiviral therapy, although this is unclear, but generally does not influence management of a disease outbreak.[21,72]

The virus can be isolated in tissue culture, chick embryos and hamsters, from either nasal washings or aborted fetuses, and has growth characteristics that differentiate it from EHV-4.[73]

Samples of nasopharyngeal exudate for virus isolation are best obtained from horses during the very early, febrile stages of disease, and are collected via the nares by swabbing the nasopharyngeal area with a 5 × 5-cm gauze sponge attached to the end of a 50-cm length of flexible, stainless steel wire encased in latex rubber tubing. A guarded uterine swab devise can also be used. After collection, the swab should be removed from the wire and transported promptly to the virology laboratory in 3 mL of cold (not frozen) fluid transport medium (serum-free minimal essential medium with antibiotics). Virus infectivity can be prolonged by the addition of bovine serum albumin or gelatin to 0.1% (w/v).

NECROPSY FINDINGS

Macroscopic findings in **aborted fetuses** include petechial and ecchymotic hemorrhages, especially beneath the respiratory mucosae. The most consistent finding is an excess of clear yellow fluid in the pleural and peritoneal cavities. Focal hepatic necrosis and slight icterus may also be present. In some aborted fetuses the cut surface of the spleen reveals unusually prominent lymphoid follicles, which are swollen from necrosis and edema. Acidophilic intranuclear inclusion bodies may be evident histologically in a variety of cell types, including the bronchiolar and alveolar epithelium, hepatocytes, and dendritic cells of the lymphoid tissues. Although the microscopic pathology is unimpressive, examination of the placenta via IHC techniques can be a useful aid in the diagnosis of EHV-1–induced and EHV-4–induced abortions. In foals that are alive at birth but die soon afterward there is usually massive pulmonary congestion and edema, with collapse of the lung and hyaline membrane development in those that survive longer.

In the **nervous or paralytic form** of the disease there is an acute disseminated myeloencephalopathy. Hemorrhages may be visible grossly but often there are no macroscopic changes. Disseminated vasculitis occurs in the experimental disease, and the malacic lesions present in the nervous tissue are the result of leakage from these damaged vessels. The virus can be isolated from the brain, and the isolation is facilitated by use of an indirect peroxidase stain to establish the location of the virus. The virus infects endothelial cells within the CNS but has also been demonstrated within neurons and astrocytes and has been linked to chorioretinitis in a foal. In rare cases the virus may cause lesions in other tissues, such as the intestinal mucosa and spleen or pharynx.

The laboratory examination of aborted fetuses should include a search for virus by tissue culture and IHC or PCR techniques, as well as a histologic examination of the lung and liver for the presence of inclusion bodies. A direct FAT has also been used. A serologic examination of the foal may provide useful information in those cases in which attempts at isolation are negative but seroconversion has occurred. However, a recent study found that fetal serology was an unreliable means of diagnosing EHV-1 abortion, and that IHC was slightly more sensitive than virus isolation.

Samples for Confirmation of Diagnosis

- **Virology:** chilled lung, liver, spleen, thymus, and thoracic fluid of aborted fetuses or neonates. Spinal cord or brain of horses with nervous disease (VI, PCR, FAT, serology).
- **Histology:** fixed lung, liver, spleen, thymus, and trachea from fetuses or neonates.
- Fixed brain and spinal cord from several sites, as well as Bouin's fixed eye should be examined in adults with nervous disease (LM, IHC).

DIFFERENTIAL DIAGNOSIS

Respiratory disease in horses is associated with a variety of agents (Table 12-14).

Abortion can be associated with leptospirosis, *Salmonella abortusequi,* placentitis associated with *Streptococcus zooepidemicus* or *Escherichia coli,* associated with mare reproductive loss syndrome, or congenital abnormalities, among other causes. When other pregnant mares are at risk, abortion in a late-term mare should always be considered to be caused by EHV-1 until proved otherwise.

Neurologic diseases with clinical presentations similar to that associated with EHV-1 include rabies, equine protozoal myeloencephalitis, neuritis of the cauda equina (equine polyneuritis), trauma, acute spinal cord compression (cervical stenotic myelopathy), and equine degenerative myelopathy. Fever is rare in other neurologic diseases of horses, and any horse with neurologic disease and fever or a history of fever within the previous week should be considered to have EHV-1 myeloencephalopathy. Outbreaks of posterior paresis or ataxia, especially in horses without fever, should prompt consideration of ingestion of intoxicants such as *Astragalus* spp., *Swainsona* spp., or sorghum. Ryegrass staggers can produce similar signs of ataxia.

Neonatal septicemia can be associated with *E. coli, Streptococci* spp., and other bacteria, especially in foals with failure of transfer of maternal immunoglobulins.

EHV-1, equid herpesvirus-1.

TREATMENT

Because of the highly contagious nature of EHV-1 infections, horses with respiratory disease, abortion, or neurologic disease, especially if these occur as an outbreak, should be isolated until the cause of the disease is identified.

There is **no specific treatment** for the diseases associated with EHV infection, although acyclovir and other antiviral drugs are used on occasion to treat horses in outbreaks of myeloencephalopathy.[46]

Horses with EHM require intense supportive care. Nursing care to prevent urine scalding, pressure sores, and pneumonia is important in horses with myeloencephalopathy. Recumbent or severely ataxic horses should be supported to stand if at all possible. Although a rope tied to the tail and slung over an overhead beam may be used to assist the horse to stand, a sling may be necessary to support more severely affected horses. Nursing care is important to prevent development of pressure sores in recumbent horses or those supported by slings. The perineum of incontinent horses should be cleaned frequently, and salves or ointments

to protect the skin applied. Some horses require catheterization of the bladder to relieve distension. Enemas, accompanied by careful manual evacuation of the rectum, might be needed to promote passage of feces.

Administration of corticosteroids to these horses is controversial, but many clinicians administer dexamethasone sodium phosphate (0.05–0.25 mg/kg intramuscularly every 12–24 hours) or prednisolone (1–2 mg/kg orally or parenterally every 24 hours) for 2 to 3 days. Administration of corticosteroids may be contraindicated because of the presence of replicating virus in affected horses. The use of antiplatelet drugs or antithrombotic compounds has received anecdotal support, but there is no evidence that they do not harm affected horses and similarly no evidence of efficacy.

Administration of drugs to inhibit viral replication has merit and is attempted during outbreaks of disease. The challenges of this approach are that the infection is well advanced by the time clinical signs of neurologic disease are detected, especially in cases early in the disease outbreak before purposeful monitoring is in place, pharmacokinetics and pharmacodynamics of the available drugs are unknown or imperfectly known, and the drugs are expensive. Antiviral drugs considered for use in horses with EHM include acyclovir, valacyclovir, penciclovir (after oral administration of its prodrug famciclovir), ganciclovir, and valganciclovir.[74-78] Acyclovir is effective against EHV-1 in vitro, and pharmacokinetic studies suggest that administration of 10 mg/kg orally every 4 to 6 hours (five times daily) or 10 mg/kg intravenously every 8 hours results in acceptable concentrations of drug in the blood. However, further investigation reveals that there is a large variation between individual horses in the absorption of acyclovir with consequent failure to obtain therapeutic concentrations in many horses.[79] The in vitro activity of acyclovir, ganciclovir, cidofovir, adefovir, 9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine (PMEDAP) and foscarnet against three abortigenic isolates and three neuropathogenic isolates of EHV-1 revealed variable activity of cidofovir and limited to no activity of foscarnet.[80]

Current recommendations for the prophylaxis and treatment of horses with EHM include administration of acyclovir (10–20 mg/kg every 5–8 hours, orally for 7 days) or ganciclovir IV at 2.5 mg/kg every 8 h for 24 h followed by maintenance dosing of 2.5 mg/kg every 12 h, or orally at 30–40 mg/kg every 8–12 h for 7 days.[72] The efficacy of these compounds has not been demonstrated in appropriate clinical trials, and earlier comments about the variability in oral bioavailability of acyclovir should be noted.

Neonatal foals with septicemia should be treated aggressively with **antibiotics** and **supportive care**, including enteral or parenteral nutrition and fluid administration (see the section Clinical Assessment and Care of Critically Ill Newborns in Chapter 19). Treatment with acyclovir has been reported. Failure of transfer of passive immunity should be rectified with oral or intravenous administration of colostrum or plasma, respectively.

CONTROL

Recommendations for programs to prevent introduction of infection and to control EHM and abortion outbreaks are available from several sources and might vary between countries.[18,21,29,81]

Prevention of Infection

The general principles include the following:

- Enhanced immunity, currently attempted by vaccination
- Subdivision and maintenance of the farm population in groups of horses to minimize spread of the infection
- Minimize risk of introduction of infection by new horses
- Minimize risk of reactivation of latent infection in resident horses
- Develop plans for implementation of these routine control measures, and for actions in the event of an abortion
- Educate management and staff as to the importance of strict adherence to these procedures

The relative importance of each of these measures has not been determined, but implementation of control measures, including allocation of mares to small bands based on anticipated foaling date, quarantine of new introductions, and vaccination of pregnant mares, has reduced the incidence of EHV-1 abortion in central Kentucky. The most striking association has been an apparent reduction in the incidence of abortion storms. It must be emphasized that vaccination does not replace any of the other management procedures in control of this disease and that abortions have occurred among vaccinated mares on farms on which the other management procedures have been ignored.

Vaccination

Vaccination against respiratory disease and abortion associated with EHV-1 is widely practiced despite lack of clear-cut evidence that vaccination reduces the incidence or severity of either of these diseases. Information regarding field efficacy of EHV vaccines is lacking, and that derived from experimental challenge models is often contradictory or incomplete. Give these caveats, the following recommendations are made based on generally accepted practices.

None of the currently available vaccines, of which there are approximately 14 worldwide, consistently prevent infection of vaccinated horses or provide complete protection against disease associated with EHV-1.[21,52,72] The principal objective of vaccination has been to protect mares against abortion associated with EHV-1, although vaccines intended to prevent rhinopneumonitis and containing both EHV-1 and EHV-4 are available. Additionally, vaccination of mares is intended to reduce transmission of EHV-1 to foals in an attempt to interrupt the cyclical nature of infection on stud farms. Vaccines consisting of a modified live EHV-1, inactivated EHV-1, or a mixture of inactivated EHV-1 and EHV-4 are available for intramuscular or intranasal administration to horses. Both inactivated and modified live EHV-1 vaccines elicit virus-neutralization and complement fixation antibody responses in horses, although high antibody titers are not necessarily related to resistance to infection.

Resistance to infection might be more closely related to cytotoxic T-cell responses. Widespread use of a combined EHV-1 and EHV-4 killed virus vaccine in Australia has not reduced serologic evidence of infection in foals on farms where mares are vaccinated, although the vaccine was effective in preventing disease induced by experimental infection. Complicating assessment of vaccine efficacy is the variable response to vaccination by some mares and foals, with certain animals having minimal responses to vaccination, which in other horses elicits a strong immune response. Efforts are underway to develop modified live vaccines that can be administered intranasally. Intranasal administration of one such EHV-1 vaccine induced protection against experimentally induced EHV-1 (and EHV-4) respiratory disease and abortion in mares, and prevented infection of foals even when administered in the presence of maternally derived antibodies. An alternative approach is the development of subunit vaccines using the envelope glycoprotein D, which has been shown to elicit protective immunity in laboratory animal models of EHV-1 disease and administration of which induces VN antibody and glycoprotein D–specific ELISA antibodies in horses. Current modified live vaccines appear to induce a more restricted IgG isotype than does natural infection, which could partly account for their limited efficacy.[53]

Despite the incomplete protection afforded by vaccines, vaccination against EHV-1 is an important part of most equine herd health programs in the vaccination of pregnant and nonpregnant mares, foals, and adult horses. The intent of vaccination of mares is to prevent abortion associated with EHV-1. One inactivated virus vaccine is reported to decrease the incidence of abortion by 65%, although others have not been able to replicate this success and there are reports of abortion storms on farms of well-vaccinated mares. An inactivated virus vaccine containing EHV-1 and EHV-4 prevented abortion in five of six mares exposed experimentally to EHV-1, whereas all six nonvaccinated mares aborted. Mares are

vaccinated with the inactivated vaccine during the fifth, seventh, and ninth months of gestation. Additional vaccinations at breeding and 1 month before foaling are recommended by some authorities.

No vaccines are currently licensed with the claim of preventing EHM, and the disease occurs in well-vaccinated horses. Concerns that the disease might represent a "second hit" as a result of vaccination and subsequent infection have not received widespread support and do not have empirical evidence that is in any way supportive.[21]

Foals are an important source of infection and control of infection in foals is considered critical to control of infection on a farm. Consequently, attention has been paid to the responses of foals to vaccination at various ages, given the risk of passive immunity interfering with vaccination and the early age at which foals are infected by EHV-1. Current recommendations vary with some authorities recommending vaccination of foals after 5 months of age, to avoid the interfering effect of passive immunity on response to vaccination. However, vaccination of foals at this age likely misses the period of time when foals are first infected by EHV-1 from their dam or other mares in the band. One recommendation is that foals should be vaccinated in their third month, with revaccination 1 month and 6 months later. Modified live virus vaccine is given to foals at 3 to 4 months of age, and nonpregnant mares and other horses are given two doses administered 3 months apart followed by revaccination every 9 months. Because of the short duration of immunity following vaccination, frequent vaccination, perhaps at intervals as short as 3 months, of horses at high risk is recommended. However, the efficacy of such a program is uncertain.

Subdivision of Horses on a Farm

Maintenance of small groups of horses of similar age and reproductive status is recommended to minimize the chances of spread of infection. Pregnant mares, after weaning of foals, should be maintained in a herd that does not have access to foals, weanlings, nonpregnant mares, or other equids (donkeys). Similarly, weaned foals should be separated from horses of other ages in recognition of the high rate of infection and viral shedding in weanlings. Failure to adhere to these procedures can result in rapid spread of infection and abortions among at-risk mares. Pregnant mares should be combined into small groups (~10) early in pregnancy based on their anticipated foaling dates. Multiparous mares should not be mixed with mares that are pregnant for the first time.

Management practices should be introduced that minimize the opportunities for viral spread. Ideally, pregnant mares are handled using facilities separate from those used to handle mares with foals or weanlings. If common facilities must be used, pregnant mares should be handled first, after thorough cleaning of the facility, followed by mares with foals and finally weanlings and other horses.

Minimize Risk of Introduction of Infection

The only sources of virus are recrudescence of latent infection and introduction by newly arrived horses shedding virus. All horses must be considered as potentially shedding EHV-1 on arrival at a farm and should be isolated from resident horses. Introduction of new horses to the small groups of pregnant mares should be avoided if at all possible, or if absolutely necessary preceded by a 21-day isolation period. If at all possible, avoid mingling resident and nonresident mares even after quarantine of nonresident animals.

Prevention of Reactivation of Latent Infection

The factors inciting reactivation of latent infection and viral shedding are unknown. However, stressful events, such as transportation or other disease, have the potential to cause reactivation of latent infection. For this reason pregnant mares should not be shipped within 8 weeks of expected foaling and all efforts, including vaccination, should be made to prevent other infectious diseases.

Control of Outbreaks

The principles underlying control of abortions or EHM caused by EHV-1 include the following:

- Early and rapid diagnosis
- Prevention of spread of infection
- Treatment of individual cases

These aims are approached through six stages:

1. **Preliminary recognition of the problem (outbreak):** typically by owners or trainers recognizing the presence of sick horses.
2. **Preliminary veterinary investigation:** conducted by a veterinarian on, usually, their first response to the owner's concerns and leading to a presumptive clinical diagnosis.
3. **Establishing the diagnosis:** use of appropriate laboratory and other testing to confirm or rule out specific diagnoses.
4. **Understanding and managing the outbreak:** this is complex because it involves an understanding of the biology and epidemiology of the disease, the financial and social context of the outbreak, and assessment of the feasibility, and cost-effectiveness, of potential interventions.
5. **Establishing freedom of infection:** documenting the end of the outbreak and confirming freedom from infection by the offending agent.
6. **Return the premise to normal function and activity**.

Control of Outbreaks of Myeloencephalopathy

Diagnostic criteria for EHM are set out in the six stages list earlier. Adult horses with rapid onset of signs of nervous system disease, with or without fever, should be considered to have EHM until proven otherwise.

Outbreaks of EHV-1–induced neurologic disease often occur in riding schools and similar situations where there is constant movement of horses on and off the property. As such it is exceedingly difficult to institute control measures that prevent introduction of the disease and that are compatible with the use of the horses. Having said that, the principles outlined earlier for preventing introduction of infection onto breeding farms also apply for prevention of myeloencephalopathy at riding stables.

Reports of outbreaks of EHM in stables and veterinary hospitals have underscored the highly infectious nature of the disease.[25,46,47] EHV-1 is spread from infected horses, which can have virus in nasal fluid before onset of clinical signs, by aerosol, and on fomites. It is critical to prevent spread by diligent attention to biosecurity, including spread by personnel and aerosol. Infected horses should be isolated in a separate air space to uninfected or at risk horses.

Detailed instructions for handling outbreaks of neurologic disease attributable to EHV-1 are available and provide advice on quarantine, disinfection, and sample collection. There is no "one size fits all," and the recommendations should be modified or adopted with a full understanding of the financial, social, and psychologic context of managing the outbreak. Guidelines for managing an outbreak of EHM include the following[21,29,72,82]:

- Affected horses should be isolated because they are infectious.
- The diagnosis should be confirmed by virus isolation, PCR, or histologic examination of tissues from affected horses that die or are euthanized.
- Potentially affected horses should be tested to determine whether they are excreting the virus (nasal swabs).
- There should be no movement of horses on or off the premises for at least 21 days after the last case has occurred.
- Movement among bands of horses on the farm should be avoided.
- Animals should leave or move between bands only when there is no evidence of continued active infection in their group.
- Vaccination in the face of an outbreak of EHM is not recommended. Clinically affected horses should not be vaccinated.
- Prophylactic use of acyclovir has been reported, although the efficacy of this practice is unknown.

Table 14-13 Three-tiered approach to managing an outbreak of equine herpesvirus myeloencephalopathy.

	Three tiers of approach		
Action	*Gold tier*	*Silver tier*	*Bronze tier*
Segregate the population into small discrete groups that can be managed discretely to avoid infection transferring between them	**Yes** The smaller the groups the better to minimize the impact of ongoing disease and possibly reduce later laboratory test costs	**Yes** The smaller the groups the better to minimize the impact of ongoing disease and possibly reduce later laboratory test costs	**Yes** The smaller the groups the better to minimize the impact of ongoing disease and possibly reduce later laboratory test costs
Collect samples	**Collect full set from all animals** NP swab in VTM, serum (5–10 mL) and heparinized whole blood (30 ml)	**Collect partial set from all animals** NP swab in VTM and serum (5–10 mL)	**Collect partial set from all animals** NP swab in VTM and serum (5–10 mL)
Test samples	**Test full set from all animals** NP swab by qPCR, serum by CFT and heparinized blood by virus isolation	**Test partial set from all animals** NP swab by qPCR and serum by CFT	**Do not test, but freeze** the partial set from all animals for possible testing later
Observe for clinical disease (neurologic disease and/or abortion noting that pregnant mares should only be considered clear once they have a foaled successfully and have a healthy foal at foot)	**Observe all groups for 3–4 weeks**: If no clinical disease is observed in a group: collect NP swabs and sera (pair with already tested sample in CFT) and test, consider EHV-1 free if all results are negative If clinical disease is observed in a group: immediately collect and test a full set of samples from all horses in the affected group Remove positives to an isolation area Repeat after 2–3 weeks and only consider EHV-1 free when all results are negative	**Observe all groups for 3–4 weeks**: If no clinical disease is observed in a group: collect NP swabs and sera (pair with already tested sample in CFT) and test, consider EHV-1 free if all results are negative If clinical disease is observed in a group: immediately collect and test a full set of samples from all horses in the affected group Remove positives to an isolation area Repeat after 2–3 weeks and only consider EHV-1 free when all results are negative	**Observe all groups for 3–4 weeks**: If no clinical disease is observed in a group: collect NP swabs and sera (pair with frozen samples in CFT) and test, consider EHV-1 free if all results are negative If clinical disease is observed in a group: immediately collect a full set of samples from all the affected group and test all, including frozen, samples Remove positives to an isolation area Repeat after 2–3 weeks and only consider EHV-1 free when all results are negative

CFT, *complement fixation test;* NP, *nasopharyngeal;* qPCR, *quantitative polymerase chain reaction;* VTM, *virus transport medium*.
Reproduced from Gonzalez-Medina S et al: Equine Vet J *2015; 47:142.*

A suggested, three-tiered approach to managing an outbreak of EHM is depicted in Table 14-13.

Abortion

Rapid Diagnosis

Every abortion in a late-term mare should be considered to be associated with EHV-1 until proven otherwise. Therefore rapid and early diagnosis of the abortion or of EHM is important to instituting control measures. In regions with large numbers of breeding mares, **all** abortions in mares should be investigated by detailed postmortem examination of the fetus and serologic examination of the mare.

Prevention of Spread

Diligent and concerted efforts must be made to prevent dissemination of infection from the initial focus in cases of abortion. Delay in doing so increases the incidence of abortion and prolongs the outbreak.[27] Infected fetal tissues and fluids, and contaminated materials such as bedding, should be placed in impervious containers and either transported to a laboratory for examination or destroyed by incineration. Samples for laboratory examination should be handled to prevent spread of infection. Facilities and equipment that might have been contaminated should be disinfected by thorough cleaning followed by application of a phenolic or iodophor disinfectant.

The mare should be isolated until results of laboratory examination are negative for EHV-1 or until the second estrus, at which time it is unlikely that there is shedding of virus from the reproductive tract. Other mares in the same band as the mare that aborted should be considered exposed and at risk of abortion. These mares should be held in strict isolation until the results of laboratory examination are negative for EHV-1, or until they foal or abort. Other recommendations for horse movement include the following:

- When an abortion occurs on the stud, no mares should be allowed to enter or leave it until the possibility of EHV-1 infection is excluded. However, maiden and barren mares, i.e., mares that have foaled normally at home but that are not in foal, coming from home studs where no signs of the disease are occurring, may be admitted because they are considered not to be infected.
- If EHV-1 infection is identified on the stud, all pregnant mares ready to foal that season (i.e., late-pregnant mares) should remain at the stud until they have foaled. The incubation period for EHV-1 abortion ranges between 9 and 121 days.
- All nonpregnant animals and mares that have foaled should remain at the stud for 30 days after the last abortion.

The main problem that arises in this program is in deciding what to do with mares that come into contact with the respiratory disease but not the abortion disease. This may occur very early in pregnancy and prolonged isolation would be onerous. The decision usually depends on the owner's risk aversion and the availability of facilities to maintain long-term isolation.

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PERUVIAN HORSE SICKNESS VIRUS

Peruvian horse sickness virus is an Orbivirus associated with causing neurologic disease in horses in Peru with a mortality rate of approximately 1.25% and a case–fatality rate of 78%.[1] A genetically identical virus has been isolated from horses dying of neurologic disease in northern Australia.[2] Serologic surveillance in that area demonstrates antibody to Peruvian horse sickness virus in 11% of horses. The disease is described as causing motor incoordination, sagging jaw, tooth grinding, and stiff neck with death in 8 to 11 days.

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POWASSAN VIRUS

The **Powassan virus**, a flavivirus that is spread by the bite of infected ticks,[1] occurs in Ontario and the eastern United States, and produces a nonsuppurative, focal necrotizing meningoencephalitis in horses. Approximately 13% of horses sampled in Ontario in 1983 were serologically positive to the virus. Experimental intracerebral inoculation of the Powassan virus into horses resulted in a neurologic syndrome within 8 days. Clinical findings include a "tucked-up" abdomen, tremors of the head and neck, slobbering and chewing movements resulting in foamy saliva, stiff gait, staggering, and recumbency. There is a nonsuppurative encephalomyelitis, neuronal necrosis, and focal parenchymal necrosis. The virus has not been isolated from the brain.

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NIGERIAN EQUINE ENCEPHALITIS

Nigerian equine encephalitis, a disease with low morbidity but high mortality, is characterized by fever, generalized muscle spasms, ataxia, and lateral recumbency of 3 to 5 days' duration. The virus has not been identified, but the only report describes the lesions as consistent with an alphavirus, although Lagos bat virus, a pathogenic lyssavirus, is highly endemic in this area.

MAIN DRAIN VIRUS ENCEPHALITIS

The **main drain virus** has been isolated from a horse with severe encephalitis in California.[1] Clinical findings included incoordination, ataxia, stiffness of the neck, head-pressing, inability to swallow, fever, and tachycardia. The virus is transmitted by rabbits and rodents and by its natural vector, *Culicoides variipennis*.

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BORNA DISEASE

Borna disease is an **infectious encephalomyelitis** of horses and sheep first recorded in Germany. It is associated with a negative sense, single-stranded RNA virus classified as *Bornavirus* within the order Mononegavirales. There is a recently recognized avian variant of Borna disease virus, which causes disease in birds.[1]

The disease and the virus in horses are indistinguishable from EEE. Borna disease is now recognized as a subacute meningoencephalitis in horses, cattle, sheep, rabbits, and cats in Germany, Sweden, and Switzerland.[2] There are reports of encephalitis with Borna disease virus genome detected in lesions by PCR in a horse and a cow in Japan. The disease apparently occurs in New World camelids.[3] Encephalitis associated with Borna disease virus was detected in young ostriches in Israel. The disease does not appear to be a common cause of nonsuppurative encephalitis in pigs.[4] Serologic evidence of infection by Borna disease virus is widespread both geographically and in the range of species.[5,6]

Borna disease virus is suspected of causing disease in humans, including lymphocytic meningoencephalitis, but infection is not associated with an increased prevalence of psychiatric disorders. Others suggest that the presence of circulating Borna disease virus immune complexes (Borna disease virus antigen and specific antibodies) is associated with severe mood disorders in humans. The role, if any, of Borna disease virus in human neurologic or psychiatric disease has not been established with any certainty and is the subject of considerable debate.[1]

Detection of Borna disease virus **genome** by PCR analysis suggests that, although the spontaneous disease in horses and sheep occurs predominantly if not exclusively in Europe, clinically unapparent Borna disease

virus infection is widespread in a number of species including horses, cattle, sheep, cats, and foxes. However, concern has been raised that some of these reports might be based on flawed laboratory results as a consequence of contamination of PCR assays. **Antibodies** to Borna disease virus in serum or CSF have been detected in horses in the eastern United States, Japan, Iran, Turkey, France, and China, and in healthy sheep and dairy cattle in Japan. In areas in which the disease is not endemic, between 3% (United States) and 42% (Iran) of horses have either antibodies or Borna disease virus nucleic acid, detected by PCR, in blood or serum. Similarly, approximately 12% to 20% of horses have serologic evidence of exposure to Borna disease virus in areas of Europe in which the disease is endemic. Antibodies to Borna disease virus and nucleic acid have been detected in humans in North America, Europe, and Japan. Closed flocks of sheep and herds of horses have evidence of persistent infection of some animals, based on serologic testing. It is worth noting that animals infected with the virus and those who are clinically ill may have undetectable to very low antibody titers.

The method of transmission of infection between animals is unknown, but it is thought to be horizontal by inhalation or ingestion. Seropositive, clinically normal horses and sheep can excrete virus in conjunctival fluid, nasal secretions, and saliva, suggesting that they might be important in the transmission of infection. Removal of all seropositive and Borna disease virus RNA-positive sheep from a closed flock did not prevent seroconversion of other animals in the flock the following year. The possibility of vertical transmission is raised by the finding of Borna disease virus RNA in the brain of a fetal foal of a mare that died of Borna disease.

There is a seasonal distribution to the prevalence of the disease, with most cases in horses occurring in spring and early summer. The virus has not been isolated from arthropods, including hematophagous insects.

The **morbidity** in Borna disease is not high, approximately 0.006% to 0.23% of horses affected per year in endemic areas of Germany, but most affected animals die.

The **pathogenesis** of the disease involves infection of cells of the CNS. It is assumed that the virus gains entry to the CNS through trigeminal and olfactory nerves, with subsequent dissemination of infection throughout the brain. Viral transcription and replication occurs within the cell nucleus. Viral replication does not appear to result in damage to the infected neuron. However, infected cells express viral antigens on their surface, which then initiate a cell-mediated immune response by the host that then destroys infected cells (immunosuppression prevents development of the disease). The inflammatory response is largely composed of CD3 lymphocytes. The disease is subacute; infection and the development of lesions may take weeks to months. Clinically inapparent infection appears to be common in a number of species, including horses.

In **field outbreaks** the incubation period is about 4 weeks and possibly up to 6 months.

Clinical signs of the disease in horses include the following:

- Moderate fever
- Pharyngeal paralysis
- Lack of food intake
- Muscle tremor
- Defects in proprioception
- Hyperesthesia
- Blindness or visual defects[7]

Lethargy, somnolence, and flaccid paralysis are seen in the terminal stages, and death occurs 1 to 3 weeks after the first appearance of clinical signs. Infection without detectable clinical signs is thought to be common on infected premises. The frequency with which Borna disease virus is detected in horses with gait deficits is greater than in clinically normal horses, suggesting a role for the virus in inducing subtle disease.

The presentation of the disease in cattle is similar to that in horses, with affected animals having reduced appetite, ataxia, paresis, and compulsive circling. The disease ends in the death of the animal after a 1- to 6-week course.

Hematology and routine serum biochemistry are typically normal, with the exception of fasting-induced hyperbilirubinemia in anorexic horses. Clinicopathologic identification of exposed animals is achieved with complement fixation, ELISA, Western blot, or indirect immunofluorescent tests.

At **necropsy** there are no gross findings, but histologically there is a lymphocytic and plasmacytic meningoencephalitis, affecting chiefly the brainstem, and a lesser degree of myelitis. The highest concentration of virus is in the hippocampus and thalamus. The diagnostic microscopic finding is the presence of intranuclear inclusion bodies within neurons, especially in the hippocampus and olfactory bulbs. The virus can be grown on tissue culture and demonstrated within tissues by immunofluorescence and immunoperoxidase techniques. Borna disease virus can also be detected in formalin-fixed, paraffin-embedded brain tissues using a nested PCR.

Specific **control measures** cannot be recommended because of the lack of knowledge of means of transmission of the virus. The role of inapparently infected horses in transmission of the disease is unknown, and there is no widespread program for testing for such horses. An attenuated virus vaccine was produced by continued passage of the virus through rabbits and used in the former East Germany until 1992. However, its use was discontinued because of questionable efficacy.

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TESCHOVIRUS INFECTIONS

Important enteric viruses of the pig belong to the Picornaviridae particularly enteroviruses, teschoviruses and sapeloviruses (formerly porcine enterovirus A or porcine enterovirus).

SEROTYPES

The most important disease of this group is Teschen itself, which was restricted to a particular region around the town of Teschen in Czechoslovakia and the surrounding parts of Eastern Europe.[1,2] The mild forms of the disease have occurred elsewhere and are referred to as Talfan or in the past poliomyelitis suum or benign enzootic paresis, and these are probably present worldwide.

SYNOPSIS

Etiology Porcine enteroviruses capable of causing encephalomyelitis. Teschen virus, Talfan virus, and others.

Epidemiology Certain European countries, Scandinavia, and North America. Morbidity 50%; case fatality 70%–90%. Teschen in Europe. Talfan in UK. Viral encephalomyelitis in North America. Transmitted by direct contact.

Signs Acute Teschen: fever, stiffness, unable to stand, tremors, convulsions, and death in few days

Subacute Talfan: milder than acute form. Most common in pigs under 2 weeks of age. Morbidity and case–fatality rate 100%. Outbreaks. Hyperesthesia, tremors, knuckling of fetlocks, dog-sitting, convulsions, blindness, and death in a few days. Milder in older growing pigs and adults.

Clinical pathology Virus-neutralization tests.

Lesions Nonsuppurative encephalomyelitis.

Diagnostic confirmation Demonstrate lesion and identify virus.

Differential diagnosis list
- Pseudorabies
- Hemagglutinating encephalomyelitis virus

Treatment None.

Control Outbreaks will cease and herd immunity develops.

ETIOLOGY

Originally, there were at least 13 enterovirus members, and these are now reclassified. The viruses are resistant to environmental effects (in one study of disinfectants only sodium hypochlorite was effective), are stable, and easily cultivated. The only known host is the pig, and the viruses are not zoonotic.

Important enteric viruses belong to the Picornaviridae and the genera *Enterovirus, Teschovirus,* and *Sapelovirus* (these were formerly known as porcine enterovirus A or porcine enterovirus serotype B.[1] In a survey of 206 viral isolates 97 (47%) were identified as teschoviruses, 18% as sapeloviruses, and 3% as adenoviruses.[3]

Porcine enteric picornaviruses produce asymptomatic infections as well as reproductive disorders, diarrhea, pneumonia, and dermal lesions. These viruses were previously classified as enteroviruses. They are now reclassified into three groups on the basis of genomic sequences: (1) porcine teschoviruses (PTVs) with 11 different serogroups; (2) porcine enterovirus B, which corresponds to the former enterovirus serotypes 9 and 10; and (3) porcine sapelovirus (PSV), which corresponds to former enterovirus type 8 and has a single serotype that is divided into antigenic variants (PEV 8a, 8b, and 9c). It is associated with reproductive disease, diarrhea, and pneumonia.

It appears that PTV-1, the most virulent type, is only found in Central Europe (there have been a number of independent isolates, such as the Konratice and Reporyje strains) and Africa. Talfan virus, isolated from England, and other unnamed isolates appear less virulent. Teschen and Talfan virus occur in subgroup 1, which is now called porcine enterovirus group 1 (PEV-1), but isolates from encephalomyelitis are also associated with other subgroups. The other PTVs and PSV are ubiquitous. Porcine enterovirus B (PEV-9 and PEV-10) is found in Italy, UK, and Japan.[4]

A PTV caused respiratory distress and acute diarrhea in China in 50-to 70-day-old pigs.[5] PTV-8 (a sapelovirus in the new classification) caused a SMEDI-like syndrome in China,[6,7] in which approximately 80 gilts aborted and many piglets were stillborn or died soon after birth; samples from most were PTV positive.

Within subgroups, strains may be further differentiated using a complement fixation test and monospecific sera. There is variation in virulence between strains, and with many strains, clinical encephalitis following infection appears to be the exception rather than the rule. Most of the infections are subclinical.

Polioencephalomyelitis is associated with PTV-1, 2, 3, and 5; reproductive disease is associated with PTV-1, 3, and 6; diarrhea is associated with PTV-1, 2, 3, and 5; pneumonia is associated with PTV-1, 2, and 3; pericarditis and myocarditis have been associated with PTV-2 and 3; and cutaneous lesions are associated with PTV-9 and 10.

EPIDEMIOLOGY

Occurrence and Prevalence of Infection

There is serologic evidence that the disease occurs throughout the world. The most severe form of the disease, Teschen disease, appears to be limited to Europe and Madagascar, but the milder forms occur extensively in Europe (Hungary, 2012), Scandinavia, and North America (2002–2007) and recently in Japan (2012). The recent outbreak in the United States (Indiana) was ascribed to porcine enterovirus Serogroup 5 or 6 with the only characteristic feature being the histologic lesions of polioencephalomyelitis. Losses caused by the disease result primarily from deaths.

Serologic surveys in areas where the disease occurs indicate that a high proportion of the pig population is infected without any clinical evidence of the disease. In the majority of field occurrences, porcine encephalomyelitis is a sporadic disease affecting either one or a few litters, or a small number of weaned pigs.

Morbidity and Case Fatality

The morbidity rate is usually about 50% and the case–fatality rate 70% to 90% in Teschen. Talfan is much milder, and the morbidity rate below 6%.

Methods of Transmission

Infection is transmitted by the fecal–oral route and therefore by ingestion and possibly by aerosol. The virus replicates primarily in the intestinal tract, particularly the lower intestine and the ileum but also in the respiratory tract. Replication is thought to be in the reticuloendothelial cells of the lamina propria. There may be a viremia in the Teschen type of disease but not in the mild forms. Piglets may pick up the infection after weaning when the maternal antibody disappears. Many strains can infect the pig. They can be infected at any age with a strain that they have not been exposed to before. When infection first gains access to a herd, the spread is rapid and all ages of pigs may excrete virus in their feces.

Risk Factors

Animal Risk Factors

Depending on the virulence of the infecting strain, clinical disease primarily affects young pigs but may occur in older pigs at the same stage. As infection becomes endemic and herd immunity develops, excretion of the virus is largely restricted to weaned and early grower pigs. Adults generally have high levels of serum antibody, and suckling piglets are generally protected from infection by colostral and milk antibody. Sporadic disease in suckling pigs may occur in these circumstances in the litters of nonimmune or low-antibody sows, and may also occur in weaned pigs as they become susceptible to infection. In the recent outbreak in the United States, the major factor was the rapid decline of the maternal antibody in the piglets (<21 days). Seroconversion then coincided with the increased mortality in the herd.

Pathogen Risk Factors

The causative viruses will infect only pigs and are not related to any of the viruses that cause encephalomyelitis in other species. They are resistant to environmental conditions, including drying, and are present principally in the CNS and intestine of affected pigs.

PATHOGENESIS

The virus multiplies in the intestinal and respiratory tracts and Teschen produces a viremia. Invasion of the CNS may follow, depending on the virulence of the strains and the age of the pig at the time of infection. There is some strain difference in the areas of the CNS primarily affected, which accounts for variations in the clinical syndrome. Histopathologic evidence of encephalitis may be the only evidence of disease.

CLINICAL FINDINGS

Acute Viral Encephalomyelitis (Teschen Disease)

An incubation period of 10 to 12 days is followed by several days of fever (40°C-41°C, 104°F-106°F). Signs of encephalitis follow, although these are more extensive and acute after intracerebral inoculation. They include stiffness of the extremities, and inability to stand, with falling to one side followed by tremor, nystagmus, and violent clonic convulsions. Anorexia is usually complete, and vomiting has been observed. There may be partial or complete loss of voice caused by laryngeal paralysis. Facial paralysis may also occur. Stiffness and opisthotonus are often persistent between convulsions, which are easily stimulated by noise and often accompanied by loud squealing. The convulsive period lasts for 24 to 36 hours. A sharp temperature fall may be followed by coma and death on the third to fourth day, but in cases of longer duration the convulsive stage may be followed by flaccid paralysis affecting particularly the hindlimbs. In milder cases, early stiffness and weakness are followed by flaccid paralysis without the irritation phenomena of convulsions and tremor. In a recent case in the UK, the pigs were off-color, showed anterior limb paralysis, and were reluctant to rise and were therefore euthanized. Pigs were bright and keen to eat and drink.

Subacute Viral Encephalomyelitis (Talfan Disease)

The subacute disease is milder than the acute form, and the morbidity and mortality rates are lower. The disease is most common and

severe in pigs less than 2 weeks of age. Older sucking pigs are affected too, but less severely and many recover completely. Sows suckling affected litters may be mildly and transiently ill. The morbidity rate in very young litters is often 100% and nearly all the affected piglets die. In litters over 3 weeks old there may be only a small proportion of the pigs affected. The disease often strikes suddenly—all litters in a piggery being affected within a few days—but disappears quickly, with subsequent litters being unaffected. Clinically, the syndrome includes anorexia, rapid loss of condition, constipation, frequent vomiting of minor degree, and a normal or slightly elevated temperature. In some outbreaks, diarrhea may precede the onset of nervous signs, which appear several days after the illness commences. Piglets up to 2 weeks of age show hyperesthesia, muscle tremor, knuckling of the fetlocks, ataxia, walking backward, a dog-sitting posture and terminally lateral recumbency, with paddling convulsions, nystagmus, blindness, and dyspnea.

The Dresden type of teschovirus caused an ataxia and recumbency in a large group of pigs about 5 days after removal of the sows and housing in the production unit. Older pigs (4 to 6 weeks of age) showed transient anorexia and posterior paresis, manifested by a swaying drunken gait, and usually recovered completely and quickly. In the Japanese outbreak, the pigs had at 40 days of age a flaccid paralysis of the hindlimbs and became recumbent, although they could move using their forelegs. After the initial group of affected piglets the disease disappeared.

Individual instances or small outbreaks of "leg weakness" with posterior paresis and paralysis in gilts and sows may also occur with this disease.

CLINICAL PATHOLOGY

Serology

Virus-neutralization and complement fixation are useful serologic tests. Antibodies are detectable in the early stages and persist for a considerable time after recovery. Because nearly all pigs are positive, it is only meaningful when paired serum samples are examined. There is a good ELISA for the detection of teschovirus serology.

Detection of Virus

It is absolutely necessary to collect tissues from acutely ill animals. If they have been ill for several days, the viruses have probably disappeared.

The virus is present in the blood of affected pigs in the early stages of the disease and in the feces in very small amounts during the incubation period before the signs of illness appear. Isolated viruses can be identified by virus neutralization, complement fixation, and immunofluorescence. Brain tissue is usually used as a source of virus in transmission experiments. A nested PCR has recently been described in which all 13 serotypes and field isolates were detected using three sets of primer pairs. It is more rapid and less time-consuming as a test than tissue culture and serotyping. Now RT-PCR can be used to detect viral RNA. New nested RT-PCRs have been developed to differentiate the viruses from each other.

NECROPSY FINDINGS

There are no gross lesions except muscle wastage in chronic cases. The lesions are only found by the microscope and are most severe in cases of Teschen. Microscopically, there is a diffuse nonsuppurative encephalomyelitis and ganglioneuritis with involvement of gray matter predominating. This takes the form of perivascular cuffing with mononuclear cells, focal gliosis, neuronal necrosis, and neuronophagia. The brainstem and spinal cord show the most extensive lesions, often with the most severe lesions in the cord. These take the form of degenerated or necrotic nerve cells in the ventral horns, glial nodules, occasional hemorrhage, and a diffuse infiltration of mononuclear cells. In the white matter the changes were not so severe. Infiltration of mononuclear cells was also seen in the dorsal root ganglia (together with degenerated ganglion cells and neuronophagia) spinal nerves, and sciatic nerves. Swollen myelin sheaths and axonal spheroids were seen in the peripheral nerves. Meningitis, particularly over the cerebellum, is an early manifestation of the disease. No inclusion bodies are visible in neurons, in contrast to many cases of pseudorabies. Virus can be isolated from the brain and spinal cord early in the disease course, and from the blood during the incubation period. Recovery of the virus from the gastrointestinal tract does not confirm the diagnosis because asymptomatic enteric infection is common. Isolation attempts may prove unrewarding, necessitating the correlation of clinical, serologic, and necropsy findings to confirm the diagnosis. Recently an experimental infection with PEV-3 produced tremors and paralysis 3 to 7 days postinfection with all the animals having pericarditis and myocarditis.

Samples for Confirmation of Diagnosis

- Histology: half of midsagittally sectioned brain, spinal cord including spinal ganglia, gasserian ganglion (LM)
- Virology: half of midsagittally sectioned brain, spinal cord (ISO, FAT)

In the recent German cases the virus was isolated from all the tissues examined but not from the blood. A technique using monoclonal antibodies has been described that can be used either as an immunofluorescent agent or for immunoelectron microscopy. In the recent Japanese description cytopathogenic agents were recovered from the tonsil, brainstem, and cerebellar homogenates. The PCR products from these were then sequenced and the isolate confirmed as PTV. Isolation of virus is not easy and needs to be from the brain and spinal cord. There are no firm indications of when to take material and a good consistent site in the brain for isolation.

DIFFERENTIAL DIAGNOSIS

The diagnosis of diseases causing signs of acute cerebral disease in pigs is difficult because of the difficulty in neurologic examination of pigs, and the diagnosis usually depends on extensive diagnostic laboratory work particularly in histopathology.

Pseudorabies and hemagglutinating encephalomyelitis virus disease are similar clinical syndromes. In general, viral diseases, bacterial diseases, and intoxications must be considered as possible groups of causes; careful selection of material for laboratory examination is essential. The differentiation of the possible causes of diseases resembling viral encephalomyelitis is described in the section Pseudorabies.

IMMUNITY

Pigs mount a classical humoral response with IgM and IgG and it may be that IgA is important to prevent entry beyond the intestinal epithelium.

TREATMENT

There is no treatment.

CONTROL

The sporadic occurrence of the disease in a herd is usually an indication that infection is endemic. When outbreaks occur, the possibility that introduction of a new strain has occurred should be considered. However, by the time clinical disease is evident, it is likely that infection will be widespread and isolation of affected animals may be of little value. A closed-herd policy will markedly reduce the risk of introduction of new strains into a herd, but there is evidence that they can gain access by indirect means. The sporadic nature of the occurrence of most incidents of porcine encephalomyelitis does not warrant a specific control program.

Teschen disease is a different problem. Vaccines prepared by formalin inactivation of infective spinal cord and adsorption onto aluminium hydroxide have been used extensively in Europe. Two or three injections are given at 10- to 14-day intervals and immunity persists for about 6 months. A modified live virus vaccine is also available.

In the event of its appearance in a previously free country, eradication of the disease by slaughter and quarantine should be attempted if practicable. Austria reported eradication of the disease, which had been present in that country for many years. A slaughter policy was supplemented by ring vaccination around infected premises.

FURTHER READING

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Prion Diseases Primarily Affecting the Cerebrum

INTRODUCTION

The transmissible spongiform encephalopathies (TSEs) are a group of progressive neurologic disorders that are transmissible and affect a number of animal species and humans (Table 14-14). They are nonfebrile with long incubation periods and a long course of disease.

There is a debate about the nature of the infective agent causing TSEs. An abnormal folded isoform, designated PrP^{Sc}, of a host-encoded cell-surface glycoprotein (prion protein, PrP^{c}) accumulates during disease and is associated closely with infectivity. The function of PrP^{C} is not known and the mechanism by which PrP^{C} is converted to PrP^{Sc} is uncertain. PrP^{Sc} is rich in β-sheets and can be isolated as insoluble aggregates. A theory is that the transmissible agent is the abnormal isoform of the prion protein and that, in the infected host, this can recruit further alternatively folded prion protein by acting as a template for protein folding. With this theory the long incubation period of prion diseases reflects the rise in level and deposition of PrP^{Sc} in a variety of tissues, including brain, eventually resulting in fatal spongiform encephalopathy.

Scrapie affects sheep and goats and is the prototypic disease for the group in domestic and wild animals.

Although scrapie in sheep has been recognized for over 200 years, the recent epidemic of Bovine Spongiform Encephalopathy (BSE) has focused public attention and scientific research on the TSEs. With scrapie, and other TSEs, transmission can be effected by crude or purified extracts of brain or other tissues from affected animals, and the infective agent is very resistant to ionizing and ultraviolet irradiation and to reagents that damage or modify nucleic acids. This, along with other experimental findings, has led to proposals that the infectious agent in scrapie, and other TSEs, is the PrP^{Sc} itself, and not a small, unconventional virus or virino as previously proposed. The structure of the infecting PrP^{Sc} is thought to imprint on the normal cellular precursor PrP^{c}, resulting in a change to the abnormal isoform, which is protease resistant and accumulates in cells.

Naturally occurring TSEs, such as sporadic Creutzfeldt–Jakob (vCJD) in humans or transmissible mink encephalopathy in mink, are associated with individual species or with closely related species as with scrapie in sheep, goats, and mouflon (*Ovis orientalis musimon*) and chronic wasting disease (CWD) in mule deer (*Odocoileus hemionus*), white-tailed deer (*O. virginianus*), and elk (*Cervus elaphus nelsoni*).

The results of attempts at interspecies transmission of these diseases are variable. Although, by definition, each TSE is transmissible, the species to which they will transmit varies between the TSE, and can be influenced by the route of challenge; the tissues that contain infection also vary according to the particular TSE. Frequently they do not transmit. Successful primary transmission between different mammalian species typically requires a larger dose to affect disease than would be required for transmission to the same species. Also, usually, parenteral or intracerebral routes are required and success is greater with young animal recipients. This is the so-called "species barrier," which may be absolute or partial because it will affect only a proportion of animals on first passage, or may result in an extended incubation period on first passage.

When using transmission studies to detect the presence of one of these agents, optimal sensitivity is with a recipient host of the same species. Transgenic mice may eliminate this barrier.

The gold-standard technique for the diagnosis of TSE agents is the passage of tissue in panels of inbred mice, which is a technique known as "strain typing." Until recently this was the only way to differentiate scrapie and BSE. BSE presents with a characteristic incubation period, pattern of distribution, and relative severity of the changes in the brain of the different mouse strains (the lesion profile), which is distinct from all scrapie strains tested.

When examining TSEs as a group, one cannot extrapolate the transmission particulars of one TSE to another and one cannot extrapolate risk factors or epidemiology from one to another, and certainly generalizations from an experimental model to a natural disease across a species barrier is scientifically inappropriate.

The literature on this subject is large. This section will discuss scrapie in sheep and goats, and BSE, which are the two TSEs of agricultural animals. It will also discuss the risk for BSE in sheep. CWD in deer is briefly described but has not shown any evidence for transmission to agricultural animals other than deer.

Table 14-14 Transmissible spongiform encephalopathies in animals and humans

Disease	Acronym	Species	Etiology	First described
Creutzfeldt–Jakob disease	CJD	Man	Sporadic familial iatrogenic	1920
Gerstmann-Straussler-Scheinker	GSS	Man	Familial	1936
Kuru		Man	Acquired	1957
Fatal familial insomnia	FFI	Man	Familial	1992
Variant Creutzfeldt–Jakob disease	vCJD	Man	Acquired	1996
Scrapie		Sheep, goats, mouflon	Natural	1738
Transmissible mink encephalopathy	TME	Mink	Acquired	1964
Chronic wasting disease	CWD	Deer, elk	Natural	1980
Bovine spongiform encephalopathy	BSE	Cattle	Acquired	1986
Zoo ungulate transmissible spongiform encephalopathy	Zoo ungulate TSE	Nyala, kudu, gemsbok, oryx	Acquired	1986
Feline spongiform encephalopathy	FSE	Zoo cats (puma, cheetah and domestic cats)	Acquired	1990

BOVINE SPONGIFORM ENCEPHALOPATHY (MAD COW DISEASE)

Classical BSE is an afebrile, slowly progressive neurologic disorder affecting adult cattle. It is a subacute TSE that is uniformly fatal once cattle show signs of nervous disease. TSEs are caused by accumulation of β-sheets of prion proteins in nervous tissue, leading to slowly progressive neurodegeneration and death. Current knowledge suggests that classical BSE originated from a sporadic spongiform encephalopathy preexistent in the cattle population, and that the causative prion was fed to genetically susceptible cattle in contaminated animal protein feeds.

SYNOPSIS

Etiology Epizootic disease was most likely caused by a bovine prion called the classical bovine spongiform encephalopathy strain that was fed back to genetically susceptible cattle in contaminated meat-and-bone meal. Major concern for zoonotic potential. Some countries have documented the presence of atypical bovine prion strains (H-type, L-type) at an extremely low prevalence.

Epidemiology Has occurred as an epidemic in Great Britain associated with the feeding of infected meat-and-bone meal. Sporadic in other countries.

Clinical findings Nonfebrile disease of adult cattle, with long clinical course. Disturbance in behavior, sensitivity, and locomotion.

Clinical pathology None specific.

Diagnostic confirmation Histology, demonstration of prion protein.

Treatment None.

Control Slaughter eradication. Avoidance of feeding ruminant-derived protein to ruminants.

The disease is of considerable importance mainly because it has zoonotic potential and has spread to many countries. The cost of control is very high.

ETIOLOGY

Classical BSE is a prion-associated TSE that causes disease primarily in cattle and also in a number of other species, including humans.

The stability of the lesion profile in cattle and experimental infection studies strongly suggests that the bovine epidemic in the UK, and the subsequent extended epizootic in other countries, was caused by transmission of a single stable bovine prion.[1]

A number of alternative hypotheses were originally offered for the epidemic in the UK. The most popular initial theory was that BSE was caused by transmission of a strain of scrapie that was modified to infect cattle. However, BSE has many characteristics that distinguishes it from conventional scrapie strains, and there is no evidence that cattle develop infection or neurologic disease after 8 or 10 years of oral administration of the scrapie agent.[1,2] Another hypothesis was that the agent could have entered into meat-and-bone meal (MBM) from the carcass of an animal that died in a zoo or a safari park in the UK. This hypothesis was based on the method of carcass disposal for these animals (many were rendered and not incinerated) and because of the high susceptibility of certain African ungulates and zoo carnivores to BSE infection. An additional hypothesis proposed that MBM from the Indian subcontinent was the source. The UK government has conducted several inquiries into the source of the BSE agent and the cause of the outbreak including the Phillips report in 2000 and the Horn report in 2001, but these reports were not conclusive.

The mass exposure of cattle in the UK to this agent, and the subsequent development of a disease epizootic in cattle in the latter half of the 1980s and the early 1990s, is currently thought to have been the consequence of a change in the method of processing of MBM prepared from slaughtered cattle latently infected with the classical BSE strain. This change in processing permitted the prion to persist in the feed, which was fed back to cattle to create a positive feedback loop. Subsequent recycling of the agent in MBM prepared from latently infected slaughter cattle amplified its occurrence until an epidemic of neurologic disease in adult cattle was identified. In hindsight, it was not a wise decision to turn an evolutionary herbivore into a carnivore by feeding contaminated MBM to cattle.

There appear to be at least three different strains of prions identified from cattle with BSE. Discriminatory testing of 370 BSE cases in the EU between 2001 and 2011 indicated that 83% were classical BSE, which transmits to humans as vCJD, 7% were atypical high-type (H-type) BSE first diagnosed in the United States in 2004, and 10% were atypical low-type (L-type) BSE.[1] The L-type has been identified in cattle from Belgium, Canada, Germany, Italy, and Japan, whereas the H-type has been identified in cattle from France, Germany, Japan, the Netherlands, Poland, Sweden, Switzerland, the UK, and the United States. It is likely that atypical forms of BSE (H-type, L-type) represent a rare, sporadic, spontaneous disease in cattle related to old age, with some similarities to sporadic CJD in humans or the Nor98 variant of scrapie in sheep and goats.[3] Only 42 cases of atypical BSE had been reported by 2010, and all were in cattle at least 8 years of age with the exception of a possible case in a 23-month-old heifer.[4]

EPIDEMIOLOGY

Occurrence

Geographic Occurrence

Classical BSE was first described in Great Britain in 1987, but the BSE inquiries considered it likely that there had been several undetected cycles of BSE in the southwest England in the 1970s and early 1980s. Following its description in 1987, the disease developed to an epizootic with over 183,000 cases, of which more than 95% were detected before 2000. The epidemic in the UK peaked at an annual total of more than 37,000 clinical cases in 1992. The disease was recognized in Northern Ireland in 1998 and in the Republic of Ireland in 1999. The disease was subsequently recognized in Switzerland, Portugal, and France in the early 1990s and then became widespread to involve 27 countries by 2015.

Cases have occurred in imported British cattle in Oman and the Falkland and Channel Islands. Countries that have had cases of BSE in native-born cattle are Austria, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Israel, Italy, Japan, Luxembourg, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Switzerland, UK, and the United States.

Occurrence in Cattle

Great Britain

In Great Britain, the first known clinical case of classical BSE probably occurred in 1985. The annual incidence subsequently increased and the disease became a major epizootic in the late 1980s. The disease was declared notifiable, and a statutory ban on the feeding of ruminant-derived protein to ruminants was introduced in 1988. A more extensive ban on feeding any animal protein to any agricultural animal was later implemented to avoid feed cross-contamination. The annual incidence peaked in 1992 and has fallen every year since to produce a bell-shaped epidemic curve at approximately the year 2000, with some cases every year since (Fig. 14-10). The reduction from the peak in 1992 is attributed to the 1988 ruminant-feed ban with the delay in response an effect of the incubation period of this disease. Britain has had the greatest number of affected cattle and, consequently, provides the majority of information on the disease.

Herd Type

A great proportion of cases have occurred in **dairy and dairy crossbred herds**, and by 2002 62% of dairy herds in Great Britain had experienced one or more cases. In contrast, 17% of **beef** herds had cases in the same time period. There has been no apparent breed predisposition. In both herd types, the risk for cases increased significantly with increasing herd size. A significant proportion of the cases in beef cattle herds have occurred in animals purchased into the herds from dairy herds. The reason for this difference in herd type is thought to be the greater use of concentrates in dairy cattle.

The disease has occurred in all regions of the country but was most prevalent in southwest England. Although the disease

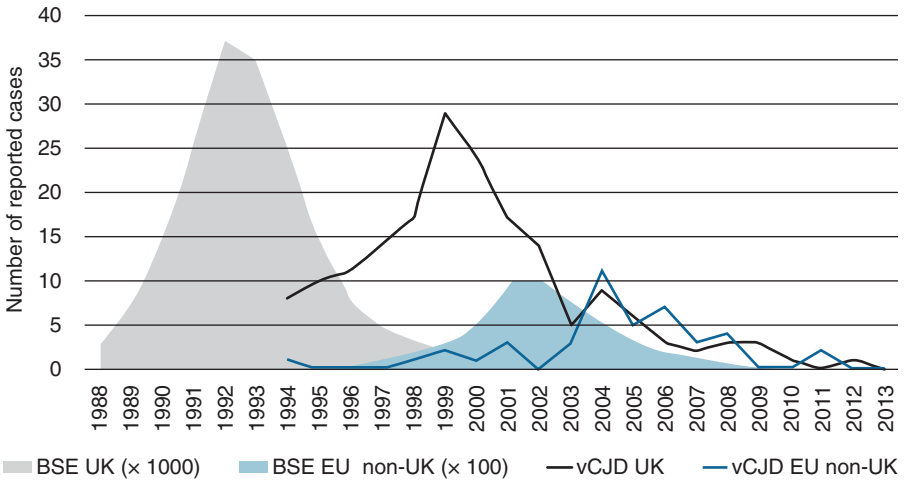

Fig. 14-10 The number of reported bovine spongiform encephalopathy (BSE) cases in cattle and variant Creutzfeldt–Jakob (vCJD) cases in humans by date of onset in the UK and in the European Union (EU) excluding the UK from 1988 to 2013. Note the different multiplier for BSE and vCJD cases in the UK and EU non-UK. (Published with permission from the European Centre for Disease Prevention and Control. http://ecdc.europa.eu/en/healthtopics/Variant_Creutzfeldt-Jakob_disease(vCJD)/Pages/factsheet_health_professionals.aspx.)

developed to an epizootic within the country, the disease does not occur as an epizootic within affected herds and most experience either single cases or a limited number of cases. The average **within-herd incidence** has remained below 2% since the disease was first described.

Northern Ireland and Republic of Ireland

In Northern Ireland classical BSE was recognized in 1998 and in the Republic of Ireland in 1999, but epizootic disease occurred Great Britain and Northern Ireland. The epidemiologic features in both countries were similar to that in Great Britain, but the incidence has been lower. In Northern Ireland the incidence was approximately one-tenth of that in Great Britain. The yearly incidence of the disease peaked in 1994 in Northern Ireland but jumped unexpectedly in the Republic of Ireland in 1996 to 1998 and has remained high since. The source of infection in both countries is thought to have been MBM imported from Great Britain. In the Republic of Ireland there has been geographic clustering with a higher incidence in two counties possibly associated with the location of feed suppliers.

European Continent and Iberian Peninsula

On the European continent classical BSE was recognized in Switzerland in 1999 and shortly after on the Iberian peninsula in Portugal. Both countries showed a case incidence with evidence of an epidemic curve. However this was not mirrored in EU member states in the continent, in which only sporadic cases were reported in the 1990s, and it appears that the disease in this region was unrecognized, underreported, and was more widespread than recorded. Apparently cattle with typical clinical manifestations and fallen stock with clinical signs that should have led to a suspicion of BSE were misdiagnosed or not reported.

Switzerland established a surveillance system in 1999 testing fallen cattle, emergency slaughter, and normal cattle using Prionics Western blot rapid testing methods. This surveillance method was rapidly adopted by EU member countries so that all but two had recorded cases by the end of 2001. In France, between the first notified case in 1991 and the establishment of mandatory testing in 2000, there were 103 cases detected by passive surveillance, but it is estimated that 301,200 cattle were infected with BSE during this period. The first report of L-type BSE was from Italy in 2004.

North America

Canada experienced a case of classical BSE in a cow imported from Great Britain in 1993, but the first case in an indigenous Canadian cow occurred in 2003 in Alberta. Trace back on 40 herds and slaughter of over 2000 suspects were all negative. The molecular profile of the BSE agent from this case was very similar to the UK BSE strains and had no relationship to the agent associated with **CWD** in deer and elk. In 2003 a Canadian cow that had been exported to the United States as a young calf developed complications at parturition, was shipped as a nonambulatory cow, and was discovered as a classical BSE case under a routine monitoring program of downer cows. Canada had two more cases of classical BSE in 2005. By 2009, Canada had reported 14 cases of classical BSE, with 1 H-type and 1 L-type.

The United States had a case of atypical H-type BSE in a native-born cow in 2004. The affected cow had a new prion coding gene (E211K) that suggested the possible existence of a genetic susceptibility to developing clinical signs.[5] A second case of atypical H-type BSE has been reported in the United States. Genetic studies have indicated that susceptibility to classical BSE does not appear to be related to genetic differences in the prion coding gene.[6]

Japan

Japan had reported 33 cases of BSE (32 classical and 1 atypical in a 16-year-old Japanese black cow) by 2007. Cases were attributed to imported infected cattle and imported fat that was used in a milk replacer formulation fed to calves.[7]

Age Incidence

TSEs as a group have long and variable incubation periods, with genetic susceptibility to clinical disease playing a major role in the age of onset of clinical signs. BSE, like scrapie, has a **long incubation period**, 2.5 to at least 8 years and possibly for the life span of cattle and is a disease that affects mature animals. Epidemiologic studies suggest that most affected cattle have been infected as calves, with the mean incubation period decreasing with increasing dose. Risk is greatest in the first 6 months of life and between 6 and 24 months of age risk is related to feeding patterns of proprietary concentrates. Adult cattle are at low risk for infection.

The **modal age at onset** of clinical signs is between 4 and 5 years, but there is a skewed distribution with the youngest age at onset recorded at 22 months and the oldest at 15 years. During the course of the outbreak in the UK there has been a change in the age distribution of cases in both Britain and Northern Ireland, consistent with a sudden decrease in exposure as a result of the bans on ruminant protein feeding. The clinical course is variable, but the case fatality is 100%. There is a variation in risk associated with the calendar month of birth-related to seasonal differences in calf management and exposure to ruminant protein in calf feeds.

The majority of the occasional cases of BSE currently being diagnosed in the UK are attributed to residual contamination of raw feed, but may also reflect a very low level prevalence of atypical BSE cases.[1,8]

Other Species

Spongiform encephalopathies have been identified in seven species of **ungulates** in zoos or wildlife parks in Great Britain since the occurrence of the disease in cattle. These animals had been fed MBM, but the apparently shorter incubation period suggests that they might be more susceptible to infection than cattle and there is evidence for horizontal transmission.

Feline spongiform encephalopathy (FSE) also has been recorded in **domestic cats** in Great Britain since 1990 and in zoo

felids. The **zoo felids** had been fed cattle carcasses unfit for human consumption, or the zoo had a history of BSE in exotic ruminants and fed culled carcasses to other zoo animals. Transmission studies in mice with the agents associated with these encephalopathies in zoo ungulates and felids suggest that they are the same strain that causes BSE. The initial concern that there would be an outbreak of FSE in domestic cats did not occur, and only 89 cases were confirmed to the end on 2003.

Method of Natural Transmission

Ingestion of Meat-and-Bone Meal

The initial epidemiologic studies suggested that the disease in the UK was an extended common-source epidemic, and the only common source identified in these initial studies was the feeding of proprietary concentrate feedstuffs. Epidemiologic studies also suggested that the presence of MBM in proprietary concentrates was the proxy for affected cattle to have been exposed to a scrapie-like agent, and this conclusion is supported by case–control studies examining feeding practices to calves that subsequently developed the disease. This hypothesis explains **breed differences** in incidence because concentrates are not commonly fed to beef calves in the UK; it also can account for geographic differences in incidence. The oral route of challenge is known to be an inefficient route for the transmission of the agents associated with spongiform encephalopathies, and this is thought to be the reason for the low within-herd incidence of the disease in the face of a common exposure.

MBM is manufactured by the rendering industry from tissues discarded in slaughterhouses and from down and dead livestock. The outbreak of BSE in Great Britain was temporarily preceded by a change in the method of processing of MBM to a continuous process with a cessation of the use of hydrocarbon fat solvents. It is postulated that this change permitted the cycling of unrecognized but extremely low-incidence cases of classical BSE. The initial exposure probably occurred from 1981 to 1982 and, subsequently, the agent recycled from infected cattle carcasses and offal used in the preparation of MBM. Rendering procedures have subsequently been devised to minimize survival of the agent.

The marked fall in disease incidence following the introduction of the feed ban in 1987 in the UK substantiated the importance of ingestion of MBM as the major method of infection. Bans in Europe were largely introduced in 1990.

Born-After-the-Ban

In the UK and in other countries a number of cattle that were born-after-the-ban (BAB; French acronym NAIF) have developed the disease. Most of these were born in the years immediately following the ban and their numbers have decreased in subsequent years but still continue at low levels. A case–control study found that vertical or horizontal transmission was not an important cause of these cases. It is thought that MBM that was already in the food chain at the time, in mills and on the farm, was fed until it was depleted.

In several countries the occurrence of BAB cases has been geographically clustered, and also associated with certain birth cohorts. In the UK the clustering was related to areas with high concentrations of pigs and poultry, and it is thought that there was cross-contamination of feedstuffs in feedmills. This is certainly possible with an infective dose of 1 g or less for cattle.

More recently, there has been concern about cattle in the UK that have developed BSE but that were born after the implementation of the reinforced feed ban in 1996 (BARBs). Up to 2005, there have been approximately 100 cases. Again there is no evidence of maternal or lateral transmission and the inadvertent use of illegal feed material residual on farms is suspected.[9]

Non–Feed-Borne Transmission

There is no epidemiologic evidence for significant horizontal or vertical transmission of the disease in cattle, although the studies suggest that minor horizontal transmission may occur to birth cohorts of calves that subsequently develop BSE. This type of transmission is of minor importance to the perpetuation of the disease in a country, but it may be of significance to human health, and birth cohorts are included in trace backs of infection in the United States and Canada.

Vertical Transmission

In the absence of other mechanisms of transmission, vertical transmission is not considered significant for the perpetuation of the disease in an epidemic form. There is an **enhanced risk** for the disease in calves born to infected cows, and this is higher in calves born after the onset of clinical disease in the cow. This may be the result of exposure, at birth, to high infectivity in birth products because there is no evidence for infection and transmission in embryo transplants. However, no detectable infectivity has been found in placentas from cows with the disease.

A very elegant experiment that examined the risk for transmission of BSE via embryo transfer that used recipient cattle sourced from New Zealand and donor cows clinically affected with BSE, bred to bulls that did and did not have clinical BSE, concluded, after a 7-year observation period on the progeny, that embryos were unlikely to carry BSE.

Modeling the BSE epidemic in the UK indicated a constant and relatively high basic reproduction number (R_0) that is defined as the expected number of secondary infections produced in a susceptible population by a typical infected host. If $R_0 > 1$, then the agent can persist indefinitely; initial estimates for R_0 before the first feed ban in 1988 ranged from 10 to 12. This degree of infectivity was consistent with the potential that a maximally infectious animal could infect up to 400 other cattle. Since the feed ban, the value for R_0 is thought to have decreased to 0 to 0.25, indicating that the disease will soon disappear.

Risk for Occurrence of Disease in Countries

Changes in the method of processing MBM have occurred in countries other than the UK, and scrapie occurs in sheep in other countries. However, the major risk for the occurrence of the disease in other countries is the importation of latently infected cattle and/or the importation of infected MBM. This risk can be substantially avoided by prohibiting the feeding of MBM to cattle.

An assessment in 1996 of risk for the occurrence of BSE in the United States concluded that the potential risk of an epizootic was small and that there are substantial differences in the strength of the risk factors between the United States and the UK. These result from differences in proportional numbers of sheep and cattle, differences in the nature of the beef and dairy industries, the type of animal used for beef production and the age at slaughter, and differences in the practice of feeding ruminant-derived protein in calf rations, which is uncommon in the United States. Thus the risk of an outbreak similar to that in the UK was considered negligible. However, a case in a native-born cow in the United States occurred in 2005. This, and contemporary cases in Canada suggested that infected MBM was imported to the North American continent at some time, or that in the United States, the case reflected the very low incidence of spontaneous atypical BSE in cattle. The cases in both countries occurred in cattle that were born before the ban on feeding MBM imposed in both countries in 1997.

Countries with largely pastoral cattle are at low risk.

The International Animal health code of the OIE describes five BSE risk categories for countries based on the importation of cattle from at-risk countries, the importation of potentially infected MBM, the consumption of MBM by cattle and other animals, animal feeding practices, livestock population structure, rendering practices, and the potential for recycling of BSE. In order of increasing incidence of BSE these categories are BSE free, BSE provisionally free, minimal BSE risk, moderate BSE risk, and high BSE risk.

Experimental Reproduction

Although studies on the transmissibility and experimental reproduction of BSE were established before the occurrence of human cases of BSE (vCJD), they have been **critical in determining the risk** of cattle products

for human disease and the risk for disease in other species.

In cattle, disease has been experimentally reproduced by oral and intracerebral inoculation with infected cattle brain homogenates.

Oral, intravenous, and intracerebral inoculation of sheep with infected cattle brain homogenates also results in disease. Disease has also been reproduced in goats and mink by parenteral challenge. In pigs, disease has been produced by intracerebral challenge with infected brain homogenates but not oral challenge. It has not been produced by any route of challenge in poultry and is not produced by oral challenge in farmed deer.

Infectivity of Tissues

Brain, spinal cord, and retina are tissues that are infective to cattle or laboratory animals from natural cases of BSE. The tissues that are infective to cattle or laboratory animals from experimentally infected cattle are brain, spinal cord, retina, distal ileum, bone marrow, trigeminal nerve, and lingual lymph tissue. The infective dose of brain material from a cow with classical BSE appears to be <1 mg of brain tissue.[10]

Parenteral injection of BSE brain:
- Transmits from cattle to cattle, mice, goats, sheep, pigs, mink, guinea pig

Orally fed BSE brain:
- Transmits from cattle to cattle, mice, mink, sheep and goats
- Not to pigs or farmed deer

Other tissues including the major visceral organs, striated muscle, and tissue common for human consumption were negative by mouse bioassay, indicating that no infectivity could be detected. These tissues are currently being reexamined for infectivity using the most sensitive assay known, intracerebral infection into the host species, which in this case the host is cattle. These studies are ongoing but, at last report have only confirmed the results of the negative mouse bioassays. There is no evidence of infectivity in milk based on the fact that calves suckling cows with clinical BSE do not themselves develop BSE when mature and also on the lack of infectivity with intracerebral injection of mice.

Strongest evidence of absence of infection in milk is the study that examined and found no increase in incidence of BSE in calves born to dams with BSE that suckled these cows during clinical disease compared with calves that suckled clinically normal dams. There is species susceptibility (no barrier) strength in this study.

BSE, *bovine spongiform encephalopathy.*

Economic Importance

BSE is not of major economic significance to individual herds in countries in which it is endemic because of the low within-herd incidence. In most countries, compensation will cover cases detected by passive surveillance and, with active surveillance, most of the costs if there is selective culling in affected and trace back herds. However, it is arguable that this disease is the **most economically devastating** agricultural animal disease in the developed world.

The disease has been of major economic importance in the UK and is estimated to have cost £600 billion. This has been from the national cost associated with detection and control procedures, the cost of compensation, and the cost of disposal of affected animals. These costs, along with the cost of loss of export markets, are very high.

Worldwide, the public has developed an extreme concern for the public health risk associated with BSE infection in cattle and, consequently, all countries have been mandated or encouraged to develop active surveillance programs. Not to do so runs the risk of loss of overseas markets and loss of home consumption of beef in favor of other meats. Further, the detection of a single case of BSE by these active surveillance programs results in the loss of export markets for the country and a severe fall in cattle prices for countries that rely on exports in their cattle industries.

BSE is also arguably the disease that has been used most to influence trade in live cattle and cattle products with no science-base or attention to the internationally adopted OIE Terrestrial Animal Health Code. This is largely because of the success of local political influence of ranches and farmers.

It is further arguable that the money spent, for reasons of public health, on this relatively minor zoonotic disease, by far outweighs its relative importance as a cause of human disease.

Zoonotic Implications

Concerns that this disease could transmit to man were raised a very short time after its initial diagnosis. These unfortunately proved true in 1996 when a new form of CJD was reported. Although, with the initial cases, there was reservation as to causality, studies showed the agent associated with this disease is similar to that associated with BSE and the FSEs; there is now no doubt that this is a form of BSE in man. It differs from CJD in that it affects young people with a mean age onset in the third decade of life. In humans there is evidence for genetic susceptibility, and all cases have been homozygous for methionine at codon 129. The disease has been termed **variant CJD** (vCJD).

The disease occurred in the UK despite the progressive bans on human consumption of beef products that contained infectivity that were implemented in 1998 and subsequently tightened further as new information on potential infectivity became available. It is possible that exposure of affected humans occurred in the early and mid-1980s, before the recognition of the disease. There was initially extreme concern that there would be a very large outbreak in humans. However, this has not occurred. The total number of deaths form vCJD in the UK has reached 150. The peak number of deaths occurred in the year 2000, and the outbreak appears to have reached a plateau and is possibly in decline, although the nature of the outbreak will be dependent on the range of incubation periods in humans. More than 200 individuals had succumbed to this infection worldwide by 2015.

Although there is no evidence of direct transmission to humans, veterinarians and animal handlers should take appropriate precautions when handling nervous system tissues of infected animals. Cow's milk appears to provide a negligible risk of contracting vCJD disease.[11]

PATHOGENESIS

Information on the pathogenesis and development of BSE in cattle was initially derived from studies published from Great Britain in the 1990s that studied the spatial and temporal development of infectivity and pathologic change in cattle after oral challenge with a 100-g dose of BSE-affected brain homogenate sourced from naturally clinically affected cattle. The experimental cattle were killed sequentially following challenge, and infectivity in tissues was subsequently determined initially by infectivity assays by intracerebral and intraperitoneal injection into panels of inbred mice and subsequently by infectivity studies by intracerebral challenge of cattle to exclude any species barrier effects.

- Long incubation period (5 years)
- Oral infection
- Infection of Peyer's patches, to brainstem via vagus nerve
- Accumulation of abnormal prions destroys brain slowly

BSE prions spread by two antegrade pathways from the gastrointestinal tract to the CNS: (1) via the splanchnic nerves, mesenteric and celiac ganglion complex, and lumbar/caudal thoracic spinal cord and (2) via the vagus nerve.[12] Following oral challenge of calves, infectivity was initially detectable in the distal ileum, in the Peyer's patches, but no infection is demonstrable in other lymphoreticular organs. Infectivity was identified at 4 months postinfection and was unchanged in magnitude at 24 months postinfection, revealing no decline or clearance of the agent from ileal Peyer's patches.[13] Infectivity was demonstrable in the cervical and thoracic dorsal root ganglia at 32 to 40

months after infection and in the trigeminal ganglion at 36 to 38 months. Traces of infectivity were shown in sternal bone marrow in cattle killed 38 months postexposure. The earliest presence of abnormal PrP and infectivity in the CNS occurred 32 months postexposure, before any typical diagnostic histopathologic changes in the brain. The onset of clinical signs and pathologic change in the brain occur at approximately the same time. Infectivity of peripheral nerves such as the sciatic nerve appears to be a secondary event after infection of the CNS.[12,13]

More recent reports of the oral experimental dosing studies have indicated that the 50% infective dose for classical BSE was 0.15 g of brain homogenate, with higher oral doses increasing the likelihood of developing BSE.[14] In addition, the incubation period decreased as the infective dose increased. In other words, an increase in the incidence of classical BSE disease indicates an increase in exposure, and a decrease in the age of clinical signs indicates a larger infective dose.

CLINICAL FINDINGS

The disease is insidious in onset and the clinical course progresses over several weeks, varying from 1 to 6 months in duration. There is a **constellation of clinical signs** with alterations in behavior, temperament, posture, sensorium, and movement, but the clinical signs are variable from day to day, although they are progressive over time Cattle that show behavioral, sensory, and locomotor abnormality together are highly suspect for BSE. The predominant **neurologic signs** are apprehensive behavior, hyperesthesia, and ataxia, and a high proportion of cases lose body condition and have a diminishing milk yield during the clinical course of the disease. Cattle with BSE do not always show neurologic signs in the initial stages of the disease, and animals with BSE may be sent to slaughter for poor production before the onset of clinical nervous signs. Cattle with vacuolar changes in the brainstem usually have more severe clinical abnormalities; this observation is consistent with vacuolar change reflecting a more advanced histologic lesion.[15]

Clinical signs in BSE
- Change in temperament and behavior
  - Apprehension, excitable, unusual kicking, head-tossing when haltered, separation from group
- Change in posture and movement
  - Abnormal posture and ataxia
- Fall in milk production
- **No antemortem test available**

Behavioral changes are gradual in onset and include changes, such as a reluctance to pass through the milking shed or to leave a vehicle or a pen, a change in milking order, and a reluctance to pass through passageways. Affected cattle are disoriented and may stare, presumably at imaginary objects, for long periods. There is hyperesthesia to sound and touch, with twitching of the ears or more general muscle fasciculation and tremors. Many throw their head sideways and show head-shaking when the head or neck is touched.

Other changes in **temperament** include the avoidance of other cows in loose housing but antagonistic behavior to herdmates and humans when in confined situations. Affected animals may kick during milking and show resistance to handling. Some cows show excessive grooming and licking and may show the equivalent of the scrapie scratch reflex.

Bradycardia, associated with increased vagal tone and not occurring because of decreased food intake, is reported and may persist despite the cow's nervousness during clinical examination.

Relatively early in the course of the disease there is **hindlimb ataxia** with a shortened stride, swaying gait, and difficulty in negotiating turns. This should be especially examined as animals exit transport vehicles or are trotted through an area. Knuckling, stumbling, and falling, with subsequent difficulty in rising, is common in the later stages of the disease. Cows show **progressive weakness**, with ataxia and weight loss, and before the common recognition of the disease, they were sent to slaughter because of locomotor disabilities or changes in temperament.

It has been recommended that the reaction of the animal to sudden noise, sudden light, sudden movement, and sudden touch be used as a test. Sudden noise is tested by clanging two metal objects together out of sight of the animal (the **bang test**), sudden light is tested with a camera flash (the **flash test**), sudden movement is tested by waving a clipboard toward the cow from a short distance (the **clipboard test**), and sudden touch is tested by touching the animal on the hindlimbs with a soft stick (**stick test**). Abnormal reactions to these tests include being startled, head-tossing, salivation, snorting, running away, or panicky circling and kicking out on touch. These tests have been found positive in BSE suspects that had a history of behavioral change but did not show abnormalities of gait.

Cattle infected with atypical BSE (H-type, L-type) appear more dull and to have a greater degree of difficulty in rising than cattle with classical BSE; otherwise they have similar clinical findings.[16] Abnormal BAEPs have been reported at the onset of neurologic signs in classical BSE-infected cattle and manifest as prolonged peak latency of waves III and V and prolonged I-V latency.[17] Prion accumulation in the auditory brainstem nuclei of BSE-infected cattle[18] may contribute to their hyperresponsiveness to the bang test.

Electroencephalographic and evoked potential diagnostic methods have been proposed as antemortem diagnostic test methods but require further evaluation and would seem impractical for routine use. Antemortem assessment of retinal function and morphology identified changes 11 and 5 months before the onset of unequivocal clinical signs in cattle experimentally infected by intracranial inoculation with classical BSE and H-type BSE.[19] Strain-specific differences in retinal function, the amount of prion accumulated in the retina, and the retinal glial response to disease were also identified.

Clinical Signs and Passive Surveillance

There is no reliable preclinical test for BSE, and clinical recognition of BSE is the major component of passive surveillance.

At the peak of the outbreak in Great Britain, BSE was confirmed in 85% of suspects picked by passive surveillance. This percentage fell to 56% later in the outbreak. Farmers were fully compensated at notification and well informed and so were probably motivated to contact their veterinarian. Veterinarians were also very aware of the clinical presentation of BSE and observant at livestock markets and while testing for tuberculosis and at abattoirs. Relatively high success rates were also found in Switzerland in which approximately 59% of animals notified with BSE were confirmed. However, in other countries, passive surveillance was an utter failure.

Although an aid to surveillance of a disease, passive surveillance of BSE based on clinical signs is an insensitive method of disease detection; targeting surveillance of emergency slaughtered cattle and fallen stock is 40 times more likely to detect cases of BSE than notification on the basis of clinical signs. One study found that the odds of finding a BSE case was 49 times higher in the fallen stock and 58 times higher in emergency slaughtered cattle greater than 24 months of age compared with passive surveillance of clinical disease.

CLINICAL PATHOLOGY

There is no specific test for the antemortem diagnosis of this disease. Apolipoprotein E and two unidentified proteins are present in the CSF from clinical cases but not normal cattle, and the presence of a 30-kDa, 14-3-3 protein in CSF in affected cows is reported, but there is no information of specificity.

NECROPSY FINDINGS

There are no abnormalities in gross pathology, and diagnosis is dependent on histologic findings or testing of brainstem samples using validated tests based on in situ IHC or Western immunoblots, with the obex and rostral brainstem being the subsampled region of choice.[12] The preferred method for determining prevalence is immunology-based rapid tests, which are validated to

detect classical BSE disease-associated prions. These tests typically apply proteinase K to destroy the cellular isoform of the prion protein (PrP^{c}) while maintaining a proteinase K–resistant disease-associated isoform (PrP^{sc}). This approach has identified three types of BSE: classical type (C-type), H-type, and L-type, with the H and L designation referring to the apparent molecular weights of the proteins.[20]

Major histologic changes are in the brainstem, and the pathognomonic lesion is a bilaterally symmetric intracytoplasmic vacuolation of neurons and gray matter neuropil. The occurrence of vacuolation in the solitary tract and the spinal tract of the trigeminal nerve in the medulla oblongata is the basis of the statutory diagnosis of the disease in Great Britain. In Great Britain, statutory diagnosis is achieved by an examination of a single brainstem section obtained via the foramen magnum and obviating the need of extracting the brain with the associated risk of aerosol production. This sampling location has the potential to miss some cattle infected with atypical BSE.[21]

Scrapie-associated fibrils can be visualized by electron microscopy. Government regulatory agencies are usually responsible for the confirmation of this diagnosis and typically distribute specific protocols regarding the collection of samples and disposal of carcasses from suspect animals.

Samples for Confirmation of Diagnosis

- Immunology-based rapid tests: fresh brainstem
- Histology: formalin-fixed brain, including midbrain and entire medulla oblongata (LM).

Note the zoonotic potential of this disease when handling carcass and submitting specimens.

DIFFERENTIAL DIAGNOSIS

The disease should be considered in the differential diagnosis of any progressive neurologic disease in cattle. Primary differentials on clinical signs include the following:

- Hypomagnesemia
- Nervous acetonemia
- Rabies
- Lead poisoning
- Listeriosis
- Polioencephalomalacia
- Tremorgenic toxins

TREATMENT AND CONTROL

There is no treatment for the disease.

Detection of BSE in Surveillance and Control Programs

Passive surveillance has been used in many countries. Suspect disease is notifiable with compulsory slaughter and compensation and disposal of the carcass by incineration. The limitations of passive surveillance were described earlier and, in most countries, passive surveillance has been replaced with some form of active surveillance.

Active surveillance was initially directed at a targeted proportion of culled animals, animals manifesting neurologic disease, rabies suspects negative for rabies, fallen (down) cattle, and emergency slaughter categories, and a proportion of cattle, or all cattle, over 24 to 30 months (depending on country) that were presented for slaughter for human consumption. In slaughter cattle, **the sampling frame was set to detect BSE at a prevalence rate of one mature animal in a million mature animals**. The ability to conduct active surveillance, particularly on slaughter cattle, has been allowed by the development of rapid tests that can be conducted and read while the carcass is being held so that positive test cattle are not released for human consumption. Positive rapid tests need to be confirmed by histology and IHC. More recently, because the average age of BSE cases has been over 11 years, meaning that they were born before the date of the reinforced feed ban, the majority of EU countries have now raised the age limit for testing to 72 months for healthy slaughtered cattle (or even stopped testing) and to 48 months for fallen stock and emergency slaughter categories.[1]

In the United States, following the case of BSE in an imported cow, the United States Department of Agriculture (USDA) implemented an intensive national testing program for BSE that concentrated on a targeted high-risk population. The purpose is to help discover if BSE is in the United States and, if so, at what level. The intention is to sample as many cattle over a 12- to 18-month period as possible with the goal of examining 268,500 cattle. This would allow a detection rate of 1 in 10 million with a 99% confidence level. The cattle will be over 30 months of age and include nonambulatory cattle, cattle that are too weak to walk, cattle that are moribund, cattle with neurologic signs, rabies suspects that are negative, and dead cattle.

Control of BSE in Cattle

Control programs use the following assumptions:

- Infection and disease in cattle is introduced through feeding contaminated feed containing infected MBM or greaves.
- The source of infection to cattle can be eliminated by effective prohibition on feeding infected feed.
- There is no significant horizontal or vertical transmission.

Based on this, most countries have established a ban on the feeding of ruminant protein to ruminants. This was done in 1987 in the UK, the mid-1990s in most European countries, and in 1997 in Canada, the United States and Mexico. There is, however, a strong argument for banning all mammalian protein for feeding to all livestock. The experience of several countries with animals that were born after the ban shows that cross-contamination in feed mills can occur. Although the removal of **specified risk materials** (SRMs), (brain, spinal cord, eyes, tonsil, thymus, spleen, and intestines) from cattle carcasses should reduce the risk of the BSE agent being in the subsequent rendered carcass, it obviously does not eliminate it. More detail of the regulations and of control procedures is available.

These control procedures, initiated in the UK, were effective in changing the course of their epidemic, which is now on the wane.

Measures to Protect Human Health

High-risk animals, such as **downer cows**, should be kept out of the human food chain and not rendered for MBM. Infection is present in the tissues listed as **SRMs** (brain, spinal cord, eyes, tonsil, thymus, spleen, and intestines), which are removed from the carcass at slaughter. The removal of SRMs also protects against the risk posed by cattle that may be incubating the disease yet do not show any clinical signs. Together with a ban on products such as mechanically recovered meat that could be contaminated with SRMs, excluding SRMs from the human food chain is the most important food safety measure to protect public health.

However, this may not be sufficient. The method of slaughter with captive bolt guns can result in the widespread dissemination of brain within the carcass with dissemination by blood into the pulmonary tissues and elsewhere. Also, the method of splitting the carcass and spinal cord can result in significant carcass contamination and contamination of the slaughterhouse environment. Methods to decrease the risk of contamination of the carcass at slaughter have been suggested.

Based on transmission and infectivity experiments cattle under 30 months of age are considered to have very low risk of being infected, but there can be a risk in endemic countries with cattle over this age. Some countries with a high incidence of BSE have banned cattle over 30 months of age for human consumption.

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BOVINE SPONGIFORM ENCEPHALOPATHY AND SHEEP

There is considerable speculation and concern that the agent of BSE could have become established in small ruminants. BSE can be readily experimentally transmitted to sheep and goats and produces clinical signs and lesions similar to scrapie. There is further concern following a recent report of the transmission of the agent from challenged ewes to their lambs. Further, the risk to human health from the ingestion of meat from sheep may be even greater than that from cattle because of the widespread distribution of the BSE agent in the lymphoid tissue of infected sheep.

In the UK and Europe concentrates are commonly fed to meat-producing breeds of sheep in late pregnancy and early lactation and less commonly to their lambs. They are also fed to milk-producing sheep breeds and to lactating goats. Concentrates fed during the 1980s and 1990s could have contained infected MBM, and this risk would have lasted until the total ban on feeding MBM to all farm animals in 1996 in the UK and 2001 in Europe.

The inclusion of MBM in concentrate rations for small ruminants was less than that for cattle, and the proportion of concentrate ration fed was also lower. This, coupled with the fact that prion diseases require a larger infective dose to produce disease in a cross-species to that required to produce the disease in the same species (the **species barrier** effect) may have resulted in an infective dose to sheep that was too low to establish infection.

The possibility that BSE did establish in sheep during the BSE epidemic in Britain is not supported by a study that examined the incidence and new infection rates of scrapie flocks in Britain covering the period from 1962 to 1998. This study found no evidence of a change in scrapie occurrence before, during, or following the BSE epidemic and no temporal or spatial correlations of scrapie occurrence with the BSE epidemic. There have been other studies that have examined the risk factors for transmission of BSE to sheep and the possibility that it could be perpetuated by sheep-to-sheep transmission. Most have concluded that the risk that BSE has established in sheep is low but, with current knowledge, cannot rule out the possibility.

There are no reports of naturally occurring cases of BSE detected in sheep. However, there is one report of a TSE in a goat in France that was found to have IHC and immunoblotting characteristics compatible with BSE, and, following injection into mice, incubation times compatible with those recorded for experimental ovine BSE.[1]

Experimental Transmission

BSE can be experimentally transmitted to sheep and goats by intracerebral, oral, and intravenous routes using BSE-infected cow brain. The PrP genotype affects the incubation period in both Cheviot and Romney sheep. PrP genotypes ARQ/ARQ and AHQ/AHQ are associated with short incubation periods (approximately 18–36 months) following challenge and also with disease susceptibility. One study further suggests that AHQ/ARQ sheep have a similar susceptibility to infection, and that sheep homozygous for alanine (A) at codon 131 and glutamine (Q) at codon 171 are more susceptible to BSE than any other genotype. In contrast, the PrP genotype ARR/ARR is associated with a long incubation period in sheep challenged intracerebrally, and ARR/ARR sheep are resistant to BSE challenged orally and do not have infectivity in their tissues. The ARR allele appears dominant in this respect because sheep carrying at least one ARR allele in combination with any other allele have a longer incubation period. PrP genotype VRQ/VRQ appears to have an intermediate incubation period.

Texel and Lacaune sheep with PrP ARQ/ARQ genotypes are susceptible. However, in these studies the survival of some sheep with susceptible genotypes suggests that factors other than the PrP genotype has influence on survival. Challenge dose in all of these studies has been high.

In a recent study, 30 ewe lambs were dosed orally, at 6 months of age, with 5 g of infected cattle brain and subsequently mated. Twenty-four developed clinical disease between 655 and 1065 days postinoculation and two lambs, born before their dams had clinical disease, also subsequently developed clinical disease. This study indicated that the agent of BSE can transmit either in utero or perinatally in sheep. There is no information on other routes of transmission and if they exist.

PATHOGENESIS

Following challenge of sheep with BSE, infectivity has been found in intestinal Peyer's patches as early as 5 months postinfection and in enteric nerves and spinal cord after 10 months with widespread dissemination throughout the lymphoreticular system and peripheral nervous system by 21 months.[1]

CLINICAL SIGNS

The clinical signs reported in affected experimental animals are not well described in many of the experimental challenge studies but have varied in different studies. In one study, sheep and goats showed sudden onset of ataxia, which progressed rapidly to recumbency. There was little evidence of pruritus and the clinical course was very short, lasting between 1 and 5 days in the majority of animals with one goat showing progressive weight loss over 3 weeks before it was culled. Genotype had no influence on the duration of the clinical course. In another study in sheep only, the clinical course was approximately 3 months and affected sheep showed pruritus with fleece loss and ataxia and behavioral change. Ataxia, weight loss, and pruritus were considered constant in another.

In an experiment designed to test specifically if clinical signs could be used for differentiation between scrapie and BSE, two different groups of sheep were inoculated with each agent. The duration of clinical signs varied quite markedly within both groups with a mean of approximately 9 days for each group but a variation in both from 1 to over 80 days. As with natural scrapie, there was considerable variation in the nature of the clinical signs, but there was no marked difference in the frequencies of clinical signs between the two groups, except that ataxia was the first sign noticed in a significantly greater proportion of the BSE-challenged group, whereas pruritus was the first noticed sign in a significantly greater proportion of the scrapie-challenged group.

DISPOSITION OF DISEASE-ASSOCIATED PRP

Genotype and route of inoculation influence the disposition of disease-associated PrP in lymphoreticular system tissues (tonsil, spleen, and mesenteric lymph node). The most conspicuous effect is the absence of disease-associated PrP in peripheral lymph tissue in ARR/ARR genotype sheep and lack of infectivity, and there appears to be an inverse relationship between this disposition and the incubation period. Route of inoculation influences the relative intensity of disposition in tonsil, spleen, and mesenteric lymph node.

Following experimental infection of sheep with BSE, disease-associated PrP can be detected in tonsil biopsies 11 to 20 months after challenge but, in contrast to scrapie, disease-associated PrP is not detected in biopsies of lymphoid tissue from the third eyelid.

DIAGNOSIS

The diagnosis of BSE in clinically affected cattle can be achieved with several techniques, including the analysis of symptoms, histopathology, and the detection of the disease-associated form of the prion protein, by immunocytochemistry, Western blot, or ELISA. The profiling of vacuoles in the affected host had shown a remarkable uniformity over the year and from different geographic regions. However, this is not true with scrapie and the variation in the host brain with scrapie would not allow differentiation from BSE on histologic findings. The diagnosis of BSE in sheep presents problems, and the similarity of the clinical signs and pathology between scrapie and BSE could easily result in naturally occurring cases of BSE in sheep being misdiagnosed as scrapie.

Strain Tying

The gold-standard technique for the diagnosis of TSE agents is the passage of tissue in panels of inbred mice, a technique known as strain typing. Until recently this was the only way to differentiate the two diseases. BSE presents with a characteristic range of incubation periods and a pattern of distribution and relative severity of changes in the brain of the different mouse strains (the lesion profile), which is distinct from all scrapie strains tested. However, this method of diagnosis is both expensive and time-consuming.

There has been a wide search for a differential test system in including prion protein profiling, studies in glycosylation and glycoform ratios, and other molecular and biochemical studies that are detailed elsewhere. A recent promising set of studies suggests that the site of truncation of disease-associated PrP during partial digestion by proteases located in lysozymes appears different for sheep scrapie and experimental BSE. After digestion by exogenous enzymes, the BSE PrP molecule is shorter than that of scrapie stains giving rise to different IHC patterns, and this is supported by Western blot studies. Unlike scrapie, the intracellular truncation site of ovine BSE PrP is influenced by the cell type in which it accumulates, giving distinct patterns of immunolabeling with different PrP antibodies. Epitope labeling shows that the shortest fragment of disease-associated PrP occurs in tangible body macrophages followed by glial cells and neurons. It appears that this difference in truncation of PrP in experimentally infected BSE sheep is not influenced by route of inoculation or by genotype or by sheep bred, and it is proposed that truncation patterns, as detected by immunoblotting and IHC, can be used in surveys for BSE in sheep.

CONTROL

If BSE is or does establish in small ruminants in a country, there is significant concern for human health. The distribution of BSE infection in the carcasses of cattle is limited and can be removed by the ban of the use of SRMs (largely brain, spinal cord, and offal). In contrast, the distribution of the BSE agent in infected sheep is widespread, and it would be virtually impossible to remove this by trimming or selective organ removal from a carcass for human consumption. Also, lymphocytes in milk could be infected.

Active surveillance for TSEs in sheep and goats has been increased in the EU, and several rapid tests for use in sheep and goats are now available.[2] In the UK, a worst-case scenario, published in 2001 in a contingency plan to address BSE in sheep, threatened the national herd with slaughter, largely on the grounds that an epidemic of BSE in sheep could be harder to contain than was the case for BSE in cattle and that lamb could present a greater risk to consumers than beef. A more recent UK contingency plan would allow PrP genotype ARR homozygous sheep and ARR heterozygous sheep for human consumption. This plan is the same as the EU, except that there are differences in the maximum age allowed at slaughter between the UK and the EU recommendations.

The risk for BSE in sheep was a major incentive for the development of national breeding programs for the control of scrapie, and possible BSE, including the National Scrapie Plan in the UK, launched in 2001, and the National Scrapie Eradication Program in the United States. The purpose in these breeding programs is to select against highly susceptible genotypes and select for the highly resistant genotype.

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SCRAPIE

SYNOPSIS

Etiology A transmissible agent (prion, a proteinaceous infectious particle) that is highly resistant to chemical and physical agents, and appears not to contain DNA. Susceptibility of sheep to developing clinical disease after infection is determined by genetics.

Epidemiology Transmitted primarily by contact with infected sheep and from environmental contamination; very long incubation period.

Clinical findings Nonfebrile disease of adult sheep, goats, and mouflons with insidious onset and long clinical course. Clinical disease is rare in goats and mouflons. Affected animals show behavioral change, tremor, pruritus and locomotor disorder, and wasting.

Clinical pathology Demonstration of scrapie prion protein by immunostaining of the obex in brain and selected lymphoid tissue elsewhere.

Lesions Vacuolation of gray matter neuropil and neuronal perikarya, neuronal degeneration, gliosis.

Diagnostic confirmation Demonstration of scrapie prion protein.

Treatment None.

Control Slaughter eradication. Genetic testing and selection/culling.

Scrapie is a nonfebrile, fatal, chronic disease of adult sheep, goats, and mouflons (one of two ancestors of all modern sheep breeds) characterized clinically by pruritus and abnormalities of gait, and by a very long incubation period. It is the prototypic disease for a group of diseases known as **TSEs**. This group also includes **CWD** of deer and elk; **transmissible mink encephalopathy;** and FSE, CJD, and other spongiform encephalopathies of humans, and the relatively new disease, **BSE**, which is described separately under that heading. In Iceland scrapie is known as ***rida***, in France as ***la tremblante*,** and in Germany as ***traberkrankheit***.

ETIOLOGY

There has been a significant historical debate over the etiology of this disease. The current consensus view is that scrapie is associated with an infectious agent, but that the incubation period for clinical manifestation of the disease and the susceptibility of the host to developing clinical disease after infection is determined by genetics. In other words, to develop clinical disease caused classical scrapie, an animal must be exposed to the infectious agent and have a susceptible genotype.

Scrapie can be transmitted experimentally to other sheep and to certain laboratory animals, and infection induces the production in the brain, and some other tissues, of amyloid fibrils called scrapie-associated fibrils or prion rods. The main constituent of these is a disease-specific, protease-resistant neuronal membrane glycoprotein termed the **prion protein**, or PrP^{Sc}. PrP^{Sc} is an abnormal isoform of a host-coded membrane glycoprotein, PrP^{C}, and the TSEs are characterized by the accumulation of PrP^{Sc} in neuronal and other tissue.

Transmission can be effected by crude or purified extracts of brain or other tissues from affected sheep, and the infective agent is very resistant to ionizing and ultraviolet irradiation and to reagents that damage or modify nucleic acids. This, along with other experimental findings, has led to the accepted view that the infectious agent in scrapie is PrP^{Sc} itself, and not a small, unconventional virus or virino as previously proposed. The structure of the infecting PrP^{Sc} is thought to imprint on the normal cellular precursor PrP^{C}, with the template resulting in a change

to the abnormal isoform which is protease-resistant and accumulates in cells.

More than 20 different **strains** of scrapie have been identified based on the following:

- Strain typing by differences in incubation time of the experimental disease in inbred strains of mice of different genotype
- The type, pattern, severity, and distribution of lesions in the brain of the different strains of experimental animals (lesion profiles)
- Resistance to thermal inactivation
- The type of disease produced in sheep and experimental animals (e.g., drowsy versus pruritic manifestations in goats)
- The ability of a strain to produce disease in different species of experimental animals

It is proposed that strain differences reflect differences in replicating information carried within the conformational state of the PrP^{Sc}. The more important strains identified are called **classical scrapie strains**, comprising strain A and strain C (thought to be the most prevalent strain in the United States), and **atypical (or discordant or nonclassical) scrapie strains**, comprising the Nor98 strain and other discordant strains. Coinfection of strains can occur with scrapie.

Nor98 was first reported in 1998 in five unrelated Norwegian sheep that had PrP^{Sc} in a different location (cerebellum) than usually reported with scrapie. Nor98 has now been identified in sheep in a number of countries. Atypical scrapie is thought to arise spontaneously and not be associated with an infective source.[1] Interestingly, atypical scrapie is usually not clinically apparent, but there are reports of sheep infected with atypical scrapie strains exhibiting some of the typical clinical signs of classical scrapie, particularly rear limb ataxia.[1,2] Atypical scrapie caused by Nor98 has been diagnosed in sheep in Australia and New Zealand; these are two countries that do not have classical scrapie.[3] Atypical scrapie is not considered rare compared with classical scrapie and appears to occur at a constant prevalence in different countries.[4]

EPIDEMIOLOGY

Occurrence

Geographic Occurrence and Incidence

Scrapie in sheep occurs enzootically in the UK, Europe, and North America. Outbreaks have been reported in Australia, New Zealand, India, the Middle East, Japan, and Scandinavia, principally in sheep imported from enzootic areas. Australia and New Zealand used vigorous importation, quarantine, and culling policies to prevent subsequent entry of the disease and are considered free of disease.

The true prevalence of the disease both within and between countries is not known because there has been no test to detect the presence of infection in individual sheep or in flocks at all stages of infection. This is further confounded by secrecy about the existence of scrapie in many flocks and breeds. This secrecy results from a fear of economic penalties that could result from the admission of infection.

In Great Britain, where the disease is enzootic and has been recognized for over 250 years, the true incidence is unknown, although a questionnaire survey in 1988 suggests that one-third of sheep flocks are infected. In infected flocks the annual incidence ranges from 0.4 to 10 cases per 100 sheep per year, with a mean of 1.1 cases per 100 sheep per year. However, the annual incidence can approach 20% of the adult flock, on occasions up to 40%, and in flocks where there is no selection against the disease the annual incidence and mortality can reach a level that results in disbandment of the flock or its nonsurvival.

Farmer consultation with a veterinarian about a case of scrapie and farmer reporting of cases of scrapie are notoriously low. Historically, this is because factors such as the stigma associated with having scrapie diagnosed in a purebred flock and concerns for future sales or, in the case of commercial flocks, a lack of incentive to consult and a lack of concern because nothing can be done to cure the present case or prevent future cases. In England, it has been estimated that only 13% of farmers who had a suspected case of scrapie in the past 12 months reported it. Possibly, the chance of improvement through genetic selection will alter this farmer trait.

In the United States the disease is thought to have been introduced in 1947, and by 1992 was found in 657 flocks in 39 states. In 2007 the prevalence of infection in the United States was estimated at 0.1% to 0.3%.

Host Occurrence

Age

Scrapie is a disease of **mature sheep,** although most are exposed as young sheep, and the incidence decreases with age at exposure. The age-specific incidence in **sheep** is highest between 2.5 and 4.5 years of age and cases rarely occur under 18 months of age. Natural disease in **goats** is rare. The age at death is similar to that in sheep, with a range from 2 to 7 years. The **case–fatality rate**, with time, is 100%. The death loss is added to by the slaughter of infected and in-contact animals in countries where control and eradication is a practice.

Breed

Scrapie occurs in both sexes and in the majority of breeds, although the incidence is higher in some breeds than others. Breed differences in prevalence occur in several countries; an example would be the high prevalence in the Suffolk breed in the United States relative to white-faced breeds and in some Hill breeds in the UK. These probably reflect breed and flock differences in genetic susceptibility to the development of clinical disease. Similarly, the occurrence of outbreaks of scrapie may result from the introduction of infection to a genetically susceptible flock or to a change in the genetic structure of flocks that are infected.

Methods of Transmission

Knowledge of transmission of scrapie is based primarily on the experimental disease and observations of the natural disease in experimental flocks.

Sources and Routes of Infection

The usual method of introduction into unaffected flocks is by the purchase of preclinically infected sheep. Infectivity can be demonstrated in the placenta, fetal fluids, saliva, colostrum, and milk of naturally occurring cases,[5-7] and in the oral cavity of sheep with preclinical scrapie,[8] but has not been demonstrated in the urine or feces of natural cases, even though it can be demonstrated in the intestine. Ingestion of infected material appears the most likely route of infection, but scarification of the skin and conjunctival inoculation will also allow infection. Hay mites have been found to harbor the agent on scrapie-infected properties and have been proposed as a reservoir for infection.

Horizontal Transmission

This is the usual method of spread, and the placenta is considered the major source of infection for the mother to her lamb, and to other lambs in close contact. Under natural conditions the disease in flocks often runs in families, and whether or not a lamb contracts scrapie appears to depend primarily on the current or future scrapie status of its dam. It is common for all the VQR/VQR lambs from dams dying of classical scrapie to develop scrapie.

Scrapie can also transmit between sheep in close contact, and this can occur from sheep in the preclinical phase of the disease. Scrapie can be transmitted by blood transfusion. The importance of this route of infection in field infections appears low because successful transmission appears to require at least 400 mL of blood.

Under natural conditions, scrapie occurs in sheep and occasionally spontaneously in goats. Under experimental conditions, scrapie has been observed to spread from sheep to goats by contact, and the little evidence available on the natural disease in goats is consistent with the view that the scrapie can be maintained by contagion in a herd of goats living apart from infected sheep.

Vertical Transmission

There is a greater risk for scrapie in lambs born to infected dams, but this most

probably reflects horizontal transmission at birth from placentas. There are conflicting results between studies that have examined transmission by embryo transfer, and the importance of vertical transmission to the epidemiology of the natural disease remains to be determined. However, epidemiologic studies suggest that it is of rare occurrence, and there is significant evidence against the occurrence of in utero transmission. The agent has not been demonstrated in the testes or semen of rams.

Environment

An infected environment can also be the source, and scrapie-free sheep can develop disease after grazing pasture previously grazed by scrapie-infected sheep, with infection by ingestion or possibly via abrasive lesions. Environmental infection can occur from the products of parturition and, although the scrapie agent has not been demonstrated in feces, it is suspected as being so in infected animals. The duration of infectivity on inanimate materials such as pasture has not been defined, but field and experimental observations indicate that it is a long time, probably in excess of 16 years under some conditions.[9,10]

Iatrogenic Transmission

An outbreak of scrapie occurred in the 1930s following the use of a vaccine against louping-ill prepared from the brains of sheep. More recently, the use of a vaccine against contagious agalactia has been epidemiologically linked to an outbreak of scrapie in sheep and goats in Italy where there was a high attack rate and high mortality affecting several birth cohorts.

Genetics

Scrapie is recorded in most breeds of sheep, but there are breed, family, and individual differences in susceptibility. There is substantial genetic control of the incidence of disease, and in both the natural and experimental disease, genetics is a major determinant of susceptibility with the susceptibility of sheep strongly linked to certain polymorphisms in the sheep PrP gene.

In earlier studies, experimental challenge and breeding showed that sheep could exhibit a long or short incubation period following challenge, and that this difference in incubation period or susceptibility was determined by a single gene called **scrapie incubation period** (*Sip*). There is a similar gene in mice (*Sinc*) that determines incubation period and susceptibility following experimental challenge. The *Sip* gene has two alleles, *sA* and *pA*, which, respectively, shorten or prolong the experimental incubation period for most strains of the scrapie agent. The subsequent recognition of prion protein (PrP) and its association with scrapie led to the recognition of the gene that encodes PrP, which was found congruent to *Sip* in sheep, and *Sip* genetics have been entirely superseded by PrP genetics.

Sheep have one pair of genes that influence susceptibility to scrapie known as the prion protein genes. These code for a normal prion protein in the cell (PrP^C), which has 254 amino acids with each codon in the gene encoding for a specific amino acid at a particular location on PrP^C. PrP^C can be converted to a scrapie prion protein molecule (PrP^{Sc}) in infected sheep which, when it accumulates in the CNS, causes disease. The susceptibility of sheep to this conversion, and thus to scrapie, is **strongly associated with certain polymorphisms at codons 136, 154, and 171**. It is thought that there are at least two groups of scrapie TSE strains, one of which is influenced primarily by the amino acid at codon 136 and the other group by the amino acid at codon 171. Within these there may be subtypes because resistance to some 136-type TSEs can be affected by the amino acid at codon 154.

- At codon 136 valine (V) is linked to scrapie susceptibility and alanine (A) is linked with resistance
- At codon 154 histidine (H) is linked to susceptibility and arginine (R) to resistance
- At codon 171 glutamine (Q) and histidine (H) are linked to susceptibility and arginine (R) to resistance.

- The notations used for descriptions of the prion protein (PrR) genotype vary in different countries.
- The susceptibility of sheep to scrapie is strongly associated with polymorphisms at codons 136, 154, and 171 in the prion protein gene.
- The amino acids associated with these polymorphisms are alanine, valine, histidine, arginine, and glutamine.
- In the description of the PrP genotype these are given the letters A, V, H, R, and Q, respectively.
- The PrP genotype is listed in the order of codon 136 followed by 154 and then 171.
- The amino acid at each codon is listed according to the letter designation for each of the two alleles separated by a backslash. Examples are ARR/ARR or ARR/VQR. These could also be expressed as $AA_{136}RR_{154}RR_{171}$ and $AV_{136}RQ_{154}RR_{171}$.
- In sheep in the United States the polymorphisms at codon 171 are the major determinant of scrapie susceptibility. Polymorphisms at codon 154 play a minor role and are usually not listed as part of the PrP genotype.
- Genotypes in the United States are usually referred to using the letters of the amino acids in numerical order codon 136 followed by codon 171.
- The previous examples would be AA RR and AV RR.
- They can also be referred to using the codon number followed by the corresponding amino acid 136AA, 171RR and 136AV, 171RR or the amino acid followed by the codon.
- Often only the amino acids at codon 171 are listed.

Of the possible alleles from these polymorphisms, only five, ARR, ARQ, VRQ, AHQ, ARH, are commonly seen. The relationship between PrP genotype and susceptibility to scrapie is shown in Table 14-15 using the groupings of the British National Scrapie Plan.

It can be seen from Table 14-15 that in the Britain, the VQR allele confers the greatest degree of susceptibility and that ARR is associated with resistance. Estimates that quantify risk in the British national flock based on genotypes of the sheep, and those of scrapie-affected sheep, are available but they are not strongly concordant. There is also an effect of PrP genotype on the incubation period, with the most susceptible genotypes (VQR) having the shortest incubation period and dying of scrapie at a younger age.

The frequency and distribution of the various PrP genotypes varies considerably between flocks and between breeds of sheep. There are also some marked between-breed differences in susceptibility with the same PrP genotype.

Susceptibility in the Suffolk and other black-faced breeds in the United States appears less complex than in other breeds and is strongly associated with sheep that are homozygous for glutamine at the 171 codon (171QQ) of the PrP gene, but is rare in sheep heterologous for glutamine and arginine (171QR) or homozygous for arginine (171RR) at codon 171. Suffolks are the predominant breed affected with scrapie in the United States. They lack the VRQ allele, and the ARQ/ARQ genotype is the genotype that confers the greatest susceptibility. The association between genotype and susceptibility, as defined in the scrapie eradication plan of the USDA, in the United Sates is shown in Table 14-16.

Factors other than the PrP genotype influence susceptibility to scrapie because not all sheep with a susceptible genotype challenged with scrapie subsequently develop the disease. Also, there are some breed differences in the level of resistance or susceptibility conferred by a given genotype. For example, ARQ/ARQ Suffolk sheep are highly susceptible to scrapie, whereas ARQ/ARQ Cheviots are relatively resistant. Breed differences in PrP genotype scrapie disease linkage and disease pattern differences with atypical strains of scrapie may be associated with polymorphisms in the PrP gene promoter. Atypical scrapie caused by to Nor98 strain is most common in sheep in Europe carrying phenylalanine (F) at position 141 or the PrP genotypes ARR/ARR, ARR/ARQ, and AHQ/ARQ.[11-13]

Table 14-15 PrP genotype and susceptibility to scrapie in national scrapie program in Great Britain

NSP Type	Main characteristic	Genotypes	Comments
1	ARR homozygous	ARR/ARR	Genetically most resistant
2	ARR heterozygous non-VQR	ARR/AHQ ARR/ARQ ARR/ARH	Sheep that are genetically resistant to scrapie, but will need careful selection when used for further breeding
3	**Non-ARR and non-VQR**	AHQ/AHQ ARQ/AHQ AHQ/ARH ARH/ARH ARQ/ARH ARQ/ARQ	Sheep that genetically have little resistance to scrapie and will need careful selection when used for further breeding Group 3 risk varies and can depend on breed, e.g., ARQ/ARQ Suffolk are highly susceptible ARQ/ARQ Cheviots are relatively resistant
4	**ARR/VQR heterozygous**	ARR/VRQ	Sheep that are genetically susceptible to scrapie and should not be used for breeding unless in the context of a controlled breeding
5	**VQR and non-ARR**	AHQ/VRQ ARQ/VRQ ARH/VRQ VRQ/VRQ	Sheep that are highly susceptible to scrapie and should not be used for breeding

NSP, *National Scrapie Program.*

Table 14-16 Scrapie susceptibility and genotype as defined by the U.S. Scrapie Eradication Plan

Genotype	Susceptibility
1. AA RR	Sheep that are resistant
2. AA QR	Sheep that are rarely susceptible
3. AV QR	Sheep that are susceptible to some scrapie strains that are thought to occur with low frequency in the United States
4. AA QQ	Sheep that are highly susceptible
5. AV QQ	Sheep that are highly susceptible
6. VV QQ	Sheep that are highly susceptible

There is less information on the genetics of scrapie in **goats**. There is high variability in the goat PrP gene that possibly can be exploited to select for goat-specific scrapie-resistant PrP genotypes. An initial report indicated that the H_{154}, Q_{211}, and K_{222} single nucleotide polymorphisms were associated with a high resistance to classical scrapie.[14]

Risk Factors

Exposure Factors

There is a dose–response relationship in naturally occurring scrapie. The high incidence in some Icelandic flocks is attributed to a high level of exposure, resulting from a long winter housing period with a higher risk for disease in lambs born in the winter housing period.

Factors that influence exposure risk will vary with the management systems, which can vary markedly between countries. With that caveat, risk factors that have been identified in case–control studies include the following:

- A higher risk for scrapie in larger flocks and in pedigree flocks
- A greater risk in flocks that lamb communally in group pens compared with those that lamb in individual pens or outside on pasture
- A greater risk in flocks that disposed of the placenta in the compost and spread sheep compost on the land
- A lower risk in flocks in which cow compost is spread on the land
- A greater risk in flocks that purchased replacement sheep through the market
- A greater risk where different flocks share pastures or rams

Age at Exposure

Lambs exposed at birth have a shorter incubation period and higher risk for scrapie than lambs exposed at 6 to 9 months of age. Similarly, lambs or goats removed from infected dams at birth to a scrapie-free environment have a lower incidence of scrapie than those removed at later times.

Infection Status of Parents

Lambs born to affected ewes are at increased risk for scrapie, and the offspring from an infected ewe and an infected ram are at greater risk than those born from an infected ewe and an uninfected ram. However, even in high-incidence herds a considerable proportion of disease cannot be attributed to parental scrapie status and results from horizontal transmission. Also, the number of genetically susceptible sheep in an affected flock can increase the infection pressure.

Goats

Scrapie in goats is rare, and most cases arise in goats that are in close contact with infected sheep. Scrapie can spread from goat to goat with no sheep contact.

Experimental Reproduction

The agent is present in the brain, spinal cord, lymph nodes, intestinal tract tissue, and spleen of infected sheep, and has been extracted from sheep and goat brain. Experimentally, the disease can be transmitted to sheep, goats, mice and other laboratory animals using these tissues, and by a variety of routes of inoculation. The experimental disease has a long incubation period that varies with the strain of the agent and the genetics of the recipient. Transmission of the disease to sheep has also been effected by the oral or intracerebral administration with fetal membrane material from known infected ewes. Accidental transmission is recorded following vaccination against louping-ill, with vaccine contaminated by the agent of scrapie, and resulted in widespread dissemination of the disease.

Pathogen Risk Factors

The scrapie agent can be maintained in tissue culture, and infectivity is retained with passage. It can also be perpetuated in experimental animals. Infectivity also survives for remarkable periods in dead and formalinized tissues; infected brain homogenates buried in soil for 3 years retain their infectivity. It is highly resistant to physical and chemical influences and can survive decontamination processes that are effective against conventional viruses. It is capable of withstanding the usual virucidal procedures and is not destroyed by boiling, by rapid freezing and thawing, or by exposure to ether or 20% formalin. Conventional heat treatments may reduce infectivity, but the agent is remarkable resistant to heat and steam sterilization at 27 psig (132°C) is required to totally destroy it. Chemical inactivation can be achieved with sodium hypochlorite providing 2% (20,000 ppm) of available chlorine acting for 1 hour, and by 4% sodium hydroxide.

Economic Importance

Scrapie is of major concern to pedigree flocks and, if present and public, will curtail the sale of sheep and effectively result in the dissolution of the flock. Some countries have, or have had, eradication schemes. The disease is also of major international importance because of the embargos maintained by several countries against sheep from enzootic areas.

Zoonotic Implications

There is no evidence for transmission of scrapie to humans or for a risk to public health.

PATHOGENESIS

In both sheep and mice, the agent shows a predilection for tissues of the lymphoreticular system in which it replicates during the incubation period before invading the nervous system. In naturally infected sheep, replication begins in the tonsil, retropharyngeal lymph node and Peyer's patches, and gut-associated lymphoid tissue, which probably reflects the oral route of infection. PrP^{Sc} subsequently becomes disseminated to other lymph nodes and the spleen. There may be a considerable period, ranging from 14 months to 7 years, before there is infection of the brain, and during this infection in the lymphoreticular system probably provides the reservoir for maternal and horizontal transmission. The action of the PrP genotype may be to delay neural invasion, in which case it is possible that a nonclinical carrier state may exist for scrapie.

How the scrapie agent reaches the CNS is not certain, but it is probably through transportation across intestinal villous enterocytes[15] and subsequent infection of the autonomic nervous system. Gut-associated lymphoid nodules in the Peyer's patches have a substantial network of nerve fibers and are probably the site for neuroinvasion. The scrapie agent has been detected in lymphoid nodules of the Peyer's patches of the gut as early as 5 months after oral infection.

Infection in the brain of sheep is initially in the diencephalon and medulla oblongata, with subsequent spread and replication in other areas of the brain. Characteristically, there is a noninflammatory, vacuolar degeneration of gray matter and the presence of PrP^{Sc} in scrapie-associated fibrils. Infection results in the posttranslational modification of this protein so that it becomes resistant to proteinases and to normal clearance and, consequently, accumulates in the cell.

PrP^{Sc} is also present in the placenta and in the trophoblast cells of the placentomes but not in the endometrium, myometrium, associated nerve plexuses, or in the fetus. The presence of PrP^{Sc} in the placenta is determined by the fetal PrP gene, and PrP^{Sc} is not present in the placenta of fetuses carrying one or two ARR alleles.

CLINICAL FINDINGS

Incubation

The incubation period varies from several months to several years. Scrapie is a nonfebrile disease and the onset is insidious, but as the disease progresses clinical signs become more obvious and severe. The **clinical course** is protracted, varying from 2 to 12 months, but lasting in most cases for about 6 months. Affected animals usually show **behavioral change, tremor, pruritus, and locomotor disorder.** A clinical examination protocol to detect classical and atypical scrapie in sheep has been developed.[16,17]

Early Signs

The earliest signs are transient, nervous phenomena occurring at intervals of several weeks or under conditions of stress. These episodes include sudden collapse and sudden changes of behavior, with sheep charging at dogs or closed gates.

Rubbing and biting at the fleece then begins but are often unobserved because of their infrequent occurrence. The apparent **pruritus** is manifested chiefly over the rump, thighs, and tail base. The poll and dorsum of the neck may also be involved and, less commonly, the neck in front of the shoulder and the ribs behind the elbow. The affected areas have approximate bilateral symmetry. In this early stage a stilted gait is often observed. A general loss of condition may also be observed as an early sign, although the appetite may not be severely affected.

Advanced Cases

More advanced cases show intense pruritus, muscle tremor and marked abnormalities of gait, and severe emaciation. **Persistent rubbing** causes loss of wool over the areas mentioned previously. Scratching with the hindfeet and biting at the extremities also occurs. Hematoma of the ears and swelling of the face may result from rubbing. Light or deep pressure, pinpricking, and application of heat or cold may elicit the characteristic "nibbling or scrapie scratch" reaction, during which the animal elevates the head and makes nibbling movements of the lips and licking movements with the tongue (Fig. 14-11). The sheep's expression suggests that the sensations evoked are pleasant ones. The reaction may not be observed consistently, often disappearing when the sheep is excited or in new surroundings.

Simultaneously with the development of pruritus there is serious **impairment of locomotion**. Hindlimb abnormalities appear first. There is incomplete flexion of the hock, shortening of the step, weakness, and lack of balance. The sense of spatial relationship appears to be lost, and the sheep is slow to correct abnormal postures. Adduction occurs during extension, and abduction occurs during flexion. When the animal is attempting to evade capture, gross incoordination of head and leg movements is likely and the animal often falls. Convulsions, usually transient but occasionally fatal, may occur at this time.

General hyperexcitability is evident. In the animal at rest an intermittent nodding and jerking of the head and fine tremor of superficial muscles may also be observed. In some cases, nystagmus can be produced by rotating the head sideways. Other clinical signs include inability to swallow, although prehension is unaffected; vomiting; loss of bleat; and blindness. A change of voice to a trembling note is often most noticeable.

Anorexia is not evident in most cases until the last 4 to 5 weeks and results in rapid loss of BW. Abomasal distension and impaction occurs in a small number of cases. Pregnancy toxemia may occur as a complication in pregnant ewes during this stage of scrapie. Finally, the sheep reaches a stage of extreme emaciation and inability to move without becoming readily fatigued. Sternal recumbency follows and lateral recumbency with hyperextension of the limbs is the final stage. Pyrexia is not evident at any time.

In a detailed study in 129 sheep with scrapie the proportional occurrence of signs was hindlimb ataxia 71%, head tremor 61%, altered mental status 57%, positive nibble reflex 51%, crouching position 51%, teeth grinding 44%, low head carriage 38%, body condition score of less than 1.5, 38%, and conscious proprioceptive deficits of limbs 36%. The occurrence of clinical signs was examined in relationship to the PrP genotype. The nibble reflex was strongly associated with PrP genotypes ARQ/ARQ and ARQ/ARH.

In goats, the clinical course in naturally occurring cases lasts from 2 to 24 weeks. Clinical signs are similar to those in sheep, and hyperesthesia, ataxia, and pruritus are common, but loss of weight is less common. In lactating goats the first sign may be a reluctance to permit milking. Dribbling and regurgitation of ruminal contents are also recorded in one-third of cases.

In most countries the disease is reportable to government authorities.

CLINICAL PATHOLOGY

There are no changes in hematologic or serum biochemistry parameters. The **IHC test on the obex** and other parts of the brain is the confirmatory test at some laboratories of the OIE and is considered the gold standard test in the United States. At least four ELISA tests are approved for scrapie surveillance at slaughter in the EU. Western blots on retropharyngeal lymph nodes obtained at slaughter have a sensitivity approaching that of IHC.[18] Atypical scrapie is best diagnosed using cerebellum as the tissue for analysis.

Until recently there has been no **antemortem** test for scrapie; however, PrP^{Sc} can be detected in cells by IHC methods and is present in the lymphoid tissue of some sheep with scrapie in the preclinical phase of the disease. **Palatine tonsillar biopsy** has detected PrP^{Sc} in lambs of susceptible genotypes as young as 5 months of age and in the tonsils of nonchallenged susceptible lambs at 9 to 10 months of age that were born and maintained in a scrapie environment. However, tonsil biopsy requires general anesthesia and is not a practical on-farm technique.

Biopsy of **lymphoid follicles in the third eyelid** or **rectum** is more practical, requires only restraint, sedation using xylazine, and local analgesia, and the techniques are being investigated for the preclinical diagnosis of scrapie in surveillance programs. In scrapie-positive sheep, PrP^{Sc} can be detected in third

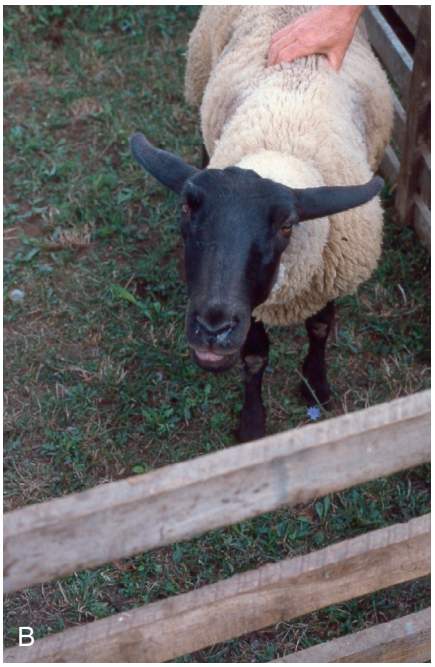

Fig. 14-11 **A,** Clinical signs of scrapie in Suffolk ewes located in the midwest region of the United States. The ewe on the left is pruritic, which is manifested as rubbing against the tree. The same ewe is also showing a positive nibble reflex (scrapie scratch reaction) with an upper lip curl and protruded tongue. The ewe on the right is losing weight and has an abnormally low head carriage. **B,** A positive result to the scrapie scratch reaction test. Rubbing/scratching the back over the thoracic vertebrae results in a slight elevation of the head, an upper lip curl, licking of the lips, and a pleasing look in the eyes of sheep with scrapie.

eyelid biopsies by 14 months of age, obtained from the palpebral side of the third eyelid. Histamine-containing eye drops improve the success of collecting a sample with adequate lymphoid follicles for examination. However, lymphoid follicles may not be present in sufficient numbers in third eyelid biopsies for evaluation in up to 60% of adult sheep sampled, and the sensitivity of third eyelid biopsy and rectal mucosa biopsy in detecting scrapie-infected sheep is 40% and 36%.[19] It is unlikely that lymphoid tissue will ever achieve an adequately high test sensitivity because a large number of infected animals have minimal or no PrP^{Sc} in lymphoid tissue.

Research is ongoing about developing an accurate test that can detect serum biomarkers of early and late phase scrapie or PrP^{Sc} in blood.[20] It has been suggested that the disease could be diagnosed antemortem by EEG, but this has been disputed.

NECROPSY FINDINGS

Significant gross findings are restricted to traumatic lesions caused by rubbing, and to emaciation and loss of wool; gross distension of the abomasum has been recorded in some natural cases.

The essential histopathologic lesion in scrapie is the **vacuolation of gray matter neuropil** in the spinal cord, medulla, pons, and midbrain, and the consequential wallerian degeneration in dorsal, ventral and ventrolateral columns of the spinal cord, and in nerve fibers in the cerebellar peduncles and the optic nerve. In addition, there is degeneration of the cerebellar and hypothalamoneurohypophyseal systems. There are different strains of the scrapie agent that can result in differing clinical signs and pathology. Scrapie-associated fibrils are present in infected brain. Histologic findings are diagnostic in many cases but can be supplemented with the immunodetection of PrP^{Sc} in brain tissue by in situ IHC and Western immunoblots. The breed of the sheep affects the magnitude of neuropil vacuolation, and variation also is associated with the PRP genotype within breeds.

Atypical strains of scrapie (Nor98) are recognized that differ from the usual strains in their vacuolation patterns and their disease-specific, protease-resistant PrP^{Sc} disposition patterns. These strains can also produce disease in PrP genotypes not normally affected, including Prp genotype ARR/ARR.

DIFFERENTIAL DIAGNOSIS

The characteristic signs of behavioral change, tremor, pruritus, and locomotor disorder occurring during a period of prolonged illness should suggest the possibility of this disease. The long incubation period, slow spread, and high case–fatality rate should also be considered when making a diagnosis. Diseases that may require differentiation include the following:

Diseases with signs of nervous dysfunction
- Louping-ill
- Pregnancy toxemia
- Rabies
- Pseudorabies
- Visna.

Skin diseases
- External parasites
- Wool loss

Treatment No treatment has proved capable of changing the course of the disease.

CONTROL

Individual Flocks

The maintenance of a closed ewe flock is critical to the control of this disease. If ewes need to be purchased from outside flocks, they should be from certified flocks or, better still, selected by PrP genotype testing for 171RR or 171QR genotype. The rams should be 171RR or 171QR genotypes. Ewes should be isolated at lambing and lambed individually with disposal of placenta by burning.

National Eradication

In countries that do not have the disease, and where it is inadvertently introduced with imported sheep, the approach is slaughter eradication of the infected flock and all in-contact animals. The aim is to eliminate the disease from the country, and the approach is usually successful because it has the full support of the sheep industry and the government.

Flock Eradication

The eradication of scrapie in countries where it is enzootic has less chance of success. Eradication programs vary and may involve the whole flock or just the family lines of the infected sheep. Programs in the United States since 1952 have varied from compulsory slaughter eradication of the affected flock and source flocks, to bloodline eradication, and finally from discontinuation to a voluntary certification scheme.

During this period there was no antemortem diagnostic test for scrapie and the identification of infected farms and flocks relied on owners submitting suspect or clinical cases for postmortem and histologic diagnosis. Owners are unlikely to put their flocks at risk if there is inadequate compensation for the results of their action, if they perceive that other flock owners are not cooperating with the control program, or if they question the validity of the eradication policy, which is attested to by the experience in the United States.

Iceland is currently attempting an eradication program that involves depopulation of infected farms and areas. The farms are left without sheep for a 2-year period during which there is extensive cleaning and disinfection of the farm area before repopulation with scrapie-free sheep. The program is a national thrust but very expensive. This approach has also been apparently successful in virtually eliminating, if not eradicating, the disease in Iceland. Norway is also attempting eradication in a similar manner. In both countries the disease was geographically clustered.

Genetic Control and National Programs

The occurrence of scrapie and the concern for BSE in sheep has led many countries to develop national breeding programs for the control of scrapie and potential BSE. Examples are the National Scrapie Plan in the UK and the National Scrapie Eradication Program in the U.S. National Scrapie Plan. The overall aim is to identify sheep genetically resistant to scrapie on the basis of their genotype (ARR) and to and breed them to create a national flock with scrapie resistance. Genetic testing will allow the selection of resistant sheep for breeding and the culling of susceptible sheep, particularly in breeds such as the Suffolk in which the genetics of susceptibility appear relatively simple.

The **UK** has a Voluntary **National Scrapie Flocks Scheme** and a National Scrapie Plan which, under EU regulations, become compulsory for flocks that have had a case of scrapie after July 2004. Under the Compulsory Scrapie Flocks Scheme farmers with confirmed scrapie cases on their farms will either have their sheep flocks genotype tested so that those animals more susceptible to disease can be identified and removed or the whole flock slaughtered and disposed of. All goats on affected holdings also will be slaughtered and disposed of. Testing of breeding rams will also become compulsory for all purebred flocks and any other flocks producing and selling homebred rams for breeding. All rams carrying VRQ PrP genotypes will be slaughtered or castrated. Allied to this will be a voluntary ewe-testing scheme.

A mathematical model of the program has examined the time that it would take to eliminate scrapie from the national flock. The results suggest eradication is feasible but the process could take decades and would be expensive. Surprisingly whole-flock culling was more efficient in terms of time to eradication than genetic typing and selective culling. Not surprising was the finding that the **most important factor** influencing the efficacy of control at the national level was the ability to identify affected flocks. It was suggested that investing money in obtaining better notifications and in conducting trace backs and active surveillance of animals slaughtered for human consumption and animals found dead on farms would be a good investment.

In the **United States**, all breeding sheep must be individually identified with a unique flock and individual number. The **Scrapie Flock Certification** program monitors flocks over time and assigns certified status to flocks with no evidence of scrapie. Although this program has strict requirements of identification and reporting, it is not based on genetic testing.

The **United States** also has a **USDA Genetics-Based Flock Cleanup and Monitoring Plan.** This program targets scrapie-infected and source flocks. The sheep in these flocks are genotyped, sheep with susceptible genotypes are removed (as are all goats), and the flock is placed under surveillance for 5 years. Flocks that are exposed to scrapie are placed on a monitoring program, and if scrapie is detected the genetics-based cleanup program would begin.

There is concern that breeding for the selection for certain PrP genotypes and reduction or elimination of other PrP genotypes could affect other **desirable genetic characteristics** and reduce the overall "genetic pool." This will need to be determined for individual breeds, but preliminary analyses that have involved several breeds suggest that reproductive traits, muscle mass, wool quality, live weight gain, and carcass characteristics are not affected, at least in some breeds.

There has also been concern that **rare breeds** could be threatened in the face of an occurrence of scrapie and subsequent disposition of the flock based on the PrP genotype. Interestingly, there is a good representation of ARR and some breeds have very high frequencies.

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CHRONIC WASTING DISEASE

CWD has recently emerged, or been recognized, in the United States as a TSE of captive and free-ranging cervids. The ability of this infection to transmit laterally between cervids, coupled with the longevity of the agent in the environment and the common grazing land of infected cervids and cattle and sheep, has resulted in concern that CWD in cervids might be a risk to livestock, and subsequently to humans, similar to BSE. There has also been concern that it might be

transmitted directly from infected cervids to hunters dressing carcasses or consuming deer meat. There is no evidence for either of these risks.

The known natural hosts for CWD are mule deer (*O. hemionus*), white-tailed deer (*O. virginianus*), Rocky Mountain elk (*C. elaphus nelsoni*), and less frequently Shiras moose (*Alces alces shirasi*). CWD was originally recorded in the late 1960s as a chronic wasting syndrome of unknown etiology in captive mule deer in research facilities in Colorado and Wyoming. It was subsequently established that the disease was a TSE, and CWD has subsequently been found affecting cervids in captivity in several states in the United States and also in the provinces of Saskatchewan and Alberta, Canada. The occurrence in captive and farmed cervids in these different geographic areas is likely the result of transfer of animals between them, and the disease has recently been reported in Korea in cervids imported from North America. The disease continues to expand in prevalence and range in North America.

CWD has a focus and may have originated in free-ranging deer and elk in north central Colorado and southeastern Wyoming; however, in recent years it has been detected in free-ranging cervids east of the Mississippi and in a much broader area of North America. It is not certain whether this is caused by spread or because of improved surveillance. Based on comparisons of the CNS lesions and the glycoform patterns, the CWD agent is the same in captive and free-ranging deer.

There is strong evidence from outbreaks in captive deer that lateral transmission is of major importance in the transmission of CWD. The agent accumulates in gut-associated lymphoid tissues early in the infection, and saliva and feces are the likely source of horizontal infection with contamination of the environment.

The disease can be transmitted experimentally between cervids, and there is evidence for genetic susceptibility. The prion associated with CWD is not the same as that associated with BSE. In a recent study, it was shown that infection, with amplification of prion protein in brain tissue, can be transmitted to cattle by intracerebral inoculation of CWD-infected deer brain. Six years following challenge less than 50% of the challenged cattle showed amplification of the infection and none had histologic evidence of spongiform encephalopathy. It was concluded that if infection via the oral route did occur in cattle it would be unlikely that it would result in amplification of the abnormal prion within the life span of cattle.

Clinically the disease in cervids is manifested initially by changes in behavior not commonly observed in free-ranging cervids, and the major manifestation is a marked fall in body condition. In the terminal stages, there may be ataxia and excitability. The clinical course varies from a few days to a year but averages 4 months. Diagnosis is by histologic examination of the brain or more commonly by the demonstration of PrP^{CWD} in brain tissue by IHC. Antemortem biopsy of lymphatic tissue in tonsils and retropharyngeal lymph nodes as well as rectal biopsy have all been proven to be useful in diagnosing preclinical and subclinically infected animals, with diagnostic performance approaching testing brain tissue. Because prions in cervids with CWD are heavily shed in saliva and ocular secretions, diagnostic tests are currently under development using these fluids.

Control of CWD appears to be unsuccessful because of its horizontal transmission, as well as occurrence in wildlife that migrate over large distances and that are naturally shy. Eradication appears very unlikely.

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Parasitic Disease Primarily Affecting the Cerebrum

COENUROSIS (GID, STURDY)

Coenurosis is the disease caused by invasion of the brain and spinal cord by the intermediate stage of *Taenia multiceps*. The syndrome produced is one of localized, space-occupying lesions of the CNS. In most countries the disease is much less common than it used to be and relatively few losses occur.

ETIOLOGY

The disease is associated with *Coenurus cerebralis,* the intermediate stage of the tapeworm *T. multiceps,* which inhabits the intestine of dogs and wild Canidae. The embryos, which hatch from eggs ingested in feed contaminated by the feces of infested dogs, hatch in the intestine and pass into the bloodstream. Only those embryos that lodge in the brain or spinal cord survive and continue to grow to the coenurid stage. *C. cerebralis* can mature in the brain and spinal cords of sheep, goats, cattle, horses, and wild ruminants, and occasionally humans, but clinical coenurosis is primarily a disease of sheep and occasionally goats[1] and cattle.[2] Infection in newborn calves, acquired prenatally, has occasionally been observed.

PATHOGENESIS

The early stages of migration through nervous tissue usually passes unnoticed, but in heavy infections an encephalitis may be produced. Most signs are caused by the mature coenurus, which may take 6 to 8 months to develop to its full size of about 5 cm. The cystlike coenurus develops gradually and causes pressure on nervous tissue, resulting in its irritation and eventual destruction. It may cause sufficient pressure to rarefy and soften cranial bones, leading to a larger volume of calvarium, compared with uninfected controls.[3]

CLINICAL FINDINGS

In acute outbreaks caused by migration of larval stages, sheep show varying degrees of blindness, ataxia, muscle tremors, nystagmus, excitability, and collapse. Sheep affected with the mature *Coenurus* show an acute onset of irritation phenomena including a wild expression, salivation, frenzied running, and convulsions. Deviation of the eyes and head may also occur. Some animals may die in this stage, but a large number proceed to the second stage of loss of function phenomena, the only stage in most affected animals. The most obvious sign is slowly developing partial or complete blindness in one eye. Dullness, clumsiness, head-pressing, ataxia, incomplete mastication, and periodic epileptiform convulsions are the usual signs. Papilledema may be present. Localizing signs comprise chiefly deviation of the head and circling; there is rotation of the head with the blind eye down, and deviation of the head with circling in the direction of the blind eye.

In young animals local softening of the cranium may occur over a superficial cyst and rupture of the cyst to the exterior may follow, with final recovery. When the spinal cord is involved, there is a gradual development of paresis and eventually inability to rise. Death usually occurs after a long course of several months.

CLINICAL PATHOLOGY

Clinicopathologic examinations are not generally used in diagnosis in animals, and serologic tests are not sufficiently specific to be of value. Radiologic examinations are helpful in defining the location of the cyst, especially if there is a prospect of surgical intervention. MRI provides more detailed information regarding cyst size and location.[3]

NECROPSY FINDINGS

Thin-walled cysts may be present anywhere in the brain but are most commonly found on the external surface of the cerebral hemispheres. In the spinal cord the lesions are most common in the lumbar region but can be present in the cervical area. Local pressure atrophy of nervous tissue is apparent, and softening of the overlying bone may occur.

DIFFERENTIAL DIAGNOSIS

The condition needs to be differentiated from other local space-occupying lesions of the

Continued

cranial cavity and spinal cord, including abscess, tumor, and hemorrhage. In the early stages the disease may be confused with encephalitis because of the signs of brain irritation. Clinically there is little difference between them and, while clinical signs and local knowledge may lead to a presumptive diagnosis, demonstration of the metacestode is essential.

TREATMENT AND CONTROL

Surgical drainage of the cyst may make it possible to fatten the animal for slaughter, and surgical removal with complete recovery is possible in a majority of cases. The life cycle can be broken most satisfactorily by control of mature tapeworm infestation in dogs. Periodic treatment of all farm dogs with a tenicide is essential for control of this and other more pathogenic tapeworms. Carcasses of livestock infested with the intermediate stages should not be available to dogs.

Anthelmintic agents appear to have efficacy in treating coenurosis in naturally infected sheep, as demonstrated by degeneration of the cysts in treated animals.[4] Best results were obtained with oral albendazole (25 mg/kg), or combined oral fenbendazole (500 mg) and oral praziquantel (500 mg) The clinical effect of such treatment is undetermined.

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HALICEPHALOBUS

H. gingivalis (*H. deletrix; Micronema deletrix*) is a small nematode that has been found in horses on rare occasions. Like *Pelodera*, it is a free-living saprophytic organism that has the ability to become an opportunistic parasite. *H. gingivalis*, however, invades the deeper tissues where it reproduces. Enormous numbers may be seen in granulomatous lesions that grow to several centimeters in diameter. Lesions may be found near the eye, in the prepuce, nares, or the maxilla. The latter may be sufficiently large to cause the hard palate to bulge, displacing the molars and causing difficulty in mastication.[1] Putative hematogenous spread gives rise to similar lesions in the kidney,[2] which may be misdiagnosed as renal neoplasia. The worm also invades the brain,[3-5] spinal cord, and heart,[6] but here the lesions are usually microscopic and consist of discrete granulomata with a vascular orientation. In the brain lesions are predominantly in the cerebrum with numerous intralesional worms.[5] Affected horses may show a wide variety of clinical signs including lethargy, ataxia, and incoordination leading to recumbency and death.[1,6] Diagnosis of superficial lesions is by demonstration of worms and larvae in biopsy samples, but more often *H. gingivalis* infection is identified retrospectively in histologic sections following necropsy.[7] The worms are 250 to 430 µm long, have a characteristic bilobed pharynx, and often contain a single large egg. PCR and sequencing have been used to identify *H. gingivalis* definitively.[3] This infection must be considered in the differential diagnosis of equine cerebrospinal nematodosis.[3,4] Treatment with ivermectin at the maximum safe dose has been attempted, although the susceptibility of the worm to this compound is uncertain.[1] Experimental tests have indicated that *H. gingivalis* adult worms and larvae have remarkable tolerance to ivermectin.[8]

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Metabolic Diseases Primarily Affecting the Cerebrum

POLIOENCEPHALOMALACIA (CEREBROCORTICAL NECROSIS) OF RUMINANTS

SYNOPSIS

Etiology Several different causes including thiamine inadequacy, sulfate toxicity.

Epidemiology Sporadic disease in young well-nourished ruminants on high-level grain diets and not synthesizing sufficient thiamine. Ingestion of preformed thiaminase in certain plants or production by ruminal microbes may also cause destruction of thiamine. May also occur in cattle and sheep of all ages ingesting excess amounts of sulfates in feed and water.

Signs Sudden blindness, ataxia, staggering, head-pressing, tremors of head and neck, ear-twitching, champing fits, clonic-tonic convulsions, recumbency, opisthotonus, rumen contractions normal initially, pupils usually normal and responsive, nystagmus, death may occur in 24–48 hours. Hydrogen sulfide odor of ruminal gas in sulfate toxicity.

Clinical pathology Erythrocyte transketolase activity decreased and thiamine pyrophosphate effect increased but both measurements difficult to interpret; blood thiamine concentrations decreased but are not reliable in thiamine inadequacy form. Increased hydrogen sulfide content in rumen gas and increased thiosulfate concentration in urine in sulfur-induced form.

Lesions Diffuse cerebral edema, flattened dorsal gyri, coning of cerebellum, multifocal to linear areas of fluorescence in gray and white matter borders of cortical gyri and sulci.

Diagnostic confirmation Fluorescence of gray and white matter of cortical gyri and sulci of brain.

Differential diagnosis list

Cattle
- Lead poisoning
- Hypovitaminosis A
- Sodium chloride toxicity
- *Histophilus somni* meningoencephalitis

Sheep
- Pregnancy toxemia
- *Clostridium perfringens* type D enterotoxemia
- Focal symmetric encephalomalacia
- Lead poisoning.

Goats
- Pregnancy toxemia
- *C. perfringens* type D enterotoxemia
- Closantel overdosage[1]
- Lead poisoning

Treatment Thiamine hydrochloride parenterally.

Control Thiamine supplementation of diet. Avoid excess feeding or access to sulfate in feed and water supplies.

ETIOLOGY

Historically, PEM was considered to be caused by a thiamine inadequacy. It is important to realize that PEM is a histologic description of a cerebral injury affecting predominantly the gray matter, and that there are several different causes of PEM in ruminants. The current preference is to discuss PEM in relationship to a suspected etiology.

Thiamine Inadequacy

Thiamine (vitamin B_1) is synthesized only in bacteria, fungi, and plants but is an essential nutrient for animals. Consequently, animals must obtain thiamine from their diet. The evidence that a thiamine inadequacy can be associated with the disease includes the following:

- Affected animals respond to the parenteral administration of thiamine if given within a few hours after the onset of clinical signs
- Affected animals have biochemical findings consistent with thiamine pyrophosphate ([TPP], also known as TDP) inadequacy (TPP is the biologically active form of thiamine)
- The clinical signs and pathologic lesions can be reproduced in sheep and cattle by the administration of large daily

doses of pyrimidine containing structural analogs of thiamine, principally amprolium, given orally or intraperitoneally.

Excess Dietary Sulfur

Elemental sulfur in the rumen is metabolized by two pathways: (1) reduction of sulfate (SO_4^{2-}) to sulfide (S^{2-}), which is then incorporated into sulfur-containing compounds such as cysteine and methionine that are used by rumen bacteria and (2) reduction of sulfate to sulfide, which is converted to hydrosulfide (HS^-) at normal rumen pH (pKa of $S^{2-} + H^+ \leftrightarrow HS^-$ is 11.96). Hydrosulfide is in equilibrium with hydrogen sulfide in the rumen because the pKa for the equilibrium reaction: $HS^- + H^+ \leftrightarrow H_2S$ is 7.04).[2] The practical significance of these equilibrium reactions is that sulfate metabolism results in higher levels of H_2S in rumen gas (and H_2S is assumed to be the toxic agent) at lower rumen values for pH. These equilibria reactions help to explain the association between high sulfate intakes, high-grain diets, and increased risk of sulfur-associated PEM. The ingestion of excessive quantities of sulfur from the diet and water supply can cause the disease in cattle and sheep without any change in the thiamine status of the tissues. An increased dietary sulfur intake may increase the metabolic demand for thiamine, possibly to offset the damaging effect of hydrogen sulfide on brain tissue.[3]

EPIDEMIOLOGY

Occurrence

PEM occurs sporadically in young cattle, sheep, goats, and other ruminants. In North America, UK, Australia, and New Zealand, the disease is most common in cattle and sheep that are being fed concentrate rations under intensified conditions such as in feedlots. An inadequate amount of roughage can result in a net decrease in the synthesis of thiamine. The disease is most common in well-nourished thrifty cattle 6 to 18 months of age (peak incidence 9–12 months of age) that have been in the feedlot for several weeks. Feedlot lambs may also be affected only after being on feed for several weeks. The disease also occurs in goats and in antelope and whitetail deer. It may affect goats from 2 months to 3 years of age and is commonly associated with milk-replacer diets in kids or concentrate feeding in older goats. The disease occurs only rarely in adult cattle, which may be a reflection of the greater quantities of roughage they usually consume. However, there are recent reports of the disease occurring in adult cows on pasture with access to drinking water containing excessive concentrations of sulfates.

Morbidity and Case Fatality

Accurate morbidity and case–fatality data are not available, but outbreaks can occur suddenly in which up to 25% of groups of feeder cattle may be affected, with case–fatality rates from 25% to 50%. Case–fatality rates are higher in young cattle (6–9 months) than in the older age group (12–18 months), and mortality increases if treatment with thiamine is delayed for more than a few hours after the onset of signs. In feedlot lambs, it has been suggested that approximately 19% of all deaths are caused by PEM.

Risk Factors

When PEM was first described in 1956, and for about 30 years, it was considered to be a thiamine deficiency conditioned by dietary factors such as high-level grain feeding and inadequate roughage. PEM was most common in well-nourished young cattle from 6 to 12 months of age that were being fed high-level grain rations. The scientific investigations centered on the effects of dietary factors, such as grain diets, and the presence of thiaminases in certain diets on thiamine metabolism in the rumen. In recent years, it has become clear that the disease is not etiologically specific because many different dietary factors have been associated with the occurrence of the disease, and in some instances the thiamine status of the affected animals is within the normal range. Notable examples are the recent observations linking dietary sulfate with the occurrence of the disease.

Dietary Risk Factors

Although there has been general agreement that thiamine inadequacy is associated with the cause of PEM, the possible mechanisms by which this occurs are uncertain. Thiamine inadequacy in ruminants could, theoretically, occur in any of the following situations in which inadequate net microbial synthesis of thiamine in the rumen may occur:

- Concentrate-fed animals receiving inadequate roughage
- Impaired absorption and/or phosphorylation of thiamine
- Presence of a thiamine inhibitor in the tissues of the host
- Lack of sufficient or appropriate apoenzyme or coenzyme-apoenzyme binding for thiamine-dependent systems
- Increased metabolic demands for thiamine in the absence of increased supply
- Increased rate of excretion of thiamine resulting in its net loss from the body

Thiamine can be destroyed by thiaminases of which significant amounts can be found in the rumen contents and feces of cattle and sheep affected with naturally occurring PEM.

Thiamine Inadequacy

In cattle under farm conditions, using erythrocyte transketolase activity as a measurement of thiamine status, up to 23% of cattle under 2 years of age and 5% over 2 years may be in a thiamine-low state. Newly weaned beef calves on a hay diet are not subject to a thiamine deficiency, but a low and variable proportion of young cattle on barley-based feedlot diets (1.7%) may have some evidence of thiamine deficiency based on a TPP activity effect in excess of 15%. The supplementation of the diet of feedlot steers on an all-concentrate barley-based diet with thiamine at 1.9 mg/kg dry matter resulted in an increase in average daily gain and final carcass weights. Thus some animals may be marginally deficient in thiamine, which may be associated with decreased performance in cattle fed all-concentrate diets. However, thiamine supplementation of cattle on all-concentrate diets does not consistently result in improved animal performance. The experimental disease can be produced in young lambs fed a thiamine-free milk diet, and it may be unnecessary to postulate that thiamine analogs produced in the rumen are essential components of the etiology.

Thiaminases

A major factor contributing to PEM in cattle and sheep is a progressive state of thiamine deficiency caused by the destruction of thiamine by bacterial thiaminases in the rumen and intestines. Certain species of thiaminase-producing bacteria have been found in the rumen and intestines of animals with PEM. *Bacillus thiaminolyticus* and *Clostridium sporogenes* produce thiaminase type I and *B. aneurinolyticus* produces thiaminase type II. Although there is good circumstantial evidence that the thiaminases from these bacteria are the real source of thiaminases associated with the disease, it is not entirely certain. The experimental oral inoculation of large numbers of thiaminase type I producing *C. sporogenes* in lambs did not result in the disease.

Certain species of fungi from moldy feed are also thiaminase producers, but the evidence that they destroy thiamine and are associated with PEM is contradictory and uncertain.

The factors that promote the colonization and growth of thiaminase-producing bacteria in the rumen are unknown. Attempts to establish the organism in the rumen of healthy calves or lambs have been unsuccessful. Thiaminases have also been found in the rumen contents and feces of normal animals, which may suggest the existence of a subclinical state of thiamine deficiency. Poor growth of unweaned and weaned lambs can be associated with a thiaminase-induced subclinical thiamine deficiency. Weekly testing of young lambs over a period of 10 weeks revealed that 90% of unthrifty lambs were excreting high levels of thiaminase in their feces; low levels of thiaminase activity were present in 20% of clinically normal animals, and there were significant differences in the mean erythrocyte transketolase activity of the unthrifty animals excreting

thiaminase compared with the thiaminase-free normal animals.

Field and laboratory investigations have supported an association between inferior growth rate of weaner sheep in Australia and a thiaminase-induced thiamine deficiency. Thiaminase activity has been detected in the feces of lambs at 2 to 5 days of age, with the levels increasing for 10 days and then declining over the next 3 to 4 weeks. Decreased erythrocyte transketolase activity indicated a thiamine insufficiency in lambs with high thiaminase activity, and mean growth rates were 17% less than lambs with low thiaminase activity. The oral supplementation with thiamine at 2 to 3 weeks of age was the most appropriate prevention and treatment for subclinical thiamine deficiency.

The parenteral or oral administration of thiamine to normal calves raised under farm conditions resulted in a marked reduction in the percentage TPP effect, which is an indirect measurement of thiamine inadequacy. Goats with PEM were found to have elevated ruminal and fecal thiaminase activities, low erythrocyte transketolase activity, elevated TPP effect, low liver and brain thiamine levels, and elevated plasma glucose levels compared with goats not affected with the disease. With the increased interest in goat farming, some breeders attempted to improve body condition of breeding stock for sale or show by feeding grain or concentrate, which creates a situation similar to feedlot rearing of sheep and cattle that is conducive to the establishment of thiaminases in the rumen and the occurrence of PEM.

High levels of thiaminase type I are present in the rhizomes of bracken fern (*Pteridium aquilinum*) and horsetail (*Equisetum arvense*). The feeding of the bracken fern rhizomes (*P. esculentum*) to sheep will cause acute thiamine deficiency and lesions similar to those of PEM, but neither of these plants is normally involved in the natural disease. The disease has occurred in sheep grazing the Nardoo fern (*Marsilea drummondii*) in flood-prone or low-lying wet areas in Australia. The fern contains a high level of thiaminase type I activity.

Amaranthus blitoides (prostrate pigweed) may contain high levels of thiaminase and be associated with PEM in sheep.

Sulfur-Induced Polioencephalomalacia

PEM has been associated with diets high in sulfur, particularly in the form of sulfate. A high concentrate of sulfates in the diet of cattle has been associated with episodes of the disease in 6- to 18-month-old cattle. Inorganic sulfate salts in the form of gypsum (calcium sulfate) added to feedlot rations to control the total daily intake of the diet may cause PEM. Seasonal outbreaks have occurred in feedlot beef cattle between 15 and 30 days after introduction to a **high-sulfur diet,** and the risk may increase when water is an important source of dietary sulfur, and during hot weather, when the ambient temperatures exceeded 32°C.

Initial outbreaks may follow the use of a **new well of water containing more sulfate** than water used previously from another well, increasing from a monthly incidence of 0.07% to 0.88%. Growing cattle consume 2.4 times more water when the temperature is 32°C than at 4°C; consequently total ingestion of sulfur by consumption of high-sulfate water increases during hot weather. The feed contained 2.4 g of SO_4/kg dry matter with a total sulfur content of 0.20%. Samples of drinking water contained between 2.2 and 2.8 g of SO_4/L. During hot weather daily sulfur ingestion from feed and water combined was estimated to be 64 g per animal corresponding to total dietary sulfur of approximately 0.67% of dry matter. Daily SO_4 ingestion was approximately 160 g per animal. The ruminal sulfide levels were much higher 3 weeks after entering the feedlot, when the incidence of the disease was greatest, than 2 months after entering the feedlot when the risk of the disease was low.

In western Canada, there is an association between PEM and high levels of sodium sulfate in water, and range cows are usually affected when certain waters become concentrated with this salt during the summer months. Water containing high levels of magnesium sulfate, often called ***gyp water*** (for gypsum water) is common in the western plains and intermountain areas of the United States and Canada. Ideally, water for livestock consumption should contain less than 500 ppm sulfate, and 1000 ppm is considered the maximum safe level in water for cattle exposed to moderate dietary sulfur levels or high environmental temperatures. A level of 2000 ppm of sulfate in drinking water is the taste discrimination threshold for cattle. Performance of feedlot cattle is reduced when offered water with sulfate levels of 2000 ppm or higher. The National Research Council states that the requirement of sulfur in feed to be 1500 to 2000 ppm for both growing and adult beef cattle; 4000 ppm is considered the maximum tolerated dose. Ruminant diets normally contain between 1500 to 2000 ppm (0.15%–0.20% sulfur).

Based on National Research Council guidelines, 30 g of sulfur is the calculated maximum tolerated dose of sulfur for a 650-lb (294-kg) steer consuming 16.25 lb (7.39 kg; 2.5% BW) of feed daily. If the ambient temperature reaches 32°C, a 650-lb steer can drink 14.5 gallons (53.9 L) of water daily, Consumption of 14.5 gallons of water containing 3000 ppm sulfate results in a daily intake of 55 g of sulfur. A feed intake of 2.5% BW would also consume 22.2 g of sulfur from feed containing 3000 ppm sulfur for a total daily intake of 77.2 g of sulfur from both feed and water, which is 2.5 times the maximum tolerated dose.

In some surveys, water supplies in western Canada contained 8447 ppm of total dissolved solids and 5203 ppm of sulfate. A survey of the sulfate concentrations in water on farms found that high levels of sulfate can have a detrimental effect on the thiamine status of the cattle on those farms. Cattle exposed to sulfate concentrations >1000 ppm had blood thiamine levels lower than those drinking water with low levels <200 ppm. This raises the possibility that a subpopulation of cattle under such circumstances could be marginally deficient in thiamine.

The total dietary intake of sulfur by cattle must be considered when investigating sulfur as a cause of PEM. In a study of one farm, water from a 6.1-m well containing 3875 mg/L of total dissolved solids with 3285 mg/L of sodium sulfate was associated with PEM in heifers 6 months of age. However, the water contributed about 20% of the total sulfur content in the diet of the heifers, and 60% of the dietary sulfur intake was supplied by the hay and 20% by the grain supplement. The hay contained 0.4% total sulfur, which is at the maximum tolerable level for cattle and at the upper limit for hay. The hay consisted of variable amounts of kochia (*Kochia scorpia*) and Canada thistle (*Cirsium arvense*). *K. scorpia* (summer cypress or Mexican fireweed) is high in sulfur content and has been associated with the disease in range cattle.

The levels of sulfate in water that have affected feed intake in cattle have varied from 2800 to 3340 mg sulfate/L, whereas other studies found no reduction in feed intake with levels up to 7000 mg/L. It appears that the different effects of sulfur toxicity for similar sulfur contents in saline water are attributed to the total sulfur intake. Outbreaks of the disease may occur in adult cattle on pasture drinking water containing 7200 ppm of sodium sulfate. Thus established guidelines for saline drinking water are not applicable when cattle are fed feeds grown in saline areas.

A combination of excessive intake of sulfur and a low dietary intake of trace minerals, especially copper, may affect the thiamine status of a cattle herd and contribute to PEM. Sulfur adversely affects both thiamine and copper status in sheep. A nutritionally related PEM has also been reproduced in calves fed a semipurified, low-roughage diet of variable copper and molybdenum concentrations and it was not related to copper deficiency. The disease has occurred in cattle in New Zealand fed chou moellier (*Brassica oleracea*), which contained sulfur concentrations of 8500 mg/kg dry matter. The morbidity was 25% and mortality 46% despite rapid conventional therapy. Sulfur-associated PEM has also occurred in Australia when cattle grazed extensive stands of *Sisymbrium irio* (London rocket), *Capsella bursapastoris* (shepherd's purse), and *Raphanus raphanistrum* (wild radish), which all contain high

sulfur content and are in the Brassicaceae (Cruciferae) family.[4]

Ammonium sulfate used as a urinary acidifier in the rations of cattle and sheep has been associated with outbreaks of PEM. Morbidity rates ranged from 16% to 48% and mortality rates from 0% to 8%. Affected animals did not respond to treatment with thiamine.

Outbreaks have occurred in sheep exposed to an alfalfa field previously sprayed with 35% **suspension of elemental sulfur**. The disease can be induced experimentally in lambs by the administration of sodium hydrosulfide into the esophagus and has occurred in lambs 3 to 4 weeks after being fed a concentrate ration containing 0.43% sulfur. Feeding experimental diets containing inorganic sulfur to young lambs was associated with PEM, and supplementation of those diets with thiamine decreased the severity of the lesions. Rumen microbes are able to reduce sulfate to sulfides, which may be directly toxic to the nervous system. Feeding calves (115–180 kg) a semipurified diet high in readily fermentable carbohydrate, without long fiber, and with added sodium sulfate for a total sulfur content of 0.36% resulted in PEM within 21 days of the introduction of the experimental diet. An odor of hydrogen sulfide was frequently detected on passage of a stomach tube into the rumen of all calves during the experiment. The total thiamine concentrations in affected and control calves remained within normal limits.

The dietary content of copper, zinc, iron, and molybdenum may also have important modifying influences on sulfur toxicosis. Molybdenum and copper can combine with sulfur to form insoluble copper thiomolybdate. Copper, zinc, and iron form insoluble salts with sulfide, and their expected effect would be to decrease the bioavailability of sulfide in the rumen. Conversely, low, but not necessarily deficient, dietary contents of these divalent metals could be prerequisites for excess absorption of sulfide to occur. PEM is not associated with copper deficiency, but copper and sulfur metabolism are interdependent. An excess of dietary sulfur may result in depression of serum copper, or alternatively, low serum copper may potentiate the actions of toxic levels of sulfur. Chronic copper poisoning in a lamb has been associated with PEM. It is suggested that the copper toxicity may have caused decreased hepatic function resulting in increased plasma concentration of sulfur containing amino acids which, may have predisposed to sulfur toxicity encephalomalacia.

Major dietary sulfur sources are inorganic salts that are fed in acidogenic diets to control periparturient hypocalcemia in dairy cattle, the by-products of grain processing, such as distillers grains, corn gluten meal, and brewers grain, and molasses, beet pulp, and alfalfa hay. Prolonged feeding of barley malt sprouts to cattle in Turkey has resulted in PEM caused by the high sulfur content of barley sprouts.[5] Similarly, molasses toxicity occurred in Cuba in cattle fed on a liquid molasses-urea feeding system with limited forage. The clinical and necropsy findings were identical to PEM; however, molasses toxicity is not thiamine responsive and can be reversed by feeding forage.

Other Dietary Circumstances

Deprivation of Feed and Water. In some outbreaks there is a history of deprivation of feed and water for 24 to 28 hours, because of either a managerial error or frozen water supplies. In other cases, a rapid change in diet appears to precipitate an outbreak. Some outbreaks are associated with a temporary deprivation of water for 24 to 36 hours, followed by sudden access to water and an excessive supply of salt, a situation analogous to salt poisoning in pigs, but these require more documentation to ensure that they indeed are not salt poisoning.

In sheep flocks, a drastic change in management, such as occurs at shearing time, will precipitate outbreaks in which only the yearlings are affected. Changing the diet of sheep from hay to corn silage resulted in a decrease in thiamine concentrations in ruminal fluid to about 25% of control values on hay. The cause of the drop in thiamine concentrations is unknown.

***Phalaris Aquatica* "PEM-Like" Sudden Death in Sheep and Cattle.** The Mediterranean perennial grass *P. aquatica* (formerly *P. tuberosa*) can cause sudden death in sheep and cattle throughout southern Australia. The nervous form of the disease is similar clinically to PEM but atypical because of the very rapid onset and the absence of either neuronal necrosis or malacia in cerebral cortical sections from affected animals. The available evidence suggests that this form of phalaris sudden death is more likely to involve a peracute form of ammonia toxicity than a peracute form of PEM.

PATHOGENESIS

Thiamine Inadequacy Polioencephalomalacia

High levels of thiaminases are formed in the rumen, which destroy thiamine that is naturally synthesized. The circumstances in the diet or in the rumen that allow for the development of high levels of thiaminases are unknown but may be related to the nature of the ruminal microflora in young cattle and sheep fed concentrate rations, which results in the development of ruminal acidosis. These rations may also allow for the development and growth of thiaminase-producing bacteria which, combined with a smaller net synthesis of thiamine in the rumens of concentrate-fed ruminants, could explain the higher incidence in feedlot animals. Experimentally PEM has been produced in lambs by continuous intraruminal infusion of a highly fermentable diet. Animals changed very rapidly to high-concentrate rations develop increased ruminal thiaminase levels.

The possibility that intraruminal thiaminases may also create thiamine analogs capable of acting as thiamine antimetabolites and accentuating the disease has been studied, but the results are inconclusive. The presence of naturally occurring second substrates (cosubstrates) in the rumen could produce, by the thiaminase type I reaction, a potent thiamine antimetabolite capable of accentuating the condition. In vitro studies have shown that thiaminase only caused rapid destruction of thiamine when a second substrate was added, and a large number of drugs commonly used as anthelmintics or tranquilizers may be active as second substrates. Many compounds found in the rumen of cattle are potential cosubstrates.

Amprolium has been used extensively to produce the lesions in the brains of cattle and sheep that are indistinguishable from the naturally occurring disease. However, because amprolium has been found in the brain tissue, the experimental disease should perhaps be known as "amprolium poisoning encephalopathy." The administration of other antagonists such as oxythiamine and pyrithiamine does not produce the disease. This suggests that PEM is a particular form of thiamine deficiency in which the supply of thiamine is reduced by the action of intraruminal thiaminase. Thus the thiamine status of the animal will be dependent on dietary thiamine intake, thiamine synthesis, the presence of thiaminase in the rumen, and the effects of possible antimetabolites. Subclinical states of thiamine deficiency probably exist in apparently normal cattle and sheep being fed diets that are conducive to the disease. This suggests that in outbreaks of the disease the unaffected animals of the group should be considered as potential new cases and perhaps treated prophylactically.

Thiamine is an essential component of several enzymes involved in intermediary metabolism and a state of deficiency results in increased blood concentration of pyruvate, a reduction in the lactate to pyruvate ratio and depression of erythrocyte transketolase. These abnormalities affect carbohydrate metabolism in general, but in view of the specific requirements of the cerebral cortex for oxidative metabolism of glucose, it is possible that a thiamine inadequacy could have a direct metabolic effect on neurons. The brain of the calf has a greater dependence on the pentose pathway for glucose metabolism, in which pathway the transketolase enzyme is a rate-limiting enzyme. Ultrastructural examination of the brain of sheep with the natural disease reveals that the first change that occurs is an edema of the intracellular compartment, principally

involving the astrocytes and satellite cells. This is followed by neuronal degeneration, which is considered secondary. It has been suggested that the edema may be caused by a reduction in ATP production following a defect of carbohydrate metabolism in the astrocyte. There are three basic lesions that are not uniform: compact necrosis, edema necrosis, and edema alone. This may suggest that a uniform etiology such as thiamine deficiency cannot be fully supported.

In the cerebral cortex of affected animals, autofluorescent spots are observed under ultraviolet 365-nm illumination and are a useful diagnostic aid. The distribution of autofluorescence corresponds to that of mitochondria in cerebrocortical neurocytes in affected calves, suggesting that metabolic impairment occurs and the autofluorescent substance is produced in the mitochondria. Mitochondrial swelling and disorganization of cristae are also observable in brain tissue, but are not specific to PEM.

Sulfate-Induced Polioencephalomalacia

Diets high in sulfur result in hydrogen sulfide production in the rumen and anaerobic bacteria from rumen samples of cattle fed high-carbohydrate, short-fiber diets with added sulfate will generate hydrogen sulfide in rumen fluid broth medium. Rumen microflora adapt to higher dietary sulfate content over a period of 10 to 12 days before they are capable of generating potentially toxic concentrations of sulfide. In experimental sulfate diets, which induce PEM, the rumen pH decreases during the transition to the experimental diet and acidic conditions in the rumen favor increased rumen gas cap concentrations of hydrogen sulfide. With a change of pH from 6.8 to 5.2, the percentage of hydrogen sulfide in the rumen gas cap increased from 47% to 97%.

Hydrogen sulfide gas concentration gradually increases in the rumen of sheep during the first 4 weeks on ingesting a medium-concentrate corn and alfalfa-based diet that contained substantial amounts of distillers grains.[6] Hydrogen sulfide is thought to be detoxified by the liver via oxidation to sulfate. Hydrogen sulfide absorbed across the ruminal wall into the portal circulation is not considered a likely mechanism of toxicity because absorbed hydrogen sulfide will be detoxified. However, a portion of the eructated hydrogen sulfide can be absorbed across the alveolar membrane directly into pulmonary capillaries, effectively bypassing hepatic detoxification before reaching the brain. If ruminants inhale 60% of eructated gases, inhalation of hydrogen sulfide could be a route of systemic sulfide absorption, in addition to gastrointestinal absorption. Sulfide inhibits cellular respiration leading to hypoxia, which may be sufficient to create neuronal necrosis in PEM. The nervous system lesions of sulfur toxicosis are indistinguishable from lesions in the naturally occurring disease.

Acute Cerebral Edema and Laminar Necrosis

Acute cerebral edema and laminar necrosis occur and the clinical signs are usually referable to increased intracranial pressure from the edema and the widespread focal necrosis. Recovery can occur with early treatment, which suggests that the lesions are reversible up to a certain point. EEGs of buffalo calves with amprolium-induced PEM found decreased frequency patterns, occasional spindles, and decreased voltage patterns during the onset of clinical signs. In the comatose stage, there was little evidence of electrical activity. EEGs of animals treated with thiamine hydrochloride found normal awake patterns.

CLINICAL FINDINGS

Cattle

Animals may be found dead without premonitory signs, especially beef cattle on pasture. The clinical findings are variable but characteristically, there is a sudden onset of **blindness; walking aimlessly; ataxia; muscle tremors**, particularly of the head with ear-twitching; **champing of the jaws** and frothy salivation; and **head-pressing** (which is really compulsive forward walking stopped by a wall), and the animal is difficult to handle or move (Fig. 14-12). Dysphagia may be present when one attempts to force feed hay by hand. Grinding of the teeth is common. Initially, the involuntary movements may occur in episodes, and convulsions may occur, but within several hours they become continuous. The animal usually then becomes recumbent, and there is marked opisthotonus; nystagmus; clonic-tonic convulsions, particularly when the animal is handled or moved; and tetany of the forelimbs is common. The temperature is usually normal but elevated if there has been excessive muscular activity. The heart rate may be normal, subnormal, or increased and is probably not a reliable diagnostic aid.

Rumen movements remain normal for a few days, which is an important distinguishing feature from lead poisoning in which the rumen is static.

The **menace reflex is always absent** in the acute stage, and its slow return to normal following treatment is a good prognostic sign. The **palpebral eye-preservation reflex is usually normal**. The pupils are usually of normal size and responsive to light. In severe cases the pupils may be constricted. Dorsal strabismus caused by stretching of the trochlear nerve is common. Nystagmus is common and may be vertical or horizontal. Optic disc edema is present in some cases but is not a constant finding.

Calves 6 to 9 months of age may die in 24 to 48 hours, whereas older cattle up to 18 months of age may survive for several days. Recovery is more common in the older age group.

In less severe cases, affected animals are blind, head-press into walls and fences, and remain standing for several hours or a few days. In outbreaks, some cattle will be sternally recumbent; others remain standing with obvious blindness, whereas others are anorexic, mildly depressed, and have only partial impairment of eyesight. Those with

Fig. 14-12 Weaned Polled Hereford calf with polioencephalomalacia. The calf has been walking in the same direction in the stall for many hours (as indicated by the straw). The diameter of the circle is determined by the width of the stall. The calf was blind and depressed, but was neurologically normal 48 hours later after aggressive treatment with intramuscular thiamine.

some eyesight will commonly return to almost normal. Some survivors are permanently blind to varying degrees but may begin to eat and drink if assisted. Some cases will recover following treatment and may grow and develop normally.

Evidence of recovery within a few hours following treatment with thiamine indicates that the disease is associated with thiamine inadequacy. A failure of response indicates the possibility of sulfur toxicity PEM.

Sheep

Sheep usually begin to wander aimlessly, sometimes in circles, or stand motionless and are blind, but within a few hours they become recumbent with opisthotonus, extension of the limbs, hyperesthesia, nystagmus, and periodic tonic-clonic convulsions (Fig. 14-13). Hoggets affected at shearing time may show blindness and head-pressing but, if fed and watered, usually recover within a few days. Occasional animals show unilateral localizing signs, including circling and spasmodic deviation of the head. In goats, early signs may include excitability and elevation of the head. Blindness, extreme opisthotonus, and severe extensor rigidity and nystagmus are common.

In sulfur-induced PEM in sheep introduced to a diet containing 0.43% sulfur, clinical signs occurred 15 to 32 days later and consisted of depression, central blindness, and head-pressing, but no hyperesthesis, nystagmus, or opisthotonus were observed. In sulfur toxicity in lambs with PEM, the rumen contents may have a strong odor of hydrogen sulfide (rotten egg smell).

There are some reports from Australia of unthriftiness in unweaned and weaned lambs associated with thiamine deficiency caused by the presence of thiaminases in the alimentary tract. In affected flocks the incidence of ill-thrift in lambs is much higher than the usual incidence and other causes of unthriftiness were ruled out. Affected lambs lose weight, may have chronic diarrhea, and become emaciated and die of starvation. In some flocks, clinical signs of PEM may occur in a small percentage of animals. The disease is most common in early July, which is the coldest part of the year in Australia for lambs that are born in May and June. In affected lambs the fecal thiaminase levels are high and the blood transketolase level activity is increased above normal. Treatment of affected lambs with thiamine resulted in an increase in growth rate.

Fig. 14-13 **A,** Weanling sheep with acute polioencephalomalacia demonstrating slow progressive walking that is interrupted by a wall. This is mistakenly called head-pressing. **B,** The same weanling sheep 24 hours later after repeated intravenous thiamine injections. The sheep has stopped progressive walking and the appetite has partially returned; however, the sheep is not fully aware and could not identify that it was still eating. It made a full recovery.

CLINICAL PATHOLOGY

Thiamine Inadequacy Polioencephalomalacia. The biochemical changes occurring in cattle and sheep with the thiamine-deficiency PEM have not been well defined diagnostically based on thoroughly investigated naturally occurring clinical cases. However, some estimates are available including the changes that occur in the experimental disease. Interpretation of the values may also be unreliable if the animals have been treated before death. Because of challenges with the availability and cost of laboratory tests, the most practical method to confirm a diagnosis of PEM caused by thiamine inadequacy is the clinical response to treatment with thiamine.

In animals, thiamine is present as free thiamine, thiamine monophosphate (TMP), TDP (more commonly known as TPP, which is the biologically active form), and thiamine triphosphate (TTP). The role of TMP and TTP is not well known at this time. The critical forms to measure are therefore free thiamine and TPP.[3] The **thiamine concentrations** of blood of animals with PEM have varied widely and may be difficult to interpret because of the possibility of thiamine analogs inducing deficiency even when blood thiamine levels are normal. However, this would not apply when blood thiamine concentrations are below normal. A normal reference range of 75 to 185 nmol/L is suggested for both cattle and sheep, and levels below 50 nmol/L are considered indicative of deficiency. In normal goats, the mean thiamine content of blood was 108 nmol/L, with a range of 72 to 178 nmol/L. In goats with PEM, blood thiamine levels were less than 66 nmol/L with a mean of 29 nmol/L. Levels as low as 1.8 to 3.6 µg/dL (6–12 nmol/L) have been found in suspected cases of PEM. The thiamine concentrations of liver, heart, and brain of cattle and sheep with PEM are decreased. The levels of blood pyruvate and lactate are also increased and thiamine pyrophosphate–dependent enzymes such as pyruvate kinase are decreased. The thiaminase activity of the feces is increased. Laboratory reference ranges should be used to evaluate blood thiamine concentrations because of analytical differences related to whether the measurement relates to free thiamine, total thiamine, or TPP.

The **erythrocyte transketolase activity** is decreased in confirmed cases of thiamine-inadequacy PEM. Transketolase is an important enzyme in the pentose pathway and requires TPP. Measurement of transketolase activity in erythrocytes is attractive because a blood sample is readily obtained and this is a biologic assay. Unfortunately, the assay must be run soon after blood collection and is not widely available. Erythrocyte transketolase activities in normal sheep range from 40 to 60 IU/mL RBCs. A variant of the transketolase test involves the addition of a standard amount of TPP, with the percentage increase in erythrocyte transketolase activity

being recorded; this is called the TPP effect. A TPP effect of 30% to 50% is commonly found in normal healthy cattle and sheep, and an increase to above 70% to 80% occurs in animals with PEM.

It is important to note that decreased erythrocyte transketolase activities, an increased TPP effect, and decreased blood thiamine concentrations would be expected in animals that have been inappetent for a number of days because thiamine is a water-soluble vitamin within minimal body stores. For example, cattle with pneumonia or simple indigestion had lower plasma thiamine concentrations (1.00 and 0.50 µg/mL, respectively) than healthy cattle (1.70 µg/mL).[7] Sheep with acute ruminal lactic acidosis had a mean TPP effect on erythrocyte transketolase activity of 109% compared with 22% in a health control group.[8] Measurements of erythrocyte transketolase activity, increased TPP effect, and blood TPP concentration should therefore be obtained from healthy animals in the same pen as the affected animal to adjust for the effect of feed intake on the measured values.

The **hemogram** is usually normal; the total and differential leukocyte counts may indicate a mild stress reaction, a finding that may be useful in differentiation from encephalopathies caused by bacterial infections.

CSF pressure taken at the cisterna magna is increased from a normal range of 12 to 16 cm H_2O to levels of 20 to 35 cm H_2O. The level of protein in the CSF may be normal to slightly or extremely elevated. A range from 15 to 540 mg/dL with a mean value of 90 mg/dL in affected cattle is recorded. There may also be a slight to severe pleocytosis in the CSF in which monocytes or phagocytes predominate.

Brain Imaging Function. MRI of a 2-month-old Holstein Friesian calf with thiamine-inadequacy PEM indicated a laminar hyperintense T2-weighted image of the cerebral cortex from the parietal to occipital lobes that predominantly affected the gray matter.[9] The visual evoked potentials are abnormal in ruminants with thiamine-responsive PEM.

Sulfate-Induced Polioencephalomalacia

Sulfur-induced PEM is most commonly differentiated from other causes of PEM in ruminants by the lack of responsiveness to thiamine injections and calculation of total sulfur intake from feed and water. Measurement of ruminal hydrogen sulfide content or urinary thiosulfate concentration offers promise as useful diagnostic tests.

Ruminal Hydrogen Sulfide Measurement. Changes in rumen gas cap H_2S concentrations are larger than changes in rumen fluid H_2S concentrations, and estimation of rumen gas H_2S concentration may be a practical method of detecting pathologic increases in ruminal hydrogen sulfide gas. A simple and rapid method has been developed for measuring the H_2S concentration of ruminal gas under field conditions, and an excellent description of the procedure is available.[2,6] In brief, the left paralumbar fossa is clipped and aseptically prepared. A sterile 7.6- to 10.2-cm 12- to 18-gauge needle with stylet is introduced into the gas cap of the rumen by way of the left paralumbar fossa. The needle is then connected to a calibrated H_2S detector tube. In cattle with sulfate-induced PEM increases in ruminal gas H_2S may be as high as 100 times more than control animals; however, ruminal pH has a marked effect on the measured value for H_2S,[2] suggesting that test interpretation needs to be adjusted for rumen pH to improve diagnostic accuracy. The hydrogen sulfide test is more accurate when applied to healthy animals in the same pen as an animal showing clinical signs of sulfate-induced PEM, because affected animals have a markedly reduced appetite and therefore lower sulfate intake and higher ruminal pH.

Urine thiosulfate concentrations appear to provide a useful diagnostic tool for sulfate-induced PEM in ruminants. Thiosulfate ($S_2O_3^{2-}$) is produced by incomplete oxidation of sulfide and by partial reduction of sulfate and therefore an increase in urine or plasma thiosulfate concentration reflects an increase in dietary sulfate intake or ruminal sulfide concentration. Thiosulfate concentrations in urine are stable for 8 hours at room temperature and 24 hours when stored at 4°C, and marked increases in urine thiosulfate concentrations occur when cattle are fed a high-sulfate diet, with the greatest increase occurring after feeding.[2] The urine thiosulfate concentration does not need to be normalized to urine creatinine concentration.

Brain Function. The effects of high dietary sulfur on brain function have been examined using evoked potentials techniques. Altered nerve conduction pathways occur in sheep fed high-sulfur diets without supplemental thiamine compared with animals that have received thiamine.

NECROPSY FINDINGS

Diffuse cerebral edema with compression and yellow discoloration of the dorsal cortical gyri is evident, and the cerebellum is pushed back into the foramen magnum with distortion of its posterior aspect.

In recovered animals, there is macroscopic decortication about the motor area and over the occipital lobes. The lesion can be identified grossly using ultraviolet illumination, which results in a fluorescence that indicates necrosis of brain and engulfment of necrotic tissue by lipophages. In general, there is a good correlation between the presence of characteristic fluorescence and the biochemical changes in cases of PEM. A small percentage of false negatives may occur.

Histologically, the lesions are widespread but most common in the cerebral cortex. There is bilateral laminar necrosis and necrosis of deeper cerebral areas. The necrosis is most prominent in the dorsal occipital and parietal cortex, but bilateral areas of necrosis are also seen less frequently in the thalamus, lateral geniculate bodies, basal ganglia, and mesencephalic nuclei. Lesions of the cerebellum are also present. The severity and distribution of the lesions probably depend on the interrelationships between clinical severity, age of affected animal, and length of illness before death.

Subnormal levels of thiamine are detectable in the liver and brain of calves with the natural disease, and low levels are also found in the experimental disease. In the molasses-induced disease in Cuba, the tissue thiamine levels were within the normal range.

In some cases of sulfur-associated PEM, the rumen contents have a strong odor of hydrogen sulfide (the rotten egg smell).

DIFFERENTIAL DIAGNOSIS

The biochemical tests described under the section Clinical Pathology are not practical. The diagnosis must be made on the basis of clinical findings and the readily available simple tests that rule out other diseases that resemble polioencephalomalacia. A careful consideration of the epidemiologic history often assists in the diagnosis.

Cattle

The differential clinical diagnosis for cattle is summarized in Table 14-12. Polioencephalomalacia in cattle occurs primarily in young growing animals 6–9 months of age on concentrate rations and is characterized clinically by a sudden onset of blindness, muscular tremors of the head and neck, head-pressing, nystagmus, and opisthotonus. The disease also occurs in mature beef cattle on pasture containing a high level of sulfate in their water and feed.

In cattle the disease must be differentiated from the following:

- **Acute lead poisoning,** which is most common in calves after spring turnout but occurs in adult cattle too and is characterized by central blindness, tremors, convulsions, uncontrollable activity with bellowing, champing fits, hyperexcitability, rumen stasis, and death in several hours. Early treatment may be successful.
- **Subacute lead poisoning** characterized by blindness, stupor, head-pressing, rumen stasis, weak palpebral reflexes, and no response to therapy.
- **Hypovitaminosis A** is characterized by a history of a vitamin A–deficient diet and nyctalopia, peripheral blindness, dilated and fixed pupils, optic disc edema, and transient convulsions followed by recovery.

- ***Histophilus somni* meningoencephalitis** characterized by sudden onset of ataxia, recumbency, fever, depression with eyes closed, lesions of the fundus, marked changes in hemogram, enlarged joints, and death in several hours if not treated early.

Sheep

In sheep polioencephalomalacia must be differentiated from the following:

- **Enterotoxemia (pulpy kidney disease) caused by *Clostridium perfringens* type D** in unvaccinated sheep, especially feedlot lambs, in which the clinical findings are almost identical; it occurs under the same management conditions as polioencephalomalacia. Enterotoxemia in lambs usually develops within several days after being placed on a grain ration, whereas polioencephalomalacia occurs after several weeks of grain feeding. Glycosuria in pulpy kidney disease may assist the diagnosis, but a necropsy is usually more informative
- **Focal symmetric encephalomalacia** also resembles polioencephalomalacia but is sporadic, usually involves only a few animals, and will not respond to treatment.

Goats

In goats the disease must be differentiated from enterotoxemia, pregnancy toxemia, lead poisoning, and meningoencephalitis.

TREATMENT

Thiamine Hydrochloride

The treatment of choice for thiamine-inadequacy PEM is thiamine hydrochloride at 10 mg/kg BW by slow intravenous injection initially and followed by similar doses every 3 hours for a total of five treatments. Bolus intravenous thiamine injections have been associated with collapse but are not usually fatal. Intramuscular injections of thiamine can be given instead of intravenous injections in animals that are difficult to handle with no discernable effect on treatment efficacy. When treatment is given within a few hours of the onset of signs, a beneficial response within 1 to 6 hours is common, and complete clinical recovery can occur in 24 hours. Goats and sheep will commonly respond within 1 to 2 hours. For those that take longer to recover, the eyesight and mental awareness will gradually improve in a few days and the animal will usually begin to eat and drink by the third day after treatment. Transfaunation of rumen fluid from roughage-fed cattle may improve appetite and rumen function in those responding slowly. In sheep, following treatment with thiamine, the blood transketolase activity begins to return to normal in 2 to 4 hours and is considered normal 24 hours after treatment.

Some cattle improve to a subnormal level within a few days and fail to continue to improve. These are usually affected with diffuse cortical and subcortical necrosis and will usually not improve further in spite of continued treatment. Those that return to a clinically normal state will usually do so by 48 hours or sooner after initial treatment. Those that are still clinically subnormal and anorexic by the end of the third day will usually remain at that level and should be slaughtered for salvage.

General treatment of cerebral edema (such as intravenous infusions of 20% mannitol at 0.25–1 g/kg BW or 7.2%–7.5% NaCl solution at 4–5 mL/kg BW, and parenteral dexamethasone (1 mg/kg BW, intravenous, see the section Increased Intracranial Pressure, Cerebral Edema, and Brain Swelling, earlier in this chapter) is theoretically indicated as part of the initial treatment of severely affected animals; however, clinical trials have not been conducted as to whether general treatment for cerebral edema provides a beneficial response above that provided by thiamine administration alone for ruminants with PEM caused by thiamine inadequacy. Both mannitol and dexamethasone are very expensive when administered to adult cattle, sheep, and goats.

Treatment is ineffective in advanced cases, but unless an accurate history is available on the length of the illness, it is usually difficult to predict the outcome until 6 to 12 hours following treatment. Thus it is usual practice to treat most cases with thiamine at least twice and monitor the response. If there is no beneficial response in 6 to 8 hours, emergency slaughter for salvage should be considered.

The oral administration of thiamine or thiamine derivatives is indicated when thiaminases are thought to be in the alimentary tract. Thiamine hydrochloride, at a rate of 1 g for lambs and kids and 5 g for calves in a drench, is recommended. However, because the action of thiaminase type I on thiamine may result in the production of thiamine analogs, which may act as inhibitors of thiamine metabolism, thiamine derivatives, which are resistant to thiaminases, lipid soluble and absorbed from the intestine, are being explored as therapeutic and prophylactic agents. Thiamine propyl disulfide can depress the thiaminase activities in the ruminal fluid of sheep with PEM within 2 hours after oral administration. The blood pyruvate levels and transketolase activities are also restored to normal and treated animals recovered clinically.

Outbreak Management

In outbreaks, the in-contact unaffected animals on the same diet as the affected animals may be on the brink of clinical disease. The diet should be changed to one containing at least 50% roughage or 1.5 kg of roughage per 100 kg BW. Thiamine may be added to the ration at the rate of 50 mg/kg of feed for 2 to 3 weeks as a preventive against clinical disease, followed by a level of 20 to 30 mg/kg of feed (cattle and sheep) if the animals remain on a diet that may predispose them to the disease.

Sulfur-Induced Polioencephalomalacia

There is no specific treatment for PEM caused by sulfate toxicity. The use of thiamine hydrochloride in doses given earlier is recommended, and may be successful in some cases, particularly when administered early in the disease course.

TREATMENT AND CONTROL

Treatment

Thiamine inadequacy form

Thiamine HCl (10 mg/kg BW by slow IV or IM every 3 hours for at least five treatments) (R-1)

In severe acute cerebral edema

20% mannitol IV (0.25–1.0 g/kg) or 7.2%–7.5% NaCl IV (4–5 mL/kg) (R-2)

Dexamethasone (1 mg/kg, IV, once) (R-2)

Rumen transfaunation if prolonged off feed (R-2)

Oral drench with thiamine (1 g to lambs/kids, 5 g to calves) if thiaminases are suspected (R-2)

Sulfur-induced form

Thiamine HCl (10 mg/kg BW by slow IV or IM every 3 hours for at least five treatments) (R-2)

Treat suspected cerebral edema (R-2)

Control

Thiamine inadequacy form

Alter intraluminal environment by increasing roughage or changing source of roughage (R-2)

Supplement ration with thiamine at 3 mg/kg dry matter of feed (R-2)

Remove amprolium from diet (R-2)

Sulfur-induced form

Decrease overall sulfur intake in ration and water (R-1)

Restrict access to pastures with Brassicaceae family plants that have high sulfur content (R-1)

BW, body weight; IM, intramuscularly; IV, intravenously.

CONTROL

Thiamine Supplementation

A rational approach to the control of PEM associated with thiamine inadequacy is to supplement the rations of concentrate-fed cattle and sheep with thiamine on a continuous basis. The daily requirements for protection have not been determined using controlled feeding trials, but a rate of 3 mg/kg dry matter of feed for cattle and sheep has been recommended. This level may not be protective in all situations, and response trials may be necessary to determine protective levels for different situations. Levels up to 20 to 30 mg/kg of feed may be necessary for protection. Most natural feedstuffs for ruminants contain thiamine at about

2 mg/kg dry matter, which when combined with the thiamine synthesized in the rumen will meet the requirements. However, the presence of thiaminases in the rumen will necessitate dietary supplementation with thiamine, but the optimal amount that will provide protection under practical conditions is uncertain.

The intramuscular injection of 500 mg thiamine three times weekly into 6-month-old calves raised under practical farm conditions will steadily reduce the percentage TPP effect to zero in about 6 weeks. The daily oral administration of 100 mg thiamine to young calves fed initially on milk substitutes and then on concentrates and hay results in a decrease in percentage pyrophosphate effect.

For animals fed diets associated with thiamine inadequacy, it is recommended that thiamine be added to the diet at the rate of 5 to 10 mg/kg dry matter. Cattle and sheep on concentrate-fed rations must also receive supplements containing all necessary vitamins and minerals, especially cobalt, a deficiency of which may be associated with some outbreaks of the disease.

Feeding Roughage

The minimum amount of roughage, which should be fed to feedlot cattle and sheep to prevent the disease and still maintain them on high levels of concentrates is unknown. A level of 1.5 kg of roughage per 100 kg BW has been recommended, but this may not be economical for the feedlot whose profits are dependent on rapid growth in grain-fed cattle. Supplementation of the diet with thiamine appears to be the only alternative.

The prevention of the disease in sheep that are being moved long distances or gathered together for shearing and other management practices will depend on ensuring an ample supply of roughage and water and avoiding drastic changes in management.

Sulfate Toxicity PEM

The prevention of the disease associated with a high sulfur intake in the feed and water supplies will depend on analysis of the feed and water for sulfate and making appropriate adjustments in the sources of feed and water to decrease the intake of sulfur to safe levels.

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THIAMINE DEFICIENCY (HYPOTHIAMINOSIS)

The disease caused by deficiency of thiamine in tissues is characterized chiefly by signs of neurologic disease. PEM of ruminants is discussed in the previous section.

ETIOLOGY

Thiamine deficiency can be primary; caused by deficiency of the vitamin in the diet; or secondary, because of destruction of the vitamin in the diet by thiaminase. A primary deficiency is unlikely under natural conditions because most plants, especially seeds, yeast, and milk contain adequate amounts.

Thiamine is normally synthesized in adequate quantities in the rumen of cattle and sheep on a well-balanced roughage diet. The degree of synthesis is governed to some extent by the composition of the ration, a sufficiency of readily fermentable carbohydrate causing an increase of synthesis of most vitamins of the B complex, and a high intake in the diet reducing synthesis. The etiology of PEM has been discussed in detail previously. Microbial synthesis of thiamine also occurs in the alimentary tract of monogastric animals and in young calves and lambs, but not in sufficient quantities to avoid the necessity for a dietary supply, so that deficiency states can be readily induced in these animals with experimental diets. Thiamine is relatively unstable and easily destroyed by cooking.

The coccidiostat, amprolium, is a thiamine antagonist and others are produced by certain plants, bacteria, fungi, and fish.

EPIDEMIOLOGY

One of the best examples of secondary thiamine deficiency is inclusion of excess raw fish in the diet of carnivores, resulting in destruction of thiamine because of the high content of thiaminase in the fish.

Two major occurrences of secondary thiamine deficiency are recorded. In horses, the ingestion of excessive quantities of **bracken fern** (*P. aquilinum*) and **horsetail** (*E. arvense*) causes nervous signs because of the high concentration of thiaminase in these plants. The disease has been induced in a pig fed bracken rhizomes, and the possibility exists of it occurring under natural conditions. It also occurs in horses fed large quantities of turnips (*Beta vulgaris*) without adequate grain. The second important occurrence of thiamine deficiency is in the etiology of PEM and is discussed under that heading.

A thiaminase-induced subclinical thiamine deficiency causing suboptimal growth rate of weaner lambs has been described. Higher levels of thiaminase activity were present in the feces and rumen contents of lambs with poor growth rate compared with normal lambs. *B. thiaminolyticus* was isolated from the feces and ruminal fluids of affected lambs and supplementation of thiaminase-excreting lambs with intramuscular injections of thiamine hydrochloride was associated with significantly improved growth rate.

Thiamine deficiency occurs in sheep being subjected to live export from Australia to the Middle East. Sheep that died or were clinically ill and euthanized had significantly lower hepatic and ruminal thiaminase concentrations than clinically healthy control sheep. A high proportion had thiamine concentrations comparable with those found in sheep that die with PEM. The evidence indicates that the thiamine deficiency is a primary one associated with deprivation of feed during transportation to the preembarkation feedlots. The low feed intake and failure of the ruminal microbes to adapt, thrive, and synthesize a net surplus of thiamine during alterations in the ruminal environment are considered to be major contributing factors.

PATHOGENESIS

The only known function of thiamine is its activity as a cocarboxylase in the metabolism of fats, carbohydrates, and proteins and a deficiency of the vitamin leads to the accumulation of endogenous pyruvates. Although the brain is known to depend largely on carbohydrates as a source of energy, there is no obvious relationship between a deficiency of thiamine and the development of the nervous signs that characterize it. PEM has been produced experimentally in preruminant lambs on a thiamine-free diet. There are other prodromal indications of deficiency disease. For example, there is a decrease in erythrocyte precursors and in erythrocyte transketolase. Additional clinical signs are also in the circulatory and alimentary systems, but their pathogenesis cannot be clearly related to the known functions of thiamine. Subclinical thiamine deficiency caused by thiaminases in the alimentary tract is associated with low erythrocyte transketolase activities and elevated TPP effects, which may explain the poor growth rate.

CLINICAL FINDINGS

Bracken Fern (*P. aquilinum*) and Horsetail (*E. arvense*) Poisoning in the Horse

Incoordination and falling and bradycardia caused by cardiac irregularity are the cardinal clinical signs of bracken fern poisoning in the horse. These signs disappear after the parenteral administration of thiamine. Similar clinical effects occur with horsetail.

Swaying from side to side occurs first, followed by pronounced incoordination, including crossing of the forelegs and wide action in the hindlegs. When standing, the legs are placed well apart and crouching and arching of the back are evident. Muscle tremor develops and eventually the horse is unable to rise. Clonic convulsions and opisthotonus are the terminal stage. Appetite is good until late in the disease when somnolence prevents eating. Temperatures are normal and the heart rate slow until the terminal period, when both rise to above normal levels. Some evidence has also been presented relating the occurrence of hemiplegia of the vocal cords in horses with a below normal thiamine status. Neither plant is palatable to horses and poisoning rarely occurs at pasture. The greatest danger is when the immature plants are cut and preserved in meadow hay.

Experimental Syndromes

These syndromes have not been observed to occur naturally but are produced readily on experimental rations.

In **pigs**, inappetence; emaciation; leg weakness; and a fall in body temperature, respiratory rate, and heart rate occur. The ECG is abnormal and congestive heart failure follows. Death occurs in 5 weeks on a severely deficient diet. In calves, weakness, incoordination, convulsions, and retraction of the head occur, and in some cases there is anorexia, severe scouring, and dehydration.

Lambs 1 to 3 days old placed on a thiamine-deficient diet show signs after 3 weeks. Somnolence, anorexia, and loss of condition occur first, followed by tetanic convulsions.

Horses fed amprolium (400–800 mg/kg BW daily) developed clinical signs of thiamine deficiency after 37 to 58 days. Bradycardia with dropped heartbeats, ataxia, muscle fasciculation and periodic hypothermia of hooves, ears, and muzzle were the common signs, with blindness, diarrhea, and loss of BW occurring inconstantly.

CLINICAL PATHOLOGY

Blood pyruvic acid levels in horses are raised from normal levels of 2 to 3 µg/dL to 6 to 8 µg/dL. Blood thiamine levels are reduced from normal levels of 8 to 10 µg/dL to 2.5 to 3.0 µg/dL. ECGs show evidence of myocardial insufficiency. In pigs, blood pyruvate levels are elevated and there is a fall in blood transketolase activity. These changes occur very early in the disease. In sheep subjected to export, liver and rumen thiamine concentrations and erythrocyte transketolase activities were all below levels found in clinically normal sheep.

NECROPSY FINDINGS

No macroscopic lesions occur in thiamine deficiency other than nonspecific congestive heart failure in horses. The myocardial lesions are those of interstitial edema, and lesions are also present in the liver and intestine.

In the experimental syndrome in pigs, there are no degenerative lesions in the nervous system, but there is multiple focal necrosis of the atrial myocardium accompanied by macroscopic flabbiness and dilatation without hypertrophy of the heart.

DIFFERENTIAL DIAGNOSIS

Diagnosis of secondary thiamine deficiency in horses must be based on the signs of paralysis and known access to bracken fern or horsetail. A similar syndrome may occur with poisoning by the following:

- *Crotalaria* spp.
- Perennial ryegrass
- *Indigofera enneaphylla*
- Ragwort (*Senecio jacobaea*)

It is accompanied by hepatic necrosis and fibrosis. The encephalomyelitides are usually accompanied by signs of cerebral involvement, by fever, and by failure to respond to thiamine therapy.

TREATMENT

In clinical cases the injection of a solution of the vitamin produces dramatic results (5 mg/kg BW given every 3 hours). The initial dose is usually given intravenously followed by intramuscular injections for 2 to 4 days. An oral source of thiamine should be given daily for 10 days and any dietary abnormalities corrected.

CONTROL

The daily requirement of thiamine for monogastric animals is generally 30 to 60 µg/kg BW. The addition of yeast, cereals, grains, liver, and meat meal to the ration usually provides adequate thiamine.

THIAMINASE TOXICOSIS

SYNOPSIS

Etiology Thiaminases occur naturally in *Marsilea* spp., *Cheilanthes* spp., *Pteridium* spp., and *Equisetum* spp. ferns or fernlike plants.

Epidemiology Horses fed hay containing bracken; pigs eating bracken, especially rhizomes.

Clinical pathology Low blood concentrations of thiamine; high blood concentrations of pyruvate.

Lesions Similar to vitamin B_1 (thiamine) deficiency in horses; cardiac lesions in pigs.

Diagnostic confirmation. Low blood and urine levels of thiamine.

Treatment Injectable thiamine gives excellent results, provided thiamine source is withdrawn.

Control Limit access to plants.

ETIOLOGY

The identified thiaminases that are important to animals occur in ferns or fernlike plants and catalyze the decomposition of thiamine. Thiaminases are of two types, methyltransferase and hydrolase. The hydrolases are not found in plants but only in the rumen, presumably as metabolites produced by ruminal bacteria from specific precursors in the plants. The thiaminase content of the ferns varies widely, being highest at a period of rapid growth and after being grazed severely. Thiaminase activity occurs in the fronds of the ferns *M. drummondii, Cheilanthes sieberi,* and *P. aquilinum* in descending order of magnitude. Plants containing thiaminases are usually deficient in thiamine.

The ferns that are sources of thiaminase and the animal species affected are as follows:

- Horses: *Pteridium* spp. (bracken fern), *E. arvense* (horsetail), *E. fluviatile, E. hyemale, E. palustre, E. ramosissimum, E. sylvaticum, M. drummondii* (Nardoo)[1]
- Sheep: *M. drummondii, C. sieberi* (mulga or rock fern)[1]
- Cattle: *C. sieberi, Dryopteris borreri, D. filix-mas*

EPIDEMIOLOGY

Occurrence

Thiaminase poisoning associated with *Pteridium* spp. and *Equisetum* spp. occurs most often in horses fed hay contaminated by the ferns and is most toxic if the hay is cut when the fronds are very young. The standing plants are unpalatable and rarely eaten by these animals unless no other feed is available. In grazing horses ingesting 20% to 25% of their diet as thiaminase-containing plants, signs occur in 3 to 4 weeks; horses grazing on a pasture with thiaminase-containing plants providing close to 100% of their diet may show signs in as little as 10 days.[2,3] Stabled horses fed heavily contaminated hay may show signs in a short period of time, depending on how much thiaminase is present in the hay.

Thiaminase deficiency is less common in pigs and the clinical signs not as obvious.[3] Grazing pigs may root out and eat *Pteridium* rhizomes, which contain a much higher concentration of the thiaminase than the fronds. Sheep grazed on pastures dominated by *M. drummondii* on floodplains in inland Australia or forced to graze *C. sieberi* are poisoned.[1]

Grazing cattle may be forced to eat the ferns because of lack of other feed and when the fern is at a toxic, rapidly growing stage, but they are not affected by thiamine deficiency. They succumb to a hemorrhagic disease.[4]

PATHOGENESIS

A state of thiamine deficiency is created by the destruction of thiamine in the alimentary

tract. The activities of enzymes that require thiamine, are impaired and there is an accumulation in tissues of pyruvate and lactate.[3] The relationship between the intake of the thiaminase and the nervous signs is not adequately explained. That a relationship exists is suggested by the development of brain lesions of PEM in sheep poisoned by *M. drummondii* and in those fed experimentally on the rhizomes of *P. aquilinum*.[3]

CLINICAL FINDINGS

Affected horses sway from side to side, show gait incoordination, including crossing the forelimbs and a wide action in the hindlimbs. Abnormal postures include a wide stance, arching of the back, and crouching. Muscle tremor, cardiac irregularity, and bradycardia are evident. Terminally, the animal falls easily, becomes recumbent and hyposensitive to external stimuli, and makes convulsive movements. The heart rate and the temperature become elevated. Additional signs seen in horses poisoned by *M. drummondii* include carrying the head close to the ground, whinnying, partial blindness, nodding of the head, twitching of the ears, and frequent yawning.

Pigs fed bracken fern rhizomes (33% of diet) developed anorexia and nonspecific signs. At 8 weeks they deteriorated rapidly and death occurred at 10 weeks.[3] Postmortem lesions were cardiac in nature. In another report, 4 of 22 piglets died when a pregnant sow was poisoned with bracken fern.[3]

Sheep poisoned by *M. drummondii* may be affected by an acute or a chronic syndrome. The acute form of the disease is characterized by the sudden onset of dyspnea, depression, and recumbency and death in 6 to 8 hours. The chronic syndrome is indistinguishable from PEM. Sheep affected by *Cheilanthes* spp. poisoning are hyposensitive to external stimuli, including being blind, and walk slowly and with an uncoordinated gait.

Cattle poisoned by *Dryopteris* spp. are also blind and hyposensitive. Many recover but remain blind.

CLINICAL PATHOLOGY

The characteristic findings attributable to a nutritional deficiency of thiamine are present. These include depression of blood levels of thiamine and transketolase and elevation of levels of blood pyruvate.

NECROPSY FINDINGS

In naturally occurring cases in horses, there are no lesions recorded other than the nonspecific ones of acute or congestive heart failure. PEM has been seen in sheep and, in pigs, an enlarged mottled heart and congestion of the lungs and liver indicate the presence of congestive heart failure.

Diagnostic confirmation is based on low blood thiamine levels.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis list

- Hepatic encephalopathy
- Infectious encephalitides
- *Crotalaria* spp., *Senecio jacobea* toxicosis
- Staggers syndromes, e.g., ryegrass staggers, paspalum staggers, phalaris staggers

TREATMENT

In the early stages, the administration of thiamine and removal of the dietary source of thiaminase are the critical procedures and recovery is to be expected. In horses, an intravenous injection of 0.5 to 1 g of thiamine followed by intramuscular administration for 3 to 5 days is recommended.[2,5] The response to treatment is usually excellent.

CONTROL

Large-scale control is attempted by a combination of pasture management, application of herbicide, and mowing in early spring, but it is expensive and subject to error; thus professional agrochemical advice is desirable. Draining water from marshy areas and improving drainage will encourage grasses and legumes to compete with and outgrow these plants.

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SALT TOXICITY (SODIUM CHLORIDE TOXICOSIS)

SYNOPSIS

Etiology Ingestion of excessive amounts of sodium chloride or normal intake of sodium but limited water intake.

Epidemiology Multiple sources of excess salt in the diet and limitations of drinking water.

Clinical pathology High serum levels of sodium and chloride; increased plasma osmolarity; eosinopenia in pigs. High salt content in water or feed.

Lesions

Acute: gastroenteritis plus neurologic abnormalities.

Chronic: eosinophilic meningitis in pigs; polioencephalomalacia in pigs and cattle. High rumen, brain, and CSF levels of sodium.

Diagnostic confirmation Elevated sodium content of rumen and brain. CSF sodium exceeds serum sodium. Elevated sodium in aqueous or vitreous humor.

Treatment

Peracute with no signs: remove source of salt and allow free choice water; monitor closely.

Acute and chronic with signs: remove source of salt, restrict water intake, IV fluid replacement.

Control Limit intake of salt-rich water, whey, concentrate mixes; ensure adequate drinking water supply at all times.

CSF, *cerebrospinal fluid;* IV, *intravenous.*

ETIOLOGY

Sodium and chloride are the main ions responsible for maintaining osmotic balance in the ECF. Any alteration in serum concentrations, either through increased salt intake or decreased water consumption is likely to result in salt toxicity.[1,2]

Feed and water containing excessive quantities of salt are unpalatable to animals but excessive quantities of salt are sometimes ingested, especially in saline drinking waters. Specific details about the degree of salinity of drinking water compatible with health in animals are difficult to provide, because of the variation in the kinds of salts that occur in natural saline waters. Hypernatremia may also occur secondary to limited water intake such as occurs in cold environments when there is no access or water has frozen.

EPIDEMIOLOGY

Occurrence

Salt poisoning will occur wherever bore water is used for livestock drinking. It is reported principally from Australia, North America, and South Africa. Other sources of excessive salt include the following:

- Saline drinking water, especially after a change from fresh water, and especially if the animals are thirsty.[3]
- Water accumulating in salt troughs during drought periods.
- Grazing on salt marshes or drinking water obtained from salt marshes.[3]
- Swill fed to pigs containing excessive amounts of salt from bakery dough residues, butcher shop brine, cheese factory salt whey, or salted fish waste.
- Excessive sodium sulfate given to pigs as treatment for gut edema if the water intake is restricted.
- Oil field brine.[2]

Salt poisoning associated with water deprivation may occur from:

- Temporary restriction of the water supply to pigs of 8 to 12 weeks of age and lambs and calves fed prepared feeds containing the standard recommendation of 2% salt; poisoning occurs when the animals are again allowed access to unlimited water.
- Pigs brought into new pens where drinking water is supplied in automatic drinking cups that are not be accustomed to their use and fail to drink for several days until they learn to operate the cups.
- Feeder lambs and calves may also be deprived of water when their water troughs are frozen over.

Risk Factors

Animal Risk Factors

Swine are the most susceptible animals and have generated the most clinical reports of toxicity.[4] Sheep, beef cattle, and dry dairy cattle appear to be less susceptible than milking dairy cows, which are in turn less susceptible than horses. Heavy milking cows, especially those in the early stages of lactation, are highly susceptible to salt poisoning because of their unstable fluid and electrolyte status.

Many animals may be clinically affected and the mortality rate may be high when animals are kept under range conditions and have to depend on saline water supplies for drinking purposes. In animals kept under intensive conditions salt poisoning occurs only sporadically, but most affected animals die and heavy losses may occur in groups of pigs.

High salt intakes may be used in sheep to restrict food intake during drought periods and in the control of urolithiasis in feeder wethers, but salt poisoning does not occur if there is free access to water. Rations containing up to 13% of sodium chloride have been fed to ewes for long periods without apparent ill-effects, although diets containing 10% to 20% and water containing 1.5% to 2% sodium chloride do reduce food consumption. This may be of value when attempting to reduce feed intake but can be a disadvantage when sheep are watered on saline artesian water.

Toxic doses for acute sodium chloride poisoning in pigs, horses, and cattle are 2.2 g/kg BW and in sheep 6 g/kg. The toxicity of salt is significantly influenced by the age and BW of the subject. For example, dose rates that kill pigs of 6.5 to 10 kg BW have little effect on pigs of 16% to 20 kg BW. Water concentrations of 1000 mg Na/L water are associated with chronic problems in dairy cattle, including decreased production.[2]

Farm Risk Factors

Saline waters often contain a mixture of salts and those containing high levels of magnesium or fluorine may be quite toxic. Water containing 0.2% to 0.5% magnesium chloride may be associated with reduced appetite and occasional diarrhea in sheep, especially if the sodium chloride content is also high, but water containing similar quantities of sodium sulfate does not have any harmful effect. Variation between bore waters includes differences in the relative proportions of the acid radicals, particularly sulfates, carbonates, and chlorides.

Environmental Risk Factors

Environmental temperatures have an effect on toxicity, with signs occurring in the summer on water containing levels of salt that appear to be nontoxic in the winter. Australian recommendations are that the maximum concentration for sodium chloride or total salts in drinking water should not exceed 1.3% for sheep, 1% for cattle, and 0.9% for horses. South African and Canadian recommended levels are much lower, but there does not appear to be any proof that such low levels of total and individual salts are necessary.

PATHOGENESIS

Acute Poisoning

When excessive amounts of salt are ingested, gastroenteritis occurs because of the irritating effects from the high concentrations of salt. Dehydration and diarrhea result and are exacerbated by the increased osmotic pressure of the alimentary tract contents. Salt is absorbed from the gastrointestinal tract and may be associated with the involvement of the CNS.

Chronic Poisoning

Where the defect is one of decreased water but normal salt intake, there is an accumulation of sodium ions in tissues, including the brain, over a period of several days. An initial high sodium accumulation may inhibit anaerobic glycolysis, preventing active transport of sodium out of the cerebrospinal compartment. When water is made available in unlimited quantities, it migrates to the tissues to restore normal salt–water equilibrium. This is associated with acute cerebral edema and the appearance of signs referable to a sudden rise in intracranial pressure. The response is the same in all species, but in pigs there is also an accumulation of eosinophils in nervous tissue and the meninges. The sodium ion is the one that accumulates in the tissues, and identical syndromes are produced by the feeding of sodium propionate or sodium sulfate. It has also been observed that the feeding of soluble substances such as urea, which are excreted unchanged by the kidney, may be associated with anhydremia and an increase in the sodium ion concentration in brain tissue and the development of encephalomalacia.

This form of salt poisoning is chronic only in the sense that the sodium ion accumulates gradually. The clinical syndrome is acute in much the same way as the syndrome is acute in chronic copper poisoning. There is an apparent relationship between this form of salt poisoning and PEM in all species.[5,6] Many outbreaks of the latter disease occur in circumstances that suggest chronic salt poisoning. Sheep adapt to a continuous high salt intake (up to 1.3% sodium chloride in the drinking water) by significant changes in numbers of microflora in the rumen, but this is not usually accompanied by any change in total metabolic activity. The same level of intake in sheep is associated with some mortality; chronic diarrhea; and reduction in fertility, weight gain, and wool growth.

CLINICAL FINDINGS

Subclinical Salt Poisoning

Lower levels of intake can suppress food intake and growth without overt clinical signs. This occurs in heifers drinking water containing 1.75% sodium chloride; the animals only maintain weight at a salt level of 1.5% and show suboptimal weight gains when the water contains 1.25% sodium chloride. Drinking water containing 0.25% salt significantly reduces the milk yield of high-producing dairy cows.

Acute Salt Poisoning

With large doses, vomiting, diarrhea with mucus in the feces, abdominal pain, and anorexia occur. The more common syndrome, occurring 1 to 2 days after ingestion, includes opisthotonus, nystagmus, tremor, blindness, paresis, and knuckling at the fetlocks.[7] There may be a nasal discharge and polyuria. A period of recumbency with convulsions follows and affected animals die within 24 hours of first becoming ill. Sheep show similar signs. In swine the signs include weakness and prostration, muscle tremor, clonic convulsions, coma, and death after a course of about 48 hours.

Subacute Poisoning

This syndrome in cattle and sheep on saline drinking water includes depression of appetite; thirst; constant bawling, especially in calves; loss of BW; dehydration; hypothermia; weakness; and occasional diarrhea. Incoordination, collapse, and tetanic convulsions with frothing from the mouth and nose may occur if the animals are forced to exercise. Acetonemia may be a complication in lactating cows.

Chronic Salt Poisoning

Chronic toxicity occurs most often in pigs. Lack of appetite, constipation, thirst, restlessness, and pruritus occur 2 to 4 days after exposure. A characteristic nervous syndrome follows within 12 to 24 hours. Initially there is apparent blindness and deafness, with the pig remaining oblivious to normal stimuli and wandering about aimlessly, bumping

into objects, and pressing with the head. There may be circling or pivoting on one front leg. Recovery may occur at this stage or epileptiform convulsions begin, recurring at remarkably constant time intervals, usually 7 minutes, accompanied by tremor of the snout and neck. Clonic contractions of the neck muscles may be associated with jerky opisthotonus until the head is almost vertical causing the pig to walk backward and assume a dog-sitting posture. This may be followed by a clonic convulsion in lateral recumbency, with jaw champing, salivation, and dyspnea. Death may occur from respiratory failure or the pig relaxes into a state of coma for a few moments, revives, and wanders about aimlessly until the next episode occurs. The pulse and temperature are normal except in convulsive pigs when both may be elevated.

CLINICAL PATHOLOGY

Serum sodium concentrations are elevated appreciably above normal levels (135–145 mmol/L) to about 160/170 to 210 mmol/L.[1,8] An eosinopenia is also evident during this stage and a return to normal levels usually indicates recovery. In cattle the same changes occur but there is no eosinopenia. CSF sodium concentration exceeds serum sodium concentration.

NECROPSY FINDINGS

In acute salt poisoning of cattle, there is marked congestion of the mucosa of the omasum and abomasum. The feces are fluid and dark. Animals that have survived for several days show hydropericardium and edema of the skeletal muscles. Gastroenteritis may be evident in some pigs poisoned with large doses of salt, but in chronic poisoning there are no gross lesions. Histologically, the neurologic lesions of acute poisoning are restricted to expansion of perivascular spaces in the brain. In contrast, the microscopic changes in chronic salt poisoning in pigs are quite diagnostic. The expansion of perivascular spaces typical of acute cerebral edema is accompanied by meningitis featuring large numbers of eosinophils, which extend along Virchow–Robin spaces into the brain tissue. In pigs that survive there may be residual PEM, especially of the cerebral cortex. Chemical estimation of the amount of sodium and chloride in tissues, especially brain, may be of diagnostic value. Brain sodium levels exceeding 1,800 ppm are considered diagnostic in cattle and swine.[2]

Samples for Confirmation of Diagnosis

- **Toxicology:** 50 g liver, skeletal muscle, brain, serum, CSF, aqueous, or vitreous humor, feed, water (assay for sodium concentration)
- **Histology:** formalin-fixed half of sagittally sectioned brain (LM)

DIFFERENTIAL DIAGNOSIS

Differential diagnosis list

Bacterial meningoencephalitis

Gut edema occurs in rapidly growing pigs

Mulberry heart disease in older pigs

Polioencephalomalacia

Pseudorabies

Viral encephalomyelitis

TREATMENT

Treatment of both acute and chronic salt poisoning is the immediate removal of the toxic feed or water.[8] Further treatment involves correcting hypernatremia and serum hyperosmolality.

Acute Toxicity

If the animals have not yet shown clinical signs, allow access to water and monitor closely for several days. In those animals showing an acute onset of clinical signs (less than 12–24 hours), serum sodium concentration may be lowered by 1 mmol/L/h.[8] Intravenous fluids of choice include 5% dextrose in water or 0.45% sodium chloride in well-hydrated animals and 0.9% sodium chloride or an isotonic crystalloid in hypovolemic animals.[1,8]

Chronic Toxicity

Initially, access to fresh water should be restricted to small amounts at frequent intervals; unlimited access may be associated with a sudden increase in the number of animals affected. In advanced cases animals may be unable to drink and water may have to be administered by stomach tube. Serum sodium levels in those animals with toxicity of several days' duration or those with an unknown duration of hypernatremia should be decreased by no more than 0.5 mmol/L/h.[8] Fluid choices again depend on whether the animal is volume depleted or well hydrated.

If possible, serum sodium concentration should be measured and the following formula used to calculate the free-water deficit:

$$\textit{Free-water deficit}\ (L) = 0.6 \times BW\ (kg) \times ([\textit{current serum sodium concentration}/\textit{reference range serum sodium concentration}] - 1)$$

No more than 50% of the free-water deficit should be replaced in the first 24 hours, with the remainder replaced over the subsequent 24 to 48 hours.

Supportive treatment includes gastrointestinal protectants, diuretics for pulmonary edema, and mannitol or hypertonic saline to decrease brain edema should it occur.

CONTROL

Both salt and water should be freely available at all times. Drinking water for all classes of livestock should not contain more than 0.5% sodium chloride or total salts. Water containing a high concentration of fluoride or magnesium is particularly dangerous to livestock and should be avoided. In cold weather, access to water should be monitored on a daily basis. Diets fed to pigs should not contain more than 1% salt. The manner in which whey is fed to pigs (with minimum water intake) makes prevention difficult unless the whey can be kept salt free at the cheese factory.

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VITAMIN A DEFICIENCY (HYPOVITAMINOSIS A)

A deficiency of vitamin A may be caused by an insufficient supply of the vitamin in the ration or its defective absorption from the alimentary canal. In young animals, the manifestations of the deficiency are mainly those of compression of the brain and spinal cord. In adult animals, the syndrome is characterized by night blindness, corneal keratinization, pityriasis, defects in the hooves, loss of weight, and infertility. Congenital defects are common in the offspring of deficient dams. Vitamin A may also provide a protective effect against various infectious diseases and enhance many facets of the immune system.

SYNOPSIS

Etiology Dietary deficiency of vitamin A or its precursors.

Epidemiology Primary vitamin A deficiency in animals fed diet deficient in vitamin A or its precursors. Common in cattle grazing dry pastures for long periods. Occurs when diet of hand-fed animals is not supplemented with vitamin A.

Signs
Cattle: Night blindness. Loss of body weight. Convulsions followed by recovery. Episodes of syncope. Permanent blindness with dilated pupils and optic disc edema.
Pigs: Convulsions, hindleg paralysis, congenital defects.

Clinical pathology Low levels plasma vitamin A.

Necropsy findings Squamous metaplasia of interlobular ducts of parotid gland. Compression of optic nerve tracts and spinal nerve roots. Degeneration of testes.

Diagnostic confirmation Low levels of plasma vitamin A and squamous metaplasia of interlobular ducts of parotid glands.

Differential diagnosis list
Cattle
- Polioencephalomalacia
- Hypomagnesemic tetany
- Lead poisoning
- Rabies
- Meningoencephalitis
- Peripheral blindness caused by bilateral ophthalmitis.

Pigs
- Salt poisoning
- Pseudorabies
- Viral encephalomyelitis
- Spinal cord compression caused by vertebral body abscess

Treatment Vitamin A injections.

Control Feed diets with adequate carotene. Supplement diet with vitamin A. Parenteral injections of vitamin A at strategic times.

ETIOLOGY

Vitamin A deficiency may be primary disease, caused by an absolute deficiency of vitamin A or its precursor carotene in the diet, or a secondary disease, in which the dietary supply of the vitamin or its precursor is adequate, but their digestion, absorption, or metabolism is interfered with to produce a deficiency at the tissue level.

EPIDEMIOLOGY

Primary Vitamin A Deficiency

Primary vitamin A deficiency is of major economic importance in groups of young growing animals on pasture or fed diets deficient in the vitamin or its precursors. In the UK, primary vitamin A deficiency occurs in housed cattle fed a ration containing little or no green forage. Animals at pasture receive adequate supplies of the vitamin, except during prolonged droughts, but animals confined indoors and fed prepared diets may be deficient if not adequately supplemented. For example, a diet of dried sugar beet pulp, concentrates, and poor-quality hay can result in hypovitaminosis A in confined beef cattle.

Ruminants on Pasture

Primary vitamin A deficiency occurs in beef cattle and sheep on dry range pasture during periods of drought. Clinical vitamin A deficiency does not always occur under these conditions because hepatic storage is usually good and the period of deprivation not sufficiently long for these stores to reach a critically low level. Young sheep grazing natural, drought-stricken pasture can suffer serious depletion of reserves of the vitamin in 5 to 8 months, but normal growth is maintained for 1 year at which time clinical signs develop. Adult sheep may be on a deficient diet for 18 months before hepatic stores are depleted and the disease becomes evident. Cattle may subsist on naturally deficient diets for 5 to 18 months before clinical signs appear. However, during the annual dry season (October to June), herds of cattle, sheep, and goats in the Sahelian region of West Africa are managed on dry grasses and shrubby ligneous plants, which fail to provide maintenance levels of crude protein and vitamin A. These substandard conditions result in vitamin A deficiency characterized by night blindness, xerophthalmia, retarded growth rates, reproductive failures, and increased mortality. The pastoral herders associate the cure of night blindness with the consumption of green vegetation and will purposefully herd livestock into green vegetation areas when available. Certain ethnic groups of pastoral herders depend on ruminant milk as their principal source of vitamin A, and night blindness in lactating and pregnant women as well as in young children appears after the onset of night blindness in their cattle and sheep during the latter half of the dry season. Therefore increasing vitamin A levels in the milk of cows may alleviate the clinical signs of vitamin A deficiency in herder families.

Primary vitamin A deficiency is still relatively common in beef cattle that depend on pasture and roughage for the major portion of their diet. Beef calves coming off dry summer pastures at 6 to 8 months of age are commonly marginally deficient.

Maternal Deficiency

A maternal deficiency of vitamin A can result in herd outbreaks of congenital hypovitaminosis A in calves. In one such occurrence, out of 240 heifers fed a vitamin A–deficient ration, 89 calves were born dead and 47 were born alive but blind and weak and died within 1 to 3 days after birth. Blindness with dilated pupils, nystagmus, weakness, and incoordination were characteristic. In another occurrence in the UK, 25% of the calves born from maternally vitamin A–deficient heifer dams had ocular abnormalities.

The status of the dam is reflected in the status of the fetus only in certain circumstances because carotene, as it occurs in green feed, does not pass the placental barrier, and a high intake of green pasture before parturition does not increase the hepatic stores of vitamin A in newborn calves, lambs, or kids and only to a limited extent in pigs. However, vitamin A in the ester form, as it occurs in fish oils, will pass the placental barrier in cows. Feeding of these oils, or the parenteral administration of a vitamin A injectable preparation before parturition, will cause an increase in stores of the vitamin in fetal livers. Antepartum feeding of carotene and the alcohol form of the vitamin does, however, cause an increase in the vitamin A content of the colostrum. Young animals depend on the dam's colostrum for their early requirements of the vitamin, which is always highest in colostrum and returns to normal levels within a few days of parturition. Pigs weaned very early at 2 to 4 weeks may require special supplementation. Pregnant beef cows wintered on poor-quality roughage commonly need supplementation with vitamin A throughout the winter months to ensure normal development of the fetus and an adequate supply of the vitamin in the colostrum at parturition.

Adequacy of Supplements

The addition of vitamin A supplements to diets may not always be sufficient to prevent deficiency. Carotene and vitamin A are readily oxidized, particularly in the presence of unsaturated fatty acids. Oily preparations are thus less satisfactory than dry or aqueous preparations, particularly if the feed is to be stored for any length of time. Pelleting of feed may also cause a serious loss up to 32% of the vitamin A in the original feedstuff.

Heat, light, and mineral mixes are known to increase the rate of destruction of vitamin A supplements in commercial rations. In one study, 47% to 92% of the vitamin A in several mineral supplements was destroyed after 1 week of exposure to the trace minerals, high relative humidity, sunlight, and warm temperatures.

Feedlot Cattle

The disease still occurs in feedlot cattle in some parts of North America when feedlot cattle are fed rations low in carotene or vitamin A over a period of several months. The onset of clinical signs in growing feedlot cattle is typically seen 6 to 12 months after feeding a diet deficient in carotene or vitamin A. Small farm feedlots may feed their cattle a cereal grain such as barley and barley straw with no vitamin supplementation or inadequate supplementation. Grains, with the exception of yellow corn, contain negligible amounts of carotene, and cereal hay is often a poor source. Any hay cut late, leached by rain, bleached by sun, or stored for long periods loses much of its carotene content. The carotene content of yellow corn also deteriorates markedly with long storage. Moreover, under conditions not yet completely understood, the conversion by

ruminants of carotene present in feeds such as silage may be much less complete than was formerly thought.

In feedlot cattle, the disease is most common in steers fed the same ration as heifers that may remain clinically normal. It is suggested that sexual dimorphism may be caused by the production of vitamin A by the corpus luteum of heifers.

Pigs

Young pigs on a deficient diet may show signs after several months, but as in other animals, the length of time required before signs appear is governed to a large extent by the status before depletion commences. As a general rule it can be anticipated that signs will appear in pigs fed deficient rations for 4 to 5 months; variations from these periods are probably caused by variations in the vitamin A status of the animal when the deficient diet is introduced. Congenital defects occur in litters from deficient sows, but the incidence is higher in gilts with the first litter than in older sows. It is presumed that the hepatic stores of vitamin A in older sows are not depleted as readily as in young pigs. Feeding white maize bran without supplementation can result in congenital defects in litters and paralysis in adult pigs.

Horses

Adult horses may remain clinically normal for as long as 3 years on a deficient diet.

Secondary Vitamin A Deficiency

Secondary vitamin A deficiency may occur in cases of chronic disease of the liver or intestines because much of the conversion of carotene to vitamin A occurs in the intestinal epithelium and the liver is the main site of storage of the vitamin. Highly chlorinated naphthalenes interfere with the conversion of carotene to vitamin A, and animals poisoned with these substances have a very low vitamin A status. The intake of inorganic phosphorus also affects vitamin A storage, low phosphate diets facilitating storage of the vitamin. This may have a sparing effect on vitamin A requirements during drought periods when phosphorus intake is low and an exacerbating effect in stall-fed cattle on a good grain diet. However, phosphorus deficiency may lower the efficiency of carotene conversion. Vitamins C and E help to prevent loss of vitamin A in feedstuffs and during digestion. Additional factors, which may increase the requirement of vitamin A, include high environmental temperatures and a high nitrate content of the feed, which reduces the conversion of carotene to vitamin A and rapid rate of gain. Both a low vitamin A status of the animal and high levels of carotene intake may decrease the biopotency of ingested carotene.

The continued ingestion of mineral oil, which may occur when the oil is used as a preventive against bloat in cattle, may cause a depression of plasma carotene and vitamin A esters and the carotene levels in buffer fat. Deleterious effects on the cattle are unlikely under the conditions in which it is ordinarily used because of the short period for which the oil is administered and the high intake of vitamin A and carotene.

PATHOGENESIS

Vitamin A is essential for the regeneration of the visual purple necessary for dim-light vision, for normal bone growth, and for maintenance of normal epithelial tissues. Deprivation of the vitamin produces effects largely attributable to disturbance of these functions. The same tissues are affected in all species. However, there is a difference in tissue and organ response in the different species and particular clinical signs may occur at different stages of development of the disease. The major pathophysiologic effects of vitamin A deficiency are as follows.

Night Vision and Ocular Abnormalities

Ability to see in dim light is reduced because of interference with regeneration of visual purple. Ocular abnormalities occur because of disruption to ocular, retinal, and optic nerve development from midpregnancy onward.[1]

Cerebrospinal Fluid Pressure

An increase in CSF pressure is one of the first abnormalities to occur in hypovitaminosis A in calves. It is a more sensitive indicator than ocular changes and, in the calf, it occurs when the vitamin A intake is about twice that needed to prevent night blindness. The increase in CSF pressure is caused by impaired absorption of the CSF from reduced tissue permeability of the arachnoid villi and thickening of the connective tissue matrix of the cerebral dura mater. The increased CSF pressure is responsible for the syncope and convulsions, which occur in calves in the early stages of vitamin A deficiency. The syncope and convulsions may occur spontaneously or be precipitated by excitement and exercise. It is suggested that the CSF pressure is increased in calves with subclinical deficiency and that exercise further increases the CSF pressure to convulsive levels.

Bone Growth

Vitamin A is necessary to maintain normal position and activity of osteoblasts and osteoclasts. When deficiency occurs, there is no retardation of endochondral bone growth, but there is incoordination of bone growth in that shaping, especially the finer molding of bones, does not proceed normally. In most locations this has little effect but may cause serious damage to the nervous system. Overcrowding of the cranial cavity occurs with resulting distortion and herniations of the brain and an increase in CSF pressure up to four to six times normal. The characteristic nervous signs of vitamin A deficiency, including papilledema, incoordination, and syncope, follow. Compression, twisting, and lengthening of the cranial nerves and herniations of the cerebellum into the foramen magnum, causing weakness and ataxia, and of the spinal cord into intervertebral foramina results in damage to nerve roots and localizing signs referable to individual peripheral nerves. Facial paralysis and blindness caused by constriction of the optic nerve are typical examples of this latter phenomenon. The effect of excess vitamin A on bone development by its interference with vitamin D has been discussed elsewhere. Dwarfism in a group of pigs in a swine herd was suspected to be caused by vitamin toxicosis.

Epithelial Tissues

Vitamin A deficiency leads to atrophy of all epithelial cells, but the important effects are limited to those types of epithelial tissue with a secretory as well as a covering function. The secretory cells are without power to divide and develop from undifferentiated basal epithelium. In vitamin A deficiency these secretory cells are gradually replaced by the stratified, keratinizing epithelial cells common to nonsecretory epithelial tissues. This replacement of secretory epithelium by keratinized epithelium occurs chiefly in the salivary glands, the urogenital tract (including placenta but not ovaries or renal tubules), and the periocular glands and teeth (disappearance of odontoblasts from the enamel organ). The secretion of thyroxine is markedly reduced. The mucosa of the stomach is not markedly affected. These changes in epithelium lead to the clinical signs of placental degeneration, xerophthalmia, and corneal changes.

Experimental vitamin A deficiency in lambs results in changes in the epithelium of the small intestine characterized by vesicular microvillar degeneration and disruption of the capillary endothelium. Diarrhea did not occur.

Embryologic Development

Vitamin A is essential for organ formation during growth of the fetus. Multiple congenital defects occur in pigs and rats and congenital hydrocephalus in rabbits on maternal diets deficient in vitamin A. In pigs, administration of the vitamin to depleted sows before the 17th day of gestation prevented the development of eye lesions but administration on the 18th day failed to do so. A maternal deficiency of vitamin A in cattle can result in congenital hypovitaminosis A in the calves, characterized by blindness with dilated pupils, nystagmus, weakness, and incoordination. Constriction of the optic canal with thickening of the dura mater results in ischemic necrosis of the optic nerve and optic disc edema resulting in blindness. Retinal dysplasia also occurs. Thickening of the occipital and sphenoid

bones and doming of the frontal and parietal bones with compression of the brain also occur. Dilated lateral ventricles may be present and associated with increased CSF pressure.

Immune Mechanisms

The effects of vitamin A and β-carotene on host defense mechanisms have been uncertain and controversial for many years. Some workers claim that the incidence and severity of bacterial, viral, rickettsial, and parasitic infections are higher in vitamin A–deficient animals. It is possible that vitamin A and β-carotene afford protection against infections by influencing both specific and nonspecific host defense mechanisms. The protective effect of vitamin A may be mediated by enhanced polymorphonuclear neutrophil function, but this effect is also influenced by the physiologic status of the animal such as lactation status in dairy cattle. Experimentally, a severe vitamin A deficiency in lambs is associated with alterations in immune function, but the exact mechanism is unknown.

CLINICAL FINDINGS

Similar syndromes occur in all species, but because of species differences in tissue and organ response, some variations are observed. The major clinical findings are set out in the following sections.

Night Blindness

Inability to see in dim light (twilight or moonlit night) is the earliest sign in all species, except in the pig, in which it is not evident until plasma vitamin A levels are very low. This is an important diagnostic sign.

Xerophthalmia

True xerophthalmia, with thickening and clouding of the cornea, occurs only in the calf. In other species, a thin, serous mucoid discharge from the eyes occurs, followed by corneal keratinization, clouding and sometimes ulceration, and photophobia.

Ocular Abnormalities

A range of ocular deformities, including cataract formation, lens luxation, microphthalmia, and reduction in the size of the optic nerve head, occurred in calves with low serum vitamin A and E concentrations (Fig. 14-14).[1] Mean vitamin A concentration was 0.47 µmol/L (reference range 0.87 to 1.75 µmol/L) and the mean vitamin E concentrations was 2.28 µmol/L (reference range 3.0 to 18 µmol/L).

Changes in the Skin

A rough, dry coat with a shaggy appearance and splitting of the bristle tips in pigs is characteristic, but excessive keratinization, such as occurs in cattle poisoned with chlorinated naphthalenes, does not occur under natural conditions of vitamin A deficiency. Heavy deposits of branlike scales on the skin are seen in affected cattle. Skin disease occurs in Angus calves (~8 months of age) with vitamin A deficiency and is characterized by alopecia, severe epidermal and follicular orthokeratosis, and acanthosis. Affected animals responded to vitamin A supplementation.[2]

Dry, scaly hooves with multiple, vertical cracks are another manifestation of skin changes and are particularly noticeable in horses.

A seborrheic dermatitis can be observed in deficient pigs but is not specific to vitamin A deficiency.

Body Weight

Under natural conditions, a simple deficiency of vitamin A is unlikely to occur and the emaciation commonly attributed to vitamin A deficiency may be largely caused by multiple deficiencies of protein and energy. Although inappetence, weakness, stunted growth, and emaciation occur under experimental conditions of severe deficiency, in field outbreaks severe clinical signs of vitamin A deficiency are often seen in animals in good condition. Experimentally, sheep maintain their BW under extreme deficiency conditions and with very low plasma vitamin A levels.

Reproductive Efficiency

Loss of reproductive function is one of the major causes of loss in vitamin A deficiency. Both the male and female are affected. In the male, libido is retained but degeneration of the germinative epithelium of the seminiferous tubules causes reduction in the number of motile, normal spermatozoa produced. In young rams, the testicles may be visibly smaller than normal. In the female, conception is usually not interfered with, but placental degeneration leads to abortion and the birth of dead or weak young. Placental retention is common.

Dairy ewes on a diet low in vitamin A have increased somatic cell counts, possibly indicating a predisposition to mastitis in animals with hypovitaminosis A.[3]

Nervous System

Signs related to damage of the nervous system include the following:

- **Paralysis** of skeletal muscles caused by damage of peripheral nerve roots
- **Encephalopathy** caused by increased intracranial pressure
- **Blindness** caused by constriction of the optic nerve canal

These defects occur at any age but are most common in young, growing animals; they have been observed in all species except horses.

Paralysis

The paralytic form is manifested by abnormalities of gait caused by weakness and incoordination. The hindlegs are usually affected first and the forelimbs later. In pigs, there may be stiffness of the legs, initially with a stilted gait or flaccidity, knuckling of the fetlocks and sagging of the hindquarters. Complete limb paralysis occurs terminally.

Convulsions

Encephalopathy, associated with an increase in CSF pressure, is manifested by convulsions, which are common in beef calves at 6 to 8 months, usually following removal from a dry summer pasture at weaning time. Spontaneously, or following exercise or handling, affected calves will collapse (syncope) and during lateral recumbency a clonic-tonic convulsion will occur, lasting for 10 to 30 seconds. Death may occur during the convulsion or the animal will survive the convulsion and lie quietly for several minutes, as if paralyzed, before another convulsion may occur. Affected calves are usually not blind and the menace reflex may be slightly impaired or hyperactive. Some calves are hyperesthetic to touch and sound. During

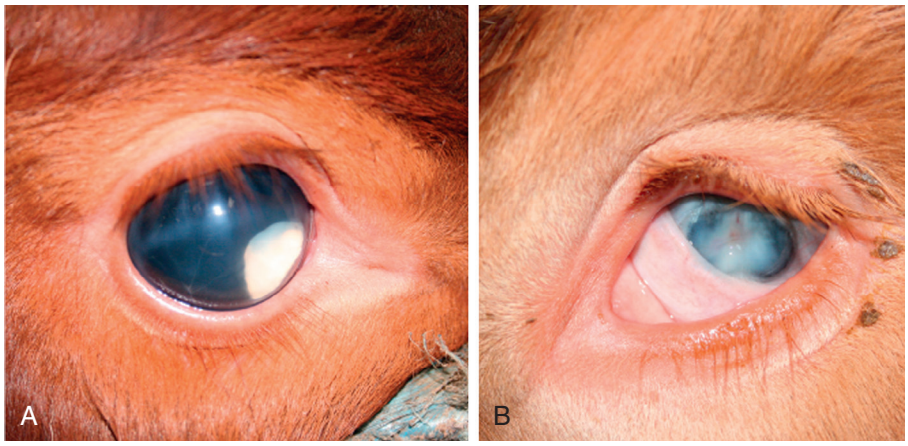

Fig. 14-14 Lens dislocation **(A)** and ocular rupture **(B)** in Simmental calves with hypovitaminosis A. (Reproduced with permission from Anon. *Vet Rec* 2014;174:244.)

the convulsion there is usually ventroflexion of the head and neck, sometimes opisthotonus and, commonly, tetanic closure of the eyelids and retraction of the eyeballs. Outbreaks of this form of hypovitaminosis A in calves have occurred and the case–fatality rate may reach 25%. The prognosis is usually excellent; treatment will effect a cure in 48 hours, but convulsions may continue for up to 48 hours following treatment.

Seizures and acute death attributable to hypovitaminosis A and D have occurred in feeder pigs fed ground red wheat and whole milk and housed in a barn with no exposure to sunlight. Lethargy, inappetence, diarrhea, and vomiting and progression to convulsions were characteristic.

Blindness

The ocular form of hypovitaminosis A occurs usually in yearling cattle (12–18 months old) and up to 2 to 3 years of age. These animals have usually been on marginally deficient rations for several months. Night blindness may or may not have been noticed by the owner. The cattle have usually been fed and housed for long periods in familiar surroundings and the clinical signs of night blindness may have been subtle and not noticeable. A computer-based algorithm for using pupillary light reflex responses to detect cattle with incipient visual loss or mild impairment of vision caused by hypovitaminosis A was not effective in detecting affected cattle.[4] The first sign of the ocular form of the disease is blindness in both eyes during daylight. Both **pupils** are **widely dilated and fixed** and will not respond to light. Optic disc edema may be prominent and there may be some loss of the usual brilliant color of the tapetum. Varying degrees of peripapillary retinal detachment, papillary and peripapillary retinal hemorrhages, and disruption of the retinal pigment epithelium may also be present. The **menace reflex** is usually totally absent, but the **palpebral and corneal reflexes** are present. The animal is aware of its surroundings and usually eats and drinks, unless placed in unfamiliar surroundings. The CSF pressure is increased in these animals, but not as high as in the calves described earlier. Convulsions may occur in these cattle if forced to walk or if loaded onto a vehicle for transportation. The prognosis for the ocular form with blindness is unfavorable and treatment is ineffective because of the degeneration of the optic nerves. Exophthalmos and excessive lacrimation are present in some cases.

Congenital Defects

Congenital defects have been observed in piglets and calves. In piglets, complete absence of the eyes (**anophthalmos**) or small eyes (**microphthalmos**), incomplete closure of the fetal optic fissure, degenerative changes in the lens and retina, and an abnormal proliferation of mesenchymal tissue in front of and behind the lens are some of the defects encountered.

Ocular abnormalities in newborn calves from maternally vitamin A–deficient heifers included corneal dermoid, microphthalmos, aphakia (absence of lens) and in some cases, both eyes covered by haired skin.[5] Cardiac defects, including ventricular septal defect and overriding aorta, are reported in a limited number of cases of calves with hypovitaminosis A, but the relationship is unclear.[5]

Other congenital defects attributed to vitamin A deficiency in pigs include cleft palate and harelip, accessory ears, malformed hindlegs, subcutaneous cysts, abnormally situated kidneys, cardiac defects, diaphragmatic hernia, aplasia of the genitalia, internal hydrocephalus, herniations of the spinal cord, and generalized edema. Affected pigs may be stillborn, or weak and unable to stand, or may be quite active. Weak pigs lie on their sides, make slow paddling movements with their legs, and squawk plaintively.

Other Diseases

Increased susceptibility to infection is often stated to result from vitamin A deficiency. The efficacy of colostrum as a preventive against diarrhea in calves was originally attributed to its vitamin A content, but the high antibody content of colostrum is most important.

Anasarca. Edema of the limbs and brisket has been associated with vitamin A deficiency in feedlot cattle, especially steers. The pathogenesis is not understood. The edema can be extensive, include all four limbs, ventral body wall, and extend to the scrotum. Heifers were unaffected.

CLINICAL PATHOLOGY

Plasma Vitamin A

Vitamin A levels in the plasma are used extensively in diagnostic and experimental work. Plasma levels of 20 µg/dL are the minimal concentration for vitamin A adequacy. Papilledema is an early sign of vitamin A deficiency, which develops before nyctalopia and at plasma levels below 18 µg/dL. Normal serum vitamin A concentrations in cattle range from 25 to 60 µg/dL. In pigs, levels of 11.0 µg/dL have been recorded in clinical cases, with normal levels being 23 to 29 µg/dL. In experimental vitamin A deficiency in lambs, serum levels declined to 6.8 µg/dL (normal lambs at 45.1 µg/dL).

The clinical signs may correlate with the serum concentrations of vitamin A. In one outbreak, feedlot cattle with serum concentrations between 8.89 and 18.05 µg/dL had only lost BW, those between 4.87 and 8.88 µg/dL had varying degrees of ataxia and blindness, and those below 4.88 µg/dL had convulsions and optic nerve constriction. Clinical signs can be expected when the levels fall to 5 µg/dL. For complete safety, optimum levels should be 25 µg/dL or above.

Plasma Retinol

Some information on the plasma retinol values in stabled Thoroughbred horses is available. The mean plasma level of retinol in 71 horses 2 to 3 years of age was 16.5 µg/dL. The serum retinol levels in racing Trotters in Finland are lower than during the summer months, which is a reflection of the quality of the diets.

Plasma Carotene

Plasma carotene levels vary largely with the diet. In cattle, levels of 150 µg/dL are optimum and, in the absence of supplementary vitamin A in the ration, clinical signs appear when the levels fall to 9 µg/dL. In sheep, carotene is present in the blood in only very small amounts even when animals are on green pasture.

Hepatic Vitamin A

A direct relationship between plasma and hepatic levels of vitamin A need not exist because plasma levels do not commence to fall until the hepatic stores are depleted. A temporary precipitate fall occurs at parturition and in acute infections in most animals. The secretion of large amounts of carotene and vitamin A in the colostrum of cows during the last 3 weeks of pregnancy may greatly reduce the level of vitamin A in the plasma.

Hepatic levels of vitamin A and carotene can be estimated in the living animal from a biopsy specimen. Biopsy techniques have been shown to be safe and relatively easy, provided a proper instrument is used. Hepatic levels of vitamin A and carotene should be of the order of 60 and 4.0 µg/g of liver, respectively. These levels are commonly as high as 200 to 800 µg/g. Critical levels at which signs are likely to appear are 2 and 0.5 µg/g for vitamin A and carotene, respectively.

Cerebrospinal Fluid

CSF pressure is also used as a sensitive indicator of low vitamin A status. In calves, normal pressures of less than 100 mm of saline rise after depletion to more than 200 mm. In pigs, normal pressures of 80 to 145 mm rise to above 200 mm in vitamin A deficiency. An increase in pressure is observed at a blood level of about 7 µg vitamin A per deciliter of plasma in this species. In sheep, normal pressures of 55 to 65 mm rise to 70 to 150 mm when depletion occurs. In the experimentally induced disease in cattle, there is a marked increase in the number of cornified epithelial cells in a conjunctival smear and distinctive bleaching of the tapetum lucidum as viewed by an ophthalmoscope. These features may have value as diagnostic aids in naturally occurring cases.

NECROPSY FINDINGS

Gross changes are rarely observed at necropsy. Careful dissection may reveal a decrease in the size of the cranial vault and

of the vertebrae. Compression and injury of the cranial and spinal nerve roots, especially the optic nerve, may be visible. In outbreaks in which night blindness is the primary clinical sign, atrophy of the photoreceptor layer of the retina is evident histologically, but there are no gross lesions.

Congenital ocular abnormalities in newborn calves from vitamin A–deficient heifer dams included aphakia, absence of a uveal tract and aqueous humor, microphthalmos, bony outgrowths of the occipital bone, compression of the cerebellum, and cardiac abnormalities similar to the tetralogy of Fallot.

Squamous metaplasia of the interlobular ducts of the parotid salivary gland is strongly suggestive of vitamin A deficiency in pigs, calves, and lambs, but the change is transient and may have disappeared 2 to 4 weeks after the intake of vitamin A is increased. This microscopic change is most marked and occurs first, at the oral end of the main parotid duct. Abnormal epithelial cell differentiation may also be observed histologically in a variety of other sites such as the tracheal, esophageal, and ruminal mucosae; preputial lining; pancreatic ducts; and urinary epithelium. Hypovitaminosis A has also been associated with an increased incidence of pituitary cysts in cattle. Secondary bacterial infections, including pneumonia and otitis media, are also common, due at least in part to the decreased barrier function of the lining epithelia.

The abnormalities that occur in congenitally affected pigs have already been described.

Samples for Confirmation of Diagnosis

- **Toxicology:** 50 g liver, 500 g feed ASSAY (Vit A)
- **Histology:** formalin-fixed parotid salivary gland (including duct), rumen, pituitary, pancreas, brain (including optic nerves), cervical spinal cord (including nerve roots); Bouin's fixed eye (LM).

DIFFERENTIAL DIAGNOSIS

When the characteristic clinical findings of vitamin A deficiency are observed, a deficiency of the vitamin should be suspected if green feed or vitamin A supplements are not being provided. The detection of papilledema and testing for night blindness are the easiest methods of diagnosing early vitamin A deficiency in ruminants. Incoordination, paralysis, and convulsions are the early signs in pigs. Increase in CSF pressure is the earliest measurable change in both pigs and calves. Laboratory confirmation depends on estimations of vitamin A in plasma and liver, with the latter being most satisfactory. Unless the disease has been in existence for a considerable time, response to treatment is rapid. For confirmation at necropsy, histologic examination of parotid salivary gland and assay of vitamin A in the liver are suggested.

The salient features of the differential diagnosis of diseases of the nervous system of cattle are summarized in Table 14-12.

Cattle

Convulsive form of vitamin A deficiency in cattle must be differentiated from the following:

- **Polioencephalomalacia**: characterized by sudden onset of blindness, head-pressing, and tonic-clonic convulsions, usually in grain-fed animals but also in pastured animals ingesting an excess of sulfate in water and grass
- **Hypomagnesemic tetany**: primarily in lactating dairy cattle on pasture during cool windy weather; characterized by hyperesthesia, champing tonic-clonic convulsions, normal eyesight and tachycardia, and loud heart sounds
- **Lead poisoning**: in all age groups, but most commonly in pastured calves in the spring; characterized by blindness, tonic-clonic convulsions, champing of the jaw, head-pressing, and rapid death
- **Rabies**: in all age groups; characterized by bizarre mental behavior, gradually progressive ascending paralysis with ataxia leading to recumbency, drooling saliva, inability to swallow, normal eyesight, and death in 4–7 days.

Ocular form of vitamin A deficiency in cattle must be differentiated from those diseases of cattle characterized by central or peripheral blindness:

- Central blindness:
  Polioencephalomalacia
  Lead poisoning
  Meningoencephalitis
- Peripheral blindness:
  Bilateral ophthalmitis caused by ocular disease

Loss of body condition in cattle, failure to grow, and poor reproductive efficiency are general clinical findings not limited to vitamin A deficiency.

Pigs

Convulsive form of vitamin A deficiency in pigs must be differentiated from the following:

- Salt poisoning
- Pseudorabies
- Viral encephalomyelitis
- Organic arsenic poisoning.

Paralytic form of vitamin A deficiency in pigs must be differentiated from the following:

- Spinal cord compression caused by vertebral body abscess.

Congenital defects similar to those caused by vitamin A deficiency may be caused by deficiencies of other essential nutrients, by inheritance or by viral infections in early pregnancy in all species. Maternal vitamin A deficiency is the most common cause of congenital defects in piglets. Final diagnosis depends on the necropsy findings, analysis of feed and serum vitamin A of the dams.

TREATMENT

Vitamin A

Animals with curable vitamin A deficiency should be treated immediately with vitamin A at a dose rate equivalent to 10 to 20 times the daily maintenance requirement. As a rule, 440 IU/kg BW is the dose used. Parenteral injection of an aqueous rather than an oily solution is preferred. The response to treatment in severe cases is often rapid and complete, but the disease may be irreversible in chronic cases. Calves with the convulsive form caused by increased CSF pressure will usually return to normal in 48 hours following treatment. Cattle with the ocular form of the deficiency and that are blind will not respond to treatment and should be slaughtered for salvage.

Hypervitaminosis A

Daily heavy dosing (about 100 times normal) of calves causes reduced growth rate, lameness, ataxia, paresis, exostoses on the planter aspect of the third phalanx of the fourth digit of all feet, and disappearance of the epiphyseal cartilage. Persistent heavy dosing in calves causes lameness, retarded horn growth, and depressed CSF pressure. At necropsy, exostoses are present on the proximal metacarpal bones and the frontal bones are thin. Very high levels fed to young pigs may cause sudden death through massive internal hemorrhage and excessive doses during early pregnancy are reputed to result in fetal anomalies. However, feeding vitamin A for prolonged periods at exceptionally high levels is unlikely to produce severe embryotoxic or teratogenic effects in pigs.

CONTROL

Dietary Requirement

The minimum daily requirement in all species is 40 IU of vitamin A per kilogram BW, which is a guideline for maintenance requirements. In the formulation of practical diets for all species, the daily allowances of vitamin A are commonly increased by 50% to 100% of the daily minimum requirements. During pregnancy, lactation, or rapid growth the allowances are usually increased by 50% to 75% of the requirements. The supplementation of diets to groups of animals is governed also by their previous intake of the vitamin and its probable level in the diet being fed. The rate of supplementation can vary from 0 to 110 IU/kg BW per day (1 IU of vitamin A is equivalent in activity to 0.3 μg of retinol; 5 to 8 μg β-carotene has the same activity as 1 μg of retinol).

Nutrient studies have indicated that preruminant Holstein calves being fed milk replacer should receive 11,000 IU of vitamin A per kilogram dry matter for optimum growth and to maintain adequate liver vitamin A stores.

The amounts of the vitamin to be added to the ration of each species to meet the requirements for all purposes should be

Table 14-17 Daily dietary allowances of vitamin A

Animal	Vitamin A (IU/kg BW daily)
Cattle	
Growing calves	40
Weaned beef calves at 6–8 months	40
Calves 6 months to yearlings	40
Maintenance and pregnancy	70–80
Maintenance and lactation	80
Feedlot cattle on high energy ration	80
Sheep	
Growth and early pregnancy and fattening lambs	30–40
Late pregnancy and lactation	70–80
Horses	
Working horse	20–30
Growing horse	40
Pregnant mare	50
Lactating mare	50
Pigs	
Growing pigs	40–50
Pregnant gilts and sows	40–50
Lactating gilts and sows	70–80

obtained from published recommended nutrient requirements of domestic animals. Some examples of daily allowances of vitamin A for farm animals are set out in Table 14-17.

Supplementation Method

The method of supplementation will vary depending on the class of livestock and the ease with which the vitamin can be given. In **pigs**, the vitamin is incorporated directly into the complete ration, usually through the protein supplement. In **feedlot and dairy cattle** receiving complete feeds, the addition of vitamin A to the diet is simple. In **beef cattle**, which may be fed primarily on carotene-deficient roughage during pregnancy, it may not be possible to supplement the diet on a daily basis. However, it may be possible to provide a concentrated dietary source of vitamin A on a regular basis by feeding a protein supplement once weekly. The protein supplement will contain 10 to 15 times the daily allowance, which permits hepatic storage of the vitamin.

Parenteral Injection

An alternative method to dietary supplementation is the intramuscular injection of vitamin A at intervals of 50 to 60 days at the rate of 3,000 to 6,000 IU/kg BW. Under most conditions, hepatic storage is good and optimum plasma and hepatic levels of vitamin A are maintained for up to 50 to 60 days. In pregnant beef cattle the last injection should not be more than 40 to 50 days before parturition to ensure adequate levels of vitamin A in the colostrum. Ideally, the last injection should be given 30 days before parturition, but this may not be practical under some management conditions. Administration of vitamin A palmitate by intramuscular injection (3500 IU/kg BW) increased plasma vitamin A concentrations by 24 hours and these elevated concentrations persisted for at least 8 days.[6] The effect of a single administration of vitamin A on liver vitamin A concentrations, the biologic reservoir for the vitamin, was not determined.

The most economical method of supplementing vitamin A is, in most cases, through the feed and when possible should be used.

The use of injectable mixtures of vitamins A, D, and E is not always justifiable. The injection of a mixture of vitamins A, D, and E of feeder cattle in northern Australia before transport did not, contrary to anecdotal evidence, reduce weight loss associated with transportation. Cattle in Queensland and northwestern Australia have very high concentrations of hepatic vitamin A and in fact, drought-stricken cattle in the terminal stages of malnutrition have also had high liver concentration. The indiscriminate use of vitamin A preparations in cattle is a public health concern because some bovine livers may contain high levels of vitamin A, which are potentially teratogenic for pregnant women.

Oral Vitamin A

The oral administration of a single bolus of vitamin A at a dose of 2.8 mg/kg BW to debilitated Sahelian cattle during the dry season was effective in raising the milk levels of vitamin A and was as effective as adding 10 g of the powder to the drinking water. Both the powder and bolus products provided high levels of vitamin A in milk within 3 days of treatment and according to herder testimonials, night-blind people consuming milk from cattle previously treated with either oral vitamin A preparation were no longer affected with night blindness.

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NICOTINIC ACID DEFICIENCY (HYPONIACINOSIS)

Nicotinic acid or niacin is essential for normal carbohydrate metabolism. Because of the high content in most natural animal feeds, deficiency states are rare in ordinary circumstances, except in pigs fed rations high in corn. Corn has both a low niacin content and a low content of tryptophan, which is a niacin precursor. A low-protein intake exacerbates the effects of the deficiency, but a high-protein intake is not fully protective.

In ruminants, synthesis within the animal provides an adequate source. Even in young calves, signs of deficiency do not occur, and because rumen microfloral activity is not yet of any magnitude, extraruminal synthesis appears probable. There are preliminary indications that dietary supplementation with niacin alters muscle fiber composition (increased type 1 (oxidative) versus type 2) in pigs and sheep.[1,2]

The oral supplementation of niacin in the diet of periparturient dairy cows may result in an increase in serum inorganic phosphorus and a decrease in serum potassium, calcium, and sodium concentrations. Niacin has been used to study the effects of artificially induced ketonemia and hypoglycemia in cattle through inducing changes in nonesterified fatty acid concentrations.[3]

The daily requirements of niacin for mature pigs are 0.1 to 0.4 mg/kg BW, but growing pigs appear to require more (0.6–1 mg/kg BW) for optimum growth.

Experimentally induced nicotinic acid deficiency in pigs is characterized by inappetence, severe diarrhea, a dirty yellow skin, with a severe scabby dermatitis and alopecia. Posterior paralysis also occurs. At necropsy, hemorrhages in the gastric and duodenal walls, congestion and swelling of the small intestinal mucosa, and ulcers in the large intestine are characteristic and closely resemble those of necrotic enteritis caused by infection with *Salmonella* spp.

Histologically, there is severe mucoid degeneration followed by local necrosis in the wall of the cecum and colon. Experimental production of the disease in pigs by the administration of an antimetabolite to nicotinamide causes ataxia or quadriplegia, accompanied by distinctive lesions in the gray matter of the cervical and lumbar enlargements of the ventral horn of the spinal cord. The lesions are malacic and

occur in the intermediate zone of the gray matter. The identical lesions and clinical picture have been observed in naturally occurring disease.

The oral therapeutic dose rate of nicotinic acid in pigs is 100 to 200 mg; 10 to 20 g/tonne of feed supplies have sufficient nicotinic acid for pigs of all ages. Niacin is low in price and should always be added to pig rations based on corn.

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PYRIDOXINE (VITAMIN B_6) DEFICIENCY (HYPOPYRIDOXINOSIS)

A deficiency of pyridoxine in the diet is not known to occur under natural conditions. Experimental deficiency in pigs is characterized by periodic epileptiform convulsions and at necropsy by generalized hemosiderosis with a microcytic anemia, hyperplasia of the bone marrow, and fatty infiltration of the liver. Less severe deficiency impairs weight gain and alters biochemical markers of sulfur-containing amino acid metabolism.[1] The daily requirement of pyridoxine in the pig is of the order of 100 µg/kg BW or 1 mg/kg of solid food, although higher levels have been recommended on occasion. Certain strains of chickens have a high requirement for pyridoxine and the same may be true of pigs.

Experimentally induced deficiency in calves is characterized by anorexia, poor growth, apathy, dull coat, and alopecia. Severe, fatal epileptiform seizures occur in some animals. Anemia with poikilocytosis is characteristic of this deficiency in cows and calves.

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PANTOTHENIC ACID DEFICIENCY (HYPOPANTOTHENOSIS)

PA is essential in metabolism because of its incorporation into coenzyme A and acyl carrier protein, both of which are central to energy metabolism. PA is ubiquitous in fodder, in addition to which microorganisms in the rumen synthesize the compound.[1] However, it is not clear if synthesis meets the requirements of dairy cows. The role of PA in ruminant nutrition is reviewed.[1]

Deficiency under natural conditions has been recorded mainly in pigs on rations based on corn.

In pigs, a decrease in weight gain caused by anorexia and inefficient food utilization occurs first. Dermatitis develops with a dark brown exudate collecting about the eyes and there is a patchy alopecia. Diarrhea and incoordination with a spastic, goose-stepping gait are characteristic. At necropsy, a severe, sometimes ulcerative, colitis is observed constantly, together with degeneration of myelin.

Calcium pantothenate (500 µg/kg BW/day) is effective in treatment and prevention. As a feed additive, 10 to 12 g/tonne of calcium pantothenate is adequate.

Experimentally induced PA deficiency in calves is manifested by rough hair coat, dermatitis under the lower jaw, excessive nasal mucus, anorexia and reduced growth rate, and is eventually fatal. At necropsy, there is usually a secondary pneumonia, demyelination in the spinal cord and peripheral nerves, and softening and congestion of the cerebrum.

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Metabolic and Toxic Encephalomyelopathies

A number of metabolic defects and a very large number of poisons, especially poisonous plants and farm chemicals, cause abnormalities of function of the nervous system. Those plants that cause degenerative nervous system disease are listed under the section Encephalomalacia; those that cause no detectable degenerative change in tissue are listed here. More detailed information on toxins that are primary neurotoxins are addressed in this chapter based on the predominant neuroanatomic location affected. This section includes those toxins that do not have a predilection for a specific neuroanatomic location.

An incomplete list of metabolic abnormalities and toxins that can cause nervous system dysfunction are as follows.

Abnormalities of Consciousness and Behavior

- Hypoglycemia and ketonemia of pregnancy toxemia (with degenerative lesions in some) and acetonemia
- Depression caused by hyponatremia and strong ion (metabolic) acidosis associated with diarrhea and dehydration, particularly in neonatal animals
- Hypomagnesemia of lactation tetany
- Hyper-D-lactatemia in neonatal calves, lambs, and kids and adult ruminants with grain overload
- Primary hyperammonemia and hepatic encephalopathy[1,2]
- Unspecified toxic substances in uremic animals
- Exogenous toxins, including carbon tetrachloride, hexachloroethane, and trichloroethylene
- Plants causing anemic and histotoxic hypoxia, especially plants causing cyanide or nitrite poisoning
- Poison plants, including *Helichrysum* spp., tansy mustard, male fern, kikuyu grass (or a fungus, *Myrothecium* sp. on the grass)

Abnormality Characterized by Tremor and Ataxia

- Weeds, including *Conium* spp. (hemlock), *Eupatorium* spp. (snakeroot), *Sarcostemma* spp., *Euphorbia* spp. and *Karwinskia* spp.
- Ivermectin toxicosis in horses[3]
- Bacterial toxins in shaker foal syndrome (probably)
- Fungal toxins, e.g., *Neotyphodium (Acremonium) lolii,* the endophyte fungus of ryegrass staggers

Convulsions

- Metabolic deficits, including hypoglycemia (piglets, ewes with pregnancy toxemia), hypomagnesemia (of whole milk tetany of calves, lactation tetany, cows and mares), hypernatremia
- Nutritional deficiencies of vitamin A (brain compression in calves and pigs), pyridoxine (experimentally in calves)
- Inorganic poisons, including lead (calves),[4] mercury (calves), farm chemicals such as organic arsenicals (pigs), organophosphates, chlorinated hydrocarbons, strychnine, urea, metaldehyde
- Bacterial toxins, including *C. tetani, C. perfringens* type D
- Fungal toxins, e.g., *C. purpurea*
- Grasses, including Wimmera ryegrass (*Lolium rigidum*) or the nematode on it, *Echinopogon ovatus*
- Pasture legumes: lupines
- Weeds: *Oenanthe* spp. (hemlock water dropwort), *Indigofera* spp. (in horses), *Cicuta* spp. (water hemlock), *Albizia tanganyicensis, Sarcostemma* spp., *Euphorbia* spp.
- Trees: laburnum, oleander, supplejack (*Ventilago* spp.)

Ataxia Apparently Caused by Proprioceptive Defect

- Grasses: *Phalaris tuberosa* (aquatica) (and other *Phalaris* spp.), *Lolium rigidum*, *E. ovatus*
- Weeds: *Romulea bulbocodium*, sneezeweed (*Helenium* spp.), *Indigofera* spp., Iceland poppy (*Papaver nudicaule*), *Gomphrena* spp., *Malva* spp., *Stachys* spp., *Ipomoea* spp., *Solanum esuriale*
- Trees: *Kalmia* spp., *Erythrophloeum* spp., *Eupatorium rugosum*
- Ferns: *Xanthorrhoea* spp., *Zamia* spp.; induced thiamine deficiency caused by bracken and horsetail poisoning

Involuntary Spastic Contraction of Large Muscle Masses

This includes, for example, acquired (Australian) equine reflex hypertonia (formerly known as Australian stringhalt) associated with ingestion of the Australian dandelion *Hypochaeris radicata,* European dandelion *Taraxacum officinale,* or mallow *Malva parviflora*).

Tremor, Incoordination, and Convulsions

There is an additional long list of plants that cause diarrhea and nervous signs, especially ataxia, together, but whether the latter are caused by the former or caused by neurotoxins is not identified.

The nervous signs include tremor, incoordination, and convulsions.

Paresis or Paralysis

Many of the toxic substances and metabolic defects listed previously cause paresis when their influence is mild and paralysis when it is severe. Some of the items appear in both lists. Because an agent appears in one list and not the other list is not meant to suggest that the agent does not cause the other effect. It is more likely that it occurs in circumstances that are almost always conducive to the development of a mild syndrome (or a severe one, as the case may be).

- **Disturbance of function** at neuromuscular junctions, e.g., hypocalcemia, hypomagnesemia, hypokalemia (as in downer cows), tetanus, botulism and hypoglycemia of pregnancy toxemia in cows and ewes, and tick paralysis. Hypophosphatemia has not been demonstrated to be a definitive cause of weakness in cattle.
- **Nutritional deficiency**, but including only experimentally induced deficiency of nicotinic and PAs: biotin and choline, cause posterior paresis and paralysis in pigs and calves.
- **Toxic diseases** of the nervous system, including disease associated with many chemicals used in agriculture, e.g., piperazine, rotenone, 2,4-D and 2,4,5-T, organophosphates, carbamates, chlorinated hydrocarbons, propylene glycol, metaldehyde, levamisole, toluene, carbon tetrachloride, strychnine, and nicotine sulfate.

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Inherited Diseases Primarily Affecting the Cerebrum

INHERITED CONGENITAL HYRDOCEPHALUS

Hydrocephalus is the distention of the ventricular system of the brain, caused by increased production of CSF by the choroid plexus, obstruction of normal CSF flow, or decreased absorption of CSF at the arachnoid villi in the venous sinuses.[1]

Cattle

Congenital hydrocephalus without abnormality of the frontal bones occurs sporadically but is also known to be an inherited defect in Holstein and Hereford and possibly in Ayrshire and Charolais cattle. Two specific inherited entities have been described. In one there is obstruction of drainage of the CSF from the lateral ventricles, which become distended with fluid and may cause bulging of the forehead, often sufficient to cause fetal dystocia. Hereford calves with this defect have partial occlusion of the supraorbital foramen, a domed skull, and poorly developed teeth; at necropsy the cerebellum is found to be small and there may be microphthalmia and skeletal muscle myopathy. They are usually born a few days prematurely, are small in size, and are unable to stand or suck. In some cows the amniotic fluid is increased in volume.

Another form of inherited hydrocephalus caused by malformation of the cranium and with no enlargement of the cranium has also been observed in Hereford cattle. The ventricular dilatation is not marked, and microphthalmia and cerebellar hypoplasia are not features. Affected calves may be alive at birth but are blind and unable to stand. Some bawl continuously and some are dumb. They do not usually survive for more than a few days. At necropsy there is internal hydrocephalus of the lateral ventricles with marked thinning of the overlying cerebrum. Other lesions include constriction of the optic nerve, detachment of the retina, cataract, coagulation of the vitreous humor, and a progressive muscular dystrophy. The condition is inherited as a recessive character.

Internal hydrocephalus inherited in combination with multiple eye defects in White Shorthorns is dealt with elsewhere, as are noninherited forms of the disease.

Sheep

A defect comparable to the Dandy–Walker syndrome in humans and characterized by internal hydrocephalus caused by obstruction of the foramina of Magendie and Lushka occurs in several breeds of sheep, especially Suffolk, and in cattle. Affected lambs are stillborn or die within a few hours of birth; because of the grossly enlarged cranium many cause dystocia, which can only be relieved by a fetotomy.

Horses

A Standardbred stallion sired a number of hydrocephalic foals in a pattern that suggested the inheritance of a dominant mutation in the germline and in the form of a single locus defect. Affected foals caused dystocia and were all stillborn. There is one report of an unsuccessful outcome following placement of ventriculoperitoneal shunt in an attempt to manage hydrocephalus in a Quarter Horse colt.[2]

Hydrocephalus has been observed more commonly in Friesian horses than other breeds. Affected foals have a malformed petrosal bone, which causes a narrowing of the jugular foramen.[1] Hydrocephalus in Friesian foals is thought to be caused by diminished absorption of CSF into the systemic circulation at the venous sinus because of the abnormally small jugular foramen. This type of hydrocephalus has been genetically linked in humans and dogs to chondrodysplasia.[1]

Pigs

Congenital hydrocephalus in Yorkshire and European pigs has been recorded. The abnormality varies from a small protrusion of dura (meningocele) to an extensive brain hernia in which the cerebral hemispheres protrude through the frontal suture, apparently forced there by increased fluid pressure in the lateral and third ventricles. The condition is thought to be inherited in a recessive manner, but exacerbated in its manifestation by a coexisting hypovitaminosis A. An outbreak of congenital meningoencephalocele in Landrace pigs is recorded in circumstances suggesting that it was inherited.

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INHERITED HYDRANENCEPHALY AND ARTHROGRYPOSIS

The defect is recorded in Corriedale sheep, and breeding trials indicate that it is inherited as an autosomal recessive character. Most affected lambs are found dead but facial deformity, including shortening of the mandible and distortion of the facial bones will be evident. At necropsy the predominant finding is the fixation and deformity of the joints of the limbs and vertebral column, and

the almost complete absence of a cerebral cortex.

INHERITED PROSENCEPHALY

Recorded in Border Leicester sheep, this defect takes the form of fusion of the cerebral hemispheres and a single lateral ventricle. It is widespread in the breed in Australia and is inherited as an autosomal recessive character. Most affected lambs are stillborn. Live ones have dyspnea caused by gross shortening of the nasomaxillary region creating a severely overshot mandible and interference with sucking. Blindness, nystagmus, and recumbency are constant signs. The cerebrum and the cranial cavity are much smaller than normal.

INHERITED MULTIFOCAL SYMMETRIC ENCEPHALOPATHY

Two forms of the disease are recorded, in **Simmental** and in **Limousin** and Limousin-cross cattle. The Limousin calves are normal at birth but from about 1 month of age develop a progressive forelimb hypermetria, hyperesthesia, blindness, nystagmus, weight loss, and behavioral abnormalities, especially aggression. The signs gradually worsen for up to 4 months when euthanasia is necessary. Necropsy lesions include brain swelling; optic chiasma necrosis; and multifocal, symmetric areas of pallor, up to 0.5 cm diameter in the brain. These lesions show partial cavitation and multiple, pathologic abnormalities, especially myelin lysis and vacuolation and demyelination. The distribution of cases suggests an inherited defect.

The disease in Simmental and Simmental-cross cattle recorded in Australia and New Zealand also has a distribution suggesting an inherited defect. The disease is clinically similar to that in Limousin cattle except that affected animals are not blind and it develops later at 5 to 8 months. Calves may survive longer, up to 12 months and, although the characteristic abnormality of gait is hypermetria, the hindlimbs are affected, not the forelimbs. Other signs observed are dullness, a swaying gait and, terminally, gradually developing opisthotonus and forelimb hypertonia in extension. Necropsy lesions are also similar to those in the Limousins, but the distribution is in the midbrain and the entire brainstem.

A multifocal symmetric necrotizing encephalomyelopathy in Angus calves has been described. Clinically affected calves exhibited ataxia, nystagmus, strabismus, muscular tremors, opisthotonus, bruxism, hyperesthesia, tetanic spasms, and episodic convulsions at 2 to 6 weeks of age. Death occurred 4 to 7 days after the onset of clinical signs. Lesions consisted of symmetric degenerative foci affecting the dorsal vagal motor, lateral cuneate, and olivary nuclei in the medulla oblongata, and occasionally in the spinal cord, substantia nigra, and cerebellar peduncles. Although an inherited basis for the disease is suspected, the etiology is unknown.

MAPLE SYRUP URINE DISEASE (BRANCHED-CHAIN KETO ACID DEHYDROGENASE DEFICIENCY)

Calves affected by this disease may be stillborn. Live calves are normal at birth and develop signs only at 1 to 3 days of age. It is inherited as an autosomal recessive and occurs principally in Poll Hereford, Hereford, and Poll Shorthorn cattle but probably also occurs in other breeds. There is molecular heterogeneity between the breeds, and tests based on detection of the mutation could be prone to error. Hair roots are good sources of target DNA for genotyping cattle for the mutation in one of the genes coding for the branched-chain α-keto acid dehydrogenase enzyme. This avoids the errors created by hemopoietic chimerism when blood is used for the test.

The disease is caused by an accumulation of branched-chain amino acids, including valine, leucine, and isoleucine. The mutation responsible for maple syrup urine disease in Poll Shorthorns and genotyping Poll Shorthorns and Poll Herefords for the maple syrup urine disease alleles has been determined. The mutations responsible for maple syrup urine disease and inherited congenital myoclonus are present in the Australian Poll Hereford population.

Clinical signs include dullness, recumbency, tremor, tetanic spasms and opisthotonus, a scruffy coat, blindness, and severe hyperthermia. When held in a standing position, some calves have tetanic paralysis and others have flaccid paralysis. Terminal coma is followed by death after a course of 48 to 72 hours. The urine smells of burnt sugar (because of the presence of branched-chain amino acids), and this smell is the source of the name.[1]

At necropsy there is a characteristic severe spongiform encephalopathy similar to that found in comparable hereditary aminoacidurias in humans.[1] Final identification can be made based on the elevated ratios of branched : straight chain amino acids in nervous tissue.

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INHERITED CITRULLINEMIA

This autosomal recessive disease is inherited in Australian Holstein Friesians, American Holstein Friesians, and Red Holstein Friesians in Europe.

Affected calves are normal at birth but develop signs in the first week of life and die 6 to 12 hours after the onset of illness. The signs are depression, compulsive walking, blindness, head-pressing, tremor, hyperthermia, recumbency, opisthotonus, and convulsions. Argininosuccinate synthetase deficiency is the likely cause. Blood citrulline levels are of the order of 40 to 1200 times normal, and the assay can be used to detect heterozygotes. The alternative method of detecting heterozygotes is to use a PCR test, which RE test designed to identify the mutation that causes the disease. Prenatal diagnosis has been achieved by examination of cell cultures derived from amniotic fluid.

INHERITED NEONATAL SPASTICITY

The defect is recorded in Jersey and Hereford cattle. Affected calves are normal at birth but develop signs 2 to 5 days later. The signs commence with incoordination and bulging of the eyes and a tendency to deviation of the neck causing the head to be held on one side. Subsequently, the calves are unable to stand and on stimulation develop a tetanic convulsion in which the neck, trunk, and limbs are rigidly extended and show marked tremor. Each convulsion is of several minutes' duration. Affected calves may survive for as long as a month if nursed carefully. There are no gross or histologic lesions at necropsy. Inheritance of the defect is conditioned by a single, recessive character.

DODDLER CALVES

This is an inherited congenital defect in Hereford cattle produced by intensive breeding of half-siblings, and it is no longer recorded. It was characterized by continuous clonic convulsions, nystagmus, and pupillary dilatation. Stimulation by touch or sound exacerbated the convulsions.

INHERITED IDIOPATHIC EPILEPSY OF CATTLE

Idiopathic epilepsy has been reported as an inherited condition in Brown Swiss cattle and appears to be inherited as a dominant character. Typical epileptiform convulsions occur, especially when the animals become excited or are exercised. Attacks do not usually commence until the calves are several months old and disappear entirely between the ages of 1 and 2 years.

FAMILIAL NARCOLEPSY

Affected horses, including Lipizzaners,[1] Shetlands, Miniature Horses, Icelandic foals, and Suffolk foals, suffer recurrent episodes of several minutes' duration during which they fall and lie motionless, without voluntary or involuntary movements except respiratory and eye movements. Between episodes there is no clinical abnormality. Handling or the excitement of feeding may precipitate

an attack, and a sharp blow may terminate one.

A genetic cause is suspected in horses based on the occurrence of the disease in three fillies born to the same sire.[1] A physostigmine provocation test (0.06 mg/kg BW intravenously) has been used, and a positive result is a cataplectic attack or clinical worsening of the sleepiness over the following hour. The genetic basis has not been confirmed in horses but is suspected to be an autosomal dominant trait with incomplete penetrance.[1]

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Congenital and Inherited Encephalomyelopathies

INHERITED LYSOSOMAL STORAGE DISEASES

These are diseases in which there is a genetically determined deficiency of a specific lysosomal hydrolase enzyme causing a defective degradation of carbohydrates, proteins, and lipids within lysosomes. These diseases are currently grouped into glycoproteinoses, mucopolysaccharidoses, sphingolipidoses, and mucopolysaccharidoses. Enzyme deficiencies associated with lysosomal storage diseases in agricultural animals include α-mannosidase, β-mannosidase, GM_1 gangliosidosis, GM_2 gangliosidosis,[1,2] β-glucocerebrosidase (Gaucher disease),[3] α-*N*-acetylglucosaminidase (NAGLU),[4] acid-sphingomyelinase (Niemann–Pick disease),[5] and an incompletely characterized form.[6,7] The lysosomes themselves are concerned with hydrolyzing polymeric material, which enters the vacuolar system, and converting it to monomeric units, such as monosaccharides, amino acids, and nucleotides, which can be dealt with by the better known metabolic processes. As a result of the deficiency, upstream metabolic substrates accumulate in the lysosomes and downstream metabolites are markedly reduced.

Lysosomal storage diseases can also be caused by poisonings, and these are addressed elsewhere in this chapter. The best known ones are caused by poisoning with *Swainsona*,[8] *Astragalus, Oxytropis,* and *Ipomoea* spp.[9-12], *Side* spp.[13], and *Phalaris* spp. (the chronic form of that disease).

The diseases included in this section are not strictly diseases of the nervous system because the lysosomes in both **neuronal** and **visceral** sites are affected, but the effects of the disease are most obvious in terms of nervous system function.

MANNOSIDOSIS

Mannosidosis is the best known group of the inherited lysosomal storage diseases in agricultural animals.

α-Mannosidosis

This is a lysosomal storage disease in which a deficiency of the enzyme α-mannosidase results in the accumulation of a metabolite rich in mannose and glucosamine in secondary lysosomes in neurons, macrophages, and reticuloendothelial cells of lymph nodes, causing apparent vacuolations in these cells. Similar vacuoles are found in exocrine cells in pancreas, abomasum, and lacrimal and salivary glands. Storage appears to be cumulative in the fetus, but after birth stored material is lost from the kidney into the urine via desquamated tubular epithelium. On the other hand, postnatal storage continues in the brain, pancreas, and lymph nodes. The disease occurs in Angus, Murray Grey, and Galloway cattle, is inherited as a simple recessive, and is recorded as occurring in the United States, Australia, and New Zealand.

Clinically it is characterized by ataxia, fine lateral head tremor, slow vertical nodding of the head, intention tremor, an aggressive tendency, failure to thrive, and death or the necessity of euthanasia at about 6 months of age. These signs appear almost immediately after birth up to several months later and worsen over a period of up to 3 to 4 months. The signs are bad enough to require euthanasia during the first week of life in many cases. The first sign observed is a swaying of the hindquarters, especially after exercise or with excitement. The stance becomes wide based and the gait jerky, stilted and high stepping, with slight overflexion of the hindquarters so that the animal appears to be squatting as it moves.

The nervous signs are exacerbated by excitement, diarrhea is common, and the calves are usually stunted and unthrifty. They are also aggressive and attempt to charge but are usually impeded by their incoordination. Many calves die after having shown general ill-thrift and with minimal nervous signs. Death may occur from paralysis and starvation, or to misadventure, and some calves appear to die during a "fit" following a period of excitement. Many others are euthanized because of persistent recumbency. The nervous syndrome of mannosidosis is well known; affected calves will die. An α-mannosidosis is recorded in Galloway cattle and is manifested by stillbirth, moderate hydrocephalus, enlargement of the liver and kidneys, and arthrogryposis.

Normal heterozygotes carrying genes for mannosidosis are identifiable because of their reduced tissue or plasma levels of α-mannosidase. The mannosidase test for α-mannosidase in goats is specific and does not cross-react with α-mannosidase.

Advances in molecular biology have now led to the development of a more accurate test based on DNA technology. DNA tests based on the PCR have been developed for the detection of two breed-specific mutations responsible α-mannosidosis. One of the mutations is responsible for α-mannosidosis in Galloway cattle. The other mutation is uniquely associated with α-mannosidosis in Angus, Murray Grey, and Brangus cattle from Australia. The latter mutation was also detected in Red Angus cattle exported from Canada to Australia as embryos. The two breed-specific mutations may have arisen in Scotland and by the export of animals and germplasm disseminated to North America, New Zealand, and Australia.

A control program can be based on the identification of heterozygotes using PCR-based assays for detection of breed-specific mutations. A program of screening cattle in herds that produce bulls for sale to commercial herds should stop the spread of the disease very quickly, because the number of heterozygous females in the population will be irrelevant to the continuation of the disease in the absence of affected sires.

The α-mannosidosis gene prevalence is now insignificant and disease incidence has been reduced from an estimated 3000 cases/year to negligible levels.

β-Mannosidosis

β-Mannosidosis occurs in Salers cattle and Anglo-Nubian goats and has been recorded in a sheep. In cattle, some affected calves are stillborn. The remainder of calves are euthanized forthwith because of the severity of the congenital defects.

Calves are affected at birth with craniofacial deformity and inability to stand. The cranium is domed and there is mild prognathism; narrow palpebral fissures; and a tough, hidebound skin. When in sternal recumbency, the head is moved in a combined motion of circling and bobbing, eventually converting the calf to lateral recumbency, in which it remains until passively returned to the sternal position, where nystagmus and tremor become evident. There is no suck reflex at any time. In lateral recumbency there is opisthotonus and paddling convulsions.

In the goats the condition is present at birth and characterized clinically by tetraplegia, tremor, deafness, and nystagmus, and an inexorably fatal termination. Additional signs include bilateral Horner's syndrome, carpal contractures, pastern joint hyperextension, thickened skin, and a dome-shaped skull. Although retinal ganglion cells are badly affected, there appears to be no defect of vision. It is an autosomal recessive defect that is very similar to α-mannosidosis.

The diagnosis is confirmed by a reduced level of β-mannosidase in the blood.

Necropsy findings include a deficiency of cerebral cortical and cerebellar substance, distended lateral ventricles, and bilateral

renomegaly. The biochemical defect is one of acidic β-mannosidase, and is conditioned by an autosomal recessive character. The carrier rate of the causative gene is very high in the Salers breed.

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GANGLIOSIDOSIS

At least five types of gangliosidosis are known to occur in humans and animals. Two (GM_1 and GM_2 gangliosidosis) have thus far been identified in agricultural animals.

GM_1 Gangliosidosis

GM_1 gangliosidosis occurs in cattle and sheep. In Friesian cattle it is inherited as a lysosomal storage disease in which the activity of an enzyme, β-galactosidase, in nervous tissue is greatly reduced. As a result, there is an accumulation of the ganglioside (GM_1) in the tissue. Clinical signs of progressive neuromotor dysfunction and a reduction in growth rate appear at about 3 months of age. The growth rate is reduced, and the animal is in poor condition, blind, and has a staring coat. The neuromotor signs include lack of response to external stimuli, sluggish mastication and swallowing, hindquarter sway while walking, a wide stance, a tendency to fall, reluctance to move, stiff high-stepping gait, aimless walking, head-pressing, and convulsions. Abnormal electrocardiogram (ECG) tracings are common. The blindness results from lesions in the retina and the optic nerve. Ophthalmoscopic examination of the retina is recommended as an aid to diagnosis. A positive diagnosis is made on the grounds of intraneuronal lipid storage plus reduced β-galactosidase activity plus identification of the stored lipid. The stored ganglioside is visible under the electron microscope as stacks and concentric whorls of lamellae. In the live animal enzyme assays are performed on leukocytes. The enzymatic defect is also detectable in liver, skin, and leukocytes.

GM_1 gangliosidosis is also present in Suffolk and Suffolk-cross sheep. Visceral and neuronal lysosomal storage are both evident but the neuronal lesion is more severe. Deficiencies of β-galactosidase and α-neuraminidase are evident. Affected sheep become ataxic at 4 to 6 months old and worsen to recumbency and death in up to 2 months.

GM_1 gangliosidosis has been reported from England in "Coopworth Romney" lambs closely related to a ram imported from New Zealand.

GM_2 Gangliosidosis

GM_2 gangliosidosis (Tay–Sachs disease) occurs in sheep and pigs and is an autosomal recessive lysosomal storage disease caused by defects in the genes that code for hexosaminidase. In Jacob sheep, progressive accumulation of GM_2 ganglioside results in in cortical blindness, proprioceptive deficits, and ataxia in all four limbs within 6 to 8 months of birth.[1,2]

GM_2 gangliosidosis has also been identified in Yorkshire pigs and also causes decreased growth rate, incoordination appearing after 3 months of age, gray-white spots in the retina and dark blue granules in neutrophils, and azurophilic granules in lymphocytes. A serum enzyme assay is a suitable method of detecting "carrier" heterozygous pigs. The test is based on the amount of *N*-acetyl-β-D-hexosaminidase in tissues.

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GAUCHER DISEASE TYPE 2

Gaucher disease is an autosomal recessive lysosomal storage disease caused by mutations in the β-glucocerebrosidase gene. Gaucher disease is the most common lysosomal storage disorder in humans and is divided into three subtypes based on the level of neurologic involvement and clinical signs: (1) type 1, nonneuronopathic; (2) type 2, acute neuronopathic; and (3) type 3 (subacute neuronopathic).[1]

Type 2 Gaucher disease has been reported in Southdown sheep in Victoria, Australia.[1] Affected lambs were unable to stand and exhibited continued shaking and shivering. Lambs could be bottle-fed but their neurologic status did not improve. Affected lambs also had a thickened leathery skin in the abdominal and cervical regions. Glucocerebrosidase activity was markedly reduced in leukocytes and cultured skin fibroblasts and glucocerebrosidase content was increased in the brain, liver, and blood.

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BOVINE MUCOPOLYSACCHARIDOSIS TYPE IIIB

Mucopolysaccharidosis IIIB is an autosomal recessive lysosomal storage disease caused by mutations in the NAGLU gene. NAGLU is intimately involved with the degradation of heparin sulfate in lysosomes; gene mutations therefore result in intralysosomal storage of heparin sulfate.

Mucopolysaccharidosis IIIB has been reported in cattle in Queensland, Australia.[1] Animals were normal at weaning at 6 to 8 months of age; clinical signs developed progressively from 12 months onward and included loss of herding instinct, aimless wandering, tendency to stand alone, becoming very placid and sedate in nature, and development of excessively hairy ears. Animals survived to 3 to 5 years of age, and terminally developed progressive ataxia, a stumbling gait, and excessive weight loss.

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SPHINGOMYELINASE DEFICIENCY (NIEMANN–PICK DISEASE TYPE A) IN CATTLE

Sphingomyelinase deficiency (Niemann–Pick disease) is a lysosomal storage disease caused by mutations in the sphingomyelinase gene and is described as three forms in humans: type A (early onset of neurologic disease in infancy), B, and C. Sphingomyelinase is involved with catalyzing the conversion of sphingomyelin to ceramide and phosphorylcholine.

Sphingomyelinase deficiency (type A) has been diagnosed in a 5-month-old Hereford calf in Virginia.[1] The calf had a 4-week history of abnormal and progressive neurologic signs, including hypermetria, wide-based stance, ataxia, and positional strabismus.

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GLOBOID CELL LEUKODYSTROPHY (GALACTOCEREBROSIDOSIS)

Globoid cell leukodystrophy has been identified in Poll Dorset sheep in Australia. Incoordination in the hindlimbs progresses until the animals are tetraplegic. Only histologic changes are evident at necropsy. These include myelin destruction and the accumulation of characteristic globoid cells in nervous tissue. There is greatly decreased galactocerebrosidase activity in affected tissue.

INHERITED NERVOUS SYSTEM ABIOTROPHIES

These diseases are characterized by **premature, progressive loss of functionally related and discrete populations of neurons.** As a result, most affected animals are born normal but develop signs of a progressive neurologic disease that is either fatal or leads to such a serious neurologic deficit that euthanasia is the only reasonable solution. In a few rare diseases the patient is abnormal at birth but worsens, and usually

dies, during the neonatal period. Again there are exceptions, and in rare cases complete recovery has been reported. The genetic nature of some of the cases included may not be certain; they are included here if the evidence that they are inherited can be reasonably presumed. An important distinction is that **abiotrophy implies premature aging,** which is different from degeneration, which is a term that implies an extrinsic etiology. From a clinical perspective nervous system degeneration can appear identical to nervous system abiotrophy, and a firm diagnosis of abiotrophy usually requires histologic examination unless the species, breed, or availability of specific diagnostic tests permits antemortem diagnosis of abiotrophy. At the moment the abiotrophic diseases cannot be treated. The lysosomal storage diseases, listed in the preceding section, represent a specific group of abiotrophic diseases.

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NEURONAL CEROID LIPOFUSCINOSIS

The neuronal ceroid lipofuscinoses are a group of inherited neurodegenerative lysosomal storage diseases of humans and other animals, inherited as autosomal recessive traits. They are grouped together because of common clinical and pathologic phenomena related to brain and retinal atrophy, premature death, and accumulation of a fluorescent lipopigment in neurons and many other cell types within the body. Molecular genetic studies have identified mutations in eight different genes (*CLN1, CLN2, CLN3, CLN5, CLN6, CLN6, CLN8,* and *CTSD*) that can result in neuronal ceroid lipofuscinoses.[1-4]

The disease is recorded in Devon cattle,[1] South Hampshire sheep,[2,3,4] Rambouillet sheep, Borderdale sheep,[5] Merino sheep, Nubian goats, and Vietnamese pot-bellied pigs.[6] It resembles neuronal ceroid lipofuscinosis of humans and is not strictly a primary lysosomal disorder; it is classified as a proteolipid proteinosis, and provides a good animal model for discussing the similar disease (Batten disease) of humans. Secondary lysosomes in animals with neuronal ceroid lipofuscinoses fill with subunit c of mitochondrial ATP synthase because of excessive peroxidation of polyunsaturated fatty acids. The mechanism of the accumulation is that protein is formed, which is normal for mitochondria, but is misdirected so that it accumulates in the lysosome. The disease in Devon cattle is caused by a single base duplication in the bovine *CLN5* gene.[1] The disease in Merino sheep is a subunit c–storing abnormality, clinically and pathologically similar to ceroid lipofuscinosis in South Hampshire sheep, which is caused by a missense mutation in the ovine *CLN6* gene.[2,3] The disease in Borderdale sheep is caused by a nucleotide substitution in the ovine *CLN5* gene.[5]

The occurrence of neuronal ceroid lipofuscinosis in South Hampshire and Borderdale sheep in New Zealand have been well described. The severity of neurodegeneration and minor differences in the ultrastructure of storage material suggests this is a different disease from other forms of ovine ceroid lipofuscinosis, which accumulate the subunit c of mitochondrial ATP synthase. An autosomal recessive mode of inheritance is considered probable.

Clinical findings include slowly progressive ataxia of the hindlimbs, commencing usually at about 4 months but possibly as late as 18 months of age, and lasting for 6 months leading to euthanasia at up to 4 years. Inability to keep up with the flock is noticed first, followed by a sawhorse stance, obvious ataxia, severe depression, and an increasing failure of the menace and pupillary light reflexes. Terminal blindness is a constant sign. Positional nystagmus, circling, and head-pressing occur in some. Eating, drinking, and defecation are normal, but there is slight weight loss. A blood test has been developed to detect the genetic mutation in South Hampshire sheep.[2] CSF is altered in sheep with advanced diseased, characterized by increased lactate, acetate, and tyrosine concentrations and decreased myo-inositol and scyllo-inositol and citrate concentrations.[3]

The lesion in lambs and calves is atrophy of the cerebrum, especially the optic cortex, with eosinophilic granulation of neurons and macrophages in the CNS followed by progressive retinal atrophy. There is a progressive storage of lipopigment in nervous tissue, especially retinal photoreceptors; its presence can be demonstrated by quantitative autofluorescence using a modified slit lamp microscope. Other clinicopathologic aids include lysosomal enzyme assay, organ biopsy, and CT, which reveals the enlargement of the lateral ventricles of the brain resulting from cerebral atrophy.

Neuronal ceroid lipofuscinosis has been described in three horses. Clinically, there was developmental retardation, slow movements, and loss of appetite at 6 months of age. Torticollis, ataxia, head tilt, and loss of eyesight were present at 1 year of age. There were abnormalities in posture and movements, decreased spinal reflexes, and some CN dysfunction, dorsal strabismus, and absence of the menace reflex. At necropsy, there was flattening of the gyri and discoloration of the brain. Histologically, eosinophilic, autofluorescent material in the perikarya of neurons was present throughout the brain, spinal cord, neurons of the retina, submucosa, and myenteric ganglia and in glial cells.

Neuronal ceroid lipofuscinosis has been described in a 2-year-old Vietnamese pot-bellied pig.[6] Ataxia had progressed to tetraparesis over a 3-month period, with terminal development of a head tilt and intermittent nystagmus. The pig did not appear to be blind.

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CONGENITAL NECROTIZING ENCEPHALOPATHY IN LAMBS

This condition, defined by its pathology, was a common diagnosis of neurologic disease in lambs under 7 days of age by the Veterinary Laboratories Agency in the north of England.[1] Affected flocks had single or multiple cases, with up to 10% morbidity of lambs in a flock. All cases came from ewes carrying multiple fetuses, but there is variation in the clinical signs of sibling lambs. The most severely affected may be stillborn, with less severely affected lambs born weak, small, and unable to rise with ataxia and head tremor. Some lambs survive but may have residual signs of cerebellar dysfunction. The common lesion is superficial cerebrocortical neuronal necrosis. A significant proportion also has necrosis of the Purkinje cells in the cerebellum and leukoencephalopathy of the thalamus and brainstem. It is possible that this syndrome reflects hypoglycemia consequent to negative energy balance in late pregnancy.

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LAVENDER FOAL SYNDROME

Lavender foal syndrome is a congenital, inherited, autosomal recessive disease of Egyptian Arab foals characterized by signs of neurologic disease evident at birth and unusual dilute coat color.[1] The disease is caused by a mutation in the MYO5A gene that is a single-base deletion in a conserved region of the tail domain.[2] The deletion produces a truncated protein product through the insertion of a premature stop codon (p.Arg1487AlafsX13). There is a prevalence of carriers in Egyptian Arabian horses of 10.3% (heterozygotes),[3] and within Arabs the allele frequency is estimated at 0.0162, with no alleles detected in Thoroughbred, Standardbred, Morgan, Quarter Horse, or Percheron horses.[4] The carrier prevalence of LFS in Arabian foals in South Africa for the 2009/2010 season was 11.7% (95% confidence interval [CI] 7.6–17.0%).[5]

There is a dilute (lavender) coat color and signs of central neurologic disease including inability to stand, paddling, opisthotonus, and torticollis with apparently normal peripheral reflexes (blink to bright light, triceps, patellar, and cutaneous truncal).[1] There are no characteristic hematologic and serum biochemical abnormalities. There is no effective treatment.

Gross necropsy examination does not reveal any consistent or diagnostic abnormalities apart from the dilute hair coat. An assay for the genetic mutation is available and provides confirmation of diagnosis. Testing of Egyptian Arabians enables avoidance of carrier-to-carrier matings, and thus the disease.[3]

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INHERITED HYPOMYELINOGENESIS (CONGENITAL TREMOR SYNDROMES OF PIGLETS)

Congenital tremor of pigs has a multiple etiology and some of the causes are not yet identified. The disease is also known as *myoclonia congenita* or trembling pig syndrome or jumpy pig disease. Gilts are particularly affected. The types are shown in Table 14-18 and the features in Table 14-19. They can only be differentiated by pathology and particularly neurochemistry. The essential lesion is the same in all cases and is a hypomyelination of the brain and spinal cord. The infectious forms are discussed elsewhere.

There are two inherited forms. One is congenital tremor Type A-III, which is found in Landrace pigs and Landrace crosses. It is sometimes known as Landrace trembles. Type A-III is a sex-linked recessive gene carried by the sow. It is associated with females, high growth rates, lean carcasses, and pale colored meat characterized by the presence of poorly myelinated axons in all parts of the CNS. It is also known as congenital cerebrospinal hypomyelinogenesis. The sows produce piglets that have reduced numbers of oligodendrocytes and therefore cannot myelinate nerve fibers. The tremor disappears when the piglets are asleep.

The other inherited form is Type A-IV of British Saddleback pigs. It is not common. The specific defect in A-IV is one of fatty acid metabolism, which results in hypomyelination and demyelination. (A similar disorder but a monogenic autosomal recessive tremor has also been described in Saddleback /Large White crosses).

The structural abnormalities in the type A-III disease have been identified; splayleg is a common accompaniment.

Both diseases are characterized by muscle tremor, incoordination, difficulty in standing, and some squealing. The A-III disease occurs only in males. Both are inherited as recessive characteristics.

Table 14-18 Diagnostic taxonomy of congenital tremor in pigs

Cause	AI	AII	AIII	AIV	AV	B
Field observations	**Virus hog cholera**	**Virus unknown**	**Genetic S-L recessive**	**Genetic autosomal recessive**	**Chemical trichlorfon**	**Unknown**
Proportion of litters affected	High	High	Low	Low	High	Variable
Proportion of pigs affected within litter (approximately)	>40%	>80%	25%	25%	>90%	Variable
Mortality among affected pigs	Medium to high	Low	High	High	High	Variable
Sex of affected pigs	Both	Both	Male	Both	Both	Any
Breed of dam (pure or crossbred)	Any	Any	Landrace	Saddleback	Any	Any
Recurrence in successive litters of same parents	No	No	Yes	Yes	Yes	?
Duration of outbreak	<4 months	<4 months	Indefinite	Indefinite	<1 month	?

Table 14-19 Key features of the six types of congenital tremor described in pigs

Type	Cause	Key features
A1	Hog Cholera	Dysgenesis Cerebellar hypoplasia Small cord Demyelination Swollen oligodendrocytes
AII	Congenital tremor virus PCV2	Swollen oligodendrocytes
AIII	Inherited autosomal recessive sex linked in landrace	Reduced oligodendrocytes Reduced myelination Hypoplasia of cord
AIV	As previously noted in Saddleback Also Landrace/Saddleback cross syndrome	Demyelination Cerebral, cerebellar and cord hypoplasia
AV	Trichlorfon toxicity	Cerebellar hypoplasia affected 45–79 days' gestation, particularly 75–79
B	Unknown	No special features

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Diseases Primarily Affecting the Cerebellum

INHERITED CEREBELLAR DEFECTS

Several inherited cerebellar defects occur congenitally in calves, lambs, and foals. Lesions of the cerebellum may or may not be grossly or clinically obvious. They all need to be differentiated from similar defects known to be caused by intrauterine viral infections such as swine fever, bovine mucosal disease, and bluetongue.

Cerebellar Hypoplasia

This occurs in Herefords, Guernseys, Holsteins, Shorthorns, and Ayrshires and appears to be conditioned by a factor inherited in a recessive manner. Most calves are obviously affected at birth. While lying down, there is no marked abnormality, although a moderate lateral tremor of the neck occurs, causing a gentle side-to-side swaying of the head. Severely affected calves are blind; they have widely dilated pupils and their pupils do not react to light. Such calves are unable to stand, even when assisted, because of flaccidity of limb muscles. When less severely affected animals attempt to rise, the head is thrown back excessively, the limb movements are exaggerated in force and range and are grossly incoordinated, and many calves are unable to rise without assistance. If they are placed on their feet, the calves adopt a straddle-legged stance with the feet wide apart and the legs and neck extended excessively. On attempting to move, limb movements are incoordinated and the calf falls, sometimes backward because of overextension of the forelimbs. Affected animals drink well but have great difficulty in getting to the teat or pail, with attempts usually wide of the mark. There are no defects of consciousness and no convulsions. Tremor may be evident while standing and there may be postrotational nystagmus after rapid lateral head movements. Sight and hearing are unimpaired and, although complete recovery does not occur, the calf may be able to compensate sufficiently to enable it to be reared to a vealing weight. Diagnosis can be confirmed by MRI.

At necropsy the most severe defect comprises complete absence of the cerebellum; hypoplasia of the olivary nuclei, the pons, and optic nerves; and partial or complete absence of the occipital cortex. Less severe defects include a reduction in size of the cerebellum and absence of some neuronal elements in a cerebellum of normal size.

Although the disease is dealt with generally as an inherited one. There is no firm evidence to substantiate this view, and there are sporadic, noninherited cases in other breeds.

Cerebellar Atrophy of Lambs (Daft Lamb Disease 1)

This has been recorded in many sheep breeds in Britain, Corriedales in Canada and New Zealand, and in Drysdales. Affected lambs are normal at birth but are weak and unable to rise without assistance. At 3 days of age it is obvious that there is severe incoordination of limb movement, opisthotonus, tremor, and a straddle-legged stance. At necropsy the cerebellum may be of normal size but on histologic examination there is gross atrophy of cerebellar neurons. The disease appears to be conditioned by a recessive gene but not as a simple homozygous recessive. A clinically similar disease has been observed in Border Leicester lambs. There is no histopathologic lesion in the cerebellum, but there are significant lesions in the cervical muscles and the nerve supply to them. The disease is inherited, most likely as an autosomal recessive trait.

Star-Gazing Lambs (Daft Lamb Disease 2)

A hereditary disease clinically similar to cerebral cortical atrophy has been described in newborn Leicester lambs in the UK but without histologic evidence of Purkinje cell loss, which is considered the hallmark of "cerebellar abiotrophy." Affected lambs exhibit "dorsal arching of the neck with the head being pressed backward," which is also described as star-gazing. Histologic lesions are present in neck muscles and nerves, but it is uncertain if these are primary or secondary.

Hereditary Lissencephaly and Cerebellar Hypoplasia in Churra Lambs

Lissencephaly is a very rare developmental intracranial disorder of animals that results from defects in neuronal migration. The gross result is a very simplified folding of the cerebrum and cerebellum with the presence of only a few broad gyri.

Lissencephaly and cerebellar hypoplasia have been identified in Churra lambs in Spain. Affected lambs were abnormal at birth, exhibiting weakness, inability to stand, and muscular rigidity. The cerebral cortex was disorganized histologically and the cerebellum was reduced in size. Pedigree analysis indicated a monogenic autosomal pattern of inheritance.[1] The genetic defect was a 31 base pair deletion in the coding area for the RELN gene, which plays an important role in neuronal migration and layer formation.[2] The deletion results in formation of a premature termination codon, resulting in the absence of protein expression.

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Inherited Ataxia of Calves

This is a true cerebellar ataxia inherited as a recessive character in Jerseys, Shorthorns, and Holsteins. Clinically the condition resembles cerebellar hypoplasia except that signs may not occur until the calves are a few days to several weeks old. At necropsy the cerebellum is normal in size but histologically aplasia of neurons is evident in the cerebellum and also in the thalamus and cerebral cortex. An inherited condition, manifested by cerebellar ataxia that does not develop until calves are 6 weeks to 5 months old, has also been recorded but the cerebellum is small and macroscopically abnormal. Conspicuous degeneration of cerebellar Purkinje cells is evident on histologic examination.

Familial Convulsions and Ataxia in Cattle

A neurologic disease is recorded as being inherited in Aberdeen Angus cattle and their crossbreeds and Charolais. In young calves there are intermittent attacks of convulsions, and in older animals these are replaced by a residual ataxia. The first signs appear within a few hours of birth; up to several months later there are single or multiple tetanic convulsions lasting for 3 to 12 hours. As these episodes disappear a spastic goose-stepping gait becomes apparent in the forelimbs and there is difficulty placing the hindlimbs. The characteristic necropsy lesion is a very selective cerebellar cortical degeneration. A proportion of cases make a complete recovery. The epidemiology of the disease is consistent with the operation of an autosomal dominant gene with incomplete penetrance.

Inherited Congenital Spasms of Cattle

This condition has been recorded only in Jersey cattle and appears to be conditioned by a factor inherited in a recessive manner. Affected calves show intermittent, vertical tremor of the head and neck, and there is a similar tremor of all four limbs that prevents walking and interferes with standing. Although the calves are normal in all other respects, they usually die within the first few weeks of life. No histologic examinations have been reported, but a cerebellar lesion seems probable.

Cerebellar Abiotrophy

This disease occurs in Holstein and Poll Hereford cross calves, Aberdeen Angus cattle and their crossbreds and Charolais cattle, Merino sheep, alpaca,[1] Arabian horses,[2-6] and pigs. The pathologic feature of cerebellar

abiotrophy is disorganization of the Purkinje cells in the granular layer of the cerebellum, with subsequent disorganization of the molecular and granular layers. The etiology is thought to be abnormal migration of the Purkinje cells through the cerebellum during development, resulting in premature neuronal degeneration of Purkinje cells.[4]

Cattle

In the calves, ataxia appears for the first time when they are 3 to 8 months old. The calves are not blind but they often fail to exhibit a menace reflex. The onset of clinical signs is sudden but progression is slow or inapparent. Some become recumbent. Those that remain standing have a spastic, dysmetric ataxia and a broad-based stance and they fall easily and have a fine head tremor. All are strong and have good appetites. Abiotrophy, or premature aging, is evident only microscopically and consists of axonal swellings and segmental degeneration and loss of cerebellar Purkinje cells. The disease appears to be inherited, but recovery of some late cases is recorded.

Familial convulsions and ataxia is characterized as being inherited in Aberdeen Angus cattle and their crossbreds and Charolais. In young calves there are intermittent attacks of convulsions, and in older animals these are replaced by a residual ataxia. The first signs appear within a few hours of birth; up to several months later there are single or multiple tetanic convulsions lasting for 3 to 12 hours. As these episodes disappear a spastic goose-stepping gait becomes apparent in the forelimbs and there is difficulty placing the hindlimbs. The characteristic necropsy lesion is a very selective degeneration of the cerebellar cortex. A proportion of cases make a complete recovery. The epidemiology of the disease is consistent with the operation of an autosomal dominant gene with incomplete penetrance.

Sheep

The disease in sheep does not appear until about 3 years of age. There is incoordination and dysmetria so that the gait is awkward and disorganized and there is frequent falling. There are also a reduced menace response, an apprehensive manner, and a wide-based stance in the hindlimbs. At necropsy there is diffuse cerebellar degeneration and severe loss of Purkinje cells.

Alpaca

Neurologic abnormalities were first detected at 18 months of age, at which time intention tremors, hypermetria, and a wide-based stance were evident.[1] CSF analysis was within normal limits and the cerebellum appeared smaller than expected on CT.

Horses

The disease is recorded principally in Arabian horses but occurs also in the Australian pony, which was developed from the Arab, and in the Gotland breed from Sweden. A similar clinical syndrome occurs in the Oldenberg breed, but the pathologic picture is quite different.

The disease may be present at birth but is often not observed until the foal is 2 to 6 months old with the latest recognition being between 9 and 24 months of age. The characteristic signs are vertical head-nodding (some cases show horizontal head tremors), especially when excited, and ataxia, which is most noticeable at a fast gait. It may not be evident while the foal is walking. Very badly affected foals are unable to stand or suckle at birth, less severe ones are normal until about 4 months of age when head-nodding becomes obvious. The degree of ataxia varies from slight incoordination to inability to stand. A goose-stepping gait, which slams the front feet into the ground, occurs in some. All foals can see but there is an absence of the menace reflex in many. Nystagmus is not recorded as occurring in this disease. The first antemortem confirmatory test to be developed was **computer-assisted MRI brain morphometry,** which is used to determine the presence of a relatively smaller cerebellum and relatively larger cerebellar CSF space compared with size-matched horses.[3] Diagnosis has historically been made on the basis of breed and age of the animal, clinical signs, slow progression of disease, and elimination of other differential diagnoses.[2] The recent development of a DNA test on hair roots that detects the presence of the putative cerebellar abiotrophy gene mutation[4-6] should make antemortem diagnosis much more straightforward in Arabian horses.

Necropsy findings are limited to histopathologic lesions in the cerebellum. These include widespread loss of Purkinje cells and the presence of a gliosis. There are no degenerative lesions in the spinal cord. In the similar disease in Oldenberg horses the cerebellum is often reduced in size. The disease is an abiotrophy—a premature aging of tissues.

The disease is inherited as an autosomal recessive trait in Arabian horses.[4] An SNP has been identified in affected Arabian horses and may induce the disease by decreasing MUTYH expression, which is a DNA glycosylase that removes adenine residues.[5] The frequency of the allele is estimated at approximately 10.5% in the U.S. Arabian population, which is high.[6] The gene mutation has been identified at a low level in three breeds with Arabian ancestry (Trakehner; Bashkir Curly Horses, also known as North American Curly horses; and Welsh ponies).[6]

Pigs

A congenital progressive cerebellar abiotrophy is also reported in piglets of the offspring of Saddleback sows and an unrelated Large White boar. The disorder behaves epidemiologically like an inherited disease conditioned by a simple autosomal recessive trait. Clinical signs include dysmetria, ataxia, and tremor at standing but not at rest. There is gradual adjustment so that the piglets can walk and stand at 5 weeks of age, but by 15 weeks they are no longer able to do so. Affected pigs also have a coarse matted hair coat caused by a disproportionate number of coarse hairs to fine hairs. Histopathologic lesions are confined to the cerebellum in which there is a significant loss of Purkinje cells.

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Diseases Primarily Affecting the Brainstem and Vestibular System

OTITIS MEDIA/INTERNA

Infection of the middle ear (**otitis media**) occurs in young animals of all species but especially dairy calves and pigs, to a lesser extent feedlot cattle and lambs, and rarely foals. The infection may gain entrance from the external ear (e.g., caused by ear mite infestation) or hematogenously, but the spread is chiefly an ascending infection of the eustachian tubes in a young animal from a respiratory tract infection. Extension of infection into the inner ear leads to **otitis interna**.

Pigs

Otitis media was present in 68% of 237 pigs that were slaughtered because of illness. It is suggested that otitis media in pigs develops first as an acute inflammation in the auditory tube and then extends to other parts of the ear and brain. When abscesses form at the ventrum of the brainstem, the vestibulocochlear nerve is usually involved in the lesion. Infection in the ear may extend into the brain by following the auditory nerve. Perilymph filling the scala vestibuli and scala tympani is also a possible tract for the extension of the infection because there is a communication between the perilymph-filled spaces of the bony labyrinth and the subarachnoid space.

Calves and Lambs

The highest prevalence is in suckling dairy calves and weaned cattle and sheep in feedlots where the disease is probably secondary to respiratory tract infection. Outbreaks of otitis media/interna have occurred in beef calves from 6 to 10 weeks of age on pasture with their dams; mixed cultures of *E. coli, Pseudomonas* spp., and *Acinetobacter*

spp. were isolated. Otitis media/interna in suckling dairy calves can also occur in outbreaks, and *M. bovis* is frequently isolated from the middle and inner ears of affected calves.

The onset of clinical signs commonly includes dullness, fever, inappetence, tachypnea, and a purulent discharge from the affected ear accompanied by rotation of the head (in otitis interna) and drooping of the ear a few days later because of involvement of the facial nerve in the inflammation. Deep palpation at the base of the ears may elicit a pain response.

Rotation of the head, with the affected side down, and facial paralysis may occur on the same side, and walking in circles with a tendency to fall to the affected side is common. In most cases the animals are normal in other respects, although depression and inappetence can occur in advanced cases (Fig. 14-15).

Fig. 14-15 Otitis media/interna on the right side of a recently weaned Suffolk sheep. Notice the marked deviation of the line between the two eyes from horizontal.

Horses

Otitis media/interna occurs in horses, and two clinical syndromes have been described. **The first syndrome** is primary otitis media characterized by abnormal behavior, including head-tossing, head-shaking, and ear-rubbing. Violent, uncontrollable behavior includes throwing themselves on the ground, rolling, and thrashing. This may progress to involve the bony structures of the temporal and proximal stylohyoid bones, resulting in a degenerative arthritis and eventual fusion of the temporohyoid bone.

The second syndrome is characterized by an acute onset of neurologic deficits. Commonly, there is vestibulocochlear nerve and often facial nerve dysfunction characterized by head tilt to the side of the lesion, nystagmus with the slow component to the affected side, and weakness of the extensor muscles on the affected side resulting in an ataxia or reluctance or refusal to stand. Horses that can stand often will lean on walls for support of the affected side.

Definitive diagnosis is dependent on either a positive tympanocentesis or, in the majority of cases, bony proliferation of the temporal bone and proximal part of the stylohyoid bone, or lysis of the tympanic bulla, as determined by radiography or CT. Otoscopic examination should be performed to determine whether there is purulent material in the auditory canal and whether the tympanic membrane is ruptured or bulging outward.

Radiography has been used to diagnose lesions of the tympanic bullae in cattle (otitis interna), characterized by thickening of the bulla wall, increased soft tissue opacity within the bulla, and osteolysis of the bulla wall and trabeculations.[1] Radiography is not as sensitive as CT for the diagnosis of otitis media; however, because CT provides more detailed information regarding the bony structures of the middle ear[2,3] and is more sensitive and specific than radiography in the diagnosis of otitis media in calves.[1] CT was used to provide an excellent anatomic description of the external acoustic meatus, tympanic cavity, and tympanic bulla of the llama.[4] Ultrasonography has also been used to diagnose otitis media in calves.[5] A 7.5-mHz linear probe is applied to the base of the ear without the use of coupling gel and the calf in a standing position. The probe is applied ventral to the base of the ear and caudal to the mandible. Abnormalities detected included anechoic to hyperechoic content; trabeculae lysis; and thinning, deformation, and rupture of the bulla wall. The lesions can be subtle in early cases and, consequently, test sensitivity is low in animals with acute or subacute clinical presentations.

Tympanocentesis is done under general anesthesia in horses or sedation in ruminants by directing a 15-cm needle through the tympanic membrane visualized with the aid of an otoscope. The technique is

somewhat difficult because of the long and angled external auditory canal. Sterile 0.9% NaCl (0.5–1 mL) is injected into the tympanic cavity and then, after a few seconds, withdrawn. A positive tap consists of withdrawal of a cloudy or yellow fluid, which on analysis may contain evidence of pus and can be sampled for culture and antimicrobial susceptibility. An alternative method uses a 15-cm sterile polypropylene catheter that has the appropriate stiffness for puncturing the tympanic membrane but sufficient flexibility to advance along the external acoustic meatus.[3]

DIFFERENTIAL DIAGNOSIS

The disease needs to be differentiated from otitis externa, in which the head may be carried in a rotated position, but usually intermittently, and this is accompanied by head-shaking and the presence of exudate and an offensive smell in the ear canal, and from cerebral injury or abscess, and similar lesions of the upper cervical cord. All of these are characterized by deviation of the head, not rotation. At necropsy the tympanic bulla contains pus, and a variety of organisms, such as staphylococci, streptococci, *Pasteurella haemolytica,* and *Neisseria catarrhalis,* may be isolated.

TREATMENT

Treatment consists of broad-spectrum antimicrobials daily for 4 weeks and antiinflammatory agents. The prognosis with treatment with fluoroquinolones is very good in calves, although a 50% mortality rate has been reported in calves that were not treated with other antimicrobial agents. The use of lincomycin at 6.5 mg/kg BW combined with spectinomycin at 10 mg/kg BW intravenously twice daily for 5 days has been reported to be successful for the treatment of otitis media in beef calves. Anecdotal reports exist of the use of a knitting needle to rupture the tympanic membrane in cattle, with rapid resolution of the head tilt because of the decreased pressure in the middle ear. Bilateral tympanic bulla osteotomy has been performed in an affected calf, resulting in a rapid resolution of the head tilt.

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LISTERIOSIS

SYNOPSIS

Etiology *Listeria monocytogenes.* Ubiquitous in farm environment.

Epidemiology Ruminants, particularly sheep. Prime occurrence is seasonal associated with feeding silage with high listerial growth. Also following management-induced stress. Commonly manifest with multiple cases in a group.

Clinical findings Most commonly encephalitis with brainstem and cranial nerve dysfunction or abortion in last third of pregnancy. Less commonly septicemia in periparturient and neonatal sheep and goats, enteritis in weaned sheep, spinal myelitis, uveitis, and occasionally mastitis.

Clinical pathology Culture, PCR. Pleocytosis and elevated protein in cerebrospinal fluid with encephalitis.

Lesions Microabscesses in brainstem in listerial encephalitis, spinal cord in spinal myelitis, abomasum, intestine, liver, and mesenteric lymph nodes in enteritis. Visceral lesions in septicemia.

Diagnostic confirmation Culture and histopathology.

Treatment Penicillin or oxytetracycline. Must be given early in clinical disease.

Control Control of listerial growth in feeds. Vaccination.

ETIOLOGY

There are currently six species classified within the genus *Listeria,* but only *L. monocytogenes* and *L. ivanovii* (previously classified as *L. monocytogenes* serotype 5) are pathogenic for domestic animals. *L. ivanovii* is only mildly pathogenic and is an occasional cause of abortion in sheep and cattle. Aborted fetuses have suppurative bronchopneumonia and lack the multifocal hepatocellular necrosis commonly seen in abortions associated with *L. monocytogenes. L. innocua* is occasionally associated with encephalitis in ruminants that is clinically and pathologically similar to that associated with *L. monocytogenes.* Most, but not all, reports of both infections record that the animals were being fed silage.

L. monocytogenes is widespread in nature and has characteristics that allow its survival and growth in a wide variety of environments. There is a highly diverse range of strains, some of which have the capability of causing disease in animals and humans.

Optimal growth temperatures are between 30°C and 37°C but the organism can grow and reproduce at temperatures between 1°C and 45°C. It can grow between pH 4.5 and 9.6 although growth at low pH is minimal at low temperatures. The organism is susceptible to common disinfectants.

L. monocytogenes can be divided into 16 serovars on the basis of somatic and flagellar antigens, and there is considerable genetic diversity between serovars. Serovars 4b, 1/2a and 1/2b, and 3 are most commonly isolated from diseased animals but there are geographic differences. Virulent strains can multiply in macrophages and monocytes and produce a hemolysin, listeriolysin O, which is thought to be a major virulence factor.

EPIDEMIOLOGY

Occurrence

Geographic

Although the organism is widespread in nature, clinical disease in animals occurs mainly in the northern and southern latitudes and is much less common in tropical and subtropical than in temperate climates. The disease is important in North America, Europe, the UK, New Zealand, and Australia.

Seasonal

In the northern hemispheres listeriosis has a distinct seasonal occurrence, probably associated with seasonal feeding of silage, with the highest prevalence in the months of December through May, but seasonal occurrence is not a feature in Australia.

Host

Listeriosis is primarily a disease of ruminants, particularly sheep, and the major diseases associated with *L. monocytogenes* are encephalitis and abortion. In ruminants it also produces syndromes of septicemia, spinal myelitis, uveitis, gastroenteritis, and mastitis. Occasional septicemic disease occurs in horses and pigs.

- **Encephalitis/meningitis** usually occurs sporadically, affecting a single animal in a herd or flock or a few individuals over several weeks. The mean attack rate in 50 affected flocks in Britain was 2.5% with a range of 0.1% to 13.3%. More serious outbreaks can occur with attack rates as high as 35% and cases occurring over a 2-month period. The disease occurs in sheep older than 6 weeks but may be more prevalent in lambs between 6 and 12 weeks of age and ewes over 2 years of age. The case–fatality is high, especially in sheep, because the short clinical course often precludes treatment.
- **Abortion** may also occur sporadically, which is usually true in cattle, but in sheep and goats it is more common as an outbreak with an attack rate that frequently approaches 10%.
- **Spinal myelitis** is an uncommon manifestation but is recorded as occurring in 0.8% to 2.5% of sheep in affected flocks and in all ages of sheep 4 weeks following spray dipping. Spinal myelitis also occurs sporadically in cattle 12 to 18 months of age.

- **Septicemic disease** is also a less common manifestation of infection with *L. monocytogenes* but can occur as an outbreak with a high case fatality in newborn lambs and kids and also in periparturient ewes and does.
- **Keratoconjunctivitis/uveitis** occurs in both sheep and cattle and has been associated with silage feeding from big bales or ring feeders. This condition presents a distinct entity that is not associated with systemic infection with *Listeria.*
- **Gastroenteritis** has been reported primarily by veterinary diagnostic labs in Great Britain and New Zealand as a sporadic disease affecting sheep after weaning. It occurs during the winter months most commonly in sheep fed baleage or silage. Cases occur 2 days or more after the onset of feeding. Less commonly, cases occur in sheep on root crops or on pasture where the quality of the pasture is poor and they are at high stocking densities.
- **Mastitis** is uncommon but can occur in cattle, sheep, and goats. It results in contamination of milk with *L. monocytogenes.* The more common source of *L. monocytogenes* in raw milk is fecal contamination. In a Danish study of quarter milk samples from over a million cows in 36,199 herds, 0.4% of cows had listerial mastitis and 1.2% of herds had infected cows.

Source of Infection

The organism is common in the environment and infection is not limited to agricultural animals. *L. monocytogenes* has been isolated from 42 species of mammals and 22 species of birds as well as fish, crustaceans, and insects. It is truly **ubiquitous in the environment** and can be commonly isolated from animal feces, human feces, farm slurry, sewerage sludge, soil, farm water troughs, surface water, plants, animal feeds, and the walls, floors, drains, and so forth of farms and other environments. The ability to form biofilms may assist in its survival in the environment and may assist in perpetuating its presence in water troughs on infected farms.

Most feed hays, grains, and formulated feeds have the potential to contain *L. monocytogenes* but, with most, low levels of available water restrict its multiplication.

In ruminants *L. monocytogenes* can be isolated from the feces and nasal secretions of healthy animals and has been isolated from the feces of cattle in 46% of 249 herds examined and from 82% of samples of feedstuffs. In a French survey 5% of small ruminant fecal samples were found positive for *L. monocytogenes.* Fecal material from wild birds in agricultural regions may also contain large amounts of *L. monocytogenes* that can contribute to the contamination of feed, water, bedding material, and soils.[1] Exposed sheep may become latent carriers, shedding the pathogen in feces and milk.[1]

In temperate climates the prevalence of *L. monocytogenes* in the feces of ruminants appears to vary with the season, being higher in the winter period. It is also increased during periods of environmental stress and in association with the stress of lambing and transport. The presence in feces and secretions can also be influenced by the number of the organism in feeds fed to the animals. In herds where there is a high proportion of cattle excreting in feces, the organism can be isolated from dried fecal dust on walls and most farm surfaces.

L. monocytogenes is not isolated from the feces or environment in all farms and its presence in isolable numbers is largely a reflection of its presence in feed, or the presence of animals with intestinal carriage. It is apparent that in some healthy herds and flocks there may be a multitude of different strains in the silage and feed, water troughs, feces, and environment in a single herd.

The presence of *L. monocytogenes* in bulk tank milk or milk filters is used as a measure of farm infection prevalence. Obviously this measure is influenced by the management and environmental conditions on farms that might result in fecal contamination of the teats. Although bulk tank and milk filter infection rates provide information of possible value to measures of environmental contamination and risk for human exposure, there is no evidence that this measure has any relationship to risk for animal disease on the farm being studied.

Silage

L. monocytogenes is commonly present in silage, but it does not multiply to any significant extent in effectively preserved silage, which is characterized by anaerobic storage, high density, a high concentration of organic acids, and a pH below 4.5. *Listeria* can multiply in silage above pH 5.0 to 5.5, the critical pH depending on the dry matter content. *L. monocytogenes* may be present in silage that is **poorly fermented,** but it can also occur in pockets of **aerobic deterioration** in otherwise good silage and this is most common. These areas are often indicated by mold growth and occur at the edges of the clamp and in the top few inches of the surface in plastic-covered clamps where air has circulated under the plastic. Thus the growth of *L. monocytogenes* is a surface problem in silage, except those that are poorly fermented, and occurs in small areas sporadically over the surface of a silage.

The risk for contamination of silage with *Listeria* is higher when it contains **soil**, which may be incorporated from molehills present in the field and in the front of the clamp during final packing. An **ash content** of greater than 70 mg/kg dry matter indicates soil contamination.

Big bale silage may have a higher risk for listerial infection than conventional silage because of its lower density, poor fermentation, greater surface area relative to clamp silage, and greater risk for mechanical damage to the plastic covering.

Moist preserved feeds other than grass silage are at risk for listerial growth; listeriosis is recorded, for example, in association with the feeding of moist brewers grains, wet spoiled hay bales, and silage made from commodity by-products such as orange and artichoke waste. A relatively rapid method for the quantitative assessment of the occurrence and distribution of *Listeria* in suspect silage is available.

Infective material also derives from infected animals in the feces, urine, aborted fetuses and uterine discharge, and in the milk. Although immediate spread among animals in a group has been demonstrated, field observations suggest that mediated contagion by means of inanimate objects also occurs. **Woody browse** may be a risk factor for goats.

Transmission

With septicemic disease and abortion, the organism is transmitted by ingestion of contaminated material. Lambs that develop septicemic disease may acquire infection from contamination on the ewe's teat, from the ingestion of milk containing the organism from ewes or does with subclinical bacteremia, through the navel from the environment, and also as a congenital infection. The encephalitic form of the disease results from infection of the terminals of the trigeminal nerve consequent to abrasions of the buccal mucosa from feed or browse or from infection of tooth cavities. Spinal myelitis is thought to result from growth up spinal nerves subsequent to body area infections.

Outbreaks of encephalitis that occur in sheep after introduction to silage usually commence about 3 to 4 weeks later, although there is wide variation, and one study of a large number of outbreaks found the median time of this period to be 44 days. This delay reflects the time for ascending infection.

Commonly, the serotype isolated from the brain of an affected animal is also present in the silage being fed. However, the recent development of methods for genetic analyses of *L. monocytogenes* has demonstrated that serotyping is a relatively crude tool for epidemiologic studies and in many instances, although the isolate from brain may be the same serotype as that from silage, there is no relationship on genetic analysis. Possibly this reflects differences in strains at different sites in silage and the difference between the time of sampling of the silage and the time when the affected cow ate it.

Septicemic disease in sheep and goats usually occurs within 2 days of introduction to silage and abortions 6 to 13 days later.

Risk Factors

Despite the ubiquity of *L. monocytogenes,* only a small proportion of animals develop clinical disease. A number of predisposing factors have been observed, or proposed, as risk factors for disease. These include factors that cause a lowering of the host animal's resistance and factors that increase the infection pressure of the organism. In farm animals the latter appear the most important.

Host Management Risk Factors

Observed risk factors include the following:

- Poor nutritional state
- Sudden changes of weather to very cold and wet
- Stress of late pregnancy and parturition
- Transport
- Long periods of flooding with resulting poor access to pasture

Differences in susceptibility between species are apparent with sheep being considerably more likely to develop clinical disease than cattle. Area outbreaks affecting several flocks can occur in sheep on poorly drained and muddy pastures following floods, but outbreaks are also described in droughts. Overcrowding and unsanitary conditions with poor access to feed supplies may predispose housed sheep.

Breed difference in susceptibility (Angora goats and Rambouillet sheep) has been observed in some studies but not in others.

Pathogen Risk Factors

Factors that increase the infection pressure largely involve a massive multiplication of *L. monocytogenes* in the feed or environment. The feeding of grass or corn silage as a major risk factor for the occurrence of listeriosis has been recognized for many decades. The increase in use of silage for feed in ruminants may be the reason for the apparent increase in the prevalence of the disease in recent years. Silage may also exert its effect by increasing the susceptibility of the host to listerial infection, although this has been disputed.

The organism persists for as long as 3 months in sheep feces and has been shown to survive for up to 11.5 months in damp soil, up to 16.5 months in cattle feces, up to 207 days on dry straw, and for more than 2 years in dry soil and feces. It is resistant to temperatures of −20°C (−6°F) for 2 years and is still viable after repeated freezing and thawing.

Experimental Reproduction

Oral or parenteral challenge of nonpregnant sheep and goats will produce a bacteremia with minor clinical signs of pyrexia and depression in animals with no preexisting antibody. Clinical disease is more severe in young animals and the infection clears with the development of an immune response. The challenge of animals with preexisting antibody is not associated with clinical disease, although there may be a bacteremia. Lactating animals secrete the organism in milk during the bacteremic period. Prior challenge of goats with *L. ivanovii* or *L. innocua* does not protect against subsequent challenge with *L. monocytogenes.*

Several studies have shown that oral, conjunctival, and parenteral challenge of **pregnant animals** results in more severe signs of septicemia and can be followed by **abortion**, although this is not an invariable sequel. Encephalitis has not been reproduced experimentally by intravenous challenge, although meningoencephalitis may occur following this route of challenge in young lambs. **Encephalitis** has been reproduced experimentally by the injection of organisms into the buccal mucosa or the tooth pulp cavity, with the organism traveling centripetally via the trigeminal nerve to reach the brainstem.

Zoonotic Implications

In humans, listeriosis is considered a foodborne infection of sporadic occurrence producing septicemia, meningoencephalitis, abortion, and infection in other organs as well as neonatal infection. Although outbreaks of listeriosis associated with contaminated food receive the most public attention, **sporadic listeriosis** is the more common presentation. Although all age groups are susceptible the disease incidence is the highest among people 65 years and older followed by young children (0–4 years) and immunocompromised patients.[2] In the EU a disease incidence of 0.3 and in the United States of 0.8 per 100,000 population have been reported.[1-4] The case fatality is high, and overall approximately 25% of reported cases die. Although the incidence increased at the beginning of the millennium, incidence rates have been stable over the last years.[4]

Although there is a potential for zoonotic transmission, the majority of human exposures to the organism, and the risk for disease, result from contamination of foods during processing and from the particular ability of the organism to grow at refrigerator temperature and in organic material with high salt content.

High disease prevalence and numbers of *L. monocytogenes* have been linked to certain foods such as soft cheese, smoked fish, pate, deli meats, unpasteurized milk, fermented raw meat sausages, hot dogs, and deli salads.[2,3]

Milk products have been incriminated in some outbreaks of the disease. Numerous studies have shown that *L. monocytogenes* is commonly present in low numbers (usually less than 1 organism per milliliter) in raw milk from some herds. In the vast majority of herds this is the result of fecal contamination during the milking process or other environmental contamination. Rarely, its presence in raw milk is from an animal with subclinical mastitis and in this case its numbers in bulk tank milk are much higher (2,000–5,000 organisms per milliliter), even when there is a single cow or goat with *L. monocytogenes* mastitis. In goats and sheep the presence in raw milk may also be the result of a subclinical bacteremia.

There have been concerns that the organism might survive pasteurization, especially if present in phagocytes. D-values for *Listeria* in milk have been determined to be in the range of 0.9 seconds at 71.1°C. The legal limit for high-temperature/short-time pasteurization in the United States is 71.7°C for 15 seconds, and this temperature is sufficient to inactivate numbers far beyond those present in raw milk. There is no evidence that the organism will survive correct pasteurization procedures.

Bulk tank infection rates are higher in winter and spring and cross-sectional and case–control studies have shown that the risk for detecting *L. monocytogenes* in bulk milk is higher in those herds that used a bucket milking system rather than a pipeline system. It is also higher in herds fed component feeds, fed leftover feed, fed from plastic feed bunks, and from feed bunks with a low frequency of cleaning, It is lower in herds that practice premilking teat disinfection.

Farmers or others who consume **raw milk** need to be aware of the risk of infection, especially if they fall within at-risk categories. There may be a particular risk with milk from goats and sheep fed silage. People associated with agriculture are also more liable to direct zoonotic transmission of listerial disease. **Dermatitis** with a papular and pustular rash occurs on the arms of **veterinarians** following the handling of infected dystocia cases and aborted fetuses. **Conjunctivitis** is also recorded in agricultural workers handling infected livestock.

Although *L. monocytogenes* rarely causes disease in **pigs,** it is present in the tonsils and feces of some pigs at slaughter and this presence is a potential source of contamination of the carcass and the slaughterhouse environment. There is a significantly higher prevalence in the tonsils of fattening pigs than in those of sows. The organism can be isolated from the floors, walls, and feed in pig units. Wet feeding, poor hygiene, and a short spelling period between batches of pigs in the finishing house have been found to be risk factors for infection in pigs. Paradoxically, disinfecting the pipeline used for wet feeding was associated with a higher risk of fecal contamination than no disinfection at all.

A further concern for indirect zoonotic risk of *L. monocytogenes* is the presence of the organism in the feces on infected farms and the potential for fecal or windborne dust spread to adjacent fields that may contain crops for human consumption.

PATHOGENESIS

In most animals, ingestion of the organism, with penetration of the mucosa of the intestine, leads to an inapparent infection with

prolonged fecal excretion of the organism and to a subclinical bacteremia, which clears with the development of immunity. The bacteremic infection is frequently subclinical and may be accompanied by excretion of the organism in milk. Septicemic listeriosis, with or without meningitis, is most common in neonatal ruminants and in adult sheep and goats, particularly if they are pregnant and when the infection challenge is large.

The organism is a facultative intracellular pathogen that can infect cells, including intestinal cells, by directed endocytosis. It can survive and grow in macrophages and monocytes. Bacterial superoxide dismutase protects against the bactericidal activity of the respiratory burst of the phagocyte and listeriolysin O disrupts lysosomal membranes, allowing the organism to grow in the cytoplasm. The experimental mouse model indicates that cell-mediated immunity is important in protection against listerial infection, but studies in goats suggest that the clearance of bacteremic infection and resistance to infection are also strongly associated with humoral antibody.

In **pregnant animals,** invasion of the placenta and fetus may occur within 24 hours of the onset of bacteremia. Edema and necrosis of the placenta lead to **abortion**, usually 5 to 10 days postinfection. Infection late in pregnancy results in **stillbirths** or the delivery of young that rapidly develop a fatal septicemia. Maternal **metritis** is constant and if the fetus is retained a fatal listerial septicemia may follow. Infection of the uterus causing abortion and intrauterine infection occurs in all mammals.

Encephalitis/Meningitis

Encephalitis/meningitis in ruminants occurs as an acute inflammation of the brainstem or the meningeal membranes and is usually focal. Invasion of the CNS can occur by at least three different mechanisms.[5] These include the following:

- Retrograde (centripetal) migration into the brain within the axon of CNs
- Transport across the blood-brain barrier within parasitized leukocytes
- Direct invasion of endothelial cells by blood-borne bacteria

In cases without systemic infection centripetal translocation of the pathogen along the trigeminal or other CNs following penetration of the traumatized buccal mucosa, the shedding of deciduous or permanent teeth, and following periodontitis may result in encephalitis. Meningitis is thought to be associated with hematogenous translocation of the pathogen through parasitized endothelial cells or leukocytes.

The incubation period after experimental inoculation of the tooth pulp was at least 3 weeks even though lesions were detectable in the brainstem within 6 days of inoculation.[5] Clinical signs are characterized most strongly by an **asymmetric** disorder of CN function, in particular the trigeminal, facial, vestibular, and glossopharyngeal nerves, but there is some variation in the involvement of individual CNs depending on the distribution of lesions in the brainstem. Lesions in the sensory portion of the trigeminal nucleus and the facial nucleus are common and lead to ipsilateral facial hypalgesia and paralysis; involvement of the vestibular nucleus is also common and leads to ataxia with circling and a head tilt to the affected side. The additional signs of dullness, headpressing, and delirium are referable to the more general effects of inflammation of the brain developing in the agonal stages. Spread of the infection along the optic nerve may result in endophthalmitis in sheep and cattle.

Spinal Myelitis

Spinal myelitis possibly results from ascending infection in the sensory nerves of the skin following dermatitis from prolonged wetting of the fleece.

Mastitis

L. monocytogenes is rarely found to be a cause of **clinical mastitis** in cattle, despite the fact that it can be common in the dairy environment, suggesting that this pathogen is not a particularly invasive or perpetuating organism for the udder. Infection of the mammary gland appears to primarily occur hematogenously.[1]

Enteritis

An acute diarrheal condition in sheep with clinical signs and morphologic changes resembling salmonellosis from which *L. monocytogenes* can be recovered has been recognized since the early 1990s.[6] Cases are frequently linked to feeding poor-quality silage and may occur within 2 days of feeding silage heavily contaminated with *L. monocytogenes.* The mechanisms through which *Listeria* invade the gastrointestinal mucosa are not yet understood, but infection seems to depend more on the ingested dose and the age of the animal than on predisposing conditions or immune status of the animal.[7] Lesions occur in the abomasum, small intestine, large intestine, mesenteric lymph nodes, and liver.[6]

CLINICAL FINDINGS

When disease occurs it is usual to have an outbreak of either encephalitis or abortion. Encephalitis is the most prevalent manifestation in sheep. Septicemia in lambs may occur in conjunction with abortion but it is rare to have all three syndromes on the same farm, at least in the same temporal period. There are always exceptions to such generalities, and the occurrence of septicemia, abortion, and encephalitis in a flock of sheep is possible.

Listerial Encephalitis/Meningitis

Sheep

In sheep, early signs are separation from the flock and depression with a hunched stance. Sheep approached during this early stage show a frenetic desire to escape but are uncoordinated because they run and fall easily. The syndrome progresses rapidly with more severe depression to the point of somnolence and the development of signs of CN dysfunction. Fever, usually 40°C (104°F) but occasionally as high as 42°C (107°F), is common in the early stages of the disease but the temperature is usually normal when overt clinical signs are present.

Signs vary between individual sheep but incoordination, head deviation sometimes with head tilt, walking in circles, unilateral facial hypalgesia, and facial paralysis are usually present. Facial hypalgesia can be detected with pressure from a hemostat, and the facial paralysis is manifested with drooping of the ear, paralysis of the lips, and ptosis on the same side of the face as the hypalgesia. This may be accompanied by exposure keratitis, often severe enough to cause corneal ulceration. Strabismus and nystagmus occur in some. Panophthalmitis, with pus evident in the anterior chamber of one or both eyes, is not uncommon in cattle that have been affected for a number of days. Also there is paresis of the muscles of the jaw, with poor tone or a dropped jaw, in which case prehension and mastication are slow and the animal may stand for long periods drooling saliva and with food hanging from its mouth.

The position of the head varies. In many cases there is deviation of the head to one side with the poll–nose relationship undisturbed (i.e., there is no rotation) but in others there is also head tilt. The head may be retroflexed or ventroflexed depending on the localization of the lesions and in some cases may be in a normal position. The deviation of the head cannot be corrected actively by the animal, and if it is corrected passively the head returns to its previous position as soon as it is released. Progression is usually in a small-diameter circle in the direction of the deviation. There is ataxia, often with consistent falling to one side, and an affected sheep may lean against the examiner or a fence. The affected animal becomes recumbent and is unable to rise, although often still able to move its legs. Death is caused by respiratory failure.

Cattle

In cattle, the clinical signs are essentially the same but the clinical course is longer (Fig. 14-16). In adult cattle the course of the disease is usually 1 to 2 weeks, but in sheep and calves the disease is more acute, with death occurring in 2 to 4 days.

Goats

In goats the disease is similar to that in the other species, but in the young goat the onset is very sudden and the course short, with death occurring in 2 to 3 days (Fig. 14-17).

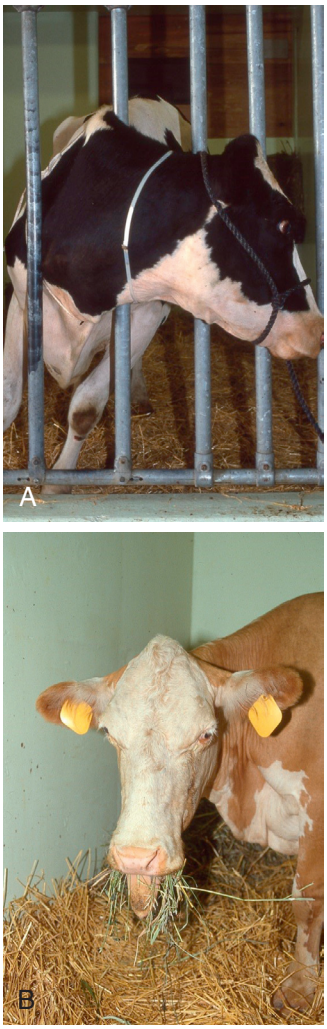

Fig. 14-16 **A,** Two-year-old Holstein Friesian heifer with listeriosis. The heifer is exhibiting clinical signs of a left brainstem lesion in the vicinity of the vestibulocochlear nerve nucleus (cranial nerve VIII) manifested as extensor thrust from the right side and tight circles to the left (circling is impeded by placement in the headgate). **B,** Three-year-old Simmental cow with listeriosis. The cow is exhibiting depression, weakness of the tongue and jaw muscles, and lack of sensation that she has hay in her mouth. Some of these clinical signs are also seen in cattle with rabies or esophageal obstruction (choke). Both animals responded well to intravenous oxytetracycline treatment.

Fig. 14-17 Two-year-old goat with listeriosis. The goat has depression of the right corneal branch of the trigeminal nerve (cranial nerve V) because it does not detect the straw on its right eye, and the right facial nerve (cranial nerve VII) because it has a right ear droop, deviation of the philtrum to the left, and flaccid right upper lip. The goat was unable to stand and appeared depressed.

Listerial Abortion

Outbreaks of abortion are recorded in cattle but are more common in sheep and in goats. Abortion caused by this organism is rare in pigs.

Cattle

In cattle, abortion or stillbirth occurs sporadically and usually in the last third of pregnancy; retention of the afterbirth is common, in which case there is clinical illness and fever of up to 40.5°C (105°F). Abortion has been observed soon after the commencement of silage feeding but does not always have this association.

Sheep and Goats

In sheep and goats abortions occur from the 12th week of pregnancy onward, the afterbirth is usually retained, and there is a blood-stained vaginal discharge for several days. There may be some deaths of ewes from septicemia if the fetus is retained. In both species the rates of abortion in a group are low but may reach as high as 15%. On some farms, abortions recur each year.

Abortion Caused by *Listeria Ivanovii*

This occurs as a sporadic disease in cattle and has no distinguishing clinical features

from that associated with *L. monocytogenes*. Outbreaks in sheep are manifested with abortion and stillbirth but particularly with the birth of live infected lambs, which seldom survive long enough to walk or suck.

Septicemic Listeriosis

Acute septicemia caused by *L. monocytogenes* is not common in adult ruminants but does occur in monogastric animals and in newborn lambs and calves. There are no signs suggestive of nervous system involvement, the syndrome being a general one comprising depression, weakness, emaciation, pyrexia, and diarrhea in some cases, with hepatic necrosis and gastroenteritis at necropsy. The same syndrome is also seen in ewes and goats after abortion if the fetus is retained. A better defined but less common syndrome has been described in calves 3 to 7 days old. Corneal opacity is accompanied by dyspnea, nystagmus, and mild opisthotonus. Death follows in about 12 hours. At necropsy there is ophthalmitis and serofibrinous meningitis. Septicemic listeriosis is recorded in a foal.

Mastitis

Infection in the udder may involve a single quarter or both quarters; it is chronic and poorly responsive to treatment. There is a high somatic cell count in milk from the affected quarter, but the milk appears normal.

Spinal Myelitis

There is fever, ataxia with initial knuckling of the hindlimbs progressing to hindlimb weakness, and paralysis. In some cases, both in sheep and cattle, there is also paresis and paralysis of the front limbs. There is no evidence of CN involvement, and affected animals are initially mentally alert, bright, and continue to eat. However, there is rapid deterioration and affected animals are commonly humanely destroyed.

Keratoconjunctivitis, Uveitis

There is swelling of the iris and constriction of the pupil; white focal lesions are evident on the internal surface of the cornea with floccular material in the anterior chamber. Advanced cases have pannus and corneal opacity.

Enteritis in Sheep

Reported clinical signs include lethargy, anorexia, and diarrhea or sudden death. Pregnant ewes may abort.

CLINICAL PATHOLOGY

The CSF in cases of encephalitis has a moderately to markedly increased protein concentration and leukocyte count. Neutrophils are the predominant cell type with lymphocytes contributing not more than 20% of cells.[8] *L. monocytogenes* is not detectable by culture or PCR.

The organism can be cultivated from vaginal secretions for up to 2 weeks after abortion, and a proportion of aborting animals also have *L. monocytogenes* in the milk and feces.

Serologic tests (agglutination and complement fixation tests) have been used but lack the predictive value required for diagnostic use. Ruminants commonly have antibody to *Listeria* and high titers are often encountered in normal animals in flocks and herds where there have been clinical cases. Nucleic acid–based techniques can be used to determine the source of a strain of *L. monocytogenes* in an outbreak.

NECROPSY FINDINGS

Typically, there are no distinctive gross changes associated with listerial **encephalitis**. Histologic examination of CNS tissue is necessary to demonstrate the microabscesses that are characteristic of the disease. These are present in the brainstem in listerial encephalitis and in the cervical and/or lumbar spinal cord in outbreaks of spinal myelitis. Sampling of the forebrain will typically result in a false-negative diagnosis. Cold enrichment techniques are advisable when attempting to isolate the organism. Gram staining of paraffin-embedded tissue may permit confirmation of the diagnosis in cases for which suitable culture material is unavailable. Alternative test methods such as fluorescent antibody or immunoperoxidase tests are available in some laboratories. In one retrospective study comparing diagnostic methods, immunoperoxidase staining was superior to bacterial culture when correlated with histopathologic changes.

Visceral lesions occur as multiple foci of necrosis in the liver, spleen, and myocardium in the **septicemic form** and in **aborted fetuses**. Aborted fetuses are usually edematous and autolyzed, with very large numbers of bacteria visible microscopically in a variety of tissues. In aborting dams, there is placentitis and endometritis in addition to the lesions in the fetus.

Sheep with **enteritis** show ulcerative and hemorrhagic abomasitis and reddening of the small intestinal mucosa.[6] In a small number of cases typhlocolitis is diagnosed at necropsy; histologically, there are microabscesses throughout the intestine and a characteristic infiltration of degenerating neutrophils in the mucosa lamina muscularis of the abomasum.[6]

Samples for Confirmation of Diagnosis

Central Nervous System Listeriosis

- **Bacteriology:** half of midsagittally sectioned brain, **including brainstem**, chilled or frozen (CULT, FAT)
- **Histology**: formalin-fixed half of midsagittally sectioned brain, **including brainstem**; appropriate segment of spinal cord if spinal myelitis suspected (LM, IHC)

Septicemia and Abortion

- **Bacteriology:** chilled liver, spleen, lung, placenta, fetal stomach content (CULT, FAT)
- **Histology:** formalin-fixed liver, spleen, lung, brain, placenta, fetal intestine (LM, IHC).

Enteritis

- **Bacteriology:** abomasum, small intestine, large intestine, mesenterial lymph nodes (CULT)
- **Histology:** formalin-fixed abomasum, small intestine, large intestine, mesenterial lymph nodes (LM, IHC).

DIFFERENTIAL DIAGNOSIS

Encephalitis
- Pregnancy toxemia in sheep
- Nervous ketosis in cattle
- Rabies
- Gid
- Polioencephalomalacia
- Middle ear disease
- Scrapie

Abortion
- Sheep
- Cattle

Gastroenteritis
- Salmonellosis

Keratoconjunctivitis/Uveitis
- Contagious ophthalmia
- Infectious bovine keratoconjunctivitis

TREATMENT

Penicillin is considered the drug of choice for treatment of listeriosis but it only has a bacteriostatic effect on *L. monocytogenes*.[2] Cephalosporins are ineffective because of minimal or nonexistent affinity of listerial penicillin-binding protein 3 and 5.[2,5]

A recent study exploring the prevalence of in vitro resistance of *L. monocytogenes* strains isolated from dairy farms found all strains to be resistant to cephalosporins, streptomycin, and trimethoprim. Over 90% of isolated strains were resistant to ampicillin and 66% were resistant to florfenicol. Resistance to penicillin G was determined for 40% of isolated strains.[9]

Penicillin administered at a dose of 44 000 IU/kg BW every 12 hours or every 24 hours given intramuscularly for 10 to 14 days is among the most commonly used treatments for listerial encephalitis/meningitis. Initiating the therapy with a loading dose of penicillin of 200,000 IU/kg as a water-soluble formulation given intravenously has been proposed.[10] The intravenous treatment of oxytetracycline (10 mg/kg BW every 12 hours or 20 mg /kg BW every 24 hours for 10 days) has been reported as being

reasonably effective in meningoencephalitis of cattle but less so in sheep.

The use of nonsteroidal antiinflammatory drugs (NSAIDs) to address pain resulting from meningitis may be indicated but warrants close monitoring of the patient's hydration status to prevent renal damage. The use of glucocorticoids has been proposed with the objective to prevent abscess formation in the CNS.[1] Concerns have been raised since increased listerial shedding through milk was reported in cattle infected with *L. monocytogenes* treated with dexamethasone.[11]

The recovery rate depends largely on the time that treatment is started after the onset of clinical signs. If severe clinical signs are already evident, death usually follows in spite of treatment. Usually the course of events in an outbreak is that the first case dies but subsequent cases are detected sufficiently early for treatment. Dehydration, acid-base imbalances, and electrolyte disturbances must also be corrected. Cases of spinal myelitis are poorly responsive to treatment.

Treatment of listerial iritis is with systemic antibiotics in the early stages coupled with subpalpebral corticosteroid and atropine to dilate the pupil.

Supportive treatment with thiamine, to compensate for decreased thiamine production during the disease, and glucocorticoids to prevent formation of microabscesses in the CNS have been proposed. Correction of metabolic acidosis, resulting from excessive bicarbonate loss with drooling saliva, may be indicated.

TREATMENT AND CONTROL

Treatment

Encephalitis

Procaine penicillin G (200,000 IU/kg IV as initial loading dose) (R-2)

Procaine penicillin G (22,000 IU/kg every 12 hours or 44,000 IU/kg every 24 hours IM, for 10–14 days (R-2)

Oxytetracycline (10 mg/kg IV every 12 hours or 20 mg/kg IV every 24 hours for 10–14 days) (R-2)

Cephalosporins (R-4)

Thiamine (10 mg/kg slow IV every 24 hours) (R-2)

Flunixin meglumine (1 mg/kg every 24 hours IV) (R-2)

Dexamethasone (1 mg/kg IV single treatment) (R-3)

Control

Ensure pH of silage is < 5.0 (R-2)

Don't feed strongly spoiled sections of silage (R-2)

IM, intramuscularly; IV, intravenously.

CONTROL

Control is difficult because of the ubiquitous occurrence of the organism, the lack of a simple method of determining when it is present in high numbers in the environment, and a poor understanding of the risk factors other than silage. Where the risk factor is silage, there may be some merit in the recommendation that a change of diet to include heavy feeding of silage should be made slowly, particularly if the silage is spoiled or if listeriosis has occurred on the premises previously. Tetracyclines can be fed in the ration of animals at risk in a feedlot. When possible, the obviously spoiled areas of silage should be separated and not fed.

Other recommendations on the feeding of silage include avoid making silage from fields in which molehills may have contaminated the grass; avoid soil contamination when filling the clamp; avoid using additives to improve fermentation; and avoid silage that is obviously decayed, or with a pH of greater than 5 or an ash content of more than 70 mg/kg of dry matter.

Silage removed from the clamp should be fed as soon as possible.

Where uveitis is a problem, feeding systems that avoid eye contact with silage should be used.

A live attenuated **vaccine** has been shown to induce protection against intravenous challenge, and a live attenuated vaccine in use in Norway for several years is reported to reduce the annual incidence of the disease in sheep from 4% to 1.5%. An economic model is available for determining whether vaccination should be practiced. Commercial killed vaccines are available for the control of the disease in some countries, and some companies will also produce autogenous vaccines on request. The efficacy of vaccination still requires further determination; however, when economics or food availability on the farm dictate that contaminated silage must be fed, consideration might be given to vaccination as a means of providing some protection.

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Diseases Primarily Affecting the Spinal Cord

TRAUMATIC INJURY

Sudden severe trauma to the spinal cord causes a syndrome of immediate, complete, flaccid paralysis caudal to the injury because of spinal shock. This is so brief in animals it is hardly recognizable clinically. Spinal shock is soon followed by flaccid paralysis in the area supplied by the injured segment and spastic paralysis caudal to it.

ETIOLOGY

Trauma is the most common cause of monoplegia in large animals. There are varying degrees of loss of sensation, paresis, paralysis, and atrophy of muscle.

Physical Trauma

- Animals falling off vehicles, through barn floors
- Osteoporotic or osteodystrophic animals, especially aged broodmares and sows, spontaneously while jumping or leaning on fences
- Spondylosis and fracture of thoracolumbar vertebrae in old bulls in insemination centers
- Cervical vertebral fractures account for a large percentage of spinal cord injuries in horses
- Trauma caused by excessive mobility of upper cervical vertebrae may contribute to the spinal cord lesion in wobbles in horses
- Dislocations of the atlantooccipital joint are being reported increasingly
- Stenosis of the cervical vertebral canal at C2-C4 in young rams, probably as a result of head-butting
- Fracture of T1 vertebra in calves turning violently in an alleyway wide enough to admit cows
- Vertebral fractures in 7- to 10-month-old calves escaping under the headgate of a chute and forcefully hitting their

backs (just cranial to the tuber coxae) on the bottom rail of the gate
- Vertebral fractures in neonatal calves associated with forced extraction during dystocia
- Lightning strike may cause tissue destruction within the vertebral canal.

Parasitic Invasion
- Cerebrospinal nematodiasis, e.g., *P. tenuis, Setaria* spp. in goats and sheep, *Stephanurus dentatus* in pigs, *P. tenuis* in moose, causing moose sickness
- *Toxocara canis* experimentally in pigs
- *S. vulgaris* in horses and donkeys
- *Hypoderma bovis* larvae in cattle

Local Ischemia of the Spinal Cord
- Obstruction to blood flow to the cord by embolism, or of drainage by compression of the caudal vena cava, e.g., in horses during prolonged dorsal recumbency under general anesthesia; in pigs caused by fibrocartilaginous emboli, probably originating in injury to the nucleus pulposus of an intervertebral disk

PATHOGENESIS
The lesion may consist of disruption of nervous tissue or its compression by displaced bone or hematoma. Minor degrees of damage may result in local edema or hyperemia or, in the absence of macroscopic lesions, transitory injury to nerve cells, classified as concussion. The initial response is that of spinal shock, which affects a variable number of segments on both sides of the injured segment and is manifested by complete flaccid paralysis. The lesion must affect at least the ventral third of the cord before spinal shock occurs. When the shock wears off, the effects of the residual lesion remain. These may be temporary in themselves and completely normal function may return as the edema or the hemorrhage is resorbed. In sheep, extensive experimental damage to the cord may be followed by recovery to the point of being able to walk, but not sufficiently to be of any practical significance.

Traumatic lesions usually affect the whole cross-section of the cord and produce a syndrome typical of complete transection. Partial transection signs are more common in slowly developing lesions. Most of the motor and sensory functions can be maintained in 3-month-old calves with experimental left hemisection of the spinal cord.

In a retrospective study of dystocia-related vertebral fractures in neonatal calves, all the fractures were located between T11 and L4, with 77% occurring at the thoracolumbar junction. All but one case was associated with a forced extraction using unspecified (53%), mechanical (28%), or manual (17%) methods of extraction. Traction is most commonly applied after the fetus has entered the pelvic canal. Manual traction varies from 75 kg of pressure applied by one man to 260 kg of pressure applied by three or more men. The forces applied in mechanical traction vary from 400 kg for a calf puller to over 500 kg for a tractor. The transfer of these forces to the vertebrae and to the physeal plates at the thoracolumbar junction could readily cause severe tissue damage. In a prospective study of vertebral fractures in newborn calves, all fractures were located at the thoracolumbar area, especially the posterior epiphysis of T13.

CLINICAL FINDINGS
Spinal shock develops immediately after severe injury and is manifested by flaccid paralysis (reflex loss) caudal to a severe spinal cord lesion. There is a concurrent fall in local blood pressure caused by vasodilatation and there may be local sweating. Stretch and flexor reflexes and cutaneous sensitivity disappear but reappear within a half to several hours, although hypotonia may remain. The extremities are affected in most cases and the animal is unable to rise and may be in sternal or lateral recumbency. The muscles of respiration may also be affected, resulting in interference with respiration. The body area supplied by the affected segments will eventually show flaccid paralysis and disappearance of reflexes and muscle wasting, all representative of a lower motor neuron lesion.

When the injury is caused by invasion by parasitic larvae, there is no stage of spinal shock but the onset is acute, although there may be subsequent increments of paralysis as the larva moves to a new site.

Neonatal calves with dystocia-related vertebral fractures are weak immediately after birth or remain recumbent and make no effort to rise.

Sensation may be reduced at and caudal to the lesion, and hyperesthesia may be observed in a girdle-like zone at the cranial edge of the lesion as a result of irritation of sensory fibers by local inflammation and edema. Because of interference with the sacral autonomic nerve outflow there may be paralysis of the bladder and rectum, although this is not usually apparent in large animals. The vertebral column should be examined carefully for signs of injury. Excessive mobility, pain on pressure, and malalignment of spinous processes may indicate bone displacements or fractures. Rectal examination may also reveal damage or displacement, particularly in fractures of vertebral bodies and in old bulls with spondylosis.

Residual signs may remain when the shock passes off. This usually consists of paralysis, which varies in extent and severity with the lesion. The paralysis is apparent caudal to and at the site of the lesion. The reflexes return except at the site of the lesion. There is usually no systemic disturbance but pain may be sufficiently severe to cause an increase in heart rate and prevent eating.

Recovery may occur in 1 to 3 weeks if nervous tissue is not destroyed, but when extensive damage has been done to a significantly large section of the cord there is no recovery and disposal is advisable. In rare cases animals that suffer a severe injury continue to be ambulatory for up to 12 hours before paralysis occurs. In such instances it may be that a fracture occurs but displacement follows at a later stage during more active movement. Recovered animals may be left with residual nervous deficits or with postural changes such as torticollis.

Fracture of the Cervical Vertebrae in Horses
In horses fracture/dislocation of cranial cervical vertebrae is fairly common. Affected animals are recumbent and unable to lift the head from the ground. However, they may be fully conscious and able to eat and drink.[1] It may be possible to palpate the lesion, but a radiograph is usually necessary. Lesions of the caudal cervical vertebrae may permit lifting of the head but the limbs are not moved voluntarily. In all cases the tendon and withdrawal reflexes in the limbs are normal to supernormal.

Spondylosis in Bulls
Old bulls in artificial insemination centers develop calcification of the ventral vertebral ligaments and subsequent spondylosis or rigidity of the lumbar area of the vertebral column. When the bull ejaculates vigorously, the calcified ligaments may fracture, and this discontinuity may extend upward through the vertebral body. The ossification is extensive, usually from about T2-L3, but the fractures are restricted to the midlumbar region. There is partial displacement of the vertebral canal and compression of the cord. The bull is usually recumbent immediately after the fracture occurs but may rise and walk stiffly several days later. Arching of the back, slow movement, trunk rigidity, and sometimes unilateral lameness are characteristic signs. Less severe degrees of spondylosis have been recorded in a high proportion of much younger (2- to 3-year-old) bulls, but the lesions do not appear to cause clinical signs.

CLINICAL PATHOLOGY
Radiologic examination may reveal the site and extent of the injury, depending on the amount of surrounding muscle mass. CSF obtained from the lumbosacral space may reveal the presence of xanthochromia or intact RBCs, suggesting preexisting hemorrhage.

NECROPSY FINDINGS
The abnormality is always visible on macroscopic examination. In neonatal calves with dystocia-related vertebral fractures, hemorrhage around the kidneys, around the adrenal glands, and in the perivertebral muscles is a common finding and a useful indicator that

a thoracolumbar fracture is present. In addition to the vertebral fracture, subdural and epidural hemorrhage, myelomalacia, spinal cord compression, severed spinal cord, and fractured ribs are common findings.

DIFFERENTIAL DIAGNOSIS

Differentiation from other spinal cord diseases is not usually difficult because of the speed of onset and the history of trauma, although spinal myelitis and meningitis may also develop rapidly. Other causes of recumbency may be confused with trauma, especially if the animal is not observed in the immediate preclinical period. In most diseases characterized by recumbency, such as azoturia, acute rumen impaction, and acute coliform mastitis, there are other signs to indicate the existence of a lesion other than spinal cord trauma. White muscle disease in foals is characterized by weakness, and the serum creatine kinase activity will be increased.

TREATMENT

Treatment is expectant only, and surgical treatment is rarely attempted. Large doses of corticosteroids or nonsteroidal antiinflammatory agents are recommended to minimize the edema associated with the spinal cord injury. Careful nursing on deep bedding with turning at 3-hour intervals (ideally, but at least 3 times a day in animals that are not "creepers"), massage of bony prominences, and periodic slinging may help to carry an animal with concussion or other minor lesion through a long period of recumbency. In well-muscled cattle especially, recumbency beyond a period of about 48 hours is likely to result in widespread necrosis of the caudal muscles of the thigh and recovery in such cases is improbable. A definitive diagnosis of a vertebral fracture with paralysis usually warrants a recommendation for euthanasia.

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SPINAL CORD COMPRESSION

The gradual development of a space-occupying lesion in the vertebral canal produces a syndrome of progressive weakness and paralysis. A preexisting inflammatory or neoplastic lesion of the vertebral body may result in spontaneous fracture of the vertebral body and compression of the spinal cord.

ETIOLOGY

Compression of the spinal cord occurs from space-occupying lesions in the vertebral canal; the common ones are as follows.

Tumors

The most commonly occurring tumor in animals is lymphomatosis in which the nerve trunks and invades the vertebral canal, usually in the lumbosacral region and less commonly in the brachial and cervical areas. This tumor is particularly common in adult cattle with multicentric lymphosarcoma caused by bovine leukosis virus infection (Fig. 14-18).

Rare tumors include fibrosarcomas, metastases, plasma cell myeloma, angioma, melanoma in a horse, hemangiosarcoma in a horse, neurofibroma, and lymphosarcoma, e.g., in horses, vascular hamartoma in a goat.

Vertebral Body or Epidural Abscess

Vertebral body abscesses (osteomyelitis) are most common in neonatal farm animals and are generally in association with a chronic suppurative lesion elsewhere in the body.

- Docking wounds in lambs, bite wounds in pigs, and chronic suppurative pneumonia in calves are common occurrences for vertebral body abscesses. Polyarthritis and endocarditis may also be present. The original site of infection may have resolved when the clinical signs referable to the spinal cord abscess appear.
- Compression of the spinal cord is caused by enlargement of the vertebral body abscess into the vertebral canal and there may or may not be deviation of the vertebral canal and its contents.[1] Epidural abscesses causing compression

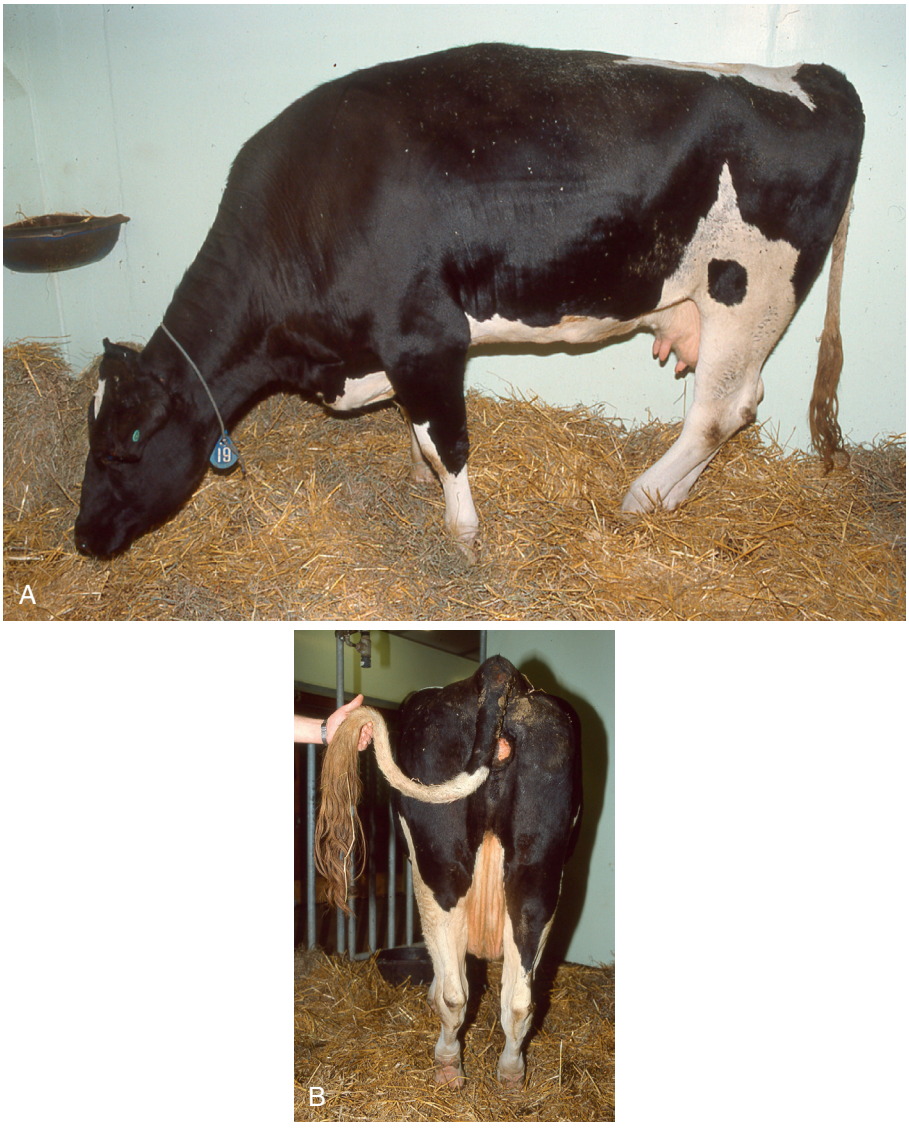

Fig. 14-18 **A,** Bilateral posterior paresis in a 5-year-old Holstein Friesian cow with spinal lymphosarcoma caused by infection with enzootic bovine leukosis virus. **B,** Caudal view of the same cow, demonstrating marked paresis of the tail and hindlegs and poor milk production.

of the spinal cord, and not associated with vertebral bodies, occur in lambs.
- Hematogenous spread may also occur from *Trueperella* (*Arcanobacterium* or *Actinomyces* or *Corynebacterium*) *pyogenes* in cattle, *A. bovis* in cattle with lumpy jaw, and *Corynebacterium pseudotuberculosis* in sheep.
- Multiple cases of compressive myelopathy have been reported in cattle following intramuscular injection of an oil containing vaccine in the lumbar area.[2]
- Cervical myelomalacia in a lamb and an alpaca developed after attempted intramuscular injections in the neck[3]
- A pyogranulomatous lesion in the sacral region of horse extended into the sacral vertebral canal, resulting in reduced anal and tail tone and urinary overflow incontinence.[4]

Bony Lesions of Vertebra

- Exostoses over fractures with no displacement of vertebral bodies.
- Similar exostoses on vertebral bodies of lambs grazing around old lead mines.
- Hypovitaminosis A in young growing pigs causing compression of the nerve roots passing through the vertebral foramina.
- Congenital deformity or fusion of the atlantooccipital axial joints in calves, foals, and goats.
- Congenital spinal stenosis of calves.
- Protrusion of an intervertebral disk is identifiable by myelogram or at necropsy,[5] although rare in large animals. The degenerative lesions in disks in the neck of the horse resemble the Hansen type 2 disk prolapses in dogs.
- Progressive paresis and ataxia also occur rarely in diskospondylitis in horses, an inflammatory condition focused on a single intervertebral joint that often results from a septic process.[6,7] Diskospondylitis has been diagnosed in a 4-month-old calf with a stiff gait and umbilical abscess,[8] an adult goat with paraplegia,[9] and an alpaca with paraparesis.[10]
- Spondylosis occurs, which is a degenerative condition characterized by extensive osteophytes on the vertebral body axis. *Spondylus* is an old Greek name meaning vertebra. Spondylosis usually affects the ventral or lateral aspects of multiple adjacent vertebrae. It is a progressive disease affecting contiguous vertebrae because of biomechanical stresses.[6] Ankylosing spondylosis typically cause lameness rather than compression of cord and paresis/paralysis.

Adult sows and boars may have degeneration of intervertebral disks and surrounding vertebral osteophytes. Less commonly are ankylosing spondylosis, arthrosis of articular facets, defects in annulus fibrosus and vertebral end plates, and vertebral osteomyelitis or fracture. These lesions of ankylosing spondylosis cause lameness in boars and sows rather than compression of cord and paresis/paralysis. These are not to be confused with the many extravertebral causes of posterior lameness or paralysis in adult pigs, which are discussed in Chapter 15.

Vertebral Subluxation or Compressive Myelopathy

- Cervicothoracic vertebral subluxation in Merino sheep in Australia and Columbia lambs in the United States
- Compressive cervical myelopathy in yearling Texel and Beltex sheep caused by fatty nodules encroaching into the dorsal vertebral canal at C6-C7[11]

Ataxia in Horses

This is a major problem and has numerous potential causes:
- Nonfatal fractures of the skull (basisphenoid, basioccipital, and petrous temporal bones)
- Nonfatal cervical fractures
- Atlantooccipital instability
- Cervical vertebral malformation (equine cervical vertebral stenotic myelopathy) caused by stenosis of the cranial vertebral orifice of C3-C7[12]; this may be effective as a compression mechanism only if the vertebrae adopt exaggerated positions
- Abnormal growth of interarticular surfaces
- Dorsal enlargement of caudal vertebral epiphyses and bulging of intervertebral disks
- Formation and protrusion of false joint capsules and extrasynovial bursae
- Spinal myelitis caused by parasitic invasion or EHV-1 virus, even louping-ill virus and probably others
- Spinal abscess usually in a vertebral body
- *Onchocerca* sp.–induced spinal cord compression and axonopathy[13]
- Spinal hematomas[14] causing ataxia, paresis, and neck pain
- Cerebellar hypoplasia (most commonly the inherited version in Arabian foals)
- Degenerative myelomalacia/myelopathy (cause unknown)
- Fusion of occipital bone with the atlas, which is fused with the axis
- Hypoxic–ischemic neuromyopathy in aortoiliac thrombosis
- Tumors of the meninges

PATHOGENESIS

The development of any of the lesions listed previously results in the gradual appearance of motor paralysis or hypoesthesia, depending on whether the lesion is ventrally or dorsally situated. In most cases there is involvement of all motor and sensory tracts, but care is necessary in examination if the more bizarre lesions are to be accurately diagnosed. There may be hemiparesis or hemiplegia if the lesion is laterally situated. Paraparesis or paraplegia is caused by a bilateral lesion in the thoracic or lumbar cord and monoplegia by a unilateral lesion in the same area. Bilateral lesions in the cervical region cause tetraparesis to tetraplegia (quadriplegia).

Vertebral osteomyelitis in young calves is most common in the thoracolumbar vertebrae and less commonly in the cervical vertebrae. The abscess of the vertebral body gradually enlarges and causes gradual compression of the spinal cord, which causes varying degrees of paresis of the pelvic limbs and ataxia. The abscess may extend into adjacent intervertebral spaces and result in vertebral arthritis with lysis of the articular facets. The onset of paresis and paralysis may be sudden in cases of abscessation or osteomyelitis of the vertebrae, which may fracture and cause displacement of bony fragments into the vertebral canal with compression and traumatic injury of the spinal cord. Vertebral body abscesses between T2 and the lumbar plexus will result in weakness of the pelvic limbs and normal flexor withdrawal reflexes of the pelvic limbs. Lesions at the site of the lumbar plexus will result in flaccid paralysis of the pelvic limbs.

In horses with cervical vertebral malformation, compression of the spinal cord results in necrosis of white matter and some focal loss of neurons. With time, secondary wallerian-like neuron fiber degeneration in ascending white matter tracts cranial to the focal lesion and in descending white matter tracts caudal to the lesion occurs. Astrocytic gliosis is a prominent and persistent alteration of the spinal cord of horses with chronic cervical compressive myelopathy and is associated with nerve fiber degeneration at the level of the compression and in well-delineated areas of ascending and descending nerve fiber tracts. It is possible that the persistent astrocytic gliosis may prevent, or slow, recovery of neurologic function in affected horses.

CLINICAL FINDINGS

Varying degrees of progressive weakness of the thoracic limbs or pelvic limbs may be the initial clinical findings. With most lesions causing gradual spinal cord compression, difficulty in rising is the first sign, then unsteadiness during walking caused by weakness, which may be more marked in one of a pair of limbs. The toes are dragged along the ground while walking and the animal knuckles over on the fetlocks when standing. Finally, the animal can rise only with assistance and then becomes permanently recumbent. These stages may be passed through in a period of 4 to 5 days.

The paralysis will be flaccid or spastic depending on the site of the lesion and reflexes will be absent or exaggerated in the

respective states. The dog-sitting position in large animals is compatible with a spinal lesion caudal to the second thoracic vertebral segment. Calves with vertebral osteomyelitis caudal to T2 are usually able to sit up in the dog-sitting position; they are bright and alert and will suck the cow if held up to the teat. In some cases, extensor rigidity of the thoracic limbs resembles the Schiff–Sherrington syndrome and indicates a lesion of the thoracic vertebrae.

Lesions involving the lumbar plexus will result in flaccid paralysis of the pelvic limbs and an absence of the flexor withdrawal reflexes. Lesions involving the sacrococcygeal vertebrae will cause a decrease in tail tone, decreased or absent perineal reflex, and urinary bladder distension.

Pain and hyperesthesia may be evident before motor paralysis appears. The pain may be constant or occur only with movement. In vertebral body osteomyelitis in the horse, vertebral column pain and a fever may be the earliest clinical abnormalities. With neoplasms of the epidural space, the weakness and motor paralysis gradually worsen as the tumor enlarges.

Considerable variation in signs occurs depending on the site of the lesion. There may be local hyperesthesia around the site of the lesion and straining to defecate may be pronounced. Retention of the urine and feces may occur. There is usually no detectable abnormality of the vertebrae on physical examination.

Calves with congenital spinal stenosis are usually unable to stand or can do so only if assisted. There are varying degrees of weakness and ataxia of the pelvic limbs. They are bright and alert and will suck the cow if assisted. Those that survive for several weeks will sometimes assume the dog-sitting position.

In the wobbler horse, circumduction of the limbs with ataxia is typical. The ataxia is usually pronounced in the pelvic limbs, and weakness is evident by toe dragging and the ease with which the horse can be pulled to one side while walking. Ataxia with hypometria is often evident in the thoracic limbs, especially while walking the horse on a slope and with the head elevated.

CLINICAL PATHOLOGY

Radiographic examination of the vertebral column should be performed if the animal is of a suitable size. Myelography is necessary to demonstrate impingement on the spinal cord by a stenotic vertebral canal. The **CSF** may show a cellular reaction if there is some invasion of the spinal canal.

NECROPSY FINDINGS

Gross abnormalities of the vertebrae and the bony spinal canal are usually obvious. Those diseases of the spinal cord characterized by degeneration without gross changes require histologic techniques for a diagnosis.

DIFFERENTIAL DIAGNOSIS

Differentiation between abscess, tumor, and exostosis in the vertebral canal is usually not practicable without radiographic examination. Vertebral osteomyelitis is difficult to detect radiographically, particularly in large animals, because of the overlying tissue. In bovine lymphosarcoma there are frequently signs caused by lesions in other organs. A history of previous trauma may suggest exostosis. The history usually serves to differentiate the lesion from acute trauma.

- Spinal myelitis, myelomalacia, and meningitis may resemble cord compression but are much less common. They are usually associated with encephalitis, encephalomalacia, and cerebral meningitis, respectively.
- Meningitis is characterized by much more severe hyperesthesia and muscle rigidity.
- Rabies in the dumb form may be characterized by a similar syndrome but ascends the cord and is fatal within a 6-day period.

In the newborn there are many congenital defects in which there is defective development of the spinal cord. Most of them are not characterized by compression of the cord, because the diminished function is caused in most cases by an absence of tissue. **Spina bifida**, **syringomyelia,** and **dysraphism** are characterized by hindquarter paralysis or, if the animal is able to stand, by a wide-based stance and overextension of the legs when walking. Some animals are clinically normal.

A generalized degeneration of peripheral nerves such as that described in pigs and cattle causes a similar clinical syndrome and so does **polyradiculoneuritis**. A nonsuppurative **ependymitis**, **meningitis,** and **encephalomyelitis**, such as occurs in equine infectious anemia, may also cause an ataxia syndrome in horses.

Paresis or paralysis of one limb (monoplegia) is caused by lesions in the ventral gray matter, nerve roots, brachial and lumbosacral plexus, and peripheral nerves and muscles of the limbs.

TREATMENT

Successful treatment of partially collapsed lumbar vertebra by dorsal laminectomy has been performed in calves.[1] Surgical treatment of cervical vertebral malformation (fusion of affected cervical vertebrae) is performed in horses, but in farm animals treatment is usually not possible and in most cases slaughter for salvage is recommended. Spinal hematomas of the cervical cord in horses can recover spontaneously but surgical decompression may be helpful in chronic cases.[14]

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BACK PAIN IN HORSES

The subject of back pain, and its relationship to lameness, is a very important one in horses. There is often a lesion in the vertebral canal and by pressing on the cord or peripheral nerves it causes gait abnormalities that suggest the presence of pain, or they actually cause pain. Spondylosis, injury to dorsal spinous processes, and sprain of back muscles are common causes of the same pattern of signs. Because these problems are largely orthopedic ones, and therefore surgical, their discussion is left to other authorities.

It is necessary in horses to differentiate spinal cord lesions from acute nutritional myodystrophy and subacute tying-up syndrome. Those diseases are characterized by high serum creatine kinase and AST activities.

Parasitic Diseases Primarily Affecting the Spinal Cord

EQUINE PROTOZOAL MYELOENCEPHALITIS

SYNOPSIS

Etiology *Sarcocystis neurona,* a protozoon. *Neospora hughesi* is an uncommon cause.

Epidemiology Sporadic disease occasionally occurring as localized epidemics. Endemic throughout most of the Americas. Disease is infectious but not contagious. The definitive host in North America is the opossum (*Didelphis* spp.), and other opossum species in South America.

Clinical signs Variable, but commonly asymmetric spinal ataxia, focal, neurogenic muscle atrophy, with or without cranial nerve dysfunction.

Clinical pathology No characteristic changes in blood or cerebrospinal fluid. Demonstration of intrathecal production of

Continued

antibodies to specific surface proteins (especially SnSAG2, 4/3) by measurement of antibodies in paired serum and CSF samples (ELISA).

Diagnostic confirmation Histologic demonstration of *S. neurona* or *N. hughesi* in nervous tissue.

Lesions Nonsuppurative myeloencephalitis with schizonts and merozoites in neurons, glial cells, and leukocytes.

Treatment Antiprotozoal agents, including ponazuril, diclazuril, or a combination of a sulfonamide and pyrimethamine.

Control Prevent exposure to *S. neurona* by minimizing fecal contamination by opossums of feed. No vaccine available.

ETIOLOGY

The cause is *S. neurona,* an apicomplexan protozoan that causes myeloencephalitis in equids, sea otters, cats, raccoons, red pandas, dogs, and a small number of other mammalian species.[1-3] Fatal encephalitis in Southern sea otters and EPM in horses is strongly linked to *S. neurona* sporocysts shed by opossums.[4,5] Isolates of *S. neurona* can vary in their antigenic composition because some immunodominant surface proteins (SnSAG 1, 2, 3, and 4) vary in either or both of their presence or antigenicity among strains of *S. neurona.* For instance, some strains of *S. neurona* (e.g., SN4), including some that are virulent in horses, lack the major surface antigen SnSAG-1.[6] This heterogeneity in the surface antigen composition of different *S. neurona* isolates could be an important consideration for development of serologic tests and prospective vaccines for EPM.[6]

Neospora spp., including *N. hughesi,* cause myeloencephalitis in horses less frequently than does *S. neurona.*[7-9]

The subsequent discussion refers to EPM caused by *S. neurona,* with specific points made in respect to *N. hughesi.*

EPIDEMIOLOGY

EPM occurs in horses and ponies in Canada, the United States, Central America, and Brazil. Reports of neurologic disease in horses with antibodies to *S. neurona* in France have yet to be confirmed but might represent cases of EPM in native horses outside of the Americas. The disease is reported in other countries in only horses imported from the Americas, and seroprevalence to *S. neurona*-specific antigens in Europe is rare in horses not imported from the Americas.[10] Distribution of the disease appears to correlate with the range of the definitive host, *Didelphis virginiana* in North America, or the related species *D. marsupialis* and *D. albiventris* in South America. The disease has not been reported in donkeys and mules. Neurologic disease associated with *S. neurona* has been reported in armadillos, sea otters, harbor seals, skunks, raccoons, zebra, lynxes, dogs, porpoises, and cats.[2,3,11,12]

The disease usually occurs sporadically in endemic areas, although epidemics on individual farms are reported. The incidence of EPM is estimated to be 14 new cases per 10,000 horses per year. The **case–fatality rate** is approximately 7%, although up to 14% of horses are sold or given away because they are affected by EPM. Approximately 40% of horses recover completely and another 37% improve but do not recover from the disease. Another study reports that only 55% of horses with EPM examined at a referral hospital were alive a minimum of 3 years after diagnosis and treatment.

Seroepidemiologic studies, based on detection by Western immunoblot test of multiple antibodies to *S. neurona* in serum, indicate that 45% to 60% of horses in the United States are exposed to the agent but do not develop disease.[13] Antibodies to *S. neurona* are present in ~49% of 495 horse sera tested with the rSnSAG2/4/3 trivalent ELISA in the Durango state of Mexico, and antibodies to *N. hughesi* are present in 3.0% of horse sera tested (rNhSAG1 ELISA and confirmed by Western blot of *N. hughesi* tachyzoite antigen) in the same region.[14] Approximately 26% of horses in Argentina have antibodies to *S. neurona,* and 39% of horses with neurologic disease are positive versus 22% of clinically normal horses.[15] Four percent of horses in southern Brazil have serum antibodies to *N. hughesi.*[16] Among horses in Israel, 12% of healthy horses are seropositive for antibodies to *N. hughesi,* and 21% of horses with neurologic disease and 38% of mares that aborted are seropositive.[17]

Rates of seropositivity to *S. neurona, N. hughesi,* or both in North America are reported, and differences in proportion of submitted samples are positive for either or both species identified based on month of submission and various animal-related factors. However, the sample was not random and results could have been heavily affected by sampling bias.[18]

Vaccination with a product containing killed *S. neurona* induces a detectable antibody response in both serum and, in approximately 50% of horses, in the CSF.

Risk Factors

Risk factors for development of EPM include season of the year, with the highest incidence of new cases in the summer and fall; age; use; protection of feed; and presence of opossums on the farm.[19] The disease occurs in horses from 2 months to 19 years of age. Horses <1 year of age are at lower risk of developing disease than are horse 1 to 4 years of age. Older horses are less likely to develop the disease. Protection of feed from contamination by opossum feces is associated with a decreased risk of disease, whereas the presence of opossums on the premises was associated with an increased risk of disease. Horses used primarily for racing and showing are at increased risk for developing EPM with an annual incidence of 38 new cases per 10,000 horses for horses used for racing compared with an incidence of 6 cases per 10,000 horses for horses used for pleasure or farm work. Horses used for showing or competition have the highest annual incidence of 51 cases per 10,000 horses per year. The presence of previous illness is a risk factor for development of EPM. Transportation for 55 hours increases the susceptibility to EPM of horses experimentally infected with *S. neurona.* Relative to neurologic (non-EPM) control horses, horses with EPM are more likely to be ≥2 years old and to have a history of cats residing on the premises. Relative to nonneurologic control horses, horses with EPM are more likely to be used for racing or Western performance.[20]

Transmission

S. neurona has the two-host life cycle (predator–prey) typical of other *Sarcocystis* and *Toxoplasma* spp.[21,22] The definitive host is the opossum, *D. virginiana,* and intermediate hosts include raccoons,[23] cats, skunks, sea otters, armadillos, and cowbirds (*Molothrus ater*).[24] The domestic cat, nine-banded armadillo, raccoon, cowbird, and skunk can be infected by ingestion of sporocysts and develop sarcocysts in muscle, which when fed to opossums, induces shedding of sporocysts, confirming the potential for these species to serve as intermediate hosts. Cats living on farms at which EPM has been diagnosed in horses have a higher rate of seroprevalence (40%) than do cats living in a city (10%), providing evidence for a role of cats in the epidemiology of the disease. However, others have detected a lower prevalence of seropositivity (5%) to *S. neurona* among cats in Texas and conclude that cats are not likely to play an important role in the epidemiology of EPM. At least in those areas where raccoons are present they are probably the most important intermediate host.

The definitive host is infected by ingestion of sarcocysts of *S. neurona* encysted in muscle of the intermediate host. The intermediate host is infected by ingestion of sporocysts derived from rupture oocysts passed in the feces of the definitive host. Sporocysts can remain infective in the environment for months, but are probably, based on behavior of other *Sarcocystis* spp. oocysts, killed by drying, high humidity, or freezing and thawing. Birds and insects also serve as transport hosts. Sporocysts ingested by the intermediate host undergo schizogony and ultimately form infective sarcocysts in muscle. *S. neurona* sarcocysts have been detected in the muscle of a 4-month-old filly, suggesting that horses might serve as intermediate hosts of the organism. This finding needs to be confirmed because the

conventional wisdom is that in horses *S. neurona* does not complete schizogony and remains as uninfective merozoites in neural tissue. *S. neurona* sarcocysts do not occur in the muscle of horses; therefore horses are not infective to other animals.

There is no evidence of transplacental infection of foals.

The definitive and intermediate hosts of *N. hughesi* have not been determined. Dogs are the definitive host of the closely related *N. caninum*. *N. hughesi* can be transmitted transplacentally from mares to foals, and it is suggested that infection with this organism can persist in a band of horses by vertical transmision.[25,26]

PATHOGENESIS

Details of the pathogenesis of EPM are unknown. It is assumed that after infection, probably by ingestion, sporocysts excyst and release sporozoites, which penetrate the gastrointestinal tract and enter endothelial cells. Subsequently, meronts (schizonts) develop and on maturation rupture and release merozoites. Schizonts are present in cells of the CNS, including neurons, glial cells, and intrathecal macrophages. Schizonts multiply in the infected cells, as evidenced by the presence of merozoites. Infection induces a nonsuppurative inflammation, characterized by accumulations of lymphocytes, neutrophils, eosinophils, and gitter cells. Infection of neurons, and the associated inflammatory reaction, disrupt normal nervous function and contribute to the clinical signs of weakness, muscle atrophy, and deficits in proprioception.

Mechanisms permitting infection and proliferation of the organism have not been well defined. Horses with EPM have lesser cell-mediated immunity than do asymptomatic horses, and the decrease in cell-mediated immunity appears to be caused by *S. neurona* suppressing immune responses to parasite-derived antigens. However, foals with severe combined immunodeficiency administered *S. neurona* do not develop neurologic disease, despite prolonged parasitemia and infection of visceral organs by the organism, whereas immunocompetent horses do not have prolonged parasitemia but do develop neurologic disease.

CLINICAL FINDINGS

The incubation period after experimental infection of young horses ranges between 28 and 42 days, but is not known for the spontaneous disease.

The clinical findings of EPM in horses are protean, and in endemic areas EPM should be considered as a diagnosis in any horse with clinical signs referable to the nervous system. *S. neurona* can infect any area of the brain and spinal cord, and may affect more than one site in an individual horse, resulting in the wide range of neurologic abnormalities associated with this disease.

Clinical signs of EPM range from barely perceptible changes in gait or behavior to recumbency, muscle atrophy, or seizures. The onset of **signs** can be insidious and gradual, or acute and rapidly progressive. Affected horses do not have increased temperature or heart rate, unless complications of the nervous disease occur.

Spinal ataxia, evident as weakness, hypometria, or hypermetria, and defects in proprioception are common manifestations of EPM. Multifocal spinal or cervical disease causes all four limbs to be affected, whereas lesions caudal to the cervical intumescence cause signs in the rear limbs only. Signs of spinal ataxia range from subtle changes in gait, which are difficult to differentiate from obscure lameness caused by musculoskeletal disease, through obvious spinal ataxia evident as truncal sway, toe dragging, and circumduction of feet, to spontaneous falling and recumbency. **Asymmetry** of clinical signs, in which one limb is affected more than the contralateral limb, is highly suggestive of EPM because CSM and equine degenerative myelopathy usually cause symmetric ataxia.

Lesions in the sacral cord cause signs of **cauda equina syndrome**, including tail paresis and urinary and fecal incontinence.

Lesions affecting spinal cord gray matter cause focal, **asymmetric muscle atrophy,** absent reflexes, or focal areas of **sweating**. Muscles frequently affected include the quadriceps, biceps femoris, epaxial muscles, and the supraspinatus/infraspinatus group. EPM can present as a brachial plexus injury evident as radial nerve paralysis.

CN disease is a common manifestation of EPM. Common syndromes include the following:

- **Vestibular disease** (CN VIII), evident as circling, nystagmus, head tilt, and falling toward the affected side
- **Unilateral facial nerve paralysis** (CN VII), evident as ear droop, lack of palpebral or corneal reflex and menace on the affected side, and displacement of the upper lip and nares away from the side of the lesion
- **Dysphagia** (CNs IX, X, XII) and persistent dorsal displacement of the soft palate
- **Tongue paralysis** (CN XII)
- **Masseter atrophy** and weakness (CN V)
- **Hypalgesia** (lack of sensation) of the nostrils and skin of the face (CN V)

EPM might also manifest as changes in personality and behavior, head-shaking, and seizures.

Clinical disease caused by infection by *N. hughesi* is clinically indistinguishable from that associated with *S. neurona*.[8,9]

CLINICAL PATHOLOGY

There are no characteristic changes in the hemogram or serum biochemical variables. **Diagnosis** has focused on the demonstration of antibodies to *S. neurona* in serum or CSF by Western blot, indirect fluorescence testing, or ELISA. The important concept is use of paired serum and CSF samples to demonstrate intrathecal production of antibodies to differentiate infection associated with neurologic disease from clinically inapparent infection.[13,27-29]

The sensitivity and specificity of Western blot (Sn 80%–89%, Sp 38%–87% on serum, and Sn ~88% and Sp 44%–89% in CSF); indirect FAT (IFAT) (Sn 59%–94%, Sp 71%–100% in serum, and Sn 65%–100%, Sp 90%–99% in CSF); SAG1 ELISA (Sn 13%–68%, Sp 71%–97% in serum); and SAG2,4/3 ELISA (Sn 30%–86%, Sp 37%–88% in serum, Sn 77%–96% and Sp 58%–96% in CSF) for detection of EPM have been recently reviewed.[13,28,29] The combination of serum and CSF testing using tests to detect antibodies to SAG2, 4/3 surface proteins were the most sensitive and specific for diagnosis of horses with clinical signs of neurologic disease.[28,29]

Interpretation of the results of **Western blot** analysis of **CSF** for IgG antibodies to *S. neurona* is problematic because of the potential for blood contamination of the sample during collection, and the high sensitivity but low specificity of the test. Blood contamination of the sample is problematic in horses that are seropositive for antibodies to *S. neurona* and in which it is desired to know if antibodies are present in CSF. Contamination of CSF with blood can introduce antibodies from serum into the otherwise antibody-free CSF, causing a "false"-positive test. Contamination of CSF with small quantities of blood with high concentrations of antibodies to *S. neurona* might not be detectable using RBCs, albumin quotient, or immunoglobulin index, but could yield a positive result on Western blot testing.

Foals of seropositive mares acquire antibodies, but not infection, by ingestion of colostrum from the dam. These antibodies can be detected in both serum and CSF of foals. The mean time for foals to become seronegative for antibodies to *S. neurona* is 4.2 months. Detection of antibodies to *S. neurona* in serum or CSF of foals less than 4 to 6 months of age, even those with neurologic disease, should be interpreted with caution as the antibodies are likely derived from the dam.

An **IFAT** reliably detects antibodies to *S. neurona* in serum and CSF of infected horses.[28] This test has the advantages of providing quantitative results, is cheaper to perform, and is more accurate than immunoblots in the detection of antibodies.

Examination of other variables in CSF is of limited use in the diagnosis of EPM, and measurement of creatine kinase activity in CSF has no diagnostic usefulness. The use of the **albumin quotient** or **IgG index** to detect blood contamination of CSF, or the

intrathecal production of IgG, is unreliable and not useful in the diagnosis of EPM.

NECROPSY

Lesions are limited to the spinal cord and brain, with the exception of neurogenic muscle atrophy. Gross lesions of hemorrhage and malacia may be visible in the CNS tissue. The lesions are asymmetric, but may be more frequently encountered in the cervical and lumbar intumescences of the spinal cord. Histologic examination reveals multifocal necrosis of the nervous tissue with an accompanying infiltration of macrophages, lymphocytes, neutrophils, and occasional eosinophils. This reaction is predomnantly nonsuppurative and usually includes a degree of perivascular cuffing. Schizonts or free merozoites may be evident in tissues but are difficult to locate without IHC stains. The sensitivity of screening for the parasite in hematoxylin and eosin–stained sections of nervous tissue from cases with histologic changes suggestive of EPM was only 20%. The sensitivity improved to 51% when IHC staining of the tissue was used. The same interpretative problems encountered when testing antemortem CSF samples apply when the fluid is collected at postmortem. Isolation in cell culture systems is possible but rarely attempted in diagnostic laboratories. PCR tests for these apicomplexan parasites can yield false negatives because of the random distribution of the parasite within CNS tissue.

Samples for Confirmation of Diagnosis

- **Histology:** fixed spinal cord (several levels, including cervical and lumbar intumescences) and half of brain, including the entire brainstem, CN VII in some cases (LM, IHC, PCR).

DIFFERENTIAL DIAGNOSIS

The clinical diagnosis of EPM should be based on the detection of unequivocal neurologic abnormalities consistent with EPM, ruling out of other causes of neurologic disease (listed next) and the detection of antibodies to *S. neurona* or N. hughesi in uncontaminated samples of cerebrospinal fluid and serum to confirm intrathecal production of specific antibodies.[13] A favorable response to treatment specific for EPM increases the likelihood that the horse has EPM. A definitive diagnosis can only be achieved by necropsy.

- Spinal ataxia.
- Cauda equina syndrome: EPM should be differentiated from polyneuritis equi, equine herpesvirus-1 myelopathy, and injection of long-acting anesthetics or alcohol around sacral nerve roots.
- Peripheral nerve lesions: other causes of focal muscle atrophy, such as brachial plexus injury, damage to the supraspinatus nerve, or disuse atrophy can be differentiated from EPM on history and clinical signs.
- Cranial nerve disease: signs of vestibular disease, facial or trigeminal nerve dysfunction, and dysphagia associated with EPM should be differentiated from the following:
  - Middle ear infection
  - Guttural pouch mycosis
  - Arthritis and fracture of the temporohyoid articulation
  - Head trauma

TREATMENT

Specific treatment of EPM involves the administration of **antiprotozoal drugs** including ponazuril, diclazuril, nitazoxanide, or the combination of pyrimethamine and sulfadiazine.

Administration of the combination of sulfadiazine (or similar drug, 20 mg/kg, orally) and pyrimethamine (1–2 mg/kg, orally) every 24 hours given 1 hour before feeding is effective in approximately 60% to 70% of cases.[13] This treatment is continued for at least 90 days if complete resolution of clinical abnormalities occurs, or longer if the signs of EPM do not resolve. **Adverse effects** of the administration of a combination of a sulfonamide and pyrimethamine include enterocolitis, anemia, and abortion. Folic acid is often added to the diet of horses being treated for EPM, but this cannot be recommended because of its lack of efficacy in preventing anemia in treated horses and its ability to cause severe congenital abnormalities in foals born to treated mares and anemia and leukopenia in adult horses. Orally administered synthetic folates interfere with normal folate metabolism in horses being administered antifolate drugs resulting, paradoxically, in folate deficiency. Adequate intake of folates in antiprotozoal-treated horses can be assured by feeding a diet containing good quality green foliage.

Ponazuril, an active metabolite of toltrazuril, is usually administered at a dosage of 5 mg/kg BW orally once daily for 28 days. At this dosage, and at 10 mg/kg orally once daily for 28 days, administration of the drug results in resolution of clinical signs in approximately 60% of horses with EPM. The initial dosage is 5 mg/kg every 24 hours, which is continued for 28 days if signs of improvement are evident after 14 days. If signs of improvement are not seen after 14 days, the dosage is increased to 10 mg/kg orally every 24 for 14 days. Few adverse effects are noted, even at 30 mg/kg orally once daily for 28 days. **Diclazuril,** which is available in the United States as a pelleted product for oral administration to horses, is similarly effective and free of serious adverse effects.[13,30-32]

Nitazoxanide administration was associated with adverse effects including fever, anorexia, diarrhea, and worsening of clinical signs of neurologic disease. It is no longer recommended for treatment of EPM.

The decision to **stop treatment** in horses that do not completely recover is difficult. Some authorities recommend resampling CSF and continuing treatment until antibodies to *S. neurona* are no longer detectable. However, given that normal horses often have antibodies in their CSF, and that some treated horses never lose their positive Western blot test, the decision to stop treatment should not be based entirely on this variable.

Some horses have a transient worsening of clinical signs in the first week of treatment. This is presumed to be from the effect of the antiprotozoal agent causing death of protozoa with subsequent inflammation and further impairment of neurologic function. Relapse of the disease occurs in some horses when administration of antiprotozoal medication is stopped.

Supportive treatment of affected horses includes antiinflammatory drugs (flunixin meglumine, 1 mg/kg intravenously, every 8–12 hours; dimethyl sulfoxide, 1 g/kg as a 10% solution in isotonic saline intravenously, every 24 hours for 3 days) and nutritional support for horses that cannot eat. Flunixin meglumine is often administered twice daily for the first 3 to 5 days of treatment with ponazuril or nitazoxanide, purportedly to reduce the inflammatory effects of death of protozoa in the CNS.

Treatment of EPM associated with infection by *N. hughesi* is based on the same principles and medications as treatment of disease associated with *S. neurona*.[8]

CONTROL

Preventing contamination of feed and water with opossum feces is essential for preventing EPM in animals. Sporocysts of *S. neurona* are resistant to the usual concentrations of many of the conventional disinfectants including sodium hypochlorite (bleach), 2% chlorhexidine, 1% betadine, 5% benzyl chlorophenol, 13% phenol, 6% benzyl ammonium chloride, and 10% formalin. The organism is killed by heating to 55°C for 15 minutes or 60°C (140°F) for 1 minute. Although survival of sporocysts in different environmental conditions outdoors has not been tested, sporocysts remained viable at 4°C (131°F) for months.[22]

Because protection of feed from contamination by opossums has been demonstrated to reduce the risk of horses developing EPM, it is prudent to use measures to reduce the exposure of animals and feed to opossum feces, and possibly feces of birds that might act as transport hosts.

There is interest in pharmacologic means of preventing infection of horses by *S. neurona*. Pyrantel pamoate has some efficacy against *S. neurona* in vitro but daily administration (2.6 mg/kg BW in feed) does not prevent *S. neurona* infection of horses. Daily

administration of low doses of **diclazuril** to foals in endemic areas significantly reduces the rate of seroconversion.[30-32]

There is no vaccine available for prevention of EPM associated with either *S. neurona* or *N. hughesi.*[22]

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CEREBROSPINAL NEMATODIASIS (ELAPHOSTRONGYLOSIS)

Cerebrospinal nematodiasis, cerebrospinal elaphostrongylosis (CSE) or neurofilariosis are disease of sheep, goats, and camelids caused by infestation of the brain and spinal cord with the nematode *Elaphostrongylus* and related genera. This genus is closely related to the lungworms of small ruminants but is found in the cranial subarachnoid space, cranial venous sinuses, and occasionally in the spinal subarachnoid space. *Parelaphostrongylus tenuis* occurs in white-tailed deer[1] and moose[2] in eastern North America and parts of western Canada, *E. cervi* in deer, sheep, and goat in Europe[3-5] and New Zealand, and *E. rangiferi* in reindeer in Scandinavia. *P. odocoilei* has been found to infect bighorn sheep in North America.[6] Eggs or larvae are carried to the lungs, undergo a tracheal migration, and the first-stage larvae are passed in the feces. The larvae are quite resistant to adverse environmental conditions and enter slugs or snails to develop into infective larvae. The lifecycle is complete when infected molluscs are ingested by deer and the larvae penetrate the abomasum and migrate, possibly along spinal nerves, to the spinal cord where they develop into adults and migrate into the subarachnoid space.

Clinical signs are not seen in infected deer, but in sheep, goats and New World Camelids the worm continually moves through nervous system tissue causing limping and incoordination followed by almost complete paralysis of the hindlimbs or of the neck, body, and all four legs.[3,7-9] There are usually no signs of cerebral involvement, and affected animals remain bright and continue to eat. If given supportive treatment, they may survive for at least 1 month. *P. tenuis* also transmits to moose and is responsible for the nervous signs in "moose sickness," including the following[4]:

- Weakness
- Incoordination
- Circling
- Impaired vision
- Blindness
- Abnormal carriage of the head
- Paralysis
- Lack of fear of man
- Aggressiveness

Histopathologic lesions include axonal degeneration and swelling, perivascular cuffing, presence of hemosiderin-laden macrophages, and increased numbers of eosinophils.[9,10]

Clinical signs of spinal cord disease attributed to Parelaphostrongylus tenuis appear to diminish after treatment with high doses of oral fenbendazole (50 mg/kg, daily for five days), although randomized clinical trials have not been completed to confirm this impression.

No reliable treatment is available for CSE. Ivermectin has no effect on the adult worms, possibly because the large molecules of this compound cannot pass the blood-brain barrier.[5] One clinical report describes the treatment of 17 light to moderately affected goats with an NSAID (flunixin meglumine) together with ivermectin and fenbendazole for 5 days.[6] Complete recovery occurred in three, partial recovery in eight, but euthanasia was necessary for the remainder.

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SETARIA

Setaria spp. are long (5- to 10-cm) thread-like filarial nematodes commonly found in the peritoneal cavity of most domestic animals. *S. labiato-papillosa* is a cosmopolitan parasite of cattle, whereas *S. digitata* and the closely related, and perhaps synonymous, species *S. marshalli* occur only in Asia.[1] *S. equina* is found worldwide in horses. *S. tundra* infects and causes significant economic losses in reindeer in Finland.[2,3] Adult females produce motile embryos (microfilariae) that circulate in the peripheral blood of the infected animal and are taken up by mosquitoes. Infective larvae develop in the intermediate host and are released when the mosquito subsequently feeds. *S. labiato-papillosa* reaches maturity in cattle in 8 to 10 months. Despite their size, the presence of these worms in the abdominal cavity causes no significant clinical effect.

Serious disease may result if *S. labiato-papillosa* or *S. digitata* infect animals other than their own natural host, especially horses, sheep, goats, and humans. In these hosts, they migrate in an abnormal manner causing epizootic cerebrospinal nematodosis (with local names including lumbar paralysis and kumri) when they invade the brain and spinal cord. Juvenile *S. digitata* may also invade the eye. Although *Setaria* is found in cattle in many countries, cerebrospinal nematodosis is largely restricted to Israel, Japan, China, Korea, India, and Sri Lanka. The incidence is increasing in Taiwan, and a single case has been reported from the United States. Ocular filariasis is seen most commonly in Japan. These diseases occur during summer and autumn when the vectors are most prevalent. The cerebrospinal form sometimes occurs in epidemic proportions, causing the death of horses, sheep, and goats.

Cerebrospinal nematodiosis may be rapid in onset with affected animals dying within a few days or it may occur gradually over a few days. There may be acute or subacute paresis with weakness and incoordination or paralysis involving the hindlegs most commonly, but sometimes all four legs are involved. Recovery is only partial in many animals but others show only a mild neurologic disorder, which gradually becomes indiscernible. There are no systemic signs and the animals may continue to eat. Other diseases causing similar clinical signs include enzootic equine ataxia in horses and paralytic rabies in sheep and goats as lesions as well as traumatic injury, spinal cord abscess, warble fly larvae, *S. vulgaris,* or *H. gingivalis.*

At necropsy, there are no macroscopic changes and sections need to be taken from many levels of the spinal cord to find histologic lesions. Focal areas of malacia or microcavitation are seen and in adjacent sites there may be loss of myelin, axonal swelling, degeneration, and gitter cell formation. Migratory pathways are indicated by necrotic tracts. Where nervous signs have been present for only a few days, a worm or worm fragments may occasionally be found. Molecular techniques have been developed for identifying the responsible species.

S. tundra causes peritonitis, perihepatitis, and significant decrease in body condition score in reindeer calves.[2,3] Treatment of infected reindeer with ivermectin (0.2 mg/kg, subcutaneously) has up to 95% efficacy of worm elimination.[2] Application of biting insect repellant (deltamethrin) significantly decreases *S. tundra* infections in reindeer.[2]

Anthelmintics will not resolve existing lesions but may prevent further damage. Little has been published on treatment or control. Ivermectin gave moderate efficacy (80%–88%) against adult *S. equina* in ponies. In a field study, none of 221 goats and sheep injected twice with ivermectin at a dose of 0.2 mg/kg developed setariasis, whereas 17 of 303 noninjected animals suffered from the disease.

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Toxic Diseases Primarily Affecting the Spinal Cord

STRINGHALT

Stringhalt is an involuntary, exaggerated flexion of the hock during walking. It can affect one or both hindlimbs. Classic stringhalt occurs sporadically, is usually unilateral, and is usually irreversible without surgical intervention. Stringhalt can also occur secondarily to injury to the dorsal metatarsus.

A clinically identical disease, Australian stringhalt, occurs in outbreaks in Australia, New Zealand, California, Japan, Europe, the UK, Brazil, and Chile.[1-5] The outbreaks tend to occur in late summer or autumn and are related to drought conditions or overgrazing of pasture with consequent ingestion of plants that would otherwise not be eaten. Outbreaks in Australia, California, and Virginia are related to the ingestion of ***Hypochaeris radicata*** (flatweed, cats ear).[4] Other plants suspected to play a role in the etiology include *Taraxacum officinale* (dandelion), *Arctotheca calendula* (capeweed), or *Malva parviflora* (mallow) but good evidence of the role of any of these latter plants is lacking.

The **pathogenesis** of the disorder is likely related to the presence of toxins in *H. radicata,* especially after it is stressed.[6] The toxin or toxins have not been identified but are unlikely to be mycotoxins.[4] The disease has been **experimentally induced** by feeding a colt 9.8 kg per day for 19 days of *H. radicata* harvested fresh from a pasture on which horses had developed disease.[5] The disease resolved when the colt was fed *H radicata* from a pasture with unaffected horses. Signs in the colt resolved within 15 days of last feeding the toxic plant.[5]

Clinical signs are distinctive. The abnormal movement is only elicited when the horse begins to move forward. The characteristic movement occurs in mildly affected horses when they are backed or turned. Most cases are manifested by a flexion of the hock that can be violent enough for the horse to kick itself in the abdomen. The hoof is held in this position for a moment and then stamped hard on the ground. If both hindlegs are affected, progress is very slow and difficult and the horses often use a bunny-hopping gait. In the most severe cases the horse is unable to rise without assistance. The horse's general health is unaffected, although it may be difficult for it to graze. Some cases have other signs of neurologic disease such as stiffness of the forelimbs or respiratory distress caused by laryngeal paralysis. Many affected horses have unilateral (usually left) laryngeal hemiplegia evident on endoscopic examination of the larynx.

EMG examination reveals markedly abnormal activity including prolonged insertion activity, fibrillation potentials, and positive waves at rest and enhanced EMG activity in the right lateral digital extensor muscle on muscle contraction consistent with denervation. The changes are most severe in the long digital extensor muscle. Most horses recover without treatment, although complete recovery might not occur for over 1 year.

Biopsy of the superficial peroneal nerve and the long digital extensor muscle can be useful in providing an antemortem diagnosis. The superficial peroneal nerve of an affected horse had loss of large myelinated fibers, axonal degeneration, and myelin splitting.[7]

There are no characteristic abnormalities in a complete blood count or serum biochemical profile. Pathologic findings are restricted to a peripheral neuropathy in the tibial, superficial peroneal, and medial plantar nerves and in the left and right recurrent laryngeal nerves. Lesions in affected muscles are consistent with denervation atrophy and fiber type grouping.

The signs of the disease are characteristic. Differential diagnosis of the disease involving one leg is ossifying myopathy of the semimembranosus and semitendinosus muscles. Lead toxicosis can induce similar signs in horses.

Recovery is spontaneous in most cases (50% over an 8-month period in one large case series).[2]

Treatment with phenytoin (15 mg/kg orally daily for 14 days) effects some improvement but the signs recur within 1 or 2 days after treatment is discontinued.[2] Myotenectomy of the lateral digital extensor muscle and tendon is reported to provide immediate relief in affected horses, even in those horses with severe bilateral disease.

Control involves the prevention of overgrazing of pastures, particularly during droughts, and restricting or eliminating access to *H. radicata.*

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Inherited Diseases Primarily Affecting the Spinal Cord

SPASTIC PARESIS OF CATTLE (ELSO HEEL)

This disease occurs in the Holstein, Aberdeen Angus, Red Danish, Ayrshire, Beef Shorthorn, Poll Hereford, Murray Grey, and many other breeds of cattle. It has been observed in crossbred Brahman cattle and in an Ayrshire × Beef Shorthorn crossbred steer. The disease occurs principally in calves, with signs appearing from several weeks to 6 months or more after birth. Occasional cases are reported as developing in adult European cattle, and there is one report of the occurrence of the disease in adult Indian cattle. The disease was first termed Elso heel based on its first description in 1922 as a heritable disease from an East Friesian bull named Elso II. The preferred name spastic paresis was first used in 1932 to emphasize the primary defect.[1]

It has been held for a long time that the disease is inherited, and the principal argument has centered on the mode of inheritance. Attempts to determine this have shown that the rate of occurrence in planned test matings is so low that, if inheritance is involved, it can only be the inheritance of a susceptibility to the disease. It is suggested that different time appearances represent a single disease entity with varying expressivity, with the late forms affected by cumulative environmental factors. A proposed hypothesis is of a gene with increased penetrance in the homozygote, with weak penetrance in the heterozygote, acting on a polygenic basis

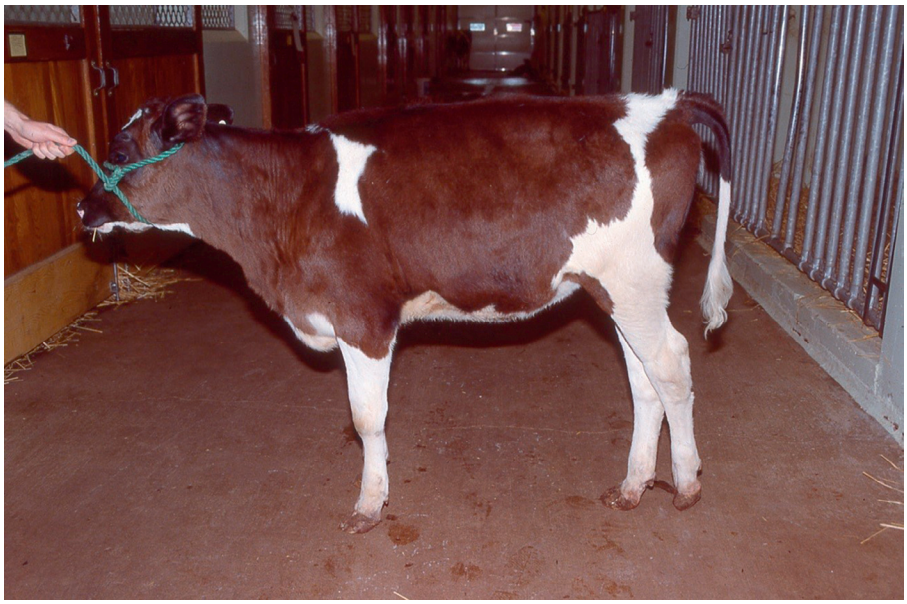

Fig. 14-19 Spastic paresis in an 8-month-old Holstein Friesian heifer. Both hindlegs are excessively straight, the left hindleg is held caudally and above the ground, and the tail is characteristically held away from the body.

dependent on external factors. Males appear to be affected more often than females, but a clear sex predilection has not been identified. The prevalence of disease appears to be <1% in all breeds.[1] Infectious agents causing transmissible subacute spongiform encephalopathies interacting with trace elements such as lithium have been suggested as etiologic agents, but there is no evidence to support this hypothesis.

In all forms of the disease in most cattle breeds (exceptions being the Belgian Blue and Romagnola in which the excessive tone occurs in the quadriceps femoris muscle; the lesion is usually bilateral) there is excessive tone of the gastrocnemius muscle and straightness of the hock, usually more marked in one hindleg. If only one leg is affected, it may be thrust out behind while the calf is walking and advanced with a restricted, swinging motion often without touching the ground. There is no resistance to passive flexion of the limb and the animal appears normal while sitting. Clinical signs are most exaggerated after immediately encouraging a sitting animal to stand. The gastrocnemius and perforatus muscles are rigid and in a state of spastic contraction. There is a characteristic elevation of the tail (Fig. 14-19). The lameness becomes progressively worse and affected animals spend much time lying down. Much BW is lost and the animal is usually destroyed between 1 and 2 years of age.

Minor lesions described as regressive changes in the neurons of the red nucleus, in the reticular substance, and in the lateral vestibular nucleus are of doubtful significance, as are the observed reduction in inorganic phosphate and ascorbic acid levels in the blood and CSF of affected calves. A lower than normal CSF concentration of a central neurotransmitter, dopamine, could also be an effect rather than a cause.

There are demonstrable lesions on radiologic examination of the tarsus with remodeling of the calcaneus bone and development of an enlarged and irregular epiphysis of the calcaneus caused by chronic and repetitive strain that straightens the hindlimb. Extensive examinations of muscles and tendons have failed to reveal histologic abnormalities. The absence of any structural lesion and the variation in intensity of the abnormality suggests that it is a functional one. An **overactive stretch reflex** is thought to be responsible for the clinical signs, possibly caused by defective glycinergic synaptic transmission and alteration of calcium signaling proteins (Fig. 14-20).[1,2]

The diagnosis of spastic paresis is based on history, signalment, clinical signs, and progressive nature of the disease. A genetic test is currently unavailable because the underlying gene defect(s) have yet to be identified. An epidural injection of 0.38% procaine solution diminishes the clinical signs of spastic contracture within 10 to 15 minute and has provided a useful supporting diagnostic test when the gastrocnemius is the principal muscle of contracture; it is less helpful in cases of spastic contraction of the quadriceps. In the latter case ultrasound-guided infiltration around the femoral nerve with local anesthetic solution may be attempted.[1,3]

In Europe, affected animals are kept for breeding purposes, especially if they are double-muscled. They are kept because of the efficacy of the curative surgical operation (partial tibial neurectomy) and for the high incidence of double-muscling in such calves. In the Holstein breed, and several German breeds, bulls that sire affected calves have been observed to have very straight hocks and to suffer from various forms of stifle and hock lameness early in life.

The only effective treatment is surgical. Several surgical techniques including tenectomy, partial tibial neurectomy, and triple tenectomy have been described. The most effective technique appears to be partial tibial neurectomy performed under caudal epidural anesthesia with electrical stimulation used to identify the tibial nerve.[4] In a large case series on 113 Belgian Blue calves with spastic paresis, a telephone follow-up of the owners 3 months later revealed good results in 83%, a considerable improvement in 4%, severe hyperflexion of the hock necessitating early culling for slaughter in 5%, and in 8% there was little or no improvement.

FURTHER READING

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INHERITED CONGENITAL MYOCLONUS (HEREDITARY NEURAXIAL EDEMA)

This congenital defect of the nervous system has been reported only in Poll Hereford cattle or their crossbreds and appears to be transmitted by inheritance in an autosomal recessive pattern. A similar disease has been tentatively recorded in Peruvian Paso horses. At birth affected calves are unable to sit up or rise and are very sensitive to external stimuli, manifested by extreme extensor spasm, including fixation of thoracic muscles and apnea, especially if lifted and held upright. The response is one of hyperesthesia with myoclonic jerks of skeletal muscles in response to external stimuli or spontaneously. The intellect of the calves seems unaffected, vision is normal, they drink well, and can be reared but at a great cost in time. Intercurrent disease is common and calves usually die of pneumonia or enteritis before they are 1 month old.

All affected calves have subluxations of the hip joints or epiphyseal fractures of the femoral head caused by muscle spasms in the fetus. Their gestation length is shorter than that of normal calves by 9 days.

There are no microscopic lesions in the CNS, but there is a biochemical defect—severe alterations in spinal cord glycine-mediated neurotransmission. The specific and marked defect in glycine receptors and the increase in neuronal uptake of glycine are

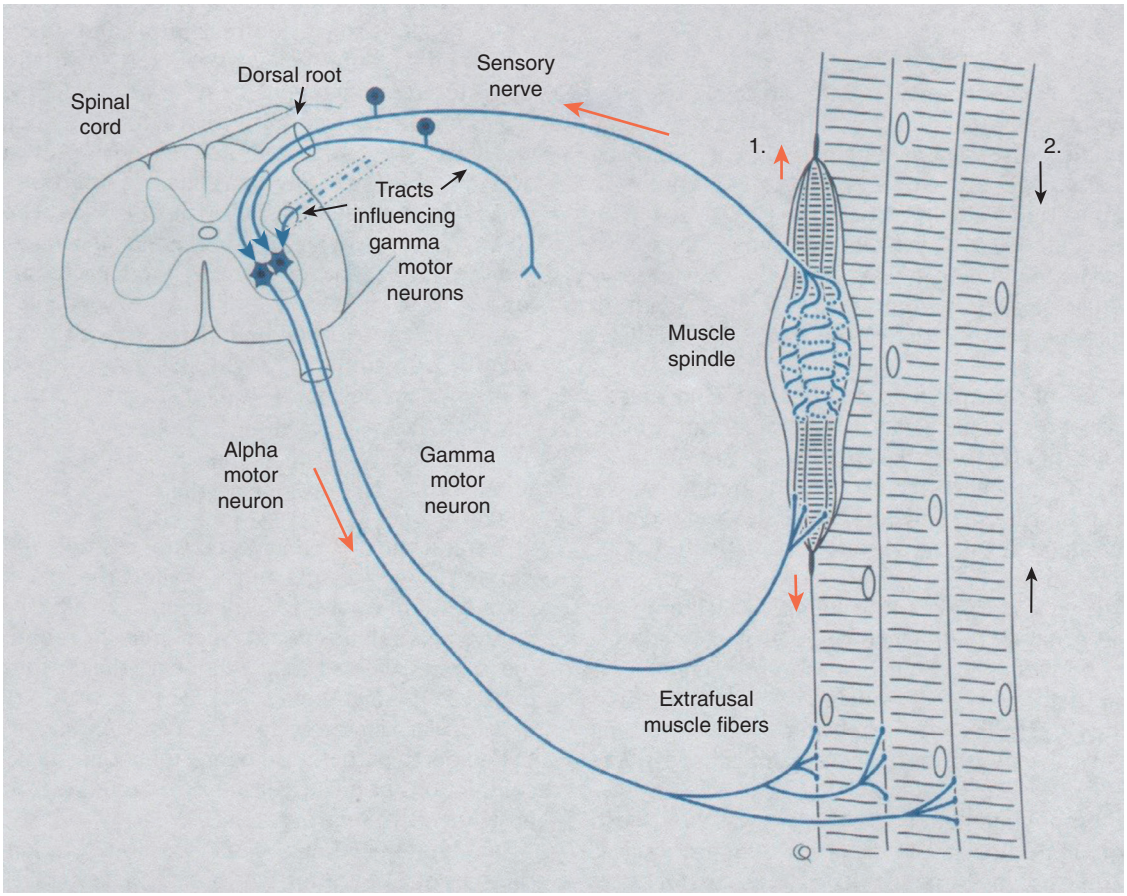

Fig. 14-20 Simplified drawing of the γ-motor neuron system. In cattle with spastic paresis, spinal cord neurons are thought to provide defective control to the γ-motor neuron system, most likely by overstimulation or sufficient inhibition. During the normal stretch reflex the extrafusal skeletal muscle fibers are lengthened, stretching the muscle spindle. This stretch is detected and a signal sent via the afferent axon to the dorsal root. The signal is then sent directly to the α-motor neurons, resulting in muscle contraction. γ-Motor neurons in the ventral spinal cord that are controlled by the central nervous system appear to inappropriately modulate the sensitivity of the stretch reflex system, resulting in sustained and excessive contraction. (Reproduced with permission from De Vlamynck C. *Vet J* 2014; 202:229-235.)

accompanied by a change in the major inhibitory system in the cerebral cortex. It has also been shown that there is a specific and marked deficit of [^{3}H] strychnine-binding sites in the spinal cord. The disease needs to be differentiated from two other congenital, presumed hereditary, diseases of newborn Herefords—maple syrup urine disease and "congenital brain edema"—in which spongy degeneration of the CNS is accompanied by severe edema of the gray and white matter. These two diseases are assumed to represent those cases of congenital disease, originally bracketed with inherited congenital myoclonus, in which there was vacuolation of nervous tissue in the CNS.

INHERITED SPINAL DYSMYELINATION

Bovine spinal dysmyelination is a congenital neurologic disease occurring in several national cattle breeds upgraded with American Brown Swiss cattle. The disease was first described in the Red Danish Dairy breed. In Denmark, all cases are genetically related to the ABS bull White Cloud Jason's Elegant. It is inherited as an autosomal recessive trait. Genetic mapping of the gene in crossbred American Brown Swiss cattle to the bovine chromosome II has been done.

Clinically, in calves there is lateral recumbency, opisthotonus, limb extension, normal to increased reflexes, and mental alertness. Dysmyelination is present, including axonal degeneration and astrogliosis, in spinal tracts, especially the ascending gracile funiculus and dorsolateral spinocerebellar tracts and the descending sulcomarginal tract. This is probably the same defect as spinal muscular atrophy.

INHERITED NEURODEGENERATION (SHAKER CALF SYNDROME)

This is an inherited, degenerative disorder of horned **Hereford** calves. Newborn calves show severe tremor, difficulty in rising, spastic gait, and aphonia. Terminally there is spastic paraplegia. Histologically, there are accumulations of neurofilaments within neurons. A similar disease in **Holstein Friesians** occurs only in males. There are severe degenerative changes in the spinal cord with spongiform lesions and some cavitation. It has the epidemiologic distribution of a sex-linked recessive mutation.

INHERITED SPINAL DYSRAPHISM

This is found as a congenital defect in Charolais calves and is associated with arthrogryposis and cleft palate. Spinal cord anomalies can be associated with a large number of vertebral abnormalities because of the close association of spinal cord and vertebral column during embryology. Other developmental defects that lead to congenital abnormalities include spinal cord hypoplasia and syringomyelia (tubular cystic cavitation containing CSF that extends over several spinal cord segments) in calves[1,2]; however, many of these developmental abnormalities are accidents of embryology and do not necessarily imply the presence of an inherited condition.

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INHERITED CONGENITAL POSTERIOR PARALYSIS

Two inherited forms of congenital posterior paralysis are recorded in cattle. In Norwegian Red Poll cattle posterior paralysis is apparent in affected calves at birth. Opisthotonus and muscle tremor are also present. No histologic lesions have been found. The disease is conditioned by an inherited recessive factor. In Red Danish and Bulgarian Red cattle a similar condition occurs but there is spastic extension of the limbs, particularly the hindlimbs, and tendon reflexes are exaggerated. Histologic examination has revealed degenerative changes in midbrain motor nuclei. Both defects are lethal because of prolonged recumbency.

An inherited posterior paralysis has been recorded in several breeds of swine in Europe. Affected pigs are able to move their hindlimbs but are unable to stand on them. They are normal in other respects. Degeneration of neurons is evident in cerebral cortex, midbrain, cerebellum, medulla, and spinal cord. The disease is conditioned by the inheritance of a recessive character. An inherited progressive ataxia is also recorded in Yorkshire pigs.

INHERITED BOVINE DEGENERATIVE AXONOPATHY

Reported in Holstein Friesian calves in Australia, most affected calves are affected at birth by recumbency; hyperesthesia or depression; rigidity of limbs; tremor, especially of the head; nystagmus, apparent blindness, and the development of opisthotonus and tetanic spasms when stimulated. At necropsy the consistent lesion is a severe, diffuse, axonal swelling and loss in the spinal cord and brainstem. The cause is unknown but the indicators point to an inherited cause.

DEGENERATIVE AXONOPATHY OF TYROLEAN GREY CATTLE

A new neurologic disease was identified in Tyrolean Grey cattle in Switzerland in 2003 and was initially named Demetz syndrome.[1] The clinical presentation is similar to that seen in weaver syndrome of Brown Swiss cattle but clinical signs are first evident at 4 to 6 weeks of age. Calves exhibit mild ambulatory paraparesis with moderate to severe ataxia being more severely affected in the hindlimbs. The disease is progressive and affected calves are usually slaughtered by 10 months of age.

A mutation in the mitofusin 2 gene (a mitochondrial membrane protein) was identified that truncates the last 22 amino acids. Pedigree analysis indicated that the gene mutation occurred before 1972, and gene testing indicated a current carrier frequency of approximately 10%. Marker assisted selection is currently being used to eliminate degenerative axonopathy from this breed.

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CENTRAL AND PERIPHERAL AXONOPATHY OF MAINE ANJOU (ROUGE-DES-PRÉS) CATTLE

A new neurologic disease was identified in Maine Anjou cattle in France in 2008. Affected calves were 1 to 4 months of age and exhibited mild to severe truncal ataxia with mild to moderate paraparesis. The pelvic limbs were much more severely affected than the thoracic limbs. Clinical signs were rapidly progressive and calves became recumbent within 1 to 3 weeks of being examined, at which time they were euthanized. Mentation remained normal for the calves.

Histopathologic examination revealed marked degeneration of axons and myelin and the dorsolateral and ventromedial funiculi of the distal spinal cord (important tracts for transmitting proprioceptive information from the hindlimbs), lateral vestibular nuclei, caudal cerebellar peduncles, and thoracic nuclei.

INHERITED PROGRESSIVE DEGENERATIVE MYELOENCEPHALOPATHY (WEAVER SYNDROME) OF BROWN SWISS CATTLE

The defect is inherited in Brown Swiss cattle. It appears first in calves when they are 6 months to 2 years old, with a small number more than 2 years, and is manifested by progressive bilateral hindlimb weakness and proprioceptive deficits causing difficulty in rising and a weaving, hypermetric gait, goose-stepping with the forelimbs, and dragging the hindlimbs. The limb reflexes are normal. The calves are bright and alert throughout. There is a broad-based stance and finally recumbency and, after a course of 12 to 18 months, inevitable euthanasia. Necropsy lesions include axonal degeneration, including spheroid formation, and vacuolation of white matter in the cerebellum and at all levels of the spinal cord but especially in the thoracic segment. There is some neurogenic atrophy of muscles but there is no muscular dystrophy. The defect can be identified by examination of chromosomes. It appears to be linked chromosomally with high milk yield traits.

INHERITED PROGRESSIVE ATAXIA

This well-recognized disease occurs in Charolais cattle. The first onset of signs is at about 12 months of age when the gait is seen to be stiff and stumbling, especially in the hindlimbs, and the hindtoes are dragged. The ataxia may be asymmetric, and the animal cannot back up. The ataxia progresses over a period of 1 to 2 years. Affected animals tend to be down a lot and have difficulty in rising and posturing for urination. Urination is abnormal; it is a squirting but continuous flow that soils the tail. Some affected animals nod their heads from side to side when excited. Both males and females are affected. It has been described occurring in 2-year-old Charolais steer in New Zealand. Characteristic necropsy lesions are confined to the CNS and are histopathologic. The white matter of the cerebellum and internal capsule contains multiple foci of oligodendroglial dysplasia. The somatic lymph nodes contain nodules of hyperplastic lymphoid follicles, some catarrh of the medullae of the nodes, and an accumulation of eosinophils.

INHERITED SPINAL MYELINOPATHY

There is a progressive spinal myelinopathy of Murray Grey cattle, similar to that seen in Charolais cattle. It is possibly genetic in origin. Some calves are affected at birth; others do not become affected until 1 year old. The syndrome is one of a progressing paresis, without significant ataxia leading to paresis and permanent recumbency. There are degenerative lesions in spinal cord, midbrain, and cerebellum. The disease is conditioned by an autosomal recessive gene.

INHERITED PERIODIC SPASTICITY OF CATTLE

Inherited periodic spasticity has been observed in Holstein and Guernsey cattle and usually does not appear until the animals are adults. A recent report described it in a Canadian Hereford bull with an early onset between 1 and 2 years of age. It is a particular problem in mature bulls maintained in artificial insemination centers. In the early stages the signs are apparent only on rising; the hindlimbs are stretched out behind and the back depressed (Fig. 14-21). Marked tremor of the hindquarters may be noted. Initially the attacks persist only for a few seconds but are of longer duration as the disease progresses and may eventually last for up to 30 minutes. Movement is usually impossible during the attacks. The tetanic episodes fluctuate in their severity from time to time but there is never any abnormality of consciousness. Lesions of the vertebrae have been recorded but no lesions have been found in the nervous system. Idiopathic muscle

Fig. 14-21 Inherited periodic spasticity in a Holstein Friesian bull. The signs are apparent only on rising; the hindlimbs are stretched out behind and the back depressed.

cramps have been suggested as a cause. The disease is familial and the mode of inheritance appears to be by inheritance of a single recessive factor with incomplete penetrance.

Administration of the spinal cord depressant, mephenesin (3–4 g/100 kg BW given orally in three divided doses and repeated for 2–3 days) controls the more severe signs. A single course of treatment may be effective for some weeks.

NEURAXONAL DYSTROPHY

Neuraxonal dystrophy represents a heterogeneous group of degenerative diseases of genetic or acquired etiology that is characterized by spheroidal swellings of axons called spheroid bodies, which is the result of accumulation of axoplasmic organelles including neurofilaments. The change may be physiologic (caused by normal aging) or pathologic and are categorized as primary (familial) or secondary (acquired).[1] EDM is considered a more severe variant of neuraxonal dystrophy and is discussed separately.

NEURAXONAL DYSTROPHY OF SHEEP (SEGMENTED AXONOPATHY)

This is reported in Suffolk, Merino, Romney, Perendale, Coopworth, and crossbred sheep.[1] An inherited defect (autosomal recessive) is suspected in all cases. Abnormalities appear related to abnormal axonal transport and the inability to maintain integrity of the axon and their associated myelin sheaths.[2]

In **Coopworth sheep** the lambs are affected at birth but have a progressive syndrome in which cerebellar and proprioceptive signs predominate. Most die by 6 weeks of age. Large axonal spheroids are present in the spinal cord and midbrain, and there is a severe depletion of Purkinje cells in the cerebellum.

In **Suffolk** sheep the disease does not appear until 1 to 6 months; signs are a gradual onset of ataxia, followed by recumbency, leading to death or euthanasia. Spheroids in CNS axons are characteristic, mostly in the spinal cord and cerebellum, and contain large amounts of amyloid precursor protein.[1]

The disease in **Merinos** is in fine-wool sheep, is probably the same disease as that previously called **Murrurrundi disease**, and does not appear until 4 to 6 years of age. Most cases require euthanasia after about 2 months but some mild cases survive for up to 3 years. The clinical signs include a wide-based stance, dysmetria of all limb movements with a pronounced hypermetria of the forelimbs resulting in frequent falling, a fine intention tremor of the head, and a diminished menace reflex. A similar disease of medium-wool Merinos, characterized by progressive posterior ataxia and degeneration of sensory tracts in thoracic segments of spinal cord, commencing after 5 months of age and terminating fatally before 2 years of age, is also recorded in Australia. It is probably also an inherited defect

NEURAXONAL DYSTROPHY OF HORSES

In horses, neuraxonal dystrophy has been reported in **Quarter Horses, Haflingers, Morgans, Appaloosas, Paso Finos, and Standardbreds** with a familial occurrence present in a number of breeds.[3,4] The onset of clinical signs can be as early as a few months of age. Common neurologic abnormalities include ataxia, proprioceptive positioning deficits, dysmetria, a wide-based stance, obtundation, and an inconsistent menace response with no detectable visual impairment.[3] Clinical progression can be very slow over a few months to years, and in some cases stabilization of clinical signs may occur.[3] It can be difficult to clinically differentiate neuraxonal dystrophy from **EDM**; however, the latter is considered a more severe clinical variant of neuraxonal dystrophy.[5] Clinical signs of ocular disease are not detectable and the results of ERG and EEG are within the normal range.[6] Lesions at necropsy are only apparent microscopically and include specific tracts and nuclei in the caudal medulla and spinal cord, with occasional involvement of the cerebellum.

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CAPRINE PROGRESSIVE SPASTICITY

A possibly inherited progressive paresis of Angora goats is recorded in Australia. Signs first appear at about 2 months of age, commencing with lethargy, followed by ataxia, then paresis progressing to sternal recumbency and eventual euthanasia. Tendon reflexes are normal but the kids have difficulty getting to their feet, especially in the hindlimbs. The gait is ataxic with frequent stumbles, and the kids are unwilling to run. At necropsy there are many large, clear vacuoles in many neurons of the spinal cord, posterior brainstem and midbrain, and degeneration of nerve fibers in the same areas and peripheral nerves.

INHERITED SPONTANEOUS LOWER MOTOR NEURON DISEASES

Motor neuron diseases involve selective degeneration of upper and/or motor neurons. Upper motor neurons originate in the cranial vault, where they stimulate contraction of muscles. In comparison, lower motor neurons connect the brainstem and spinal cord to the muscle fibers.[1] Effective treatments for motor neuron diseases have yet to be identified.

A lower motor neuron disease in newborn Romney lambs has been described.[1] Lambs are normal at birth but within 1 week they developed weakness and ataxia, which progressed until they were unable to stand. The principal histologic lesions were degeneration and loss of neurons in the ventral horns of the spinal cord and brainstem, wallerian degeneration of ventral rootlets and motor nerves, and associated denervation atrophy of skeletal muscle fibers. Large fibrillar spheroids were found in white and gray matter including nuclei in the brainstem. One missense mutation on the sheep called the ATP/GTP-binding protein 1 gene was identified in all affected animals, exhibiting recessive pattern of inheritance.[1] This binding protein plays a role in protein turnover by cleaving peptides into amino acids. A similar, though not identical, disease of newborn lambs has been recorded in a Dorset Down flock affecting about 20% of lambs. They lay with hindlimbs tucked under the body and forelimbs splayed sideways.

This progressive disease of Yorkshire piglets 5 to 10 weeks of age is presumed to be inherited. Clinical signs include hindlimb tremor, weakness, and ataxia appearing at 2 to 5 weeks of age. The gait includes fetlock knuckling, short choppy steps, and a tendency to collapse after a few steps. Segmental and postural reflexes are normal. By 10 weeks there is complete hindlimb paralysis, the pig is in sternal recumbency, and front limb paralysis has begun. The appetite is good and the pig is bright and alert. On necropsy there is symmetric degeneration and loss of motor neurons in the spinal cord in some ventral spinal nerve roots.

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INHERITED SPINAL MUSCULAR ATROPHY

A progressive ataxia, weakness, muscle atrophy, and recumbency develops in young calves, mostly during the first 2 weeks of life.

Sensory functions are unimpaired. Some are already affected at birth and some may be stillborn. No new cases occur after 3 months of age. Conditioned by an autosomal recessive gene the defect occurs in Red Danish cattle, which originated from Brown Swiss, German Braunvieh, and American Brown Swiss. The primary lesion is degeneration of ventral horn cells of the spinal cord, without involvement of the brainstem or cerebellum. The visible lesion is the secondary atrophy of the denervated muscles.

INHERITED HYPOMYELINOGENESIS (CONGENITAL TREMOR OF PIGS)

Congenital tremor of pigs has a multiple etiology and some of the causes are not yet identified. The two inherited diseases are noted here: congenital tremor type A-IV of British Saddleback pigs and congenital tremor type A-III, a sex-linked inherited form of cerebrospinal hypomyelinogenesis of Landrace pigs. The A-IV disease is characterized by the presence of poorly myelinated axons in all parts of the CNS. The specific defect in A-IV is one of fatty acid metabolism. The structural abnormalities in the A-III disease have been identified; splayleg is a common accompaniment.

Both diseases are characterized by muscle tremor, incoordination, difficulty in standing, and some squealing. The A-III disease occurs only in males. Both are inherited as recessive characters.

PORCINE CONGENITAL PROGRESSIVE ATAXIA AND SPASTIC PARESIS

This is an autosomal recessive disorder of pigs in Switzerland with a yet to be identified gene defect. Clinical signs of a spastic gait with progressive ataxia become evident within 3 days of birth, and the condition is lethal. Male and female pigs are equally affected. Pedigree analysis has identified a boar born in 1978 that was used widely for artificial insemination as the originator of the genetic defect.

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EQUINE DEGENERATIVE MYELOENCEPHALOPATHY (EQUINE NEURAXONAL DYSTROPHY)

EDM is characterized by **symmetric, slowly progressive spasticity and ataxia** in foals and horses less than 2 years of age. The disease occurs in most breeds in North America and Europe and is reported in captive zebra and Mongolian Wild Horses in North America. Neuronal dystrophy of the cuneate and gracilis nuclei is considered a form of EDM and is likely the underlying pathophysiologic process of EDM.[1]

The prevalence of the disease varies widely, with up to 40% of susceptible animals on a farm being affected, although the disease is usually sporadic. There is a familial predisposition to the disease apparently involving an increased requirement for vitamin E, although other factors, including housing, are contributory. Foals from dams that had an EDM-affected foal were at a significantly higher risk (relative risk = 25) of developing EDM than foals from other dams. The occurrence of clusters of cases involving related horses is supportive of a genetic component with inheritance as in an autosomal dominant with variable expression or polygenic manner, although this has not been confirmed in all breeds.[2-4] The disease in Quarter Horses is highly heritable and appears to be polygenic.[2,4]

EDM occurs in Standardbreds, Paso Finos, Quarter Horses, Mongolian horses, Appaloosas, Haflingers, Arabians, Morgans, Lusitanos, Thoroughbreds, Paint horses, Tennessee Walking Horses, Norwegian Fjord Horses, Welsh Pony, and various mixed breeds.[1] There is no sex predilection.

The pathogenesis of the disease is unknown. Abnormal expression of integral synaptic vesicle, synaptic vesicle-associated presynaptic plasma membrane, and cytosolic proteins was observed in two Arabian horses with equine degenerative myeloencephalopathy; however, abnormal α-tocopherol transfer protein does not appear to contribute to the disease.[4] These proteins have a role in trafficking, docking, and fusion of neuronal synaptic vesicles, and this finding suggests that there is disruption of axonal transport in equine degenerative myeloencephalopathy. A role for oxidative stress and damage to neurons is supported by documentation of markers of oxidative stress in nervous tissue and low serum and/or CSF vitamin E concentrations in two horses with EDM and not in healthy control horses.[5] Low vitamin E concentrations in serum are often associated with the disease, but in one small study only foals with a genetic predisposition to the disease, and having a low serum vitamin E concentration, developed the disease. Foals with low serum vitamin E concentrations that did not have the genetic predisposition to the disease did not develop EDM.[6] Loss of axons leads to defects in neurologic function and consequent gait abnormalities.

The clinical signs are those of a slowing progressive spinal ataxia that stabilizes when the animal is 2 to 3 years of age. Age of onset ranges from birth to 36 months, although most cases have clinical signs by 6 to 12 months of age. Affected foals and yearlings have symmetric signs that are most severe in the hindlimbs, of ataxia characterized by pivoting, circumduction, truncal sway, and difficulty performing complex movements such as backing or walking with the head elevated. At rest, severely affected horses may have an abnormal posture. The cutaneous trunci reflex may be absent. Spontaneous recovery does not occur, but progression to death is unusual. Radiography and myelography of the cervical spine does not reveal evidence of compression of the spinal cord. The disease is not associated with abnormalities detected on ocular examination, ERG or EEG.[7]

Serum vitamin E concentrations can be normal or low in affected horses, and this is not a reliable test for diagnosis of the disease.[1-3] The hemogram, serum biochemical profile, and CSF analysis are normal. There are no gross lesions on necropsy. Histologic lesions include neuronal atrophy, accumulation of lipofuscin-like pigment, and glial cell proliferation.

Differential diagnoses are listed in Table 14-20 later in the chapter, under the Equine Cervical Vertebral Compressive Myelopathy section. Diagnosis is achieved by exclusion of other causes, of abnormal gait without fever or disease in other body systems in horses, such as compressive myelopathy and equine protozoal myeloencephalopathy.

No treatment is curative, but vitamin E (6000 IU orally once daily) may prevent progression of signs. Supplementation of at-risk foals and yearlings with vitamin E can prevent the disease, although results are not equivocal.[1,6]

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EQUINE CERVICAL VERTEBRAL COMPRESSIVE MYELOPATHY (WOBBLER, "WOBBLES," FOAL ATAXIA, EQUINE SENSORY ATAXIA, CERVICAL VERTEBRAL INSTABILITY)

SYNOPSIS

Etiology Unknown. The clinical signs are the result of cervical spinal cord compression as a result of abnormalities in the cervical spine.

Epidemiology Two predominant manifestations. Sporadic or endemic disease of young horses with young, rapidly growing male horses most commonly affected. Separate presentation in middle-aged and older horses in which it is sporadic.

Clinical signs Spinal ataxia evident as truncal sway, ataxia, and paresis usually more

Continued

severe in the hindlimbs. Radiographic evidence of narrow spinal canal.

Clinical pathology None.

Lesions Malacia and wallerian degeneration in the cervical spinal cord.

Differential diagnosis Equine degenerative myelopathy, equine protozoal myeloencephalitis, trauma, equine infectious anemia, cerebrospinal nematodiasis, West Nile encephalomyelitis, equine herpesvirus-1 myelopathy, osteomyelitis, cervical vertebral epidural hematoma, aortoiliac thrombosis, congenital vertebral malformation, diskospondylitis, and ryegrass staggers.

Diagnostic confirmation Radiography. Positive contrast myelography. Necropsy.

Treatment Antiinflammatory drugs. Surgical fusion of vertebrae.

Control None.

ETIOLOGY

The cause of neurologic disease is extradural compression of the cervical spinal cord, hence the term **compressive myelopathy.** The compression may be **static**, that is, the compression is present constantly with the neck in a neutral position, or **dynamic** and only present intermittently when the neck is either flexed or extended. The second situation is often referred to as cervical vertebral instability.

The etiology of CSM in most cases is not known. The disease in young horses is caused by malformation and malarticulation of the cervical vertebrae and could represent part of the osteochondritis dissecans spectrum of diseases.[1,2] There can be combinations of articular process osteophytosis, interarcuate ligament hypertrophy, dorsal laminal thickening, vertebral body end plate flaring, and synovial cysts. Importantly, changes in soft tissue associated with the bony lesions can contribute to the compressive myelopathy. Dynamic instability is associated with vertebral instability and subluxation and is most common in the cranial vertebrae (C3-C5).

Copper deficiency has been mooted as one cause of the bony lesions, as have high calorie rations and diets high in soluble carbohydrate.[2]

The disease in older horses is secondary to osteoarthritis of the articular processes. An inciting cause has not been identified.

Several basic syndromes of compressive myelopathy, based on age of occurrence, are recognized:

- CSM in immature horses (<3 years of age, depending on breed) that is often associated with developmental joint disease in the axial and appendicular skeleton. A fundamental underlying predisposing defect appears to be a narrow diameter of the cervical vertebral canal. Compression is a result of the lesions described earlier.
- Cervical vertebral instability is a disease of horses less than 1 year of age that is often associated with malformations of one or more of the cervical vertebrae.[3]
- Compressive myelopathy in mature horses, >4 years (usually >7 years) of age, associated with osteoarthritis of the articular facets of the caudal cervical vertebrae, with subsequent impingement of the vertebral canal by bony and soft tissue proliferative lesions.
- Miscellaneous causes of cervical cord compression by neoplasia (melanoma, sarcoma, lymphoma), trauma (cervical vertebral fractures), arachnoid or synovial cysts, epidural hematoma[4] or, rarely, discospondylitis.[5]

An alternative categorization is based on the nature of the bony lesion and not on the cause of compression of the spinal cord. **Type 1 cervical vertebral malformation** occur in horses <2 years of age that have vertebral changes that likely began in the first few months of life, including malformations causing stenosis of the vertebral canal, malformations at the articulations of the vertebrae including osteochondrosis, and enlarged physeal growth regions. **Type II cervical vertebral malformations** tend to occur in older horses with severe osteoarthritic lesions of the vertebral articulations.

EPIDEMIOLOGY

Occurrence

The disease in mature horses occurs sporadically throughout the world.

The disease in young horses is sometimes endemic on farms or studs and in particular lines of horses. There is a suggestion of a familial tendency for the disease, although this has not been well documented.

The **morbidity rate** can be as high as 25% of each foal crop on individual Thoroughbred farms, although the overall frequency of the disease in the general horse population is much lower. Among Thoroughbreds born on four stud farms in Europe and North America, the disease has an annual prevalence of diagnosis of 1.3% (range of 0.7%–2.1% over the study period) and annual prevalence on farms varying from 0% to 5.8%.[6]

Compressive myelopathy was detected in 83 of 4318 horses subject to necropsy examination in Normandy, France.[7] Fifteen percent of horses with a diagnosis of neurologic disease had cervical compressive myelopathy. There were more males affected than females.[7]

Risk Factors

Animal Risk Factors

Risk factors for CSM identified in a study of 1618 horses at 22 veterinary teaching hospitals in North America are summarized in Table 14-20.

The **disease in young horses** is commonly recognized in Thoroughbred, Standardbred, Warmblood, and Quarter horses, with Arabians and other breeds less likely to be diagnosed with the disease.[8] Ponies are rarely, if ever, affected. Horses less than 4 years of age are at greater risk of the disease, with most cases occurring in 1- to 3-year-old horses. Males, either intact or gelded, are more likely to be affected than are females.[8]

Table 14-20 Association of horse factors associated with a diagnosis of cervical stenotic myelopathy in 811 horses with cervical stenotic myelopathy and 805 control horses

Variable	Or (95% CI)	*P* value
Sex		
Gelding	2.0 (1.5–2.6)	<0.001
Sexually intact male	2.4 (1.8–3.2)	<0.001
Female	1 (Referent)	NA
Breed		
Arabian	0.6 (0.3–0.9)	0.035
Standardbred	0.5 (0.3–0.7)	<0.001
Thoroughbred	1.7 (1.3–2.3)	<0.001
Tennessee Walking Horse	2.3 (1.1–4.7)	0.019
Warmblood	1.9 (1.1–3.1)	0.020
Other breeds	0.6 (0.4–0.8)	0.006
Quarter Horse	1 (Referent)	NA
Age		
<6 mo	2.4 (1.4–3.9)	<0.001
6–11 mo	6.6 (3.8–11.5)	<0.001
12 to 23 mo	16.4 (10.5–25.8)	<0.001
2 to <4 y	7.2 (4.9–10.5)	<0.001
4 to <7 y	3.1 (2.1–4.6)	<0.001
7–10 y	1.1 (0.7–1.8)	0.65
≥10 y	1 (Referent)	NA

OR, *odds ratio;* NA, *not applicable.*
From Levine JM, et al. JAVMA 2008;233:1453

The **disease in older horses** is characterized by a slight predominance of male horses with overrepresentation of Warmbloods, which could represent a breed or use predisposition, and median age at diagnosis of 8 years.[1]

Horses with CSM have a narrower spinal canal than do unaffected animals and this condition, with degenerative joint disease of the articular facets and thickening of the ligamentum flavum, contributes to the greater likelihood that the horse will have spinal cord compression.

It is suspected that predisposition to the disease is heritable, but this has not been demonstrated by appropriate studies.

The disease in mature horses tends to be in horses used for athletic endeavors and is uncommon in broodmares or retired animals.

PATHOGENESIS

The disease is attributable to injury to the spinal cord as a result of compression by either soft tissue (joint capsule, intervertebral ligaments, or, rarely, intervertebral disk material) or cartilage and bone.

Constant or intermittent pressure on the spinal cord causes dysfunction or necrosis of white matter and neurons at the site of compression, degeneration of fibers of ascending tracts cranial to the site of compression, and of descending tracts caudal to the compression. The ascending tracts are those associated with general proprioception, whereas the descending tracts are upper motor neurons. These tracts are located superficially in the dorsolateral aspect of the cervical spinal cord and damage to them results in signs of ataxia and weakness. Tracts from the caudal limbs are more superficial, and therefore more easily injured, than tracts associated with the cranial limbs. Consequently, clinical signs are usually more severe in the hindlimbs. The spinal cord lesions are usually, but not always, bilaterally symmetric, as are the clinical signs. Proprioceptive pathways are disrupted, causing the signs of ataxia (incoordination) typical of the disease. Clinical signs vary depending on the site of the lesion (see later).

CLINICAL FINDINGS

The onset of clinical signs is sometimes acute in young horses with CSM and there can be a history of trauma, such as falling. However, the onset of clinical signs of CSM in both young and mature horses is usually gradual and insidious, and in mildly affected horses the nervous disease can be mistaken for lameness of musculoskeletal origin. Affected horses are bright and alert and have a normal appetite. There can be evidence of pain on manipulation of the neck or on firm pressure over the lateral facets, especially in mature horses with osteoarthritis of the caudal cervical vertebral facets.[1] There can be focal muscle atrophy adjacent to affected cervical vertebrae in older horses.

The severity of clinical signs varies from barely detectable to recumbency. There are no defects of al nerves, with the occasional exception of the cervicofacial reflex. The severity of signs of CSM are often graded according to the following:

Grade 0: no gait deficits at the walk
Grade 1: no gait deficits identified at the walk and deficits only identified during further testing (head elevation, backing, walking on a slope, stepping over obstacles, circling, tail pull at rest and while walking)
Grade 2: deficits noted at the walk
Grade 3: marked deficits noted at the walk
Grade 4: severe deficits noted at the walk and might fall or nearly fall at normal gaits
Grade 5: recumbent and unable rise without assistance

The **two primary defects in gait** in affected horses are related to defects in upper motor neuron function and general proprioception. These two primary deficiencies in neurologic function contribute to clinical signs characterized as ataxia, paresis, dysmetria, and spasticity. **Ataxia** is the incoordinated movement of limbs and is evident as interference of one limb with another (such as one foot stepping on another when the horse is tightly circled), knuckling of the fetlock joint (which can also be a sign of weakness), unusual placement of feet (excessively wide-based or narrow-based stance, incomplete or delayed return of the foot to its normal position after it is relocated to an abnormal position, excessive circumduction of the outside foot during tight circling), stumbling, and/or swaying of the trunk during walking in a straight line. **Paresis** is weakness and is evident in its most extreme form as inability of the horse to rise. In less extreme manifestations it is evident as knuckling of the fetlock joint, stumbling when walking downhill or over obstacles, and ease of pulling the horse to one side by the tail when it is walking. **Dysmetria** refers to uneven gait typified by undershoot or overshoot of the limb such that the hoof is in an incorrect position. **Spasticity** is a result of loss of inhibition of lower spinal reflexes by the upper motor neurons and results in a stilted or stiff gait.

Mildly affected horses may have deficits that are difficult to detect and only apparent under saddle or at high speed. The owner might complain of poor performance of a racehorse or dressage animal, of an animal that frequently changes leads, or that is poorly gaited. Careful examination can reveal excessive circumduction of the hindfeet, stumbling, and pacing when the head is elevated.

Moderately affected animals have truncal sway (the body of the horse and hindquarters swaying laterally when the horse is walked in a straight line) and excessive circumduction of the hindfeet. There can be a floating gait of the hindlimbs and scuffing of the toe. Having the horse move in a very tight circle about the examiner often causes the circumduction to become worse in the outside hindleg and the horse to place one foot on top of the other. Affected horses will sometimes pace when walked in a straight line with the head elevated. Blindfolding the horse does not exacerbate the signs. Affected horses will stumble when walked over low objects, such as a curb, and will knuckle at the fetlocks and stumble when walked down a steep hill.

Severely affected horses often fall easily when moved or are unable to stand. The horses are bright and alert, but anxious, and display marked truncal sway and ataxia. When standing, they will often have their legs in markedly abnormal positions.

Horses with lesions in the cervical spinal cord cranial to C6-C7 have signs in both forelimbs and hindlimbs. The hindlimbs are more severely affected and the signs are usually, but not always, bilaterally symmetric.[9] Approximately 43% of affected horses have asymmetric gait abnormalities.[9] Lesions of the cervical intumescence (C6 to T2) may cause signs that are more severe in the forelimbs than in the hindlimbs. Lesions at this site may also cause signs typical of brachial plexus injury. Focal muscle atrophy is not characteristic of CSM or cervical vertebral instability and there are never signs of CNC, cerebral, or cerebellar disease.

After initial progression the clinical signs usually stabilize or partially resolve. However, complete spontaneous recovery is very unusual. Death is unusual unless it is by misadventure, although many affected animals are killed for humane or economic reasons.[8]

Neurologic Examination

A tentative diagnosis of cervical compressive myelopathy is often made based on the clinical examination. Although this assessment is relatively straightforward for severely affected horses, the detection of neurologic abnormalities on physical examination is more challenging for horses with milder forms of the disease. This becomes important as additional diagnostic investigations might not be warranted in all cases of horses with clear-cut signs of cervical compressive myelopathy, but might be indicated in horses with less severe signs of the disease.

The reliability of the neurologic examination of horses has been investigated very little. The agreement between expert or trained observers for overall grade of neurologic abnormality was good (intraclass correlation coefficient of 0.74) when horses of all grades were considered (grades 0–4), but very poor for horses ≤ Grade 1 (intraclass coefficient (ICC) = 0.08) and only moderate (0.43) for horses ≥ Grade 2.[10] The higher ICC for the overall assessment was because observers could easily agree on differences

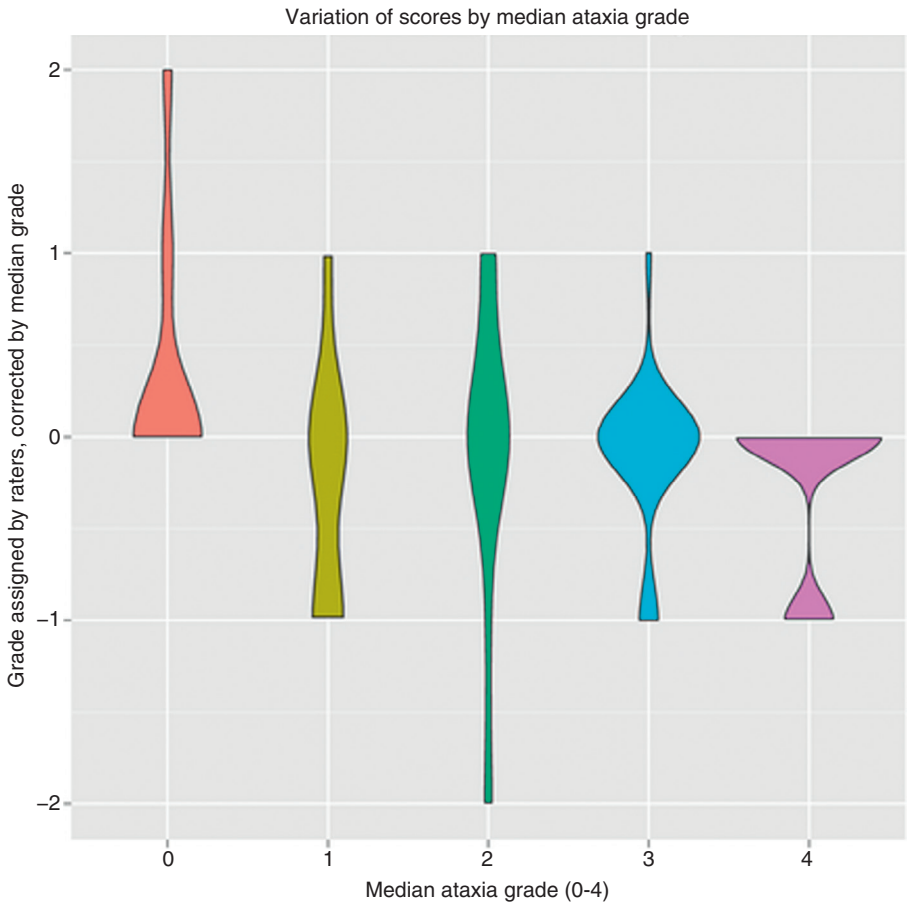

Fig. 14-22 Violin plot of the variation in individual ratings grouped by the median rating for each horse during live scoring only. To align the ratings around 0, each score was subtracted from the median score of the horse. A violin plot is similar to a boxplot, with the addition of the density of data points illustrated by an increase in width. This figure reveals that most grades have a fluctuation of 1 degree more or less than the median; however, grades 0 and 3 are condensed around the median illustrating better agreement, whereas grade 2 stretches from –2 to + 1 grades from the median. (From Olsen E, Dunkel B, Barker WHJ, et al. Rater Agreement on Gait Assessment During Neurologic Examination of Horses. *J Vet Int Med* 2014;28:630.)

between severely affected and unaffected horses. Greatest lack of agreement was for horses that had Grade 2 neurologic signs (Fig. 14-22).[10]

It is recommended in human medicine that an ICC must be >0.9 for it to be useful for decision making in individual patients,[11] and on this basis the current methods for neurologic examination for horses are not acceptable for clinical use.[10] It is the authors' opinion that the current neurologic grading system for examination of horses continue to be used because it provides a structured way of completing the examination. The results of the examination should be considered in light of its poor reliability, especially for horses with severity of median Grade 2, and interpreted with caution.

Ancillary Diagnostic Tests

The "slap test," in which the response of the arytenoid cartilages to a slap on the thorax is examined through an endoscope, has poorer sensitivity and specificity for detecting spinal cord disease than does a routine neurologic examination.

Acupuncture has no proven value in the diagnosis of cervical compressive myelopathy and should not be used for this purpose.

Radiographic Examination

Radiographic examination of the cervical vertebral column of potentially affected horses is often undertaken because there are frequently lesions of the bone associated with cervical compressive myelopathy. Radiographic examination includes plain radiographs taken from the lateral aspect with the horse standing or myelography using injection of radiopaque dye to allow visualization of the subarachnoid space and detection of extradural compression of this space.

Examination of both plain and contrast radiographs is potentially enhanced by use of one or more of a number of measures and ratios intended to detect and quantify extradural compression of the cord.

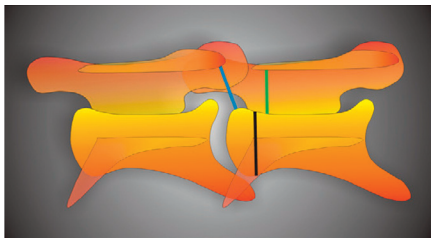

Fig. 14-23 Schematic drawing of the cervical vertebrae illustrating the sagittal ratios: the intravertebral sagittal ratio is calculated as the ratio of the minimum sagittal diameter of the spinal canal (green line) to the maximum sagittal diameter of the vertebral body, taken at the cranial aspect of the vertebra and perpendicular to the spinal canal (black line). The intervertebral sagittal ratio is the ratio of the minimal distance taken from the most cranial aspect of the vertebral body to the most caudal aspect of the vertebral arch of the more cranial vertebra (blue line) and the maximal sagittal diameter of the vertebral body (black line). (Reproduced with permission from Van Biervliet J. An evidence-based approach to clinical questions in the practice of equine neurology. *Vet Clin Nth Am Equine Pract* 2007;23(2):317-328.)

Radiographic signs detectable on plain radiographs of the cervical spine in horses with compressive myelopathy include the following:

- Encroachment of the caudal vertebral physis dorsally into the spinal canal ("ski jump lesion") caused by physeal enlargement
- Extension of the arch of the vertebra over the cranial physis of the next vertebra
- Sclerosis of the spinal canal
- Kyphosis, or subluxation, between adjacent vertebra
- Degenerative joint disease of the articular facets evident as osteoarthritis and bony proliferation

However, these signs are also common in normal horses and have poor predictive value. The overall agreement, relative sensitivity, and relative specificity, respectively, for identification of radiographic abnormalities (compared with the gold standard of necropsy examination) in affected horses is 66% (76/116 horses); 63% and 67% for identification of articular process osteophytosis; 61% (71/116), 42%, and 83% for vertebral canal stenosis; and 78% (91/116), 56%, and 85% for vertebral column subluxation.[9] Radiography appears to have useful specificity but limited sensitivity in the diagnosis of bony lesions associated with cervical compressive myelopathy. Use of additional views, such as oblique views of the caudal cervical vertebrae. can enhance the diagnostic value of radiography.[12]

Intervertebral and **intravertebral** ratios have been calculated to assist with diagnosis of CSM (Fig. 14-23). The ratios in and of

themselves have variable intraobserver and interobserver reliability with ratios varying by 5% to 10% within and between observers.[13,14] Interobserver agreement in measurements is poor and intraobserver agreement is good across the six most cranial sites but poor for caudal sites.[14] Intraobserver and interobserver variability is sufficient to affect clinical interpretation of radiographs and should be considered when interpreting radiographic examinations with suspected spinal cord disease.

An intravertebral sagittal ratio of the spinal canal to vertebral body diameter of less than 50% for C4-C6 is associated with a 26- to 41-fold increase in the probability of a compressive myelopathy for horse >320 kg; in a separate study all horses with a value of this ratio of less than 0.485 had at least one compressive lesion.[15] An intervertebral ratio can also be calculated and it has diagnostic utility that might be slightly greater than that of the intravertebral ratio.[2,15] The results of these tests are not definitive and a healthy horse can have ratios below this cutoff and affected horses can have normal ratios.[16,17] It is important to recognize that the utility of **intravertebral** (and other) ratios is dependent on the pretest likelihood that the horse has cervical compressive myelopathy. The ratios should therefore be considered in light of other clinical findings. Importantly, neither the intravertebral nor intervertebral ratios predict the site of compression, which can only be detected by myelographic examination.[2]

Myelography has been considered to provide the definitive antemortem confirmation of spinal cord compression, but recent studies demonstrate that it is not a perfect diagnostic test and that results should be interpreted cautiously.[2] The sensitivity of this technique, using a 50% reduction in the width of the dorsal dye column as a cutoff for diagnosis of the disease, is 53% (95% CI 34%–72%, $n = 22$) and the specificity is 89% (95% CI of 84%–93%, $n = 228$) (Fig. 14-24).[2] Others have found similar values for sensitivity and specificity with values of 47% and 78%, respectively, for older horses with compressive myelopathy at caudal cervical sites.[1] These values indicate a test with a relatively high false-negative rate but low false-positive rate for neutral views and indicate that a positive finding on myelography is highly suggestive of the disease, but that a negative finding does not eliminate the possibility of the disease. The **false-positive rate** is increased to 12% to 27% for compression at midcervical sites during neck flexion. Myelography is superior in diagnosing compressive lesions at C6-C7 than at more proximal sites. Occasionally the compression is lateral rather than dorsoventral and is not readily apparent on routine myelography.

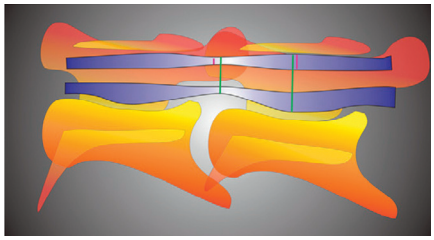

Fig. 14-24 Schematic drawing of cervical myelogram illustrating the dural diameter reduction (green lines) and the dorsal myelographic column reduction (pink lines). (Reproduced with permission from Van Biervliet J. An evidence-based approach to clinical questions in the practice of equine neurology. *Vet Clin Nth Am Equine Pract* 2007;23(2):317-328.)

Myelography has been described in standing, conscious horses, but this technique is not sufficiently well described to allow its recommendation at this time.[18]

Ex situ (postmortem) MRI examination of cervical vertebrae and spinal cord of normal and CSM-affected horses is more accurate than is interpretation of standing lateral radiographs.[17] However, both **CT and MRI** of horses with CSM are limited by the restricted views of the neck of adult horses. This prevents comprehensive examination of the cervical spine.[19,20]

Endoscopy of the epidural and subarachnoid spaces is reported in a horse with confirmed cervical compressive myelopathy.[21,22] The diagnostic or therapeutic value of this procedure is yet to be established.

The **prognosis** for horses with CSM is guarded. Sixty-four percent of affected horses were euthanized, presumably for economic or humane reasons.[9] However, the prognosis depends on the severity of clinical signs and the intended use of the horse. The criteria for euthanasia depend on the danger of the horse to itself (for instance, falling and injuring itself) or its attendants. Horses that are at high risk of self-injury or of injuring their attendants might qualify for humane euthanasia. However, horses with milder signs of disease compatible with their intended use, such as stallions or females with low-grade signs of the disease and reproductive potential, can be treated conservatively and live long lives.

It is imperative to consider the risk to riders or handlers associated with care or competing the horse when deciding on the fate of an affected horse.

The prognosis for horses intended for **athletic use** is less clear. Twenty-one of 70 Thoroughbred racehorses with cervical compressive myelopathy went on to race.[23] The likelihood of a horse racing was inversely related to the severity of its clinical signs.[23]

CLINICAL PATHOLOGY

Hematologic and serum biochemical values are usually within reference ranges in affected horses. CSF from affected horses can have increased protein concentration, but this finding is neither characteristic nor specific for compressive myelopathy. However, other causes of spinal ataxia can cause characteristic changes in the CSF and examination of the fluid might assist in ruling out these diseases.

Measurement of creatine kinase activity in CSF has no diagnostic value in horses.

NECROPSY FINDINGS

Gross examination reveals degeneration of the articular facets in many affected horses.

Impingement of soft tissues, especially the ligamentum flavum and joint structures, or cartilage and osteophytes into the spinal canal may be apparent. The spinal canal may be narrow. It may be indented and soft at the site or sites of compression. Histologically, there is nerve fiber swelling, widespread degeneration of myelin, and astrocytic gliosis. Cranial to the compressive lesion, wallerian degeneration is evident in the dorsal and lateral funiculi, although caudal to the compression these changes are most evident in the ventral and central lateral funiculi. Slight atrophy of cervical muscles is sometimes evident. There is histologic evidence of stretching and tearing of the ligamentum flavum and joint capsule at affected joints, especially C6 or C7.

DIFFERENTIAL DIAGNOSIS

Equine degenerative myelopathy, equine protozoal myeloencephalitis, trauma, equine infectious anemia, cerebrospinal nematodiasis (*Hypoderma* spp., *Setaria* sp., *Halicephalobus deletrix*), equine herpesvirus-1 myelopathy, aortoiliac thrombosis, West Nile encephalomyelitis, congenital vertebral malformation (especially in Arabian foals), discospondylitis, tumors involving the spinal canal (melanoma, lymphoreticular neoplasia, hemangiosarcoma),[5,24] extradural hematoma,[25] vertebral osteomyelitis, fibrocartilaginous embolic, postanesthetic myelopathy,[26] and ryegrass staggers (see Table 14-21).

TREATMENT

Medical treatment of the acute disease consists of rest and administration of antiinflammatory drugs (dexamethasone 0.05–0.25 mg/kg intravenously or intramuscularly every 24 hours; flunixin meglumine 1 mg/kg intravenously every 8–12 hours; phenylbutazone 2.2–4.4 mg/kg orally every 12–24 hours; and/or dimethyl sulfoxide, 1 g/kg as a 10% solution in isotonic saline intravenously every 24 hours for three treatments).

Treatment of arthritis of the facets of mature horses can be achieved by injection of the articular facet joints with corticosteroids (40 mg of methylprednisolone acetate).[27] Injection of the joint is facilitated by ultrasonographic guidance. Injection of the joints with antiinflammatory drugs is assumed to result in reduction in inflammation and soft

Table 14-21 Differential diagnosis of disease causing spinal ataxia in adult horses

Disease	Etiology and epidemiology	Clinical signs and lesions	Treatment and prognosis
Cervical compressive myelopathy (cervical stenotic myelopathy, cervical vertebral instability)	Sporadic; young, rapidly growing males; more common in Thoroughbreds, Standardbreds, and Warmblood horses; syndrome in mature horses caused by arthritis or articular facets.	Symmetric ataxia often of sudden onset; may be associated with trauma; hindlimbs most severely affected; compression of cervical spinal cord demonstrated by myelography; CSF normal	Medical treatment of rest and antiinflammatory drugs; poor prognosis; surgical correction by ventral stabilization
Equine degenerative myelopathy	Young horses (<3 years); familial incidence of increased requirement for vitamin E	Gradual onset symmetric ataxia that stabilizes at about 3 years of age; no radiographic abnormalities in cervical spinal cord; CSF normal	Guarded prognosis; vitamin E 5–20 IU/kg per day in feed may prevent progression; no cure; death uncommon
Equine protozoal myeloencephalitis	*Sarcocystis neurona* or *Neospora hughesi* in spinal cord or brain; Americas only; infectious but not contagious	Any sign of central nervous system dysfunction; usually gradual onset of asymmetric spinal ataxia, focal muscle atrophy or weakness; CSF contains antibody to *S. neurona,* but also found in normal horses	Ponazuril 5–10 mg/kg orally daily for 28 days; older, but effective, treatment is pyrimethamine, 1 mg/kg orally and sulfadiazine, 20 mg/kg orally every 24 hours for 90–120 days; Nitazoxanide 25 mg/kg orally once daily for 2 days followed by 50 mg/kg orally for 26 days; Vaccination not recommended
Equine herpesvirus-1 myeloencephalopathy	EHV-1; infectious and contagious. Sporadic; outbreaks occur often preceded by fever or upper respiratory tract disease	Ascending paralysis with fecal and urinary incontinence, recumbency, normal mentation; CSF xanthochromic and increased protein concentration; lesion is vasculitis and malacia	Valacyclovir for prophylactic therapy at a dose of 30 mg/kg orally every 8 hours for 2 days, then 20 mg/kg every 12 hours for 1–2 weeks Corticosteroids controversial Nursing care; poor prognosis Vaccination potentially effective
West Nile encephalitis	West Nile virus; transmitted by bite of infected mosquito; horse is dead-end host and does not develop sustained viremia; enzootic to Mediterranean littoral and North America; Increased recognition in other areas (Australia, Kunjin); peak disease risk is late summer	Weakness, muscle fasciculations, altered mentation; recumbency	No specific treatment; nursing care; corticosteroids controversial; hyperimmune serum available in some areas; interferon has been used but efficacy uncertain
Trauma	Sudden onset; more common in young horses	Spinal ataxia, varying degrees of weakness and proprioceptive deficits; recumbency Radiographic lesions present occasionally CSF may contain red blood cells	Antiinflammatory drugs; rest
Ryegrass staggers	Intoxication by lolitrems produced by *Acremonium lolii* growing on perennial ryegrass; outbreaks of disease in horses on affected pasture	Ataxia, stiff gait, tremor, hypersensitivity, recumbency; no histologic lesions	Remove source of toxin; rapid recovery without other treatment
Parasite migration	Sporadic. *Strongylus* sp., *Hypoderma* sp., and filaroids (*Setaria* sp.).	Wide variety of clinical signs; progressive ataxia; CSF may contain eosinophils	Ivermectin 0.2 mg/kg orally Antiinflammatory drugs
Congenital anomalies	Sporadic; cause spinal cord compression or lack of neural tissue, e.g., spina bifida	Recumbency, ataxia present at birth	No treatment
Neoplasia	Melanoma, lymphosarcoma, hemangiosarcoma, metastatic neoplasia, multiple myeloma	Variable depending on site; usually extradural tumor although can be secondary to vertebral body involvement and pathologic fracture	No practicable treatment

tissue swelling with consequent reduced compression of the cervical spinal cord. There is no objective prospective assessment of the efficacy of this treatment

A "paced growth" program of slowed growth achieved by nutritional restriction of young horses (foals and weanlings) has been suggested as conservative treatment for immature horses with compressive myelopathy or at high risk of developing the disease.

Surgical fusion of cervical vertebrae is useful in the treatment of mild to moderately affected horses, although because of issues of safety of future riders there are concerns by some authorities about the advisability of this treatment.

CONTROL

Control measures are not usually used, although ensuring an appropriate diet and

growth rate of at-risk animals would be prudent.

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EQUINE MOTOR NEURON DISEASE

Equine motor neuron disease is a **neurodegenerative disease** of horses in the United States, Canada, Europe, UK, and South America.[1-3] The disease is associated with low intake, and abnormally low serum concentrations, of vitamin E, possibly exacerbated by excessive intake of copper or iron.[4-6] The disease can be induced by feeding horses a diet with a low concentration of vitamin E, with development of clinical signs of the disease taking at least 18 months and up to 38 months.[5,7]

The disease affects horses of all breeds, with Quarter Horses most commonly affected, and the incidence of the disease increases with age (horses older than 2 years). The disease is associated with stabling and lack of access to pasture, and the risk of the disease increases with decreasing serum vitamin E concentration.

The pathogenesis of the disease is unknown but is suspected to be caused by oxidative injury to neurons subsequent to vitamin E deficiency. However, not all horses that develop the disease have a clear oxidant stress or decrease in antioxidant capacity.[8] The clinical signs are attributable to degeneration of motor neurons in the ventral horns of the spinal cord, with subsequent peripheral nerve degeneration and widespread neurogenic muscle atrophy.

The onset of **clinical signs** is usually gradual, but in a small proportion of affected horses the first sign is an acute onset of profound muscle weakness. Chronically affected horses have weight loss in spite of a normal or increased appetite, pronounced trembling and fasciculation of antigravity muscles, increased recumbency, and a short-strided gait. They often assume a posture with all feet under the body and a low head carriage, and frequently shift weight, which are all signs attributable to muscle weakness. The tail head is elevated in a large proportion of severely affected horses, which is likely a result of atrophy of the sacrocaudalis dorsalis medialis muscle. Profound flaccidity (weakness) of the tongue with lesions in the hypoglossal nuclei is reported and must be differentiated from botulism.[9] Retinal examination often reveals accumulation of lipofuscin-like pigment in the tapetal fundus.

EMG, under either general or regional anesthesia, is a useful diagnostic aid.[8] Characteristic findings include spontaneous fibrillation potentials and trains of positive sharp waves.

Lesions of redistribution of mitochondrial enzyme stain and anguloid atrophy of myofibers in sacrocaudalis dorsalis medialis muscle of adult horses with vitamin E–responsive muscle atrophy might represent a variant, or early stage, of equine motor neuron disease.[10]

The prognosis is poor for horses with advanced disease and most of these horses do not return to normal function and are destroyed, although the disease stabilizes in some cases that can then live for a number of years after diagnosis. Approximately 40% of cases will have stable clinical signs (no improvement) and 20% will continue to deteriorate after diagnosis and initiation of treatment. Early recognition and correction of diet with or without supplementation with vitamin E can result in recovery.

There is often a mild increase in serum creatine kinase activity. Horses with equine motor neuron disease have abnormal oral and intravenous glucose tolerance tests characterized by peak glucose concentrations that are lower than expected. The lower peak plasma glucose concentration is attributable to a 3× greater rate of glucose metabolism (removal from blood) in affected horses compared with normal horses. There is also evidence that horses with equine motor neuron disease are more sensitive to insulin than are normal horses.

Affected horses often have **serum vitamin E concentrations** that are below the reference range (<1.0–2.0 µg/dL, <1.0–2.0 µmol/L). Horses with equine motor neuron disease have higher spinal cord copper concentrations than do normal horses, but the diagnostic or clinical significance of this observation is unclear.

Examination of CSF is not useful in arriving at a diagnosis.

Examination of muscle from horses with equine motor neuron disease reveals a coordinated shift from characteristics of slow muscle to those of fast twitch muscle including contractile and metabolic functions of muscle. There is a lower percentage of myosin heavy chain type 1 fibers, higher percentages of hybrid IIAX and IIX fibers, atrophy of all fibers, and reduced oxidative capacity, increased glycolytic capacity, and diminished intramuscular glycogen concentrations, among other changes, in affected horses compared with normal horses.

The disease must be differentiated from botulism and other causes of weakness in adult horses. **Diagnostic confirmation** can be achieved by examination of a biopsy of the sacrocaudalis dorsalis medialis muscle or the spinal accessory nerve. The sacrocaudalis dorsalis medialis muscle is preferred because that muscle is predominantly composed of type 1 fibers and is severely affected by the disease. Examination of biopsy of this muscle has a sensitivity of approximately 90%.

Necropsy examination reveals moderate to severe diffuse muscle atrophy. Predominant histologic findings at necropsy examination include degeneration of neurons in ventral horns at all levels of the spinal cord. Muscle atrophy is evident because angular fibers, with predominantly type 1 fibers, or a combination of type 1 and type 2 fibers, are affected. There is accumulation of lipofuscin in the fundus and in capillary endothelium of the nervous tissue.

Treatment consists of administration of vitamin E. There are eight isoforms of vitamin E, and RRR-α-tocopherol, the naturally occurring form, is the most potent antioxidant. Synthetic vitamin E contains all isomers, whereas "natural" vitamin contains only one, the RRR isomer. Administration of lyophilized, water-soluble D-α-tocopherol (RRR-α-tocopherol) is apparently superior to administration of the DL-α-tocopherol acetate in increasing concentrations of vitamin E in blood of horses.[4] The usual dose is 4 IU of D-α-tocopherol (RRR-α-tocopherol) per kilogram BW orally once daily or 5000 to 7000 IU of α-tocopherol per 450-kg horse per day.[4] Supplementation results in improvement in 40% of affected horses within 6 weeks, with some appearing normal at 12 weeks.[4]

Control measures should ensure that horses have adequate access to pasture or are supplemented with good quality forage and/or vitamin E. Horses without access to green pasture should be supplemented with 1 U of vitamin E per kilogram BW per day.[4]

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Diseases Primarily Affecting the Peripheral Nervous System

The **peripheral nervous system** consists of **cranial** and **spinal nerve** components. As such, the peripheral nervous system includes the dorsal and ventral nerve roots, spinal ganglia, spinal and specific peripheral nerves, CNs and their sensory ganglia, and the peripheral components of the autonomic nervous system.

ETIOLOGY

There are several different causes of peripheral nervous system disease.

Inflammatory

Polyneuritis equi, also known as **neuritis of the cauda equina** or **cauda equina syndrome**, is a rare and slowly progressive demyelinating granulomatous disease affecting peripheral nerves in the horse. Polyneuritis equi is characterized by signs of lower motor neuron lesions, primarily involving the perineal region but also affecting other peripheral nerves, especially CNs V and VI. CNs VIII, IX, X, and XII also may be involved. Clinical signs of perineal region paresis/paralysis predominate and manifest as varying degrees of hypotonia; hypalgesia; and hyporeflexia of the tail, anus, and perineal region. Degrees of urinary bladder paresis and rectal dilatation are also present. Differential diagnoses include sacral or coccygeal trauma, equine herpes myeloencephalopathy, equine protozoal myeloencephalitis, rabies, and equine motor neuron disease.

Cranial neuritis with guttural pouch mycosis and empyema in the horse may cause abnormalities of swallowing, laryngeal hemiplegia, and Horner's syndrome if the glossopharyngeal and vagal nerves are involved in the inflammatory process of the guttural pouch.

Acquired **myasthenia gravis** has been diagnosed in a 7-month-old Hereford heifer with a 5-day history of recumbency caused by symmetric generalized neuromuscular weakness.[1] The heifer stood with no assistance within 1 minute of edrophonium chloride (0.1 mg/kg intravenously) and was able to stand for 24 hours. Three additional episodes of prolonged recumbency responded to edrophonium, with an increasing period between episodes. Additional treatment was dexamethasone intramuscularly for 5 days. Acquired myasthenia gravis was diagnosed and attributed to an autoimmune disease directed against acetylcholine receptors at the neuromuscular junction. Congenital myasthenia gravis, caused by a homozygous mutation in the acetylcholine receptor gene, has been diagnosed in Braham calves in South Africa.[2]

Degenerative

Equine laryngeal hemiplegia, often called roaring, is a common disease of the horse in which there is paralysis of the left cricoarytenoid dorsalis muscle resulting in an inability to abduct the arytenoid cartilage and vocal fold, which causes an obstruction in the airway during inspiration. Endoscopic examination reveals asymmetry of the glottis. On exercise, inspiratory stridor develops as the airflow vibrates a slack and adducted vocal fold. The abnormality is caused by idiopathic distal degeneration of axons in the left recurrent laryngeal nerve, with the disease characterized as a bilateral mononeuropathy.[3] The left recurrent laryngeal nerve is more severely affected than the right because it is longer and is the longest nerve in the horse (see Chapter 12 for more details).

Diaphragmatic paralysis has been identified in 11 alpacas aged 2 to 12 months. Respiratory dysfunction was present, manifested as tachypnea, pronounced inspiratory effort, and arterial hypercapnia and hypoxemia.[4] The paralysis appeared bilateral in all seven alpacas imaged using fluoroscopy. Histologic examination revealed phrenic nerve degeneration in all six alpacas necropsied, with long nerves also demonstrating degeneration in two alpacas. The etiology was not identified.[4]

Traumatic

Injection injuries to peripheral nerves may result from needle puncture, the drug deposited, pressure from an abscess or hematoma, or fibrous tissue around the nerve. The sciatic nerve has been most commonly affected in cattle because historically most intramuscular injections were given deep in the hamstring muscles. Young calves were particularly susceptible because of their small muscle masses. Current recommendations in cattle are that intramuscular injections should be administered cranial to the shoulder.

Femoral nerve paralysis in calves occurs in large calves born to heifers with dystocia. The injury occurs when calves in anterior presentation fail to enter the birth canal because their stifle joints become engaged at the brim of the pelvis. Traction used to deliver these calves causes hyperextension of the femur and stretching of the quadriceps muscle and its neural and vascular supplies. In most cases the right femoral nerve is affected. Such calves are unable to bear weight on the affected leg within days after birth, the quadriceps muscle is atrophied, and the patella can be luxated easily. The patellar reflex is absent or markedly reduced in the affected limb because this reflex requires an intact femoral nerve and functional quadriceps muscle. Varying degrees of rear limb paresis result, accompanied by varying degrees of hindlimb gait abnormality. Skin analgesia maybe present over the proximal lateral to cranial to medial aspect of the tibia. At rest, the affected leg is slightly flexed and the hip on the affected side is held slightly lower. During walking, the animal has difficulty in advancing the limb normally because the limb collapses when weight bearing. In severe cases of muscle atrophy, the patella is easily luxated both medially and laterally. Injury to the femoral nerve is relatively easy to clinically identify, and there is usually no need to perform EMG studies of atrophied quadriceps muscle to document denervation.

Calving paralysis is common in heifers that have experienced a difficult calving. Affected animals are unable to stand without assistance; if they do stand, the hindlimbs are weak and there is marked abduction and inability to adduct. It has always been erroneously thought that traumatic injury of the obturator nerves during passage of the calf in the pelvic cavity was the cause of the paresis; however, detailed pathologic and experimental studies have demonstrated that most calving paresis/paralysis is caused by damage to the sciatic nerve. Experimental transection of the obturator nerves does not result in paresis. The term **obturator nerve paralysis** should only be used for postparturient cattle with an inability to adduct one or both hindlimbs, and calving paralysis in the preferred descriptive term for hindlimb paresis/paralysis occurring in the immediate postparturient period.

Damage to the sciatic nerve results in rear limb weakness and knuckling of the fetlocks; the latter clinical sign is an important means for differentiating sciatic nerve damage from obturator nerve damage (Fig. 14-25). The patellar reflex in ruminants with sciatic nerve damage is normal or increased, because the reflex contraction of the quadriceps muscle group by the femoral nerve is unopposed by the muscles of the hindlimb innervated by the sciatic nerve.

The peroneal nerve is most frequently damaged by local trauma to the lateral stifle where the peroneal nerve runs in a superficial location lateral to the head of the fibular bone. Damage to the peroneal nerve leads to knuckling over of the fetlock joint from damage to the extensor muscles of the distal limb, resulting in the dorsal aspect of the hoof resting on the ground when the animal is standing. Full weight can be borne on the

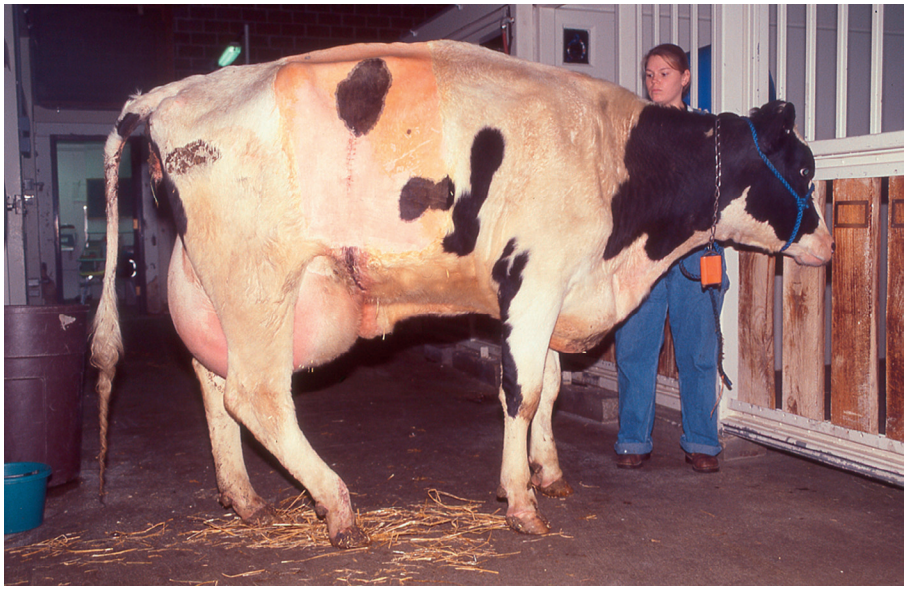

Fig. 14-25 Three-year-old Holstein Friesian cow with mild paresis of the right sciatic nerve. The hock is dropped relative to the normal unaffected left leg, and the fetlock has the characteristic knuckling. The cow has had a left displaced abomasum surgically corrected by a right flank incision and is being treated for concurrent mastitis.

affected limb when the digit is placed in its normal position, but immediately on walking the digit is dragged. There is a loss of skin sensation on the anterior aspect of the metatarsus and digit.

Damage to the tibial nerve causes mild hyperflexion of the hock and a forward knuckling of the fetlock joint. Tibial nerve damage is very rare, and most cases described as tibial nerve damage are actually sciatic nerve damage.

The radial nerve is most susceptible to traumatic damage because it courses distally and laterally over the later condyle of the humerus. Radial nerve paresis is most common when heavy adult cattle are placed in lateral recumbency, such as corrective foot trimming in bulls. Care must be taken in these animals to pad the area around the elbow and to ensure that the time spent in lateral recumbency is minimized. Clinical signs of radial nerve paresis include inability to advance the front limb with the ability to bear weight when the limb is placed directly under the animal in the normal position (Fig. 14-26). In advanced cases, the cranial aspect of the fetlock is dragged along the ground and the area needs to be protected from severe abrasion injury using a splint or cast.

Brachial plexus injury, including avulsion, is rare in large animals, because the muscle mass is usually sufficient to prevent overextension of the front limb. It is a rare outcome of correction of dystocia in goats, particularly when relatively excessive traction is applied to one front limb during delivery. Clinical signs of brachial plexus avulsion include a complete inability to bear weight

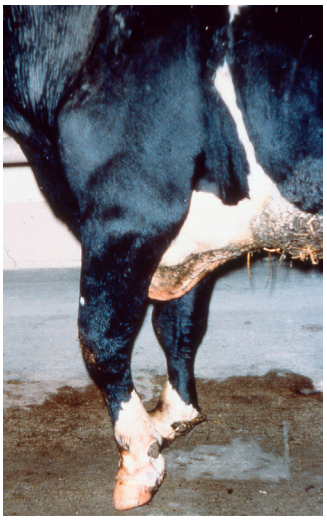

Fig. 14-26 Mild radial nerve paresis in a Holstein Friesian bull. Swelling is present over the lateral aspect of the elbow. Paresis was present immediately after taking the animal off a foot table for corrective foot trimming.

on the limb and a dropped elbow relative to the unaffected limb (Fig. 14-27).

Metabolic and Nutritional

PA deficiency may occur in pigs fed diets based solely on corn (maize). Affected animals develop a goose-stepping gait caused by degenerative changes in the primary sensory neurons of the peripheral nerves.

Toxic

Heavy metal poisoning including **lead and mercury poisoning in horses** has been

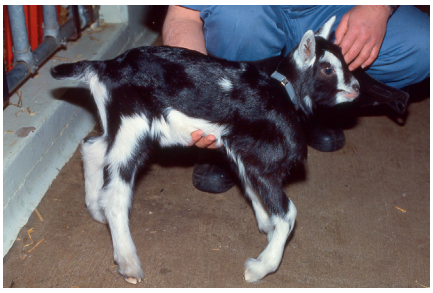

Fig. 14-27 One-week-old kid with brachial plexus avulsion of the right forelimb. The right limb "appears" longer than the unaffected left limb and the right elbow appears dropped. The right front leg cannot support weight and is not advanced in a normal manner during walking. The right leg received excessive traction during correction of a dystocia.

associated with clinical signs of degeneration of peripheral CNs, but these are not well documented.

Tumors

A multicentric schwannoma causing chronic ruminal tympany and forelimb paresis has been recorded in an aged cow. Neoplastic masses were present throughout the body, and both right and left brachial plexuses were involved. The peripheral nerves of each brachial plexus were enlarged. Large tumor masses were present on the serosal surfaces of the esophagus, pericardial sac and epicardium, and within the myocardium, endocardium, and the ventral branches of the first four thoracic spinal nerves. A large mass was present in the anterior mediastinum near the thoracic inlet.

Autonomic Nervous System

Equine grass sickness (equine dysautonomia, grass sickness, mal Seco) in the horse is a polyneuropathy involving both the peripheral nervous system (autonomic and enteric nervous systems) as well as the CNS.[5-7] Equine grass sickness occurs primarily in Scotland, although cases have been reported elsewhere in Europe, and in Patagonia and the Falkland Islands.[8] The disorder is characterized by a peracute to chronic alimentary tract disease of horses on pasture (hence the name). Gastrointestinal stasis is partial or complete. Peracute cases are in shock and in a state of collapse with gastric refluxing. Acute, subacute, and chronic cases also occur. Degenerative changes occur in the autonomic ganglia (especially the celiac–mesenteric, and stellate), thoracic sympathetic chain, ciliary, cranial and caudal cervical, the craniospinal sensory ganglia, and selected nuclei in the CNS. EMG reveals the presence of a neuropathy of skeletal muscles.[8] The etiology is unknown but neurotoxin involvement is suspected, possibly *Clostridium botulinum* type C/D.

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TETANUS

ETIOLOGY

Tetanus is caused by *C. tetani,* a gram-positive, spore-forming obligate anaerobe bacillus. It is a ubiquitous organism and a commensal of the gastrointestinal tract of domestic animals and humans. The organism forms highly resistant spores that can persist in soil for many years. The spores survive many standard disinfection procedures, including steam heat at 100°C (212°F) for 20 minutes but can be destroyed by heating at 115°C (239°F) for 20 minutes. After a period of anaerobic incubation spores germinate to their vegetative form, which starts replicating and producing a complex of exotoxins causing the clinic signs characteristic for this condition. The toxins produced are **tetanolysin, tetanospasmin,** and **neurotoxin** or nonspasmolytic toxin.

SYNOPSIS

Etiology Muscle spasm from action of the exotoxin tetanospasmin produced by the vegetative stage of *Clostridium tetani.*

Epidemiology Marked difference in species susceptibility with horses being most and cattle being least susceptible. Usually a history of a wound or other tissue trauma. Occurs as isolated cases but also as outbreaks in young ruminants following castration and docking.

Clinical findings Generalized muscular rigidity and spasms, hyperesthesia, prolapse of third eyelid, trismus, ears pulled caudally, bloat in ruminants, convulsions, respiratory arrest, and death. High case fatality.

Necropsy findings None. May demonstrate the organism in necrotic tissue in some cases.

Diagnostic confirmation Diagnosis is based on characteristic clinical signs and wound history. No definitive antemortem test or pathognomonic postmortem lesion. A bioassay consisting of injecting mice with infectious material to induce characteristic clinical signs is used.

Treatment Objectives are to prevent further production of exotoxin, neutralize residual toxin, control muscle spasms until the toxin is eliminated or destroyed, maintain hydration and nutrition, provide supportive treatment.

Control Regular prophylactic vaccination with tetanus toxoid of susceptible animals, vaccination and administration of tetanus antitoxin to unvaccinated animals with fresh wounds, antibiotic therapy in animals with wounds that are contaminated or at risk to be contaminated.

EPIDEMIOLOGY

Occurrence

Tetanus occurs in all parts of the world and is most common in closely settled areas under intensive cultivation. It occurs in all farm animals, mainly as individual, sporadic cases, although outbreaks are occasionally observed in young cattle, young pigs, and lambs following wound management procedures.[1]

Case–Fatality Rate

In young ruminants the case–fatality rate is over 80%, but the recovery rate is high in adult cattle. In horses it varies widely between areas. In some areas almost all animals die acutely, and in others the mortality rate is consistently about 50%.[2,3]

Source of Infection

C. tetani organisms are commonly present in the feces of animals, especially horses, and in the soil contaminated by these feces. Surveys in different areas of the world show it is present in 30% to 42% of soil samples. The survival period of the organism in soil varies widely from soil to soil.

Transmission

The **portal of entry** is usually through deep puncture wounds, but the spores may lie dormant in the tissues for some time and produce clinical illness only when tissue conditions favor their proliferation. For this reason, the portal of entry is often difficult to identify. Puncture wounds of the hooves are common sites of entry in horses. Introduction to the genital tract at the time of parturition is the usual portal of entry in cattle. A high incidence of tetanus may occur in young pigs following castration and in lambs following castration, shearing, docking, vaccinations, or injections of pharmaceuticals, especially anthelmintics. Docking by the use of elastic band ligatures is reputed to be especially hazardous. **Neonatal tetanus** occurs when there is infection in the umbilical cord associated with unsanitary conditions at parturition. Cases of tetanus in ruminants after thermic dehorning and ear-tagging have been reported.[1]

Outbreaks of **"idiopathic tetanus"** occur occasionally in young cattle without a wound being apparent, usually in association with the grazing of rough, fibrous feed, and it is probable that toxin is produced in wounds in the mouth or gastrointestinal tract or is ingested preformed in the feed. Proliferation in the rumen may also result in toxin production.

Animal Risk Factors

The neurotoxin of *C. tetani* is exceedingly potent, but there is considerable variation in susceptibility between animal species, and horses are the most susceptible and cattle the least susceptible. The variation in prevalence of the disease in the different species is partly caused by this variation in susceptibility but is also because exposure and wound management practices are more likely to occur in some species than in others.

Importance

Tetanus is important because of its high case fatality and the very long convalescence in the survivors. In regions of the world where horses, donkeys, and mules still play an important role in the rural economy and where vaccination is uncommon, the economic impact of tetanus can be considerable.[2]

PATHOGENESIS

The tetanus spores remain **localized** at their site of introduction and do not invade surrounding tissues. Spores germinate to their vegetative form to proliferate and produce **tetanolysin, tetanospasmin,** and **neurotoxin** only if certain environmental conditions are attained, particularly a lowering of the local tissue oxygen tension. Toxin production may occur immediately after introduction if the accompanying trauma has been sufficiently severe, or if foreign material has also been introduced to the wound, or may be delayed for several months until subsequent trauma to the site causes tissue damage. The original injury may be inapparent by then. Of the three mentioned exotoxins, **tetanospasmin is the most relevant** for the pathophysiology of the condition. Although **tetanolysin** was found to promote local tissue necrosis, its role in the pathogenesis of tetanus remains doubtful. The role of the more recently identified neurotoxin, or nonspasmogenic toxin, which is a peripherally active for the pathophysiology of tetanus, is currently unknown.

Tetanospasmin diffuses to the systemic circulation, is bound to motor end plates, and travels up peripheral nerve trunks via retrograde intraaxonal transport to the CNS. The exact mechanisms by which the toxin exerts its effects on nervous tissue are not known, but it blocks the release of neurotransmitters such as GABA and glycine, which are essential for the synaptic inhibition of gamma motor neurons in the spinal cord. There it leads to an unmodulated spread of neural impulses produced

by normally innocuous stimuli, causing exaggerated responses and a state of constant muscular spasticity. No structural lesions are produced. Death occurs by asphyxiation caused by fixation of the muscles of respiration.

CLINICAL FINDINGS

The **incubation period** varies between 3 days and 4 weeks, with occasional cases occurring as long as several months after the infection is introduced. In sheep and lambs cases appear 3 to 10 days after shearing, docking, or castration.

Clinical findings are similar in all animal species. Initially, there is an increase in **muscle stiffness**, accompanied by muscle tremor. There is **trismus** with restriction of jaw movements; **prolapse of the third eyelid;** stiffness of the hindlimbs causing an unsteady, straddling gait; and the tail is held out stiffly, especially when backing or turning. Retraction of the eye and prolapse of the third eyelid (a rapid movement of the third eyelid across the cornea followed by a slow retraction) is one of the earliest and consistent signs (with the exception of sheep) and can be exaggerated by sharp lifting of the muzzle or tapping the face below the eye. Additional signs include an anxious and alert expression contributed to by an erect carriage of the ears, retraction of the eyelids and dilation of the nostrils, and hyperesthesia with exaggerated responses to normal stimuli (Fig. 14-28).

The animal may continue to eat and drink in the early stages but mastication is soon prevented by tetany of the masseter muscles and saliva may drool from the mouth. If food or water is taken, attempts at swallowing are followed by regurgitation from the nose. Constipation is usual and the urine is retained, partly as a result of the inability to assume the normal position for urination. The rectal temperature and pulse rate are within the normal range in the early stages but may rise later when muscular tone and activity are further increased. In cattle, particularly young animals, bloat is an early sign but is not usually severe and is accompanied by strong, frequent rumen contractions.

As the disease progresses, muscular tetany increases and the animal adopts a **sawhorse posture** (Figs. 14-29 and 14-30). Uneven muscular contractions may cause the development of a curve in the spine and deviation of the tail to one side. There is great difficulty in walking and the animal is inclined to fall, especially when startled. Falling occurs with the limbs still in a state of **tetany** and the animal can cause itself severe injury. Once down it is almost impossible to get a large animal to its feet again. Tetanic convulsions begin in which the tetany is still further exaggerated. Opisthotonus is marked, the hindlimbs are stuck out stiffly behind and the forelegs forward. Sweating may be profuse and the temperature rises, often to 42°C (107°F). The convulsions are at first only stimulated by sound or touch but soon occur spontaneously. In fatal cases there is often a transient period of improvement for several hours before a final, severe tetanic spasm during which respiration is arrested.

Fig. 14-28 Polled Hereford cow exhibiting early signs of tetanus with healthy calf. The tail is held slightly away from the perineum, the ears are back, the eyes have a surprised expressed with slight prolapse of the nictitating membrane, and saliva is drooling from the mouth. The cow calved 7 days previously and had a retained placenta and metritis.

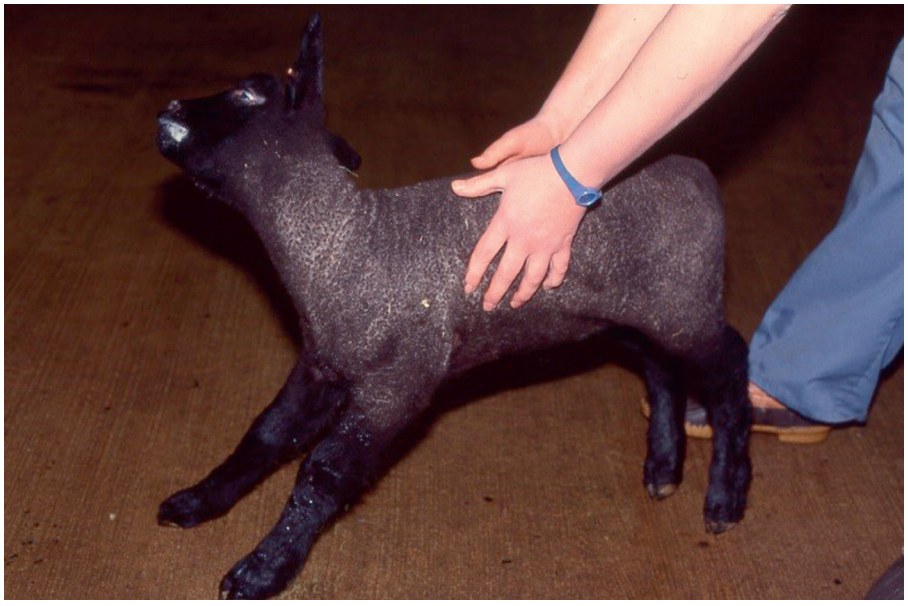

Fig. 14-29 Suffolk lamb with tetanus after castration using a band. The lamb is exhibiting a sawhorse stance caused by generalized muscle rigidity and drooling of saliva.

The **course of the disease** and the **prognosis** vary both between and within species. The **duration** of a fatal illness in horses and cattle is usually 5 to 10 days, but sheep usually die on about the third or fourth day. A long incubation period is usually associated with a mild syndrome, a long course, and a favorable prognosis. **Mild cases** that recover usually do so slowly, with the stiffness disappearing gradually over a period of weeks or even months. The prognosis is poor when signs rapidly progress. Animals vaccinated in the past year have a better prognosis, as do horses that have received parenteral penicillin and tetanus antitoxin and in which the wound was aggressively cleaned when fresh.

CLINICAL PATHOLOGY

There are no specific abnormalities in blood or CSF and no antemortem test confirming

Fig. 14-30 Corriedale lamb with tetanus after tail docking. Note the ear and eyelid retraction and generalized stiffness.

the diagnosis. Blood levels of tetanus toxin are usually too low to be detected. Gram-stain of wound aspirates is considered of limited value because sporulated as well as vegetative forms of *C. tetani* resemble other anaerobic bacteria. Culturing the pathogen is difficult because of the low number of organisms normally present and the strict anaerobic conditions required for culture. Culture in combination with PCR has been used for identification of *C. tetani.*[1] A bioassay consisting of injecting infectious material into the tail base of mice and observing for onset of characteristic clinical signs is possible.[2]

NECROPSY FINDINGS

There are no gross or histologic findings by which a diagnosis can be confirmed, although a search should be made for the site of infection. Culture of the organism is difficult but should be attempted. If minimal autolysis has occurred by the time of necropsy, the identification of large gram-positive rods with terminal spores ("tennis-racket morphology") in smears prepared from the wound site or spleen is supportive of a diagnosis of tetanus.

Samples for Confirmation of Diagnosis

- Bacteriology: air-dried impression smears from spleen, wound site (cyto, Gram stain), culture swab from wound site in anaerobic transport media; spleen in sterile, leak-proof container (anaerobic CULT, bioassay).

DIFFERENTIAL DIAGNOSIS

Fully developed tetanus is so distinctive clinically that it is seldom confused with other diseases. The muscular spasms, the prolapse of the third eyelid, and a recent history of accidental injury or surgery are characteristic findings. However, in its early stages or mild forms, tetanus may be confused with other diseases.

All species
- Strychnine poisoning
- Meningitis

Horses
- Hypocalcemic tetany (eclampsia)
- Acute laminitis
- Hyperkalemic periodic paralysis
- Myositis, particularly after injection in the cervical region.

Ruminants
- Hypomagnesemia (cows, sheep and calves)
- White muscle disease
- Polioencephalomalacia
- Enterotoxemia.

TREATMENT

These are the main principles in the treatment of tetanus:
- Eliminate the causative bacteria
- Neutralize residual toxin
- Control muscle spasms until the toxin is eliminated or destroyed
- Maintain hydration and nutrition
- Provide supportive treatment

There are no structural changes in the nervous system, and the management of cases of tetanus depends largely on keeping the animal alive through the critical stages.

Elimination of the organism is usually attempted by the parenteral administration of penicillin in large doses (44,000 IU/kg), preferably by intravenous administration. Other antimicrobials that have been proposed include oxytetracycline (15 mg/kg), macrolides, and metronidazole. If the infection site is found, the wound should be aggressively cleaned and debrided but only after antitoxin has been administered, because debridement, irrigation with hydrogen peroxide, and the local application of penicillin may facilitate the absorption of the toxin.

The objective of administering **tetanus antitoxin** is to neutralize circulating toxin outside the CNS. The use of tetanus antitoxin is most appropriate in wounded animals that are susceptible to but unvaccinated against tetanus or with uncertain vaccination history. Because binding of tetanospasmin to neural cells is irreversible and because the tetanus antitoxin is unable to penetrate the blood-brain barrier, administration of antitoxin is of little value once signs have appeared. After the experimental administration of toxin, antitoxin is of limited value at 10 hours and ineffective by 48 hours. The recommended doses vary widely and range from 10,000 to over 300,000 IU per treatment, given intravenously, intramuscularly, or subcutaneously once or repeatedly, but reported treatment outcomes are inconsistent. Local injection of some of the antitoxin around the wound has also been proposed. There have been a number of attempts to justify the treatment of early cases of equine tetanus by intrathecal injection of antitoxin, but there is limited evidence of therapeutic value and the procedure carries risk.

The use of **tetanus toxoid** has also been recommended for patients with tetanus, but an antibody response may take 2 to 4 weeks and a booster vaccination is required in previously unvaccinated animals. The effectiveness of this treatment in previously unvaccinated animals is therefore doubtful. When combining tetanus toxoid and antitoxin, both compounds should be administered on different sites using different syringes.

Relaxation of the muscle tetany can be attempted with various drugs. Chlorpromazine (0.4–0.8 mg/kg BW intravenously, or 1.0 mg/kg BW intramuscularly, three or four times daily) and acepromazine (0.05 mg/kg BW three to four times daily) administered until severe signs subside, are widely used in horses. A combination of diazepam (0.1–0.4 mg/kg) and xylazine (0.5–1.0 mg/kg intravenously or intramuscularly) may be effective in horses refractory to phenothiazine tranquilizers.

Hydration can be maintained by intravenous or stomach-tube feeding during the critical stages when the animal cannot eat or drink. The use of an indwelling tube should be considered because of the disturbance caused each time the stomach tube is passed. Feed and water containers should be elevated, and the feed should be soft and moist.

Additional supportive treatment includes slinging of horses during the recovery period, when hyperesthesia is diminishing. Affected animals should be kept as quiet as possible and provided with dark, well-bedded quarters with nonslip flooring and plenty of room to avoid injury if convulsions occur. Administration of enemas and catheterization may relieve the animal's discomfort. This level of nursing, plus penicillin, ataractic drugs, and antitoxin for an average of 14 days, can deliver something like a 50% recovery by an average of 27 days, but the cost is high. A rumenostomy may be required in ruminant patients with recurrent bloat.

Horses that fall frequently sustain bone fractures and may need to be destroyed.

TREATMENT AND CONTROL

Treatment

Penicillin G (30,000 IU/kg IM or IV every 12–24 hours) (R-1)

Procaine penicillin (44,000 IU/kg IM every 12–24 hours) (R-1)

Oxytetracycline (15 mg/kg IV every 24 hours) (R-2)

Tetanus antitoxin (10,000–50, 000 IU per dose IM or IV once or repeatedly) (R-2)

Tetanus antitoxin (30,000–50,000 IU per dose intrathecal) (R-3)

Sedation horses

Chlorpromazine (0.4–0.8 mg/kg IV or IM every 6–8 hours) (R-1)

Acepromazine (0.05–0.1 mg/kg IV or IM every 6–8 hours) (R-1)

Diazepam (0.01–0.4 mg/kg IV or IM) (R-1)

Xylazine (0.5–1 mg/kg IV or IM) (R-1)

Sedation cattle

Diazepam (0.5–1.5 mg/kg IV or IM)

Xylazine (0.05–0.15 mg/kg IV or 0.1–0.3 mg/kg IM)

Sedation sheep

Acepromazine (0.05–0.1 mg/kg IV or IM every 6–8 hours) (R-1)

Diazepam (0.2–0.5 mg/kg IV or IM (every 6–8 hours) (R-1)

Control

Regular vaccination if tetanus toxoid (R-1)

Tetanus antitoxin (1500 IU per dose IM in unvaccinated animals with fresh wounds) (R-1)

IM, intramuscularly, IV, intravenously.

CONTROL

Many cases of tetanus could be avoided by proper skin and instrument disinfection at castrating, docking, and shearing time. These operations should be performed in clean surroundings; in the case of lambs docked in the field, temporary pens are preferred over permanent yards for catching and penning.

Passive Immunity

Short-term prophylaxis can be achieved by the injection of 1500 IU of tetanus antitoxin. The immunity is transient, persisting for only 10 to 14 days.

Tetanus Antitoxin

Tetanus antitoxin should be given to any horse with a penetrating wound or deep laceration, and the wound should also be cleaned aggressively. Tetanus toxoid can be administered at the same time as tetanus antitoxin, provided they are injected at different sites and using different syringes. Animals that suffer injury are usually given an injection of antitoxin and one of toxoid to ensure complete protection.

Tetanus antitoxin is often routinely given to **mares** following foaling and to newborn foals. In some areas the risk for tetanus in young foals is high and repeated doses of antitoxin at weekly intervals may be required for protection.

On farms where the incidence of tetanus in **lambs** is high, antitoxin is usually given at the time of docking or castration; 200 IU has been shown to be effective. The risk for tetanus in calves is lower than in lambs and tetanus antitoxin is not commonly given at the time of castration.

There is a risk for **serum hepatitis** in horses that have been given tetanus antitoxin and, while this risk is small, a policy of routine active immunization of the mare to provide the mare with active immunity and the foal with passive colostral immunity is preferred to one that relies on antitoxin. Provided foals get an adequate supply of colostrum they are protected during the first 10 weeks of life by active vaccination of the mare during the last weeks of pregnancy. Prevention of tetanus in newborn lambs is also best effected by vaccination of the ewe in late pregnancy.

Active Immunity

Available vaccines are formalin-inactivated adjuvanted toxoids; they induce long-lasting immunity. Primary vaccination requires two doses 3 to 6 weeks apart. Protective titers are obtained within 14 days of the second injection and last for at least a year and up to 5 years.

Traditionally **foals** have received primary vaccination at 3 to 4 months of age; however, there is evidence that maternal antibodies acquired by foals born to mares vaccinated shortly before parturition significantly inhibit the antibody response of the foal to primary vaccination until it is 6 months of age and that primary vaccination should be delayed until that age.

Although immunity lasts longer than 1 year, it is common to revaccinate horses yearly with a single booster injection. Pregnant mares should receive a booster injection 4 to 6 weeks before foaling to provide adequate colostral immunity to the foal.

Ewes are immunized with a similar schedule except that the primary doses are usually given at a managementally convenient time when the flock is yarded. A prelambing booster vaccination is given yearly. Commonly, commercial vaccines for sheep also contain antigens for other clostridial diseases for which sheep are at high risk.

Vaccination of **cattle** is usually not considered unless an outbreak of the disease has occurred in the immediate past and further cases may be anticipated.

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BOTULISM

SYNOPSIS

Etiology Neurotoxin produced by *Clostridium botulinum* during vegetative growth. *C. botulinum* types B, C, and D and, on rare instances, type A are associated with disease in animals but the type prevalence varies geographically.

Epidemiology Ingestion of preformed toxin in which feed preparation or storage allows multiplication of the organism in the feed with toxin production. Contamination of feed with carrion containing toxin. Consumption of carrion on pasture by phosphorus-deficient animals. Risk factors often result in multiple cases. Toxicoinfections with toxin production from organisms in the intestine or wounds are more uncommon.

Clinical findings Early muscle tremor, progressive symmetric weakness, and motor paralysis leading to recumbency. Mydriasis, ptosis, weak tongue retraction; sensation and consciousness retained until death.

Necropsy findings None specific.

Diagnostic confirmation Demonstration of toxin in intestinal contents, serum, or feed. Demonstration of organisms in feed, intestinal contents, or wounds.

Treatment Type-specific antiserum and supportive treatment.

Control Avoidance of exposure by feed management. Vaccination.

ETIOLOGY

The causative organism *C. botulinum,* a spore-forming obligate anaerobe, produces neurotoxins during vegetative growth. Spores can survive in the environment for over 30 years. Under favorable conditions of warmth and moisture the spores germinate and vegetative cells multiply rapidly, elaborating a stable and highly lethal neurotoxin (BoTN) which, when ingested, or absorbed from tissues, causes the disease. The toxin is also capable of surviving for long periods, particularly in bones. Seven antigenically distinct **toxin types** (A-G), some with subtypes, have been identified. Farm animal disease is produced primarily by types B, C, D, and occasionally type A. Type A, B, E, and F toxins are generally related to human botulism.[1] Botulinum neurotoxin forming *C. botulinum* species are divided into groups I to IV depending on their physiologic properties.[1]

- **Group I**: proteolytic *C. botulinum* type A, B and F. These types degrade protein such as milk, serum, meat, and chicken protein
- **Group II**: nonproteolytic *C. botulinum,* includes nonproteolytic type B and F and all type E
- **Group III:** *C. botulinum* type C and D
- **Group IV:** *C. botulinum* type G.

The **geographic distribution** of these types varies considerably. In a study in the United States, type A was found in neutral or alkaline soils in the west, whereas types B

and E were in damp or wet soil all over, except that B was not found in the south. Type C was found in acid soils in the Gulf coast, and type D in alkaline soils in the west. Microorganisms capable of inhibiting *C. botulinum* were present, with or without the clostridia, in many soils. Type B is also common in soils in the UK and in Europe. Types C and D are more common in warm climates.

The organism is present in the **alimentary tract** of animals that have recently ingested contaminated material and may be introduced into new areas in this way, or by birds and blowflies. In healthy animals with normal intestinal fauna and motility *C. botulinum* does not multiply in the gastrointestinal tract

EPIDEMIOLOGY

Occurrence

Botulism has **no geographic limitations**, with isolated cases and sporadic outbreaks occurring in most countries. The source of exposure to toxin and the risk for disease differ between regions because of differences in food storage, feeding, and management practices. **Outbreaks** associated with ingestion of toxin in conserved feeds are more common in the northern states of the United States and in Europe, whereas outbreaks in animals on pasture are reported primarily from South Africa, Australia, and the Gulf coast area of the United States. The disease usually occurs in a number of animals at one time and has a high case–fatality rate.

Source of Infection

Most incidents of botulism are associated with the ingestion of preformed toxin (**forage botulism**). Toxin in feeds may result from the primary growth of *C. botulinum* in the feed or from the contamination of the feed with toxin-containing carrion (**carrion-associated botulism**). Less common sources are growth with toxin production in wounds (**wound botulism**) or growth and toxin production in the alimentary tract (**toxicoinfectious botulism**).

Forage Botulism

Forage botulism occurs when pH, moisture, and anaerobic conditions in the feedstuff allow the vegetative growth of *C. botulinum* and the production of toxin. This can occur in a number of spoiled stored forages. Cereal silages carry a risk in the United States. Silage and hay may spoil to a stage suitable for the growth of *C. botulinum*. This is most likely if the forage is very succulent or is wet by rain when it is made.

Big bale silage is a particular risk. The type of forage ensiled in big bales often has insufficient water-soluble carbohydrate for adequate lactic acid fermentation to achieve a stable low pH, and the higher dry matter content can also lead to a higher pH. Clostridial multiplication is inhibited below pH 4.5. Most non–carrion-associated botulism is caused by type B strains, and horses appear to be especially susceptible.

Proliferation of the organism can occur in **decaying vegetable material**. The disease has also occurred in horses fed on spoiled vegetables and potatoes contaminated by *C. botulinum* and on alfalfa haylage packed in airtight aluminum foil envelopes. Grass clippings allowed to accumulate and decay in a pile have poisoned horses, as has round bale hay that spoiled after rain. Decaying grass at the base of old tussocks and in trampled stubble are known to be suitable sites for growth of *C. botulinum*. Cases have occurred with brewers grains, and high-moisture grain has the potential for toxicity.

Carrion-Associated Botulism

This is almost always the cause of botulism in animals on pasture, and carrion is also a common cause of botulism in animals on conserved feeds. Carrion includes domestic and wild animals and birds. In endemic botulism areas, the carcasses of dead animals are invaded by *C. botulinum,* and high concentrations of toxin are produced such that very small amounts of flesh or bone have lethal concentrations. Most outbreaks of carrion-associated botulism are associated with **type C and D strains**; these strains produce much higher concentrations of toxin in carrion than type A and B strains. Toxin can persist in carrion for at least 1 year. Where the carcasses of rodents, cats, and birds contaminate hay or silage, toxin can leach out and contaminate surrounding hay or other feeds to cause multiple cases of botulism. In one instance a single mouse carcass is thought to have contaminated 200,000 tons of alfalfa cubes. A common source in Australia is hay made at the time of a mouse plague. At such times even good, fresh hay can contain a great deal of carrion. In another recorded incident 427 of 444 dairy cattle died after ingesting feed contaminated with BoTN type C from a cat carcass.

Poultry manure and ensiled **poultry litter** have caused outbreaks of botulism when used as fertilizers, as has poultry litter used for bedding cattle.[2] Outbreaks of botulism have occurred in cattle and sheep grazing pastures that have been fertilized with poultry manure or poultry litter. Cattle and sheep may eat poultry litter piled on a pasture before disposal. It is probable that the source of toxin in poultry litter is from poultry carcasses. Disease is usually caused by *C. botulinum* type D and occasionally type C.[2]

Direct carrion ingestion can occur where **cattle** subsist on a **chronically phosphorus-deficient diet** and manifest osteophagia, with subsequent ingestion of carrion. The disease is likely to occur in outbreak form. In **sheep**, pica is more usually associated with a dietary **deficiency of protein** or net energy. Occasional outbreaks occur that are caused by drinking of **water** contaminated by carcasses of dead animals. A not uncommon occurrence is livestock drinking lake water contaminated by the carcasses of ducks and other waterfowl that have died of botulism. Wetlands where outbreaks of avian botulism have occurred are likely to have repeated occurrences because of soil contamination.

Wound Botulism

Wound botulism is a **toxicoinfectious form of botulism** where the toxin is produced in wounds infected by *C. botulinum*.[3] Wound botulism is rare but is recorded in horses following castration, with omphalophlebitis, umbilical hernias treated with clamps, with an infected wound and in association with an injection abscess.

Toxicoinfectious Botulism

This results when toxin is produced by *C. botulinum* present in the intestine. Two conditions in horses, **equine grass sickness** (see Equine grass sickness in Chapter 7) and the **shaker foal syndrome,** are potential forms of toxicoinfectious botulism. The **shaker foal syndrome** is a disease of young foals up to 8 months of age with the highest prevalence in foals 3 to 8 weeks of age.

The disease occurs sporadically in the United States, Australia, and the UK but may occur repeatedly on some farms. *C. botulinum* type B has been isolated from the feces of naturally occurring cases of the disease, and the condition has been produced experimentally by the intravenous injection of *C. botulinum* toxin.

In cattle a toxicoinfection with *C. botulinum* is suspected to be the cause of a CWD reported to occur with increased incidence in northern and eastern Germany.[4,5] The condition was coined as **chronic or "visceral" botulism** and is thought to be caused by an enteral dysbiosis, allowing *C. botulinum* to grow in the ruminant intestinal tract and to expose the organism to subclinical doses of BoTN over a long time.[4,5] Symptoms associated with this condition are very unspecific including indigestion, lameness and ataxia, weight loss and drop in milk production, tucked-up abdomen, labored breathing, edema in brisket and legs, recumbency, and even death in advanced stages.[4] Although in many reported cases of herd outbreaks the diagnosis was solely based on clinical presentation and by ruling out other differential diagnosis, in several cases feces and intestinal content of affected or death animals were positively tested for *C. botulinum*.[4] The causative relationship is nonetheless under contentious debate because *C. botulinum* spores can routinely be isolated from feces of clinically healthy cattle.[6]

Experimental Reproduction

Cows challenged with type C botulinum toxin intravenously showed initial signs of

constipation and straining at defecation 48 hours after injection and weakness, decreased tail tone, decreased tongue tone, and muscle fasciculation of large-muscle groups between 76 and 92 hours. Weakness progressed to total posterior paresis between 80 and 140 hours in these cattle. On a weight-for-weight basis, cattle were considered to be 13 times more sensitive than mice to type C botulinum toxin.

Risk Factors

Animal Risk Factors

Botulism is most common in birds, particularly the domestic chicken and wild waterfowl. Cattle, sheep, and horses are susceptible but pigs, dogs, and cats appear to be resistant. The horse appears to be particularly susceptible to type B toxin. Cattle and sheep are usually affected by types C and D.

Environment Risk Factors

Botulism in range animals has a seasonal distribution. Outbreaks are most likely to occur during drought periods when feed is sparse, phosphorus intake is low, and carrion is plentiful. Silage-associated botulism is also seasonal with the feeding of silage. A key epidemiologic factor identified during recent botulism outbreaks in Europe and Great Britain was the proximity to broiler chicken litter.[2] The variation that occurs in the geographic distribution of the various types, and in carrion versus non–carrion-associated botulism is an important factor when considering prophylactic vaccination programs.

Importance

Severe outbreaks with high case–fatality rates can occur when contaminated feed is fed to large numbers of animals. Under extensive grazing conditions massive outbreaks of carrion-associated botulism also occur unless the animals are vaccinated.

Zoonotic Implications

BoTN is identified as a possible agent for bioterrorism. Furthermore an increasing number of large botulism outbreaks in cattle herds in the past decades have raised public health concerns associated with the consumption of meat or milk originating from affected herds.[1,7,8] In Germany, anecdotal reports of farmers having developed clinical signs resembling symptoms observed in their livestock suspected to suffer of a chronic form of botulism have contributed to these concerns.[9] Notwithstanding there is no evidence to support the assumption that there could be transmission between humans and animals.[1,7] Even the cases in which farm personnel and cattle were affected by a condition thought to be associated with *C. botulinum* different types of *C. botulinum* were isolated from people and cattle.[4,9]

The available evidence for the occurrence of human cases associated with meat and milk consumption has been reviewed.[7] No human cases of clinical botulism that were associated with the consumption of meat or milk derived from animals with botulism or healthy animals from herds affected by botulism were identified.[7] No cases of calves contracting clinical botulism from the consumption of raw milk in herds affected by botulism or cases of other species (dogs) contracting botulism from the consumption of fresh meat were available.[7]

Only one report of a cow affected by clinical botulism has been published in which BoTN was found in one mastitic quarter. The interpretation of this result is complicated by the fact that the BoTN affecting this animal was BoTN type C, whereas the BoNT type E was isolated in milk.[1] Furthermore the toxin was retrieved in a mastitic quarter but not the remaining three clinically healthy quarters. It has therefore been suggested that the BoNT retrieved in this quarter was either produced locally or is the result of contamination.[1] Cows are relatively sensitive to BoTN, whereas the toxin is rarely detectable in the blood of clinical cases. The excretion of BoTN in relevant amounts through the mammary gland is therefore considered to be unlikely. Nonetheless because of the mentioned uncertainties the meat and milk from cattle that have botulism should not be used for human consumption.

PATHOGENESIS

The toxins of *C. botulinum* are neurotoxins and produce functional paralysis without the development of histologic lesions. Botulinum toxins are absorbed from the intestinal tract or the wound and carried via the bloodstream to peripheral cholinergic nerve terminals including neuromuscular junctions, postganglionic parasympathetic nerve endings, and peripheral ganglia. The heavy chain of the toxin is responsible for binding to the receptors and translocation into the cell and the light chain of the toxin for resultant blockade of the release of acetylcholine at the neuromuscular junction. Flaccid paralysis develops and the animal may die of respiratory paralysis.

CLINICAL FINDINGS

Cattle and Horses

Signs usually appear 3 to 17 days after the animals gain access to the toxic material, but occasionally as soon as day 1, the incubation period is shorter as the amount of toxin available is increased. **Peracute cases** die without prior signs of illness, although a few fail to take water or food for a day beforehand. The disease is not accompanied by fever, and the characteristic clinical picture is one of progressive symmetric muscular paralysis affecting particularly the limb muscles and the muscles of the jaw, tongue, and throat. Muscle weakness and paralysis commence in the hindquarters and progress to the forequarters, head, and neck. The onset is marked by very obvious muscle tremor and fasciculation, often sufficient to make the whole limb tremble. Colic may be an initial sign in horses.

In most cases the disease is **subacute**. Restlessness, incoordination, stumbling, knuckling, and ataxia are followed by inability to rise or to lift the head. Mydriasis and ptosis occur early in the clinical course; mydriasis can be prominent in type C botulism in the horse. Skin sensation is retained. Affected animals lie in sternal recumbency with the head on the ground or turned into the flank, not unlike the posture of a cow with parturient paresis. Tongue tone is reduced, as is the strength of tongue retraction. In some cases the tongue becomes paralyzed and hangs from the mouth, the animal is unable to chew or swallow, and it drools saliva. In others there is no impairment of swallowing or mastication and the animal continues to eat until the end. This variation in signs is often a characteristic of an outbreak; either all the cases have tongue paralysis or all of them do not have it. Ruminal movements are depressed. Defecation and urination are usually unaffected, although cattle may be constipated. Paralysis of the chest muscles results in a terminal abdominal-type respiration. Sensation and consciousness are retained until the end, which usually occurs quietly, and with the animal in lateral recumbency, 1 to 4 days after the commencement of illness.

Occasional field cases and some experimental cases in cattle show **mild signs** and recover after an illness of 3 to 4 weeks. These chronic cases show restlessness and respiratory distress followed by knuckling, stumbling, and disinclination to rise. Anorexia and adipsia are important early signs but are often not observed in pastured animals. In some there is a pronounced roaring sound with each respiration. The roaring persists for up to 3 months. During the major part of the illness the animals spend most of their time in sternal recumbency. In some animals there is difficulty in prehending hay but concentrate and ensilage may be taken. This disability may persist for 3 weeks.

A syndrome ascribed to toxicosis with BoTN type B and manifested with anorexia, decline in milk production, dysphagia, a fetid diarrhea, regurgitation, and profuse salivation without myesthesia, paresis, and recumbency is reported in cattle in the Netherlands and Israel. In these cases death occurred as a result of aspiration pneumonia.

With **toxicoinfectious botulism** in foals, muscle tremor is often a prominent early sign. If the foal can walk, the gait is stiff and stilted and the toes are dragged. If the foal sucks, milk drools from the mouth; if it attempts to eat hay some of the material is regurgitated through the nostrils. Constipation occurs consistently. There is a rapid progression to severe muscular weakness and prostration, with the foal going down and

being unable to rise. If it is held up, there is a gross muscle tremor, which is not evident when the foal is lying down. Prostrate foals are bright and alert, have normal mentation and pain perception, and have dilatation of the pupils with a sluggish pupillary light reflex. During the latter period of the illness there is a complete cessation of peristalsis. The temperature varies from being slightly elevated to slightly depressed. Death occurs about 72 hours after the onset of signs and is caused by respiratory failure.

Sheep

Sheep do not show the typical flaccid paralysis of other species until the final stages of the disease. There is stiffness while walking and incoordination and some excitability in the early stages. The head may be held on one side or bobbed up and down while walking (**limber neck**). Lateral switching of the tail, salivation, and serous nasal discharge are also common. In the terminal stages there is abdominal respiration, limb paralysis, and rapid death.

Goats

Because of different feeding habits of sheep and goats the risk of exposure to BoTN of goats is considerably lower compared with sheep or cattle. Although goats look for bushes and shrubs on which to browse, cattle and sheep graze along the ground and are therefore more likely to ingest BoTN from contaminated waste spread over pasture.[8]

Pigs

Authentic reports in this species are rare. Clinical signs include staggering followed by recumbency, vomiting, and pupillary dilatation. The muscular paralysis is flaccid and affected animals do not eat or drink.

CLINICAL PATHOLOGY

There are no changes in hematologic values or serum biochemistry that are specific to botulism. In many cases under field conditions the diagnosis is solely based on clinical presentation and by ruling out potential differential diagnoses.

Laboratory diagnosis of botulism in the live or dead animal is difficult because of the lack of sensitive confirmatory laboratory tests. Laboratory confirmation is attempted by the following:

- Detection of preformed toxin in serum, intestinal tract contents, or feed
- Demonstration of spores of *C. botulinum* in the feed or gastrointestinal contents
- Detection of antibody in recovering or clinically normal at-risk animals.

Detection of toxin using bioassay in mice where mice are inoculated intraperitoneally coupled with toxin neutralization with polyvalent antitoxin is considered the most sensitive test currently available. Nonetheless the rate of positivity in clinical cases particularly when testing serum is low, which has been explained by the much higher sensitivity to BoNT of cattle and horse compared with mice and the rapid binding of BoNT in the neuromuscular junctions, leaving low to no amounts of free BoNT in blood. Currently gastrointestinal content or fecal material is preferred over fecal material for the detection of BoNT.[5,7]

In outbreaks of botulism it is not uncommon to have only a proportion of clinically affected animals, or none, test positive. Protection with monovalent antitoxin allows type identification. Toxin detection by an ELISA test appears less sensitive than mouse bioassay. Toxin production or carrion contamination can potentially occur in a number of feeds; however, the majority of outbreaks are associated with contamination in hay or silage and suspect feeds should be tested in mice for toxin. To get around the problem of lack of sensitivity with the mouse test, suspect feed has been fed to experimental cattle. Alternatively, one can make an infusion of the feed sample and use this as the sole drinking water supply for experimental animals. The problem with all feeding experiments is that the BoTN is likely to be very patchy in its distribution in the feed.

Failure to produce the disease in animals vaccinated against botulism, when deaths are occurring in the unvaccinated controls, has also been used as a diagnostic procedure.

Demonstration of spores of *C. botulinum* in the feed being fed or the feces of affected animals supports a diagnosis of botulism because botulism spores are rarely detected in the feces of normal foals and adult horses. Although the testing of gastrointestinal contents from clinically suspect cases in cattle is frequently used as diagnostic tool particularly when toxicoinfectious botulism is suspected, this approach is considered to lack specificity because the postmortem growth of environmental *C. botulinum* spores would result in false-positive results.[2,4,9] Furthermore *C. botulinum* can be isolated from the majority of fecal samples of healthy slaughter cows.

The detection of antibody in chronically affected animals and at-risk herdmates or as retrospective diagnosis by an ELISA test has been used to support a diagnosis in outbreaks of type C and type D botulism. Increased antibody prevalence over time or increased antibody prevalence in an affected group compared with a similar group nearby was reported by some authors.[10]

NECROPSY FINDINGS

There are no specific changes detectable at necropsy, although the presence of suspicious feedstuffs in the forestomachs or stomach may be suggestive. There may be nonspecific subendocardial and subepicardial hemorrhages and congestion of the intestines. Microscopic changes in the brain are also nonspecific, consisting mainly of perivascular hemorrhages in the corpus striatum, cerebellum, and cerebrum. Nonetheless, unless classic flaccid paralysis was observed clinically, the brain should be examined histologically to eliminate other causes of neurologic disease. The presence of *C. botulinum* in the alimentary tract is a further test. The presence of toxin in the gut contents is confirmatory if found but is often misleading, because the toxin may have already been absorbed. The presence of the toxin in the liver at postmortem examination is taken as evidence that the disease has occurred. In addition to traditional bioassays, such as the mouse protection test, newer methods for toxin detection include ELISA techniques, and a recently described immuno-PCR assay.

Samples for Confirmation of Diagnosis

- Bacteriology: suspected contaminated feed material, feces, rumen and intestinal contents, plus serum from clinically affected herdmates (bioassay, anaerobic CULT, ELISA)
- Histology: formalin-fixed brain.

DIFFERENTIAL DIAGNOSIS

A presumptive diagnosis is made on the clinical signs and history, occurrence in unvaccinated animals, and the ruling out of other diseases with a similar clinical presentation. The symmetric motor paralysis of botulism with muscle paralysis that progresses to recumbency in 1–4 days is a major differential for botulism from other causes of neurologic dysfunction in large animals.

Ruminants

- Periparturient hypocalcemia, characterized by low serum calcium concentrations and responsiveness to parenteral calcium administration
- Hypokalemia, characterized by marked hypokalemia
- Tick paralysis
- Paralytic rabies
- Poisoning by *Phalaris aquatica*
- Organophosphate/carbamate poisoning
- Louping-ill in sheep

Horses

- Equine encephalomyelitis
- Equine herpesvirus-1 myeloencephalopathy
- Atypical myopathy of unknown etiology; the condition that presents frequently fatal myopathy can be differentiated by the characteristic increase in serum creatine kinase activity and the presence of hemoglobinuria
- Equine motor neuron disease
- Hyperkalemic periodic paralysis
- Hepatic encephalopathy
- Paralytic rabies
- Ionophore toxicity
- Myasthenia gravis

TREATMENT

Recent studies report a survival rate in foals of 96% which was achieved by the early administration of antitoxin (before complete recumbency) coupled with a high quality of intensive care fluid therapy, enteral or parenteral feeding, nasal insufflation with oxygen, and mechanical ventilation if required. Duration of hospitalization was approximately 2 weeks. Antitoxin was considered essential to the high success rate in this report and this would limit the success of treatment geographically because antitoxin to the various BoTN types is not available universally. Specific or **polyvalent antiserum** is available in some countries and, if administered early in the course at a dose of 30,000 IU for a foal and 70,000 IU for adult horses, can improve the likelihood of survival. A single dose is sufficient, but it is expensive.

Animals should be confined to a stall with **supportive fluid therapy** and enteral feeding. Muzzling may be required to prevent aspiration pneumonia and frequent turning to prevent muscle necrosis and decubital ulcers. Bladder catheterization may be required in horses that do not urinate, and mechanical ventilation may be necessary for recumbent horses. Mineral oil is used to prevent constipation, and antimicrobial drugs are used to treat secondary complications such as aspiration pneumonia. Therapy should avoid the use of drugs that deplete the neuromuscular junction of acetylcholine, such as neostigmine, and those, such as procaine penicillin, tetracyclines, and aminoglycosides, that potentiate neuromuscular weakness.

A rapid progression of signs suggests a poor prognosis, and treatment should only be undertaken in subacute cases in which signs develop slowly and there is some chance of recovery. The prognosis in recumbent horses is grave.

Where groups of animals have had the same exposure factor, the remainder of the animals in the group should be vaccinated immediately.

Vaccination with either type-specific or combined BoNT toxoid in clinically affected animals is ineffective because binding of BoNT to neuromuscular junctions is irreversible.

TREATMENT AND CONTROL

Treatment

Polyvalent antiserum (30,000 IU for a foal and 70,000 IU for an adult horse, single dose) (R-2)

Control

Vaccinate with multivalent BoTN toxoid IM (R-2)

BoTN, botulin toxin, IM, intramuscularly.

CONTROL

In range animals, **correction of dietary deficiencies** by supplementation with phosphorus or protein should be implemented if conditions permit. Hygienic **disposal of carcasses** is advisable to prevent further pasture contamination but may not be practicable under range conditions. **Vaccination** with type-specific or combined (bivalent C and D) toxoid is practiced in enzootic areas in Australia and southern Africa. Type B and C vaccines would be more appropriate for prevention of disease in North America and Europe. The immunity engendered by vaccination is type specific. The number and interval of vaccinations required varies with the vaccine, and the manufacturer's directions should be followed. In horses, the disease is usually sporadic and caused by accidental contamination of feed or water; vaccination is seldom practiced in this species. Some local reactions are encountered after vaccination in horses but they are seldom serious. Vaccination of the mare may not prevent the occurrence of botulism in foals.

A common problem that arises when the disease appears to have resulted from feeding contaminated silage, hay, or other feed is what to do with the residue of the feed. In these circumstances the stock should be vigorously vaccinated with a toxoid on three occasions at 2-week intervals and then feeding of the same material can be recommenced.

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TICK PARALYSIS

Infestations with a several species of ticks are associated with paralysis of animals. Dogs are most commonly affected but losses can occur in cattle, sheep, goats, llamas, horses, and a variety of wild animals. At least 31 species in seven genera of ixodid ticks and seven species in three genera of argasid ticks have been implicated in tick paralysis. The most important tick species for livestock are given in Table 14-22. *D. andersoni* is the most common cause of tick paralysis in livestock in North America; *D. occidentalis* is associated with paralysis in cattle, horses, and deer.[1] In Australia, *I. holocyclus* is the predominant tick associated with paralysis, whereas *I. rubicundus* and *Rhipecephalus evertsi* are common in Africa.[1] Animals in Europe and Asia have developed tick paralysis from *I. ricinus* and *Hyalomma punctata*.[1]

The toxin of *D. andersoni* interferes with liberation or synthesis of acetylcholine at the muscle fiber motor end plates.[2] The disturbance is functional and paralysis of the peripheral neurons is the basis for clinical

Table 14-22 Ticks reported to cause paralysis in livestock

Animal	Tick	Country
Sheep, calves, goats	*Dermacentor andersoni* *D. occidentalis*	United States, Canada United States
Calves, lambs, foals, goats	*Ixodes holocyclus*	Australia
Sheep, goats, calves	*I. pilosus*	South Africa
Sheep, goats, calves, antelopes	*I. rubicundus*	South Africa
Sheep, goats	*I. ricinus*	Crete, Israel
Lambs	*Rhipicephalus evertsi*	South Africa
Calves, sheep, goats	*Hyalomma punctata*	South Africa, Europe, Japan
Sheep	*H. aegyptium*	Yugoslavia
Sheep	*Ornithodorus lahorensis*	Central Asia
Cattle, sheep, goats	*Amblyomma cajannense*	Central, South America
Cattle	*R. evertsi*	Africa

signs. Continuous secretion of toxin by a large number (35–150) of partly engorged female ticks that have been attached for 5 to 8 days is necessary to produce paralysis, with complete recovery occurring within 24 hours when the ticks are removed. The disease is generally confined to calves and yearlings. Clinically, there is an ascending, flaccid paralysis commencing with incoordination of the hindlimbs, followed by paralysis of the forelimbs and chest muscles, causing lateral recumbency.[1] Respiration is grossly abnormal; there is a double expiratory effort and the rate is slow (12–15 breaths per minute) but deep. Death, caused by respiratory failure, may occur in 1 to 2 days, but the course is usually 4 to 5 days. The mortality rate may be as high as 50% in dogs, but is usually much lower in farm animals.

I. holocyclus have been shown to paralyze calves of 25 to 50 kg BW. Between 4 and 10 adult female ticks are required to produce this effect and paralysis occurs 6 to 13 days after infestation occurs. The ticks under natural conditions parasitize wild fauna, and infestations of other species occur accidentally. The disease is limited in its distribution by the ecology of the ticks and the natural host fauna. The paralysis characteristic of the disease is associated with a toxin secreted by the salivary glands of female ticks, which is present in much greater concentration in the glands of adults than in other stages. The severity of the paralysis is independent of the number of ticks involved; susceptible animals may be seriously affected by a few ticks.[1]

Hyperimmune serum is used in the treatment of dogs, but in farm animals removal of the ticks in the early stages is usually followed by rapid recovery. Control necessitates eradication of the ticks or host fauna. The general principles of tick control are outlined in Chapter 11. The use of appropriate insecticides is an effective preventive.

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OVINE "KANGAROO GAIT" AND FENUGREEK STAGGERS

SYNOPSIS

Etiology Not known.

Epidemiology Seasonal occurrence involving only adult female sheep that are lactating, or in some cases, pregnant. Spontaneous recovery following cessation of lactation in most cases, but sometimes only 50%, but not always all affected sheep.

Clinical findings Bilateral forelimb locomotor disorder.

Lesions Edema of brain and spinal cord in early cases; axonal degeneration of the radial nerve followed by regeneration in more chronic cases (those greater than 6 weeks' duration).

Treatment Supportive.

Control None recognized.

ETIOLOGY

This is a neuropathy with no known cause. In Australia similar clinical and pathologic signs are associated with grazing mature plants or the stubble of fenugreek (*Trigonella foenum-graecum*), which is an annual winter-spring legume from which the seed is harvested as a condiment for human food.[1]

EPIDEMIOLOGY

Occurrence

This condition is recorded in Australia, New Zealand, and the UK. It is manifested by incoordination, including an acute onset of a high-stepping forelimb gait and bounding hindlimb gait.

Risk Factors

It occurs only in adult ewes with an onset in late pregnancy or early lactation. Spontaneous recovery occurs following cessation of lactation, and occasionally while ewes are still nursing lambs, although in Australia often only 50% of ewes recover completely.[1] The cumulative annual incidence varies between flocks but is usually less than 1%.

In the areas of northern England and southern Scotland the condition is significantly more common in upland and lowland flocks than in those hill grazing. Stocking density is higher in affected flocks than that in nonaffected flocks. Onset occurs while on pasture between March and June with a separate smaller peak in October. This seasonal occurrence could be a reflection of the parturition status of flocks or an effect of seasonal influences.

In Australia cases have been recorded in lactating ewes grazing improved pastures from June (winter) to February (summer) and the grazing of fenugreek crop or stubble in summer.

PATHOGENESIS

Clinical signs can be attributed to the generalized neuropathy affecting principally the radial nerves. Subsequent to the axonal degeneration a remyelination of the radial nerve occurs, explaining the clinical recovery. For cases not associated with ingestion of fenugreek, bilateral compression of the radial nerves is suggested as a cause, but there is no knowledge of how such an injury can occur. Despite the differences in diet, the similar clinical and pathologic presentation of kangaroo gait and fenugreek staggers has prompted the suggestion that these may be related entities.[1] Nevertheless there are some key differences; the initial acute stage of fenugreek staggers in Merino sheep is sometimes lethal and is later associated with weight loss, whereas kangaroo gait is not and seems to be restricted to larger meat breeds.

CLINICAL FINDINGS

These include incoordination, a high-stepping forelimb and bounding hindlimb gait, arched back, and proprioceptive deficits (knuckling of fore and occasionally hind fetlocks). There is bilateral forelimb paresis and palpable loss of muscle bulk in the forelimbs. The forelimbs and hindlimbs of affected sheep are positioned centrally under the body and so when they are pressed affected sheep move with a characteristic hopping or kangaroo gait. Affected ewes lie down more frequently and may graze on their knees but continue to eat and effectively suckle their lambs.

CLINICAL PATHOLOGY

There are no consistent abnormalities in hematology, blood biochemistry, or trace element analysis of affected sheep.

NECROPSY FINDINGS

In early cases there are signs of acute edema in the brain and spinal cord (wallerian degeneration of ventral motor tracts, spongy changes in the neuropil, and swollen astrocytes). This progresses to a peripheral neuropathy, with axonal degeneration of the myelinated fibers of the radial nerve fibers in longer standing cases (6 weeks or more), and then regeneration in recovering cases.

DIFFERENTIAL DIAGNOSIS

Romulosis, a condition associated with grazing fungus-infected onion grass (*Romulea rosea*), can cause incoordination and a similar hopping gait (bunny-hopping).

Foot rot or foot abscess involving the front feet can induce the same grazing behavior, but there is no problem in differentiation when the limbs and feet are examined.

Hypocalcemia in sheep occurs in late pregnancy or during lactation, and in the developing stages there is incoordination and muscle weakness. However, there is rapid progression to complete muscular paresis and a dramatic response to treatment.

Spinal abscess or fracture.

TREATMENT

Without the knowledge of etiology there is no specific treatment. Easy access to food and water should be provided.

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POLYNEURITIS EQUI (CAUDA EQUINA SYNDROME)

Polyneuritis equi (formerly cauda equina neuritis) is a demyelinating, inflammatory disease of peripheral nerves of adult horses. The **etiology** of the disease is unknown although infectious (adenovirus, EHV-1), immune (autoimmune disease), and toxic etiologies have been suggested, without conclusive substantiation. Adenovirus was isolated from two of three horses with the disease, but this observation has not been repeated, and it appears unlikely at this time that adenovirus is the cause of polyneuritis equi. EHV-1 is not consistently isolated from affected horses.

The disease occurs in adult horses in Europe and North America but has not been reported from the Southern Hemisphere. The prevalence in a group of 4319 horses subject to postmortem examination in Normandy was 0.2% (one case).[1] The disease is usually sporadic with single animals on a farm or in a stable affected. However, outbreaks of the disease can affect multiple horses from the same farm over a number of years.

The **pathogenesis** of the disease involves nonsuppurative inflammation of the extradural nerves and demyelination of peripheral nerves. Initial inflammation of the nerves causes hyperesthesia, which is followed by loss of sensation as nerves are demyelinated. Both motor and sensory nerves are affected, with subsequent weakness, paresis, muscle atrophy, urinary and fecal retention and incontinence, and gait abnormalities.

The inflammatory response is characterized by an abundance of **T lymphocytes**, in addition to B lymphocytes, macrophages, giant cells, eosinophils, and neutrophils in the perineurium and endomeurium.[2] The T cells are CD8+ cytotoxic T lymphocytes with rare CD4+ helper T lymphocytes.[3] This, with electron microscopic imaging, evidence of "myelin stripping" by macrophages and the presence of antibodies to the myelin P2 protein has been interpreted as indicative of immune-mediated activity against myelin.[2,4] This immune response might be toward the myelin as a primary target or could be the result of bystander activity in which other agents, potentially viruses, induce an immune response that is directed against myelin.

The **acute disease** is evident as abrupt onset of hyperesthesia of the perineum and tail head, and perhaps the face, evident as avoidance of touching, and chewing or rubbing of the tail. The hyperesthesia progresses to hypalgesia or anesthesia of the affected regions.

The disease usually has a more **insidious onset** with loss of sensation and function occurring over days to weeks. The most common presentation is that of cauda equina syndrome with bilaterally symmetric signs of posterior weakness, tail paralysis, fecal and urinary incontinence and retention, and atrophy of the gluteal muscles. Tail tone is decreased or absent and the tail is easily raised by the examiner. The anus is usually atonic and dilated. There are signs of urinary incontinence with urine scalding of the escutcheon and hindlegs. Rectal examination reveals fecal retention and a distended bladder that is readily expressed. Male horses can have prolapse of the penis with maintained sensation in the prepuce, which is a finding consistent with the separate innervation of these anatomic regions. Affected horses can also have ataxia of the hindlimbs, but this is always combined with signs of cauda equina disease.

Signs of **CN dysfunction** occur as part of the disease, but not in all cases. CN dysfunction can be symmetric, but is usually asymmetric. Nerves prominently involved in the genesis of clinical signs are the trigeminal (CN V), facial (CN VII), and hypoglossal nerve (CN XII), although all CNs can be affected to some extent. Involvement of the CNs is evident as facial paralysis (CN VII), weakness of the tongue (CN XII), and loss of sensation in the skin of the face (CN V). There can be loss of movement of the pinnae (CN VII) and head tilt (CN VIII). Laryngeal paralysis can be present (CN X). The buccal branches of CN VII can be enlarged and palpable over the masseter muscles ventral to the facial crest.

Not all clinical signs occur in all horses and, depending on the stage and severity of the disease, some animals can have loss of sensation as the only abnormality, especially during the early stages of the disease.

EMG is consistent with denervation with prolonged insertion potentials, positive sharp waves, and fibrillation. Per rectal **ultrasound examination** of the extradural sacral nerve routes as they exit the ventral sacral foramina reveals enlargement and a diffusely mottled, hypoechoic appearance.[3]

Biopsy of the sacrocaudalis dorsalis lateralis muscle can provide antemortem diagnosis of the disease. Affected horses have intense lymphocytic and histiocytic infiltration around the terminal nerves within the muscle, often obliterating architecture of the nerves but sparing the myofibers.[3] There is neurogenic atrophy of the muscle fibers.

The disease is inexorably progressive, the prognosis for life is hopeless, and the course of the disease is usually less than 3 months.

Clinical pathologic abnormalities are not diagnostic. There is sometimes a mild neutrophilic leukocytosis and hypergammaglobulinemia. Serum vitamin E concentrations are usually normal. Analysis of CSF demonstrates mild mononuclear pleocytosis and increased protein concentrations, but these changes are not diagnostic of the disease. Horses with polyneuritis equi have antibodies to P2 myelin protein in serum, but the diagnostic value of this test has not been determined.

Necropsy findings are definitive for the disease. Gross findings include thickening of the epidural nerve roots that is most severe in the cauda equina. The bladder and rectum can be distended. There can be evidence of fecal and urine scalding and self-trauma of the perineum. There can be thickening of the facial nerves. Microscopic changes are characterized by a granulomatous inflammation of the extradural nerves, although radiculoganglioneuritis and myelitis can also occur. There is loss of axons with demyelination and signs of remyelination. There is profound infiltration of nerves by macrophages, moderate to marked infiltration of cytotoxic T lymphocytes, and lesser infiltration of B lymphocytes.[3] Inflammatory cells are initially lymphocytes, plasma cells, and macrophages. As the inflammation becomes more severe or chronic there is extensive proliferation of fibroblasts and fibrocytes in addition to infiltration of lymphocytes and macrophages. There is axonal degeneration with proliferation of the perineurium. The chronic inflammatory changes result in loss of peripheral neural architecture. Lesions are present in many regions of the spinal cord, but are most severe in the sacral division and cauda equina. Lysosomal accumulations are present in the semilunar, geniculate, and sympathetic chains and granulomatous lesions in the celiac-mesenteric ganglion. Lesions of the CNs similarly involve infiltration with lymphocytes and histiocytes, and the inflammation can extend to the terminal branches of the nerves.

The **diagnosis** of polyneuritis equi is based on the presence of clinical signs of the disease, ruling out other diseases causing similar clinical signs, and necropsy examination. Diseases with manifestations similar to polyneuritis equi include the following:

- EHV-1 myeloencephalopathy
- Migrating parasites (Table 14-21, **differential diagnosis of disease causing spinal ataxia in horses**)
- Sorghum-Sudan grass neuropathy
- Equine protozoal myeloencephalitis
- Ryegrass staggers (*A. lolii*)
- Dourine
- Trauma to the sacral vertebral column
- Abscess or neoplasia involving the sacral or caudal lumbar vertebral column
- Meningitis
- Intentional alcohol sclerosis of tail head nerves in Quarter Horses.

There is no definitive **treatment** for polyneuritis equi. Administration of antiinflammatory agents, including corticosteroids, appears to be without sustained benefit.

Supportive care includes evacuation of the rectum and bladder and maintenance of hydration and provision of adequate nutrition. Feeding a diet that softens feces, or administration of fecal softeners or lubricants, can be beneficial. Bethanecol (0.05–0.1 mg/kg every 8–12 hours, orally) might increase bladder tone. Topical administration of petroleum jelly or similar products can protect the skin of the perineum and escutcheon from fecal and urine scalding.

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SCANDINAVIAN KNUCKLING SYNDROME (ACQUIRED EQUINE POLYNEUROPATHY)

This is a recently recognized syndrome of metatarsophalangeal joint extensor paresis in horses in Scandinavia.[1-3] The disease appears to be widespread in Sweden, Norway, and Finland occurring as clusters of disease outbreaks on farms.[1] The etiology is uncertain, although preserved feed is considered the source of an unidentified toxin.

A report described the risk factors and outcome of 42 cases distributed over 13 farms in Scandinavia from 2007 to 2009. Cases occurred between December and May with an overall prevalence of 27% and on-farm prevalence of 11% to 71% (for farms with >6 horses) although the number of cases, and affected farms, varies markedly from year to year.[2,4] The case–fatality rate was 29% in the epidemiology study[1] and 53% (40 of 75) in a case series.[2] The disease was less prevalent in horses >12 years of age, and younger horses had a greater chance of surviving the disease.

Clinical signs were typified by bilateral knuckling of the hindlimbs, which was most apparent on circling. Mild to moderate pelvic limb weakness was detected in 16 of 42 horses.[1] A small proportion of cases (3/42) had mild forelimb signs of weakness and knuckling. There was focal muscle atrophy of hindlimb musculature in seven cases. Mentation and vital signs (temperature, pulse, and respiratory rate) were within normal limits. The disease usually has a slow onset, but some affected horses developed severe signs with hours.[2] The median duration of clinical signs in affected horses that recover is 4.4 months (range 1–17 months) and survivors can recover completely.

Routine hematology and serum biochemical analysis do not reveal consistent abnormalities, apart from increased creatine kinase and AST activity in recumbent horses.[2]

Lesions are restricted to the peripheral nervous system and are evident in sciatic, peroneal, radial, and plantar digital nerves.[2,3] Lesions include areas of thick, swollen axons with subperineural accumulation of mucoid material. There is lymphohistiocytic infiltration of nerves and mild to moderate loss of myelinated nerve fibers.[3] Swollen axons and large vacuoles were present in sections of the lumbar tumescence. There are no lesions detected in the brain.[2]

Treatment consists of supportive and nursing care. Control measures are not reported.

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PERIPHERAL NERVE SHEATH TUMORS

PNSTs are most commonly benign tumors of the peripheral nervous system with a rare occurrence in veterinary medicine.[1] Most commonly affected species are dogs and cattle.[1] Tumors are composed of components of the peripheral nerve, including Schwann cells, perineural cells, fibroblasts and collagen. While in human medicine PNSTs are subdivided into **neurofibromas** and **schwannomas**, dependent on the predominant cell type and other histologic characteristics, this distinction is less clearly defined in veterinary medicine.[2,3] The existence of true neurofibromas as described in humans has been questioned.[1,2] PNSTs that can occur on any location of the peripheral nervous system most commonly originate from autonomic nerves such as cardiac and intercostal nerves or the brachial plexus.

CLINICAL FINDINGS

In cattle, PNSTs are generally asymptomatic and found incidentally during physical examination or slaughter. Clinical signs are uncommon but can include limb paresis or paralysis, recurrent bloat and vagal indigestion, cardiac insufficiency, and chronic wasting.[1,3,4] The cutaneous presentation is rare but can present as single or multiple indolent cutaneous masses between 1 and over 15 cm in diameter that are well demarcated. In some instances PMSTs may infiltrate surrounding tissue, immobilizing the mass and complicating surgical excision.

CLINICAL PATHOLOGY

Diagnosis must be confirmed histologically. Important features included the concurrent presence of highly and poorly cellular areas of Schwann cells. Nerve fibers are absent in schwannomas but may be found in neurofibromas. Immunohistostaining is used to confirm the presence of Schwann cells and to differentiate between schwannomas and neurofibromas.[1,2]

TREATMENT

Treatment of accessible masses (cutaneous form) is rarely required but may be indicated either for cosmetic reasons as an excisional biopsy or to remove the mass integrally. Although the prognosis in most cases is excellent, tumors with infiltrative growth may recur because of incomplete excision of abnormal c ells.

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