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Chapter 48

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Virus Infections of the Central Nervous System

Although virus infections of the central nervous system (CNS) are relatively rare, they are responsible for some of the most devastating and diverse effects of disease in humans and animals. Nevertheless, almost all the families of viruses have members associated with CNS disorders in humans. In this chapter we also briefly discuss prion diseases although these diseases are not strictly 'viral'.

CNS viral infections were first reported in Babylonian times, and trepanning in early times was possibly the earliest treatment for such diseases. Fortunately, the explosion in advances in the field of virus isolation techniques, immunology and molecular biology in addition to detailed knowledge of viral replication have enabled the rational control of CNS viral infections by prophylactics such as immunization and vector control, or following pharmacological intervention.

The broad spectrum of clinical manifestations of CNS infections (outlined in Table 48.1) poses the clinician not only a problem of prompt diagnosis but also that of treatment and aggressive management to allow recovery with little chance of sequelae. In many cases CNS diseases due to viral infections were thought to be more common in tropical regions but are now posing serious problems in Europe in recent years. With the increase in travel and changing climates due to global warming humans are becoming increasingly exposed to infections that were otherwise specific of tropical regions. This is particularly true for West Nile virus (WNV) disease, Toscana virus (TOSV) disease, avian influenza virus (H5N1) as well tick-borne encephalitis virus and arboviruses that have been frequently reported in several European countries.

Viral spread to the CNS

Consideration of how viruses enter the CNS is paramount to developing therapies through determining the methods by which such potential infections may be avoided or controlled. Space does not allow detail on entry of viruses and the reader is referred to Berger and Nash 2003[1] and *Fields Virology* by Knipe et al. 2007.[2]

For a virus to enter the CNS, it must first enter the host. The skin is the most extensive barrier to the entry of viruses but once it is broached by injury or piercing, for example by arthropod bites, viruses may rapidly invade. Similarly, entry may be via the mucosal surfaces of the respiratory, gastrointestinal and genitourinary tracts, which form the most formidable barrier due to mucous film and secretory immunoglobulin but may, nevertheless, be permeable to acid-resistant viruses, such as the enteroviruses. The major portals of entry of viruses causing human CNS infections are summarized in Table 48.2.

Following entry into the host and assuming the infection is not adequately controlled by the innate and adaptive immunity, the virus may gain access to the CNS either through the neural route via axonal transport, through the olfactory route, or via the blood across the blood–brain barrier (BBB).

Neural route

Retrograde transmission along the axon is a well-recognized route for rabies virus and has since been described for several other neurotropic viruses such as, varicella zoster and herpes simplex viruses (HSV), Herpes B virus and polio. For rabies, the neurological disease often precedes widespread dissemination in the host and the site of entry determines the incubation period. Moreover, experimental rabies and polio are prevented when the infected nerve is severed. Both retrograde and anterograde transneuronal and non-neuronal (ependymal cells and cerebrospinal fluid) pathways are utilized by vesicular stomatitis virus (VSV) within the CNS.

Olfactory route

Olfactory transmission of viruses to the CNS is well-known.[3] Experimental intranasal infection with HSV and togaviruses such as Semliki Forest virus (SFV) shows that virus is spread to the CNS via the olfactory route. In contrast to rabies virus and HSV-1, VSV does not use the trigeminal nerve for entry into the brain, as the trigeminal ganglion remains virus free following intranasal infection. Rather VSV has a tropism for olfactory receptor cells, using them for entry into the CNS.

Haematogenous route

The majority of viruses that induce CNS infection are acquired from the blood and must cross the BBB – an anatomical structure composed of endothelial cells joined by tight junctions, pericytes that form a discontinuous layer around the endothelial cells and astrocytic foot processes that surround the pericytes. The first

Table 48.1 Clinical manifestations of viral infections of the CNS

Disease	Duration	Clinical signs	Examples
Acute meningitis	Days	Rapid onset of high fever, stiff neck, altered mental state, photophobia, raised intracranial pressure	Viral meningitis
Chronic meningitis	Months	Gradual onset of signs associated with the above	Enteroviruses
Acute encephalitis	Days	Association with systemic illness, nausea, vomiting, seizures. Specific signs associated with tropism of virus, e.g. temporal lobe lesions following HSV infection	Measles, herpes simplex
Chronic encephalitis	Months to years	Gradual onset of signs as above, progressing to severe disability and death. General debility and dementia may develop	SSPE, HIV encephalitis
Post-infectious	Days to weeks	Onset of signs following recovery from viral infection. Such signs include the development of chronic fatigue syndrome or Guillain–Barré syndrome	Post-infectious encephalomyelitis
Slow viruses	Months to years	Progressive signs of neuronal destruction. Observed following immunosuppressive therapy	PML
Prion diseases	Months to years	Progressive signs of neurological dysfunction. Not associated with conventional virus	Creutzfeldt–Jakob disease, Kuru

HSV, herpes simplex virus; SSPE, subacute sclerosing panencephalitis; HIV, human immunodeficiency virus; PML, progressive multifocal leukoencephalopathy.

Table 48.2 Routes of entry of neurotropic viruses

Route of entry	Example
Inoculation	
Arthropod bite	Arboviruses
Animal bite	Rabies
Blood transfusion	Cytomegalovirus
Transplantation	Creutzfeldt–Jakob disease
Respiratory	Influenza
Enteric	Polio
Venereal	HIV
Transplacental	Cytomegalovirus

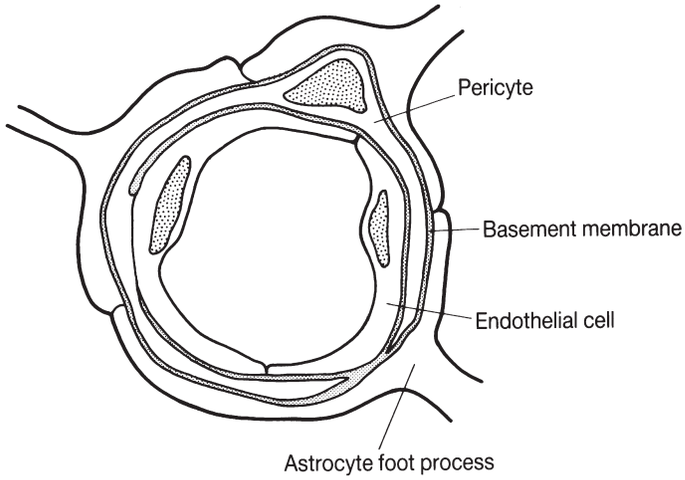

Figure 48.1 The blood–brain barrier.

description of the BBB was made in the late nineteenth century by Paul Ehrlich, who noticed that certain dyes stained all organs except the brain in an intact animal. A diagrammatic representation of the BBB is shown in Figure 48.1.

In general, the physical and chemical nature of the molecule determines its ability to cross the BBB; for example, lipid-soluble molecules are readily transferred across the BBB whereas charged non-lipid-soluble molecules are less effective. The BBB also forms a barrier for the entry of viruses; nevertheless, most viruses invade the CNS. Transfer of viruses across the BBB may take place either after infection of leukocytes, as is observed for measles and mumps virus, or following adherence of virus to erythrocytes, as is seen with togaviruses and paramyxoviruses. The infected cells migrate across the BBB and although such traffic is limited in the normal situation, it is severely augmented during injury or infection.[4] Alternatively, viruses may be taken up by receptors, induce the formation of pinocytotic vesicles on the endothelial cells and be actively transported, as in Semliki Forest virus infection (Figure 48.2).

Spread within the nervous system

Whether viruses reach the CNS via the haematogenous, olfactory or neural route, the progression of clinical signs is dependent on the subsequent spread of virus within the tissue. Additionally, the tropism of viruses for different cells determines the characteristic clinical signs and manifestation of disease associated with specific viruses (Table 48.1). For example, the spread of HSV within the temporal lobes leads to temporal lobe seizures, whereas infection of oligodendrocytes by JC papovavirus induces lesions of demyelination.

Attachment of viruses to cells prior to entry is obviously important in the development of disease, and binding domains or receptors for numerous viruses have been identified, such as the

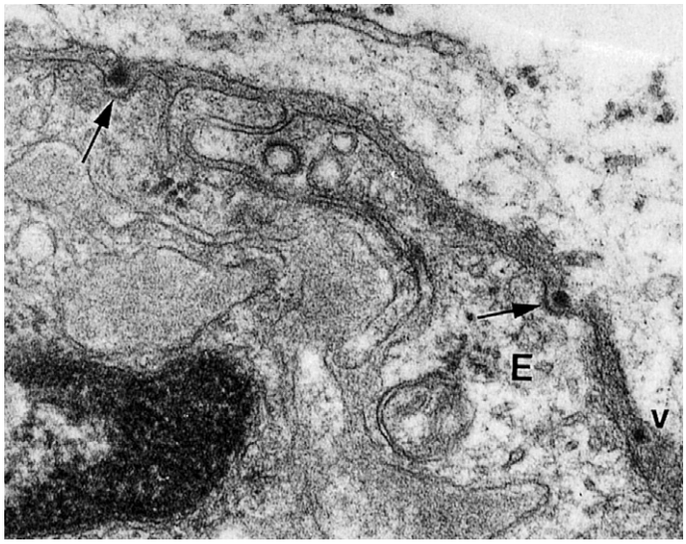

Figure 48.2 Brain capillary endothelial cell (E) showing the formation of coated vesicle containing mature virus (arrows). Mature virus (V) is also present in the basement membrane. Semliki Forest virus ×60 000. (Kindly provided by L. Pathak, St Thomas's Hospital.)

β-adrenergic receptor for reoviruses. The utilization of neurotransmitter receptors by viruses and interference in the functioning of specific neurones may explain why viruses have been implicated in chronic fatigue syndrome.[5] Other receptors include the CD4 receptor for the human immunodeficiency virus (HIV), acetylcholine receptor for rabies virus, and fibroblast growth factor receptor for HSV-1.

Once the virus has gained entry into the cell, replication and dissemination are necessary for progression of disease. Although cell-to-cell spread is the most obvious, there is little evidence for any virus that this occurs. Viruses have been observed in the extracellular spaces (Figure 48.3) and reduction of togavirus titres by specific antibody[6] suggests that extracellular movement must occur. Alternatively, transport via glial cells and axons has been suggested.[7]

As with entry of viruses into the CNS, the infiltrating leukocytes may be important in the spread of virus within the tissue. This is observed in human herpesviruses and especially with cytomegalovirus (CMV). Additionally, the role of the immune response in the progression of the disease must be considered, since autoimmune responses initiated by viruses are an important phenomenon.

ADENOVIRIDAE

While adenoviruses have been found in patients with encephalitis, these have often been cases of meningoencephalitis in immunocompromised hosts and rarely in immunocompetent patients.[8] Such associations have been carried out using nested polymerase chain reaction (PCR) and genotypes using partial gene sequence analysis to detect presence of virus in the brain or CSF, while virus in the brain was also identified by immunohistochemical staining.

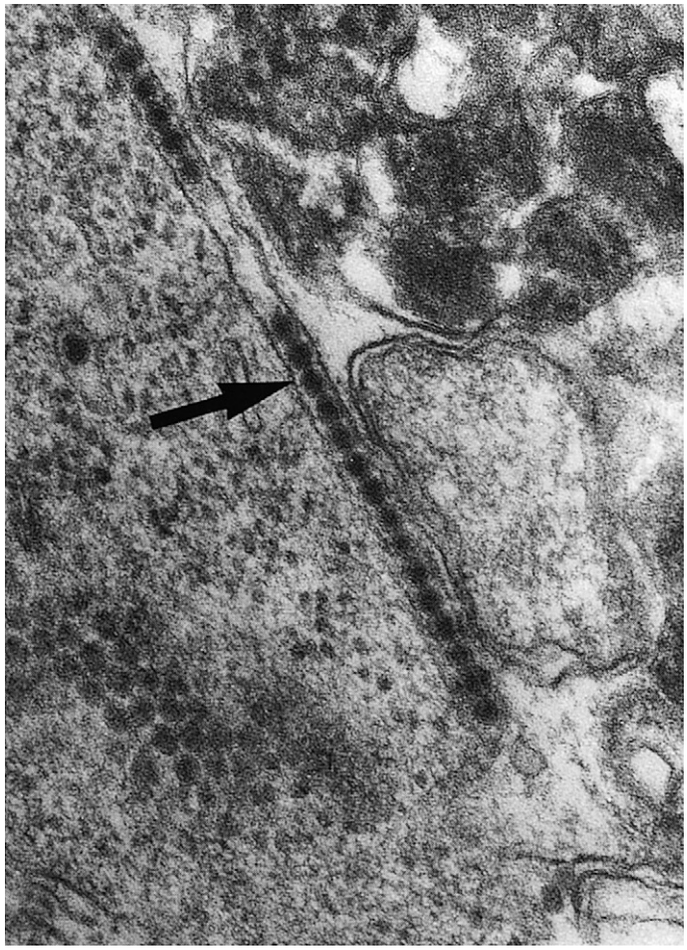

Figure 48.3 Langat virus (family Flaviviridae) (arrow) within the extracellular space of CNS tissue.

ARBOVIRUSES

The vast majority of CNS infections are due to viruses transmitted by arthropod vectors, such as mosquitoes, ticks, fleas and midges, that are termed arboviruses (*ar*thropod-*bo*rne viruses). The arbovirus group, which includes over 550 viruses, spans both DNA and RNA viruses belonging to several families: i.e. Bunyaviridae, Togaviridae, Flaviviridae, Reoviridae, Rhabdoviridae and Orthomyxoviridae (Table 48.3). These arboviruses and viruses of other families implicated in CNS disorders are discussed under the virus family heading(s).

ARENAVIRIDAE

The name is derived from the Latin arena, meaning 'sand', to describe the granules observed inside the virions. The two major groups within this family are the lymphocytic choriomeningitis (LCM) group, comprised of LCM and Lassa, in which aseptic meningitis, encephalomyelitis and meningoencephalomyelitis have been described, and the Tacaribe complex, which are distinguished on the basis of antigenic reactivity. These viruses are single-stranded RNA viruses of various sizes.

Table 48.3 Arthropod-borne viruses responsible for CNS diseases

Arbovirus	Genus	Family
California encephalitis	Bunyavirus	Bunyaviridae
La Crosse	Bunyavirus	Bunyaviridae
Crimean haemorrhagic fever	Nairovirus	Bunyaviridae
Tensaw	Bunyamwera group	
Bunyaviridae		
Rift Valley fever	Phlebovirus	Bunyaviridae
Toscana	Phlebovirus	Bunyaviridae
Inkoo		Bunyaviridae
Oropouche		Bunyaviridae
Colorado tick fever	Orbivirus	Reoviridae
Chikungunya	Alphavirus	Togaviridae
Eastern equine encephalitis (EEE)	Alphavirus	Togaviridae
O'nyong-nyong	Alphavirus	Togaviridae
Semliki Forest	Alphavirus	Togaviridae
Venezuelan equine encephalitis (VEE)	Alphavirus	Togaviridae
Western equine encephalitis	Alphavirus	Togaviridae
Rubella	Rubivirus	Togaviridae
Dengue		Flaviviridae
Ilheus		Flaviviridae
Japanese B		Flaviviridae
Kunjin		Flaviviridae
Kumlinge		Flaviviridae
Langat		
Flaviviridae		
Louping Ill		Flaviviridae
Kyasanur Forest Disease		Flaviviridae
Murray Valley encephalitis		Flaviviridae
Negishi		Flaviviridae
Powassan		Flaviviridae
TBE – western subtype; Russian spring–summer encephalitis		Flaviviridae
TBE – eastern subtype		Flaviviridae
Rocio		Flaviviridae
St Louis encephalitis		Flaviviridae
West Nile		Flaviviridae
Wesselsbron		Flaviviridae
Yellow fever		Flaviviridae
Thogoto	Ungrouped	

Lymphocytic choriomeningitis (LCM) group

LCM virus (LCMV) was the first virus isolated from aseptic meningitis in humans. The other members of this complex, namely Ippy, Mopeia and Mobala, are not associated with human disease.

Epidemiology and mode of transmission

LCMV is transmitted to humans by rodents such as the common house mouse, via exposure of open wounds or by contamination of food by infected animal excrement. Human-to-human contact is not common although it has recently been described following organ transplant[9] and is also recognized as an emerging cause of congenital defects in children and abortions.[10] Due to the nature of transmission, animal handlers or those living in impoverished conditions are at higher risk. Although LCMV infections are rare, the seroprevalence varies worldwide, one of the highest being 36% in Croatia and the lowest in France of 0.33% (in 2007). LCMV infection in humans ranges from asymptomatic infection, mild systemic illness to CNS involvement. The severity of the illness may depend on dose, route of infection and host immunogenetic background. In mice fetal infection, in the absence of a sufficient immunological response induces a persistent infection. The damage within the CNS is primarily due to the immunopathological effect.

Clinical features

The incubation period in humans is approximately 10 days and disease begins with fever, malaise, weakness, headache and myalgia, which is most severe in the lumbar region. Anorexia, nausea and dizziness are also common and the patients may have any combination of sore throat, vomiting and arthralgia with chest pain and pneumonitis. In some cases, haematological disturbances such as leucopenia are observed. The second phase occurs after a few days, with headache, stiff neck and typical signs of encephalitis in approximately 15% of infections, of which some are severe encephalitis and the mortality rate is <1.0%.

The white blood cell count is often 3000/mm^3 or less, with a mild thrombocytopenia. CSF from patients with meningeal signs contains several hundred white cells, predominantly lymphocytes (>80%), with increased protein and occasionally low sugar levels. Virus is often found in the spinal fluid during acute disease.[11] Convalescence is prolonged, with persistent fatigue and dizziness although most people recover completely.

Prevention

All persons in contact with rodents should practise safe handling procedures, avoiding eating and drinking around pets and washing and cleaning up thoroughly. Children should be educated to avoid hand to mouth contact around pets.

Lassa fever

Epidemiology

Lassa fever[12] was first described in West Africa in the 1950s, although the virus was not isolated until 1969. The only known

reservoir of Lassa fever virus in Central and West Africa is *Mastomys natalensis*, one of the most commonly occurring rodents in Africa. The virus is rapidly spread from person to person by direct contact with blood tissues or needle-stick, giving rise to a mortality rate of 30–66%. Consequently, knowledge of the pathological features is limited. Rates of seroconversion to Lassa virus range from 5% to 20% in populations of Sierra Leone villages with the highest rates in crowded, highly mobile, populations. In recent years Lassa fever has reached Europe and the USA due to air travel from Africa. Clinically, infection gives rise to haemorrhage, nephropathy, myocarditis and encephalitis.

Pathogenesis and pathology

The most common and consistently observed lesions in fatal human Lassa fever are focal necroses of the liver, adrenal glands and spleen.[13,14] Although high virus titres occur in other organs, such as the brain, ovary, pancreas, uterus and placenta, no lesions have been reported in humans, while infected monkeys have been reported to have CNS lesions.

Clinical diagnosis

Lassa fever begins 7–18 days after primary infection, leading to onset of fever, headache and malaise. Patients with Lassa fever show features of anxiety and there is a raised respiratory rate. In 15–20% of patients, bleeding occurs from gums and nose. Oedema of the face and neck are commonly seen in severe cases. Important clinical events in fatal disease are intractable hypovolaemic shock and/or severe CNS involvement, bleeding and oedema of the face. There is also endothelial and platelet dysfunction and mild thrombocytopenia.

Prevention

The ideal method of prevention is to prevent contact between rodents and humans. This can be achieved by improving the housing and food storage, which might reduce the domestic rodent population. There are two vaccines for arenaviral diseases. A live attenuated vaccine has been used extensively. A second vaccine has been made by cloning and expressing Lassa virus glycoprotein gene into vaccine virus. This vaccine has proven highly successful in preventing severe disease and death in challenged monkeys and may be relevant for treating humans.[15] Ribavirin can prevent death in Lassa fever when given at any point in the illness, but is more effective when given early and administered intravenously.[16]

Bornaviridae

In the seventeenth century, Borna disease was known as the 'disease of the head' affecting horses and was later ascribed to Borna disease virus (BDV), an unsegmented, single- and negative-stranded, enveloped RNA virus. In humans the virus has been associated with psychiatric diseases. This has been based on studies in rats infected with BDV that show behavioural changes and emotional and learning deficits and by the presence of viral nucleic acid in the blood or brain.

Table 48.4 Genera and serogroups within the family Bunyaviridae

Genus	Serogroups
Orthobunyavirus	*Anopheles A., Anopheles B.*, Bunyamwera, Bwamba
(Bunyavirus)	California, Capim, Gamboa, Guama, Koongol, Olifantsvlei, Patois, Simbu, Teteu, Turlock
Nairovirus	Crimean–Congo, Dera Gharzi Khan, Hughes, Nairobi SD, Qalyub, Sakhalin Uukuniemi
Phlebovirus	Phlebotomus
Hantavirus	*Hantaan* and *Sin Nombre*
Tospovirus	Does not infect mammals

Bunyaviridae

The Bunyaviridae family is taxonomically divided into five genera: Hantavirus, Nairovirus, Orthobunyavirus, Phlebovirus and Tospovirus, and viruses that are not assigned. The family is comprised of over 250 viruses (Table 48.4) between 90 and 100 nm in size that have a lipid envelope derived from the host cell membranes during maturation. (For more information on the structure and replication of Bunyaviruses, see references.[2,17])

This section will concentrate on those viruses within the genera that are important with respect to causing significant human disease involving the CNS.

Orthobunyaviruses

The most important serogroup with respect to induction of human diseases is the California (CAL) group, which includes California encephalitis (CE) and La Crosse (LAC) viruses. This group of viruses has 14 serotypes, the prototype virus being La Crosse virus, first isolated from a child in La Crosse, Wisconsin, in 1960.[18]

Epidemiology and mode of transmission

Members of the CE virus serogroup were first recognized in California in 1943 and have since been isolated in Canada, the USA, Trinidad, Europe, Africa and Finland, although each has a very narrow host range and geographical distribution. More recently in western Europe, two viruses of the California group – Tahyna virus and Inkoo virus – have been associated with CNS involvement, such as encephalitis.

Animals such as chipmunks and squirrels are commonly involved. La Crosse virus, the prototype virus, is transmitted by the mosquito *Aedes triseriatus*, which is the most important vector in California, although other *Aedes* species may be involved. Children and young adults aged 1–19 years are at greatest risk of exposure to this vector, which is a woodland mosquito, during activities such as camping and hiking.[19]

La Crosse infection is the second most prevalent mosquito-borne viral infection in the USA and accounts for approximately 75 definite cases a year, although seroprevalence may reach 20% in older persons. La Crosse virus is transmitted mainly by *Ae.*

triseriatus, a treehole-breeding woodland mosquito that frequently feeds on small mammals, particularly chipmunks and squirrels.[20] An alternative mosquito habitat is provided by discarded tyres that hold rainwater on which egg rafts may be laid. This virus produces acute encephalitis in children. The acute illness lasts 10 days or less in most cases. The first symptoms are non-specific and last for 1–3 days, followed by involvement of the CNS. The symptoms include stiff neck, lethargy and seizures. Earlier examination shows high counts of both polymorphonuclear neutrophil leukocytes and mononuclear cells in about 65% of patients. The most important sequela of La Crosse encephalitis is epilepsy, which occurs in about 10% of the children, and learning disabilities and other objective cognitive deficits have been reported in a small proportion of patients. A few patients (2%) have persistent paresis.

Pathology

The lesions induced by bunyaviruses are typical of acute viral encephalitis. Examination of the CNS reveals perivascular cuffing of mononuclear cells and, in severe cases, necrotic areas. Histopathologically the lesions, which consist of scattered glial nodules, perivascular cuffs, mild leptomeningitis and occasional areas of focal necrosis, are found more often in the cerebral cortex and to a lesser extent in the brain stem and medulla.

Clinical features

Following an incubation period of 3–7 days, features associated with acute encephalitis are observed. Brief 'flu-like' symptoms and primary viraemia, which follow the arthropod bite, are observed. The secondary phase is marked by fever and a secondary viraemia coinciding with CNS involvement. Clinical expression includes headache, fever and meningoencephalitis, with upper motor neuronal signs and occasionally chorea. Neurological sequelae may occur, in which persistent seizures are observed, although lasting cognitive deficits are rare. Onset of seizures may be rapid with no other signs of disease. Acute arthritis is observed, with Tahyna virus, whereas respiratory system involvement is more commonly seen in Jamestown Canyon virus infections.

Diagnosis

Clinical diagnosis of La Crosse virus may be made as a result of localization of neurological lesions. Specific diagnosis is based on complement fixation (CF) or haemagglutination inhibition (HI) assays, although neutralization tests (NTs) are also used. Artsob[21] has described an enzyme-linked immunosorbent assay (ELISA) for serotyping. Isolations in suckling mice and Vero cells have been used for virus typing.

Prevention and control

To date, apart from mosquito repellents, no specific prevention is available. Anticonvulsants are used to control seizures. Recently, reports in mice have suggested that plasmid DNAs, encoding either of the virus surface glycoproteins G1 and G2, efficiently blocked the spread of virus from the primary replication site to the brain, suggesting that such approaches may be beneficial in patients.

Phleboviruses

Rift Valley fever

Rift Valley fever (RVF) virus is a prototype Bunyavirus and the most notable virus in the genus Phlebovirus. It was first reported after an epidemic of fever and myalgia in which a few people developed encephalitis in Egypt in 1979.[22] Additional outbreaks have been observed throughout Africa, including Nigeria, Egypt, Sudan and Kenya. More than 20 species of mosquitoes have been implicated as possible vectors. *Culex pipiens*, *Cx. theileri*, *Ae. caballus* and other mosquitoes of the *Culex* and *Aedes* group may be involved. The major sources of reservoirs are animals such as cows, sheep, and goats, although camels and antelopes can be infected. Transmission of the virus from animal to animal during epidemics may result from biting flies.

Clinical features

RVF in the human illness is biphasic. The primary phase is associated with fever, back and joint pains, and headaches that last about 1 week. After 1–2 days' remission, the second phase consists of similar symptoms for 1–2 days, with nausea and sometimes a haemorrhagic diathesis with evidence of liver and renal damage. The mortality rate is <1.0%. Occasionally disturbed vision, with evidence of a retinitis and cotton-wool exudates in the region of the macula, is observed. Altered levels of consciousness are observed with, in some cases, persistent fever. Meningeal irritation occurs, with focal motor signs and hallucinations.[23]

Diagnosis

Identification of increasing levels of IgM-specific antibodies in the CSF is used for the specific diagnosis.

Treatment and prevention

No specific treatment exists for Rift Valley fever, although a formalin-inactivated vaccine may be of use for laboratory workers and troops who may be exposed to this virus. More recently an inactivated RVF vaccine TSI-GSD-200 has been found beneficial. Ribavirin may be effective if administered in time and passive neutralizing antibody is effective in protecting from disease.

Hantaviruses

Epidemiology and mode of transmission

Hantaviruses are human pathogens that are prevalent worldwide and consist of more than 16 different viruses including Puumala, Hantaan, Dobrava-Belgrade, Seoul, Sin Nombre. The predominant serotype is Puumala (PUUV), which causes encephalitis and is endemic in western Russia, Finland, Sweden, France, Belgium, Germany and former Yugoslavia but has also been reported in Denmark, Norway, the Netherlands and Austria. Puumala virus is spread by rodents and is transmitted to humans by inhalation or ingestion of food contaminated with rodent excreta. The seroprevalence in Finland is 5% and 1.8% in Austria. The incidence of NE in a cyclic fashion, with peaks occurring every 3rd to 4th year, coinciding with peaks in vole populations.

Pathology

Infection with PUUV may also lead to neurological symptoms including meningoencephalitis, polyradiculitis, seizures, cerebral haemorrhage, urinary bladder paralysis, and hypopituitarism.

Clinical features

The most common symptoms of PUUV infection are red throat, fever, nausea, vomiting, headache, stomach ache and back pain usually associated with kidney infection. Most patients recover in 7–10 days without sequelae and the mortality is less than 0.2%.

Diagnosis

Diagnosis is by an immunocytochemistry test called immunochromatographic rapid test (POC PUUMALA) by Erilab Ltd, Kuopio, Finland, that uses a highly purified baculovirus-expressed PUUV nucleocapsid protein antigen to detect IgM to PUUMV in the blood.

Treatment and prevention

Aside from avoiding contact with infected animals there is little in terms of control and treatment. A vaccine against PUUV, as well as specific treatment for the encephalitis, is still lacking.

CALICIVIRIDAE

The Caliciviridae family is comprised of Norwalk virus and hepatitis E virus. Norwalk-like viruses are the major cause of gastroenterovirus although to date only one case of encephalopathy has been possibly linked with Norwalk virus infection when the viral genome was detected in CSF by reverse transcription PCR.

CORONAVIRIDAE

Members of the Coronaviridae family are pleomorphic RNA viruses, 80–130 nm in diameter, which replicate within the cytoplasm. The family includes several animal viruses, including murine hepatitis virus known to induce demyelination in the CNS of infected mice. The neurotropic strain of mouse hepatitis virus, JHM, was first isolated from a spontaneously paralysed mouse. The virus induces lesions of acute demyelination in the brain and spinal cord.[24] The relevance of this to human disease is the finding of coronaviruses in the CNS of some patients with multiple sclerosis. More recently, the outbreak of severe acute respiratory syndrome (SARS) due to the human coronavirus (SARS-CoV) has also been associated with virus in the CNS.[25]

FILOVIRIDAE

The family Filoviridae contains a single genus *Filovirus* with subgroups *Marburg* and *Ebola*, both associated with severe haemorrhagic fevers (see Chapter 42). The mortality is high and varies between 30% and 90%, in which clinical signs develop early, with death occurring between days 6 and 16. Due to the high pathogenicity few tissues have been studied. In *Ebola*-infected monkeys, coagulation is seen in the brain and in human patients, haemorrhages in the brain induce strokes.

FLAVIVIRIDAE

Formerly classified as Group B arboviruses, the Flaviviridae were re-classified as an independent family. The family Flaviviridae are composed of the genera Flavivirus, Hepacivirus and Pestivirus. The genus Flavivirus comprises the largest group of viruses known to induce CNS diseases and is subdivided according to the mode of transmission, i.e. mosquitoes or ticks (Table 48.5).[26] Further serological subgroups may be distinguished on the basis of reactivity in HI and neutralization assays. Flaviviruses are small icosahedral enveloped viruses that replicate and mature cytoplasmically, deriving the lipid envelope from the internal membrane of the host cell. While yellow fever virus, the prototype Flavivirus (*L. flavus* = yellow), is a serious haemorrhagic disease inducing heart and kidney failure – its name derived from the jaundice induced following infection – very few reports describe encephalitis. Rather, encephalitis following vaccination with the attenuated yellow fever Asibi 17D virus is described in the elderly and immunocompromised patients.[27]

Vector control by water drainage is not feasible in most cases due to the terrain, i.e. jungle areas, but has been used successfully in urban areas when combined with insecticides. Inactivated vaccines, live attenuated vaccines and subunit vaccines using recombinant DNA technology have been utilized and developed for several Flaviviruses. Ongoing research has identified possible targets for inhibition, including binding and uptake of the virus to cells together with the viral proteases and some factors governing replication, and these may be useful in the future development of antiviral therapeutic strategies.

As seen in Table 48.5, many Flaviviruses induce CNS diseases, some of which are discussed in other chapters.

Dengue virus

Dengue and Dengue haemorrhagic fevers (see Chapter 41) also involve the CNS and several reports suggest that the incidence of Dengue fever is rising. For example, in Vietnam the death rate for Dengue fever increased by 83% in 2006. The encephalitis is confirmed by CSF microscopy, immunoglobulin in the CSF, as well as MRI, CT and EEG changes, although in some patients no alteration was observed in the CSF.[28]

Japanese encephalitis

A disease resembling Japanese encephalitis (JE) was recorded as early as 1871. In 1935, an infectious agent was recovered from the brain of a person in Tokyo and was virologically and serologically established as the prototype (Nakayama) strain. JE virus is the prototype of the JE antigenic complex. The complete nucleotide sequence of the JE viral genome has been determined. Antibody adsorption HI, CF, kinetic neutralization, agar gel diffusion and monoclonal antibody analysis have demonstrated antigenic variations. At least two immunotypes have been identified: Nakayama and JaGAr-01 (isolated from *Culex* mosquitoes). The virus replicates in a number of primary and continuous cell cultures of

Table 48.5 Classification of neurotropic Flaviviruses where known

Genus: Flavivirus	Neurotropic
A. MOSQUITO-BORNE VIRUSES	
Aroa virus group	
Aroa virus (AROAV)	
Dengue virus group	
Dengue virus (DENV)	Humans
Kedougou virus (KEDV)	
Japanese encephalitis virus group	
Cacipacore virus (CPCV)	
Koutango virus (KOUV)	
Japanese encephalitis virus (JEV)	Humans
Murray Valley encephalitis virus (MVEV)	Humans
Alfuy virus (ALFV)	
St Louis encephalitis virus (SLEV)	
Usutu virus (USUV)	Owls
West Nile virus (WNV)	Humans
Yaounde virus (YAOV)	
Rocio (ROC)	Humans
Kokobera virus group	
Kokobera virus (KOKV)	
Ntaya virus group	
Bagaza virus (BAGV)	
Ilheus virus (ILHV)	Humans
Israel turkey meningoencephalomyelitis virus (ITV)	Turkeys
Ntaya virus (NTAV)	
Tembusu virus (TMUV)	
Spondweni virus group	
Zika virus (ZIKV)	
Yellow fever virus group	
Banzi virus (BANV)	Sheep, experimental mice
Bouboui virus (BOUV)	
Edge Hill virus (EHV)	
Jugra virus (JUGV)	
Saboya virus (SABV)	
Sepik virus (SEPV)	
Uganda S virus (UGSV)	
Wesselsbron virus (WESSV)	Goats, cows
Yellow fever virus (YFV)	Mice (vaccine in humans)
B. TICK-BORNE VIRUSES	
Mammalian tick-borne virus group	
Gadgets Gully virus (GGYV)	
Kadam virus (KADV)	
Kyasanur Forest disease virus (KFDV)	Humans, mice
Alkhurma haemorrhagic fever virus (AHFV)	Humans
Langat virus (LGTV)	Mice, humans
Omsk haemorrhagic fever virus (OHFV)	
Powassan virus (POWV)	Humans
Tick-borne encephalitis virus (TBEV)	Humans
Eastern type – Russian Spring-Summer (RSSE)	Humans, macaques
Western type	
Royal Farm virus (RFV)	
Louping ill virus (LIV)	Sheep, goats
Seabird tick-borne virus group	
Meaban virus (MEAV)	
Saumarez Reef virus (SREV)	
Tyuleniy virus (TYUV)	
C. VIRUSES WITH NO KNOWN ARTHROPOD VECTOR	
Entebbe virus group	
Entebbe bat virus (ENTV)	
Yokose virus (YOKV)	
Modoc virus group	
Apoi virus (APOIV)	
Cowbone Ridge virus (CRV)	
Jutiapa virus (JUTV)	
Modoc virus (MODV)	Experimental hamsters, mice
Sal Vieja virus (SVV)	
San Perlita virus (SPV)	
Rio Bravo virus group	
Bukalasa bat virus (BBV)	
Carey Island virus (CIV)	
Dakar bat virus (DBV)	
Montana myotis leukoencephalitis virus (MMLV) small rodents	
Phnom Penh bat virus (PPBV)	
Rio Bravo virus (RBV)	

hamster, pig, monkey, Vero and mosquito. JE virus produces lethal encephalitis in infant mice by any route, whereas weanling mice succumb to intracerebral virus inoculation. Hamsters and monkeys die after intracerebral inoculation but develop asymptomatic viraemia after intraperitoneal inoculation. JE virus does not cause death in rabbits and guinea pigs after inoculation by any route.

Epidemiology

JE continues to be the major type of encephalitis in eastern, southeastern and southern Asia including Japan, the Far East, Guam, the former USSR, Malaysia, India and western Pacific island areas. In endemic areas, children are affected most, with attack rates in the 3–15 years age group 5–10 times higher than those in older people because of the higher incidence of protective immunity in older age groups. Among factors that influence mortality are age, different virus strains and cross-protective immunity to other flaviviruses, especially dengue. The *Cx. tritaeniorhynchus* and *Cx. vishnui* mosquitoes are the most important vectors. Other species of *Culex, Aedes, Anopheles* and *Mansonia* have been implicated. Pigs and many birds, including herons and egrets, may be the chief source of virus. Other domestic animals can become infected and humans may play a part in epidemics. More recently, the emergence of flaviviruses including JE has been reported in Europe.[29]

Clinical illness

Clinical illness is characterized by headache, fever and other signs of meningitis. Convulsions occur in children. Upper motor neurone involvement with extrapyramidal disturbances is a feature of this disease. The mortality rate of those with meningoencephalitis is around 20% in children and up to 50% in those over 50 years of age. Motor and psychological disturbances are common sequelae.

Pathogenesis and pathology

Pathogenicity in mice varies with different strains of JE virus. During the acute stage, oedema and small haemorrhages are found in the brain. Destruction of cerebellar Purkinje cells may occur. Lesions include neuronal degeneration and necrosis, glial nodules and perivascular inflammation. These changes occur mainly in grey matter and predominantly affect diencephalic, mesencephalic and brain stem structures. In the extraneural tissue a variety of pathological features, including hyperplasia of germinal centres of lymph nodes, enlargement of malpighian bodies in the spleen, interstitial myocarditis and focal haemorrhages in the kidneys, are seen. Transplacental infection in swine results in abortion and stillbirth. Pregnant mice inoculated intraperitoneally also transmit JE virus to the fetus, with subsequent abortion.

Diagnosis

The IgM-capture ELISA is especially well suited for diagnosis by detection of locally synthesized antibody in the CSF. The HI, CF assays and NT are applicable. More recently, the potential application of JE non-structural protein (NS) 1-specific indirect ELISA to differentiate infection from vaccination has been described. More specifically imaging of the brain using MRI has proven useful to examine the impact of JE infection.

Prevention and control

Formalin-inactivated vaccines for use in humans are prepared from infected adult mouse brains or infected primary hamster kidney cell cultures in Japan and China, respectively.[30–32] Primary immunization requires two doses at a 7–14-day interval. Booster vaccinations are given during the first year after primary immunization and then at 3–4-year intervals. A bivalent vaccine has been developed incorporating Nakayama and JaGAr-01 (the two subtypes of JE virus). This vaccine has also proved to be effective although it may not provide complete protection. Vaccination of horses with formalin-inactivated vaccines has been successful. Use of pesticides in rice-growing areas has reduced populations of *Cx. tritaeniorhynchus*. Spraying of residual insecticides in livestock pens has reduced the case incidence in China.[32] Treatment consists of good general management and nursing care, especially in the semicomatose and comatose patient. Hyponatraemia secondary to inappropriate antidiuretic hormone secretion is managed with water restriction. Increased intracranial pressure should be considered in severely ill patients with deepening coma and loss of brain stem reflexes. Anticonvulsant therapy may be required.

Murray Valley encephalitis virus

Between 1917 and 1925 and from 1950 to 1951 severe encephalitis called Australian X disease outbreaks occurred in the Murray Valley region. In 1951 Murray Valley encephalitis (MVE) virus was first isolated from human brain and found to be a member of the JE antigenic complex. The host range of MVE virus is wide, being found in humans,[33] monkeys, horses, sheep and some birds, that all develop encephalitis after intracerebral inoculation. A closely related virus, Kunjin, has also been implicated in encephalitis in the same region as MVEV.

Epidemiology

MVE virus is endemic to tropical North Australia, particularly Western Australia and the Northern Territory, but can occur in other parts of Australia, and Papua New Guinea. *Cx. annulirostris* is the major mosquito vector. *Ae. normanensis* may be involved. Birds, including herons, cormorants and other water birds, are the major reservoir of this virus.

Clinical illness

Onset is sudden, with headaches, fever and symptoms of a meningoencephalitis. Paresis of both upper and lower motor neurones may occur and breathing and swallowing may become impaired. With modern intensive care the fatality rate has been reduced dramatically to 20%. However, as a result of the increased survival rate, the number of people with both upper and lower motor neurone and psychiatric sequelae has increased.[33]

Prevention and control

Detection of flavivirus seroconversions in sentinel chicken flocks has been used as an early warning of increased levels of MVE and Kunjin virus activity. No specific treatment for MVE exists although vector control is as with other members of this family, and massive insecticide programmes are deployed when vector breeding is increased.

St Louis encephalitis virus

St Louis encephalitis (SLE) virus was first identified as the cause of human encephalitis in 1933 in Missouri and since then many outbreaks have been reported. SLE virus is transmitted by the mosquitoes *Cx. tarsalis* and *Cx. pipiens*, giving rise to one of the most common and important epidemic arbovirus infections in the USA. Since the 1930s numerous outbreaks have been described in Texas, Ohio and Florida. Occasional cases have been reported in Canada and Mexico.

Epidemiology

SLE in central USA is commonly dependent on *Cx. pipiens* and *Cx. quinquefasciatus*, whereas in Florida *Cx. nigripalpus* is the principal vector. The virus is transmitted from mosquitoes that are infected by feeding on birds. In western USA *Cx. tarsalis* is the major vector. Epidemic outbreaks appear every 10 years and appear to be dependent on the breeding of *Cx. pipiens*. Disease occurs in late summer and early autumn, and the number of affected humans ranges from 0.1% to 8%.

Clinical illness

SLE induces febrile headache, aseptic meningitis and encephalitis. Although persons of all ages are affected, morbidity and mortality is seen more commonly in the elderly. Following a 3–4-day incubation a generalized illness is observed, with malaise, fever, myalgia, headache and vomiting.[34] After a similar period the symptoms may resolve or progress to clinical findings indicative of neurological involvement. Of patients with neurological signs, 50% die within 7 days of exhibiting signs and a further 30% succumb in the second week. Many patients who survive neurological involvement have persistent headaches and memory loss, and others have overt neurological sequelae such as speech or sensory disturbances.

Diagnosis

Patients exhibiting signs of encephalitis in SLE endemic areas, particularly in late summer and early autumn, should be investigated for SLE. Virus isolation from biological specimens such as blood and urine may be difficult, although virus has been isolated from brain tissue. Confirmation of SLE infection is made by HI or CF tests. IgM-capture ELISA is useful for diagnosis.

Prevention and control

There is no specific treatment or vaccine for SLE. Education of individuals within infected areas and vector control have been shown to be useful following detection of SLE virus activity.

West Nile virus

Epidemiology

West Nile Virus (WNV) is widely distributed in Africa, Europe, Asia,[33] Mexico, the Caribbean islands and Colombia and has emerged as the most common cause of epidemic meningoencephalitis in North America. A study in Germany showed that migrating birds have been in contact with WNV although no outbreaks have been reported in Europe. The outbreak in New York City in 1999 was the first time WNV was detected in the Western hemisphere and led to 20 000 confirmed cases. Given the subsequent rapid spread of the virus, which led to the hospitalization of 59 patients, of whom 37 (63%) had clinical signs of encephalitis and seven (12%) died, this infection should now be considered as a serious threat. From 1999–2005. more than 8000 cases of neuroinvasive WNV disease were reported in the US, resulting in over 780 deaths.

The vector for WNV is *Culex* species and other ornithophilic mosquitoes. Birds, including domestic poultry, are the reservoirs and horses and dogs have also been reported to develop WNV. In 2002, WNV transmission through blood transfusion and organ transplantation, and intrauterine transmission were first documented.

Clinical illness

Following WNV infection symptoms including fever, headaches, retrobulbar and muscular pain, sore throat, nausea and vomiting occur. Development of a maculopapular rash on the trunk, face and limbs may be seen. Occasionally arthralgia may occur and involvement of ophthalmic tracts has been reported. The disease is usually mild in the young, but in older age groups a second phase with mild meningoencephalitis may develop with no sequelae. Many patients with WNV neurological disease have abnormal MRI in the basal ganglia, thalamus, cerebellum, and brainstem. In some cases movement disorders have been described due to lesions in the substantia nigra. Examination of the CSF reveals increased cell counts with predominance of neutrophils. WNV disease has also been reported in immunosuppressed patients. Recovery from neurological sequelae of WNV infection including cognitive deficits and weakness may be prolonged and incomplete.[34,35]

Diagnosis

Since clinical manifestations are difficult to differentiate from other infections, diagnosis should be made from WNV-specific IgM detectable in the CSF and serum, which is nearly 100% positive after the 8th day of infection and can persist for up to 16 months. CT and MRI again cannot accurately diagnose WNV infection although the virus does have predilection for the brainstem.

Prevention and control

Although there is no proven therapy for WNV disease, several vaccines and antiviral therapy with antibodies, antisense oligonucleotides, and interferon preparations are currently undergoing human clinical trials. As with other mosquito-borne diseases, insect repellents are crucial to prevent infection and avoidance of areas where infected mosquitoes may be present is advisable. Arboviral surveillance and vector control programmes are essential.

Rocio encephalitis

Epidemiology

In March 1975, an outbreak of encephalitis was recorded in São Paulo, south-east Brazil, in 465 cases with 61 deaths recorded.[36]

The majority of those affected were workers who frequented the forest areas; this was suggestive of an arbovirus infection. In 1975, an unknown arbovirus was isolated from the cerebellum and spinal cord of a 39-year-old farmer and referred to as Rocio virus. Further analysis identified 47 arbovirus isolates in an area previously unknown for arbovirus infections. Rocio (ROC) virus is typical of flaviviruses, being spherically shaped with a diameter of 43 nm and cross-reacting with other members of the group (i.e. SLE, Ilheus, JE and MVE virus). Since 1980, no human disease caused by this virus has been diagnosed.

Pathogenesis

The pathology has been detailed by Rosenberg.[37] Interstitial mononuclear infiltration, microglial proliferation and perivascular cuffing are observed. In acute disease neuronophagia is evident with a distinctive topographical pattern in which the dentate nucleus is more susceptible and the brainstem less so.

Clinical diagnosis

In humans the incubation period is between 7 and 14 days. The clinical features include headache, fever, vomiting, anorexia and nausea, hyperaemia of the oropharynx and conjunctivae, and photophobia. Involvement of the CNS includes meningeal irritation, alteration in consciousness, motor abnormalities and abnormalities in cranial nerve function.

Diagnosis

Epidemiological background and clinical history are paramount. Diagnosis is by cytochemical analysis of the CSF and isolation of the virus in 2-day-old mice from infected tissue. Haemagglutination, CF and plaque reduction techniques in Vero cells, IgM antibody-capture ELISA and ultimately histological examination confirm infection.

Prevention and control

The use of larvicides in ditches and flooded areas, and sanitary measures to drain stagnant waters, have decreased the incidence of infection. Formalin-treated extract of infected mouse brain is used as a vaccine.

Tick-borne encephalitis

The tick-borne encephalitis (TBE) virus complex consists of 14 antigenically closely related viruses, eight of which cause human disease. Russian spring-summer encephalitis (RSSE) and central European encephalitis virus (CEE) are very closely related antigenically and are considered to be subtypes of the same virus. They are separated on the basis of kinetic HI and CF tests and at the molecular level. Peptide maps of both the E and the largest non-structural protein (NS-5) of the two subtypes show some differences.

TBE complex viruses grow in a variety of cell cultures, including pig, bovine and chick embryo, HeLa, human amnion, Hep2, Vero, and primary reptilian and amphibian cells.[38] Cytopathic effect and plaquing are variable. TBE viruses cause encephalitis in rats, guinea pigs, sheep, monkeys and swine after intracerebral inoculation. Infant and weanling mice develop fatal encephalitis by all routes of inoculation. Experimental inoculation of wild vertebrate species, including rodents, foxes, birds, hares and bats, results in viraemia and antibody formation. Cows, goats and sheep infected by inoculation or tick bite develop viraemia and secrete virus in their milk. The Far Eastern virus type (RSSE) is more virulent for sheep and monkeys inoculated intracerebrally than the Western (CEE) subtype virus.

Epidemiology

TBE encompasses a wide area including Siberia across to Scandinavia, through Vienna into Belgium, to Scotland and Northern Ireland, across Canada, the USA and Japan. The disease occurs in areas that are favourable for ticks. The virus is maintained in nature in a cycle involving ticks and wild vertebrate hosts. Small rodents such as shrews, moles and hedgehogs are believed to be important reservoirs. Large mammals, such as goats, sheep and cattle, serve as host for adult Ixodes ticks. *I. ricinus* and *I. persulcatus* are responsible for transmission in Europe and the former Soviet Union, respectively.[39] Other tick species, of the genera Dermacentor and Haemaphysalis, have been implicated in transmission, especially in areas that do not support *Ixodes* ticks. Transmission to humans occurs mainly in adults over 20 years old, who come in contact with infected animals. The disease occurs in two peaks (May–June and September–October) coinciding with the activity of adult *Ixodes* ticks. Small outbreaks involving all age groups result from consumption of raw sheep or goat's milk or cheese.

Pathogenesis and pathology

In monkeys, the anterior horn cells of the spinal cord and cerebellar cortex appear to be more affected than other neuronal cells. Members of the TBE complex cause persistent infection in experimental animals. For instance, CEE virus has been isolated from monkey tissues by co-cultivation and explant techniques long after infection. Mice infected with Kyasanur Forest virus are shown to survive for months, with paralysis, low titres of virus in the brain and absence of detectable neutralizing antibodies.[40] Monkeys infected with TBE complex develop chronic encephalitis with degenerative spongiform lesions and astrocytic proliferation. Chronic progressive human encephalitis and seizure disorders have been associated with RSSE virus.

Histopathological findings consist of meningeal and perivascular inflammation, neuronal degeneration and necrosis, and glial nodule formation in areas such as the cerebellar cortex, brainstem, basal ganglia, cerebrum and spinal cord. The anterior horn cells of the cervical cord are especially vulnerable, which may result in the lower motor neurone paralysis seen in many cases.

Clinical features

The clinical characteristics of TBE infection in humans vary depending on the age of the patient.[41] Most of the tick-borne viruses have been associated with human disease, but there is a gradation of virulence. The Far Eastern (Siberian) strains (formerly called RSSE virus) cause severe encephalitis, often with bulbar and cervical cord involvement, a high fatality rate and frequent sequelae. The disease seen in central Europe is frequently biphasic, with influenza-like symptoms and signs of mild encephalitis.

Diagnosis

Definitive diagnosis depends on virus isolation or serology. The virus may be isolated from the blood during the first phase of illness and from brain tissue of patients dying early in the infection. Suckling mice, embryonated eggs and chick embryo cell cultures (with detection of virus by interference assay or immunofluorescence) have been used for virus isolation. Serological diagnosis including HI, CF, single radial haemolysis and NT have been used. Diagnosis by estimation of IgM antibodies is valuable for rapid diagnosis and is applicable to both serum and CSF.

Prevention and control

In the former USSR, formalin-inactivated mouse brain vaccines were used before World War II (1939–1945). Recently, vaccines have been produced in embryonated eggs or chick embryo cell cultures. However, the most effective vaccine is derived from chick embryo cell culture-grown virus which is highly purified and inactivated by formalin. The vaccine produces serological conversions in over 95% of recipients and has provided 99% protection in field trials. Preventive measures include pasteurization or boiling of raw milk, avoidance of tick bite by use of repellents and protective clothing. More recently, as with other viral therapeutic strategies, DNA vaccine encoding TB viral components has been shown to be effective in mice and offers the possibility of rational therapy in humans.[42]

Other tick-borne viruses

Kyasanur forest disease (KFD) caused by KFD virus (KFDV) was first recognized as a febrile illness in the Karnataka state of India in the 1950s it induces a haemorrhagic disease in human beings in which encephalopathy is observed in some patients. A variant of KFDV, Alkhurma haemorrhagic fever virus (AHFV), has been recently identified in Saudi Arabia. KFD is known to be encephalitogenic in mice and rodents.

Langat virus (LGT) is a naturally attenuated member of the tick-borne encephalitis virus (TBEV) complex. While LGT infects humans; there are no cases of disease recorded from tick bites. In the 1970s, Langat was briefly used as a live vaccine against more virulent tick-borne encephalitis viruses in Russia but caused encephalitis complications in about one of every 10 000 people. Injection of LGT virus in mice induces severe encephalitis.

Omsk haemorrhagic fever virus (OHFV) is principally restricted to western Siberia and is seen mostly in muskrat trappers. The disease is manifested by fever, chills, headache, pain and rash on the soft palate. CNS abnormalities develop after 1–2 weeks. The disease is fatal in up to 10% of people. To date, there are no antivirals available.

Powassan virus (POWV) was first identified in Powassan, Ontario, Canada, in 1958 and only 12 cases were reported between 1958 and 1999 and four cases were fatal. The disease, transmitted by tick bites, leads to inflammation of the brain.

Louping ill virus (LIV) infects sheep reared in Scotland, northern England, Wales and Ireland. The virus is excreted in faeces and saliva. The first report of human infection was in 1934 and to date 31 cases of human infection have been reported. Encephalitis in man is seen with LIV.[43]

HERPETOVIRIDAE

Herpesviruses are double-stranded DNA viruses approximately 100–110 nm in diameter and able to establish latency and reactivation. Of the nearly 100 herpesviruses that have been characterized at least partially, the following have been associated with CNS infections particularly in humans:[44]

- Herpes simplex virus 1 (HSV-1) (HHV-1)
- Herpes simplex virus 2 (HSV-2) (HHV-2)
- Varicella-zoster virus (VZV) (HHV-3)
- Epstein-Barr virus (EBV) (HHV-4)
- Human cytomegalovirus (HCMV) (HHV-5)
- Human herpesvirus 6 (HHV-6)
- Human herpesvirus 7 (HHV-7)
- Human herpesvirus 8 (HHV-8)

The simian herpesvirus, B virus (*Cercopithecine* herpesvirus-1 herpes simiae) in macaque monkeys results in severe pathogenesis and often death in untreated humans.[45]

Herpes simplex virus (HHV-1 and HHV-2)

Infections caused by HSV have been known since the time of ancient Greece, where the name herpes was used to mean 'creep' or 'crawl' and probably described the spreading nature of some of the skin lesions resulting from infections. Mouth ulcers and lip vesicles associated with fever were referred to as *herpes febralis* by the Roman scholar Herodotus. It was only later that herpetic lesions and genital infections were associated and by the late nineteenth century the vesicular nature of the lesions was characterized. Histological descriptions of herpes infections were identified in the early twentieth century including the encephalitogenicity of herpesviruses.[44]

Epidemiology

HSV are distributed worldwide by humans, who are deemed the sole reservoir for transmission during close personal contact. There is no seasonal variation in infections and, because of the nature of infection, it is estimated that more than one-third of the world's population is infected. Antibody prevalence studies have demonstrated that geographical location, socioeconomic status and age influence the frequency of infection. HSV-1 encephalitis is the more common and has a high mortality while HSV-2 is involved in 4–6% of cases.[45]

Pathogenesis

The pathogenesis of both HSV types is unclear, although it is apparent that both primary and recurrent HSV infection may result in CNS disease. Experiment has shown that HSV gains entry to the CNS via the olfactory and trigeminal nerves although whether primary or recurrent HSV is reactivated within the CNS are unknown in humans. In mice HSV-1 has been shown to be transmitted vertically, possibly explaining how neonatal infection occurs that causes severe disease and death in newborns.[46]

Pathology

Acute necrotizing encephalitis is the most common type of acute encephalitis and is observed in all age groups, with the exception

of young children. The gross appearance of the brain in adults shows acute inflammation, congestion and softening. The necrosis is widespread and asymmetrical, associated predominantly with the temporal lobes. The necrotic tissue is sometimes haemorrhagic. In patients who survive for more than several weeks, the brain tissue starts to disintegrate. Severe microglial reactivity is observed and in cases of disseminated HSV infection mononuclear infiltrates and perivascular cuffing are observed. Viral inclusion bodies may be detected in the nuclei of neurones and to a lesser extent in oligodendrocytes and astrocytes.

Clinical features

The effects of HSV encephalitis on the CNS vary with the type of infection. Patients present with the sudden onset of an acute febrile encephalitic illness characterized by headaches, confusion and meningeal irritation. This is rapidly followed by deterioration in consciousness and may include focal epilepsy and focal motor neurological signs. Disseminated HSV infection is commonly observed in neonates and is related to HSV-2.

Diagnosis

Patients presenting with neurological involvement and suspected herpes simplex encephalitis may be evaluated by scanning procedures such as computed tomography or magnetic resonance imaging, together with CSF analysis. Imaging often shows evidence of oedema and a midline shift in cortical structures. However, virus isolation remains the definitive diagnosis for HSV and allows for typing of the virus. The most commonly used tests are CF, NT and ELISA although the use of polymerase chain reaction (PCR) gives definitive confirmation of infection in the CSF.

Prevention and control

Owing to the high risk of infection during birth in women with active genital HSV, infants born to such mothers should be isolated and cultures obtained at intervals to exclude infection; otherwise therapy should be administered.

HSV infections may be controlled by avoidance of infectious secretions, vaccination or antiviral therapy. Patients thus presenting with obvious HSV sores should avoid contact with persons at risk, particularly neonates. The antiviral agents, vidarabine and aciclovir,[47] have proved useful in the therapy of HSV encephalitis, although the outcome is dependent on factors of age, level of consciousness and disease duration. Such agents have also been suggested to be of use prophylactically for the newborn and for women at the onset of labour. Vaccination remains the preferred method for the prevention of virus infection, although recurrent episodes of infection occur in the presence of antibody and this introduces problems. However, protection from life-threatening infections has been achieved in experimental animal models.[48]

Varicella-zoster virus (VSV; HHV-3)

VZV causes two distinct diseases: chickenpox and 'shingles'. Chickenpox (varicella) is the primary disease, generally of children, and results in a highly contagious, generalized exanthem which occurs in epidemics. (The disease should not be confused with smallpox (variola) with which there is no relation.) The name 'chickenpox' is thought to be derived from the French chick (chickpea), referring to the appearance of the vesicle or pox. Shingles (herpes zoster) is a less common disease that occurs in immunocompromised or older individuals and is characterized by dermatomal vesicular rashes. Herpes zoster is regarded as a secondary infection associated with the reactivation of VZV that has remained latent since an earlier attack of varicella. The name 'shingles' is derived from the Latin *cingulum*, meaning girdle, which is the appearance of the lesions on the dermatome.

The association between varicella and zoster was described in 1888 by von Bókay, who noted the appearance of chickenpox in a family after exposure to zoster. Furthermore, serological testing could not distinguish between the viruses and the ultimate confirmation came from studies by Weller and Stoddard,[49] who isolated virus from varicella lesions and zoster lesions, and determined that the recovered viruses were identical.

Epidemiology

Varicella is endemic in the population and epidemic in late winter and early spring. The disease affects 90% of children under the age of 10 years and intimate contact is necessary for infection. In contrast, zoster infections are a consequence of reactivation of VZV. Patients at greatest risk are those with Hodgkin's and non-Hodgkin's lymphoma and immunosuppressive conditions, such as AIDS. The incidence of CNS complications following varicella is unknown but has been reported as between 0.1 and 0.75%.[50] In contrast, the incidence of encephalitis following zoster is much higher, particularly in immunosuppressed patients.

Pathogenesis

Primary infection with VZV results from respiratory droplet transmission. The virus enters the mucosa of the upper respiratory tract, and to a lesser extent the conjunctiva, and disseminates via the blood. Cycles of replication occur, giving rise to a secondary viraemia from which the virus becomes widespread before the formation of cutaneous lesions. The complications of neurological involvement following varicella infection are classified into: (1) cerebellar ataxia, (2) generalized meningoencephalitis, (3) transverse myelitis, and (4) aseptic meningitis. The pathogenesis of these conditions is unknown, although immunological mechanisms of tissue damage, as a result of infection, have been suggested.[51] In general, the CNS involvement following zoster infections is associated with higher mortality rates than varicella. Complications following infection include encephalitis, ophthalmic zoster, myelitis, multifocal leukoencephalopathy, Guillain–Barré syndrome, and cranial and peripheral nerve palsies. VZV has been isolated from several patients with zoster encephalitis, and inclusions have been found in the glial cells and neurones. Antiviral antibodies have been demonstrated in the CSF of such patients.

Pathology

The neuropathological changes observed in varicella or zoster virus infections depend on the complication induced. In fatal varicella encephalitis, mononuclear infiltration and demyelination have been reported.[52] More detailed pathological findings have been reported for zoster complications because of the higher

incidence of death. Zoster meningoencephalitis includes mononuclear infiltration of the meninges, necrosis and axonal degeneration. Degeneration may also involve the posterior columns where neurophagia is observed.

Clinical features

The incubation period for varicella in children is between 14 and 15 days, and is associated with malaise and mild fever. Anorexia and a sore throat are additional clinical features of adult varicella infection. The rash proceeds to the characteristic vesicles that crust. CNS involvement occurs more often in children who present with cerebellar ataxia a few days after the onset of the rash.[50]

The rash of zoster is preceded by pain in the dermatome affected. The lesions, which resemble varicella, appear unilaterally and generally do not cross the midline. Crusts appear up to 1 week after eruption and last for approximately 2 weeks. Neurological complications of zoster may precede the appearance of the rash or appear as late as 10 months afterwards. Complications are observed in immunosuppressed patients as a result of persistence of virus within the CNS.

Diagnosis

The onset of neurological signs concomitant with appearance of varicella or zoster rash would suggest such infection of the CNS. However, infection is not usually verified by virus isolation from the brain tissue, the exception being at necropsy. The new guidelines recommend that where CNS infection due to VZV is suspected, the CSF should be analysed by PCR for VZV DNA. As VZV antibodies may be present in the CSF in the presence or absence of detectable VZV DNA, CSF should also be analysed for VZV-specific antibody.[53]

Prevention and control

There is generally no specific treatment, apart from antipyretics (not aspirin) for varicella in the immunocompetent host. Neurological complications of varicella, particularly in the immunocompromised host, are important because of the high morbidity and mortality rates. Although α-interferon is effective, two nucleoside analogues, vidarabine and aciclovir, are also employed, although side-effects have been reported. The possibility that immune-mediated reactions contribute to the CNS manifestations has given rise to the use of corticosteroids as a treatment of CNS involvement. In contrast, as evidence suggests active viral replication within the CNS, it would appear that antiviral agents should be employed.

Epstein–Barr virus (HHV-4)

Epstein–Barr virus (EBV) (see also Chapter 43) gives rise to CNS complications such as meningoencephalomyelitis, encephalitis and neuropsychiatric syndromes, although the frequency of such manifestations is extremely low. The CSF of patients with CNS disorders following EBV infection shows an increased protein level. In patients dying from EBV infection, the CNS is more often affected and shows perivascular cuffing, oedema and demyelination. In the X-linked lymphoproliferative disease (Duncan syndrome), a rare inherited disorder, patients are unable to clear Epstein–Barr virus infection. In these patients EBV encephalitis is observed as well as CNS lymphoproliferative disease, and lymphoma. EBV seropositivity has also been linked with multiple sclerosis.

Other herpesvirus infections

Human cytomegalovirus (HCMV) (HHV-5). HCMV is the most frequent infectious cause of developmental brain disorders and causes brain damage in immunocompromised individuals; for example, HCMV infection of the CNS occurs in at least 50% of AIDS patients. Although the brain is one of the main targets of CMV infection, little is known about the neuropathogenesis of the brain disorders caused by CMV in humans because of the limitations in studying human subjects. For diagnosis, the PCR recommended for viral DNA is performed on CSF. Treatment should be directed toward the prevention of CMV disease using ganciclovir.

Human herpesvirus 6 (HHV-6). Like other herpesviruses, HHV-6 infects virtually all children within the first few years of life and establishes latency after primary infection. In immunocompromised hosts HHV-6 has been linked with CNS disease. In particular, longitudinal studies have established a correlation between systemic HHV-6 reactivation and CNS dysfunction such as limbic encephalitis and temporal lobe epilepsy.

Human herpesvirus 7 (HHV-7). Infections of the CNS have rarely recently been reported in children although, like HHV-6, there are several reports linking these infection with multiple sclerosis, chronic fatigue syndrome and epilepsy.

Human herpesvirus 8 (HHV-8). This has also been linked with demyelinating diseases using PCR to detect virus in the blood of patients.

Cercopithecine herpesvirus 1 (B virus)

The non-human primate Cercopithecine herpesvirus 1 (B virus) is highly pathogenic to humans. Originally transmitted by the bite of rhesus or macaque monkeys, the virus is now thought to be transmitted from person to person. In 1932, following the bite from a monkey, a physician developed a localized reaction, lymphangitis, lymphadenitis and transverse myelitis, and died. The virus was subsequently recovered from the CNS of the patient and found to be lethal to rabbits following injection.

Epidemiology

The B virus is indigenous to Old World monkeys. Although B virus has been reported in only 22 human cases and is generally transmitted via a bite, individuals in Florida have been affected (two fatally), suggesting person-to-person spread of the virus.[54] Virus is secreted in the saliva and stools of infected animals and these must therefore be considered as potential sources of infection for humans.

Pathogenesis

After the bite, a local reaction occurs, followed by lymph node involvement. The course of the disease is dependent on the route of inoculation (as determined from animal studies), although transverse myelitis is a prominent neurological finding before invasion of the CNS. As with other herpesviruses, the B virus

becomes latent and may be reactivated under certain conditions.[55] Virus spread to the brain is suggested to occur via the neural routes, as with HSV.

Pathology

All regions of the brain may be infected by B virus and show haemorrhagic foci, necrosis and inflammation in the form of perivascular cuffing of mononuclear cells. Motor neurones are affected and show degeneration. Astrocytosis is observed, with gliosis.

Clinical features

Incubation of B virus varies from 2–3 to 24 days. The neurological involvement is observed 3–7 days after the appearance of the vesicular rash. Death may ensue within 10–14 days, although the progression of the disease depends on the age, site of bite and immunological status of the patient. Clinically, the patients present with a localized inflammatory reaction at the site of the bite, or with a respiratory illness: such responses have been described in two individuals.

Diagnosis

Although serological tests demonstrate the presence of B virus, a significant problem is the cross-reactivity with HSV antigens. Diagnosis is therefore dependent on the isolation of virus, particularly from the CSF of humans suspected of being infected, and the use of cell lines susceptible to B virus infection. These include rabbit kidney cells or cell lines such as BSC or LLC-RK1. Definitive diagnosis may be made using molecular methods and neutralization of isolates in serological assays.

Prevention and management

Procedures that limit the transmission of the virus should be adhered to. These include limited contact with macaque monkeys and the routine screening of such animals. The use of hyperimmune serum has not proved effective in controlling human infection, although some success has been achieved in experimental infections.[56] Antiviral therapy has concentrated on the nucleoside analogues: vidarabine, aciclovir and ganciclovir. The use of aciclovir in humans has been reported to slow the infection.[57]

ORTHOMYXOVIRIDAE

Orthomyxoviruses (Greek 'myxa' meaning mucus) are large enveloped RNA viruses and include the influenza A, B and C viruses which infect swine, horses, seals and a large variety of birds as well as humans. Influenza type A viruses are divided into subtypes based on two proteins on the surface of the virus, the haemagglutinin (H) and neuraminidase (N). There are 15 different haemagglutinin subtypes and nine different neuraminidase subtypes, all found among influenza A viruses in wild birds. Genetic reassortment produces subtypes that give rise to epidemics of highly contagious, acute respiratory illness afflicting humans.

Epidemiology

Influenza viruses are unique among the respiratory tract viruses in that they undergo significant antigenic variation. Antigenic drift involves minor antigenic changes in H and N proteins. Wild birds are the primary natural reservoir for all subtypes of influenza A viruses and are thought to be the source of influenza A viruses in all other animals. Most influenza viruses cause asymptomatic or mild infection in birds; however, the range of symptoms in birds varies greatly depending on the strain of virus. Infection with certain avian influenza A viruses (e.g. some strains of H5 and H7 viruses) can cause widespread disease and death among some species of wild and especially domestic birds such as chickens and turkeys. In May 1997, a young child in Hong Kong died of complications of influenza H5N1 – the first case in humans. The subtype H5 causes lethal avian influenza (bird flu) but did not cause an epidemic in humans since it was thought that the strain was poorly adapted to humans.

Pathogenesis and pathology

A wide spectrum of CNS involvement has been shown during influenza A virus infection in humans, ranging from irritability, drowsiness and confusion to more serious manifestations of psychosis and coma. There are two specific CNS syndromes: influenza encephalopathy and postinfluenza encephalitis. Encephalopathy occurs at the height of the influenza illness and may progress to death.[58] Histological changes are minimal. The CSF is usually normal and the brain shows severe congestion at autopsy. The post-encephalitis syndrome is extremely rare and occurs 2–3 weeks after recovery from influenza. The CSF findings suggest that inflammatory changes have occurred. Influenza A virus has only rarely been isolated from the brain or CSF. It has been suggested that the syndrome of encephalitis lethargica followed by post-encephalitic Parkinson's disease was associated with the influenza epidemics of 1918.[59]

Clinical features

Influenza A virus infections in avian species vary with the strain of the virus. Infections with most strains of influenza virus are asymptomatic. However, some strains cause chronic respiratory infections and a minority lead to a rapidly fatal infection accompanied by CNS involvement, with death occurring within 1 week. Febrile convulsion may occur in children with and without underlying CNS abnormalities. Pregnant women in the second or third trimester also have an increased risk of developing fatal influenza disease,[60] and increased incidences of congenital abnormalities and haematological malignancies have been reported following influenza virus infection in pregnancy.[61] Acute necrotizing encephalopathy manifesting with coma, convulsions and hyperpyrexia has been associated with Influenza B in children.[62]

Prevention and control

Antivirals

Several antiviral drugs are used for influenza virus infections e.g. amantadine hydrochloride is effective against all subtypes of influenza A virus but not B or C viruses.[63,64] The antiviral activity is exerted after adsorption, penetration and uncoating have taken

place but before primary transcription.[65] Zanamivir is the first widely approved neuraminidase inhibitor for the treatment of influenza. It is delivered directly to the primary site of viral replication, the respiratory tract, and is well tolerated and effective in the treatment of both influenza A and B. Oseltamivir is the second antiviral drug, after amantadine, to be marketed in the European Union for the prevention of influenza in children aged from 1 to 12 years.[66]

Vaccines

Inactivated influenza A and B virus vaccines are designated either whole virus (WV) or split product (SP). The WV vaccines contain intact formalin-treated virus, whereas SP vaccines contain purified formalin-treated virus disrupted with chemicals that solubilize the lipid-containing viral envelope. In addition, experimental vaccines containing the isolated haemagglutinin (HA) and neuraminidase (NA) surface proteins are called subunit vaccines. Other types of vaccine are those that contain a monovalent influenza A H1N1 virus of a mixture of H1N1, H3N2 and B viruses.

PAPOVAVIRIDAE

The family Papovaviridae is divided into the two subfamilies: polyomaviruses and papillomaviruses, which, although they share several properties, are not related immunologically or genetically.

Polyoma viruses

The first human disease associated with a polyomavirus was a rare demyelinating disease of the CNS, progressive multifocal leukoencephalopathy (PML). The disease is observed in immunodeficient individuals and was suggested, in 1961, to be due to a common virus which in the immunocompromised host runs an atypical course of infection. In 1971 two viruses implicated in PML were isolated from the brain (JC virus) of a patient with PML and the urine (BK virus) of a renal transplant patient.[67] JC and BK viruses are contracted in early childhood, persist in the host and are reactivated in cases of immunocompromise, such as in AIDS.

Epidemiology

Polyomaviruses are widely distributed in many species of animals, although they are generally species specific. BK and JC viruses do not naturally infect species other than humans. Antibody titres to BK virus are acquired by 50% of children by 3 years of age and against JC virus by 50% at 6 years of age.[68] It is estimated that 60–80% of adults in Europe and the USA have antibodies to JC virus. PML is worldwide in distribution and occurs as a complication in lymphoproliferative disorders, and chronic disease such as sarcoidosis, in immunodeficiency diseases and in patients on long-term immunosuppressive therapy. Reactivation of both JC and BK viruses is also known to occur in pregnancy, diabetes, chronic disorders and old age. Approximately 20% of patients with PML have AIDS, whereas PML is reported to occur in as many as 3.8% of patients with AIDS presenting with neurological disorders.[69] More recently, PML has been identified in some patients with MS prescribed Tysabri.[69]

Pathogenesis

Primary JC infections of healthy individuals are not associated with illness, although BK virus has been linked with mild respiratory illness. The mode of transmission of BK and JC viruses is unknown, although the rapid acquisition of antibodies has been suggested to be consistent with respiratory disorders. Following primary infection the virus remains latent in the kidney and is reactivated under immunosuppression.

Pathology

The PML brain is characterized by foci of demyelination that are widespread and vary in size. In advanced cases the areas may be necrotic. The lesions occur in the absence of inflammatory cells and are more frequent in the white matter of the cerebrum. Nuclear changes in the oligodendrocytes at the edge of the demyelinated plaques are associated with the presence of JC virus. The lesions are also marked with bizarre giant astrocytes and oligodendrocytes with enlarged nuclei which, at light microscopical level, are deeply basophilic and may contain inclusion bodies. Neurones are unaffected.

Clinical features

Symptoms such as cognitive changes, ataxia, aphasia and sensory deficits characteristic of a multifocal brain disease observed without signs of raised intracranial pressure in an immunocompromised host suggest PML. Generally, people with PML deteriorate rapidly and death occurs within 6 months, although in rare cases patients experience fluctuating symptoms over 2–3 years.

Diagnosis

Computed tomography or magnetic resonance imaging of the brain will detect lesions of demyelination. Verification of PML may be carried out following examination of brain tissue in which JC virus may be identified by electron microscopy, immunohistological identification as well as in CNS sections, cultivation of the virus in fetal glial cells and characterization of viral DNA by in situ hybridization and PCR.[70]

Management and control

There is no certain treatment for PML, although the accepted regimen is to discontinue the immunosuppressive therapy in combination with the use of antiviral drugs. Attempts at treatment with nucleic acid-based analogues have been reported. See also under HIV infections, as PML is more prevalent in patients with AIDS.

Papillomaviruses

While not commonly associated with CNS diseases, recently pregnant women infected with the human papilloma virus may give birth to children with pathologies of the nervous system.

PARAMYXOVIRIDAE

The Paramyxoviridae family consists of negative-stranded enveloped RNA viruses classified as three genera: *Morbillivirus*, *Para-*

myxovirus, and *Pneumovirus*, and includes four important human pathogens: measles, mumps, parainfluenza (types 1–4) and respiratory syncytial viruses.

Morbillivirus

The Morbillivirus genus is important in that it contains the human neurotropic virus measles and the canine distemper virus.

Measles

Measles (see also Chapter 47) as a disease was first described by Sydenham in the early seventeenth century and the implication that this was a virus infection was established in the 1920s. The disease is generally a childhood illness and is not fatal, although it may be serious in the very young or elderly. Great epidemics of measles have been described, such as the 'black measles' of the eighteenth century. Waves of measles infection are occasionally observed, with the greatest incidence between November and March.

Epidemiology

In the less developed countries, measles is the most important cause of death between the ages of 1 and 5 years. Death occurs predominantly from respiratory and CNS complications. Measles does not have animal reservoirs and no vectors are involved. The principal mode of transmission is via droplets of infected respiratory tract secretions inhaled as a consequence of face-to-face exposure. However, air-borne transmission may be important in certain settings, including schools, hospitals and other institutions. Virus is present in respiratory secretions and in the conjunctivae during the latter part of the incubation period. Viraemia is also present during this time and virus is present in the urine for 4 or more days after the onset of rash.[71] Patients are considered infectious from the onset of symptoms through the fourth day of rash. Maternal antibodies provide protection during the first 6 months of life and, although cell-mediated immunity is required to clear measles virus infection, both humoral and cell-mediated immunity are able to prevent disease in normal individuals. The slow infection of measles in humans (i.e. subacute sclerosing panencephalitis, SSPE) is a rare disease in which virus persists in the CNS. The incidence of SSPE is more common in males than females, and is more prevalent in rural areas. The average age of onset is between 5 and 15 years, and infection with measles before the age of 15 years increases the risk of developing SSPE. In the USA the mean annual incidence rate of SSPE was estimated at 0.06 cases per million (aged under 20 years) in 1980.

Clinical features

Measles begins, after an incubation period of 8–12 days, with fever, malaise and anorexia followed by conjunctivitis and cough. The infection then spreads to the epithelial surfaces of the mouth, nasopharynx, respiratory tract and gastrointestinal tract. Two to three days before the onset of the rash, Koplik's spots appear on the buccal mucosa. Koplik's spots are small (1–3 mm), irregular, bright red spots, each of which has a minute bluish-white speck at its centre. The temperature reaches 39.4–40.6°C at the height of the eruption on the 5th day of the illness. The rash starts around day 3 or 4 of prodromal symptoms and spreads downward over the face, neck and trunk, continuing downwards until it reaches the feet by the third day. Cough and coryza follow as a result of an intense inflammatory reaction that involves the mucosa throughout the respiratory tract. The most common complications involve the middle ear, CNS, eyes and skin.[72]

The three forms of measles encephalitis are:

1. Acute post-infectious measles encephalitis; the most common neurological complication of measles. Children under the age of 2 years are rarely affected but it occurs in older children in the ratio of 1 in 1000. It appears a short time after the rash. Between 10% and 20% die and the majority of the survivors have some neurological sequelae. Histopathological examination shows perivascular inflammatory changes and demyelination.
2. Acute progressive infectious encephalitis which is generally observed in immunosuppressed patients. Exposure to measles leads to seizures, motor and sensory deficits, and lethargy. The clinical progress and pathology are a result of unrestricted cytolytic replication of the virus.[73]
3. Late complication of measles. The symptoms develop over months, reflecting loss of cerebral cortical function.[74] In the early stage subtle mental changes and diminishing intellectual capacity are seen. Later, myoclonic jerks occur and progress to choreoathetosis, ataxia and finally coma. Focal retinitis occurs in the majority of the cases, leading to blindness.

Pathogenesis and pathology

Measles virus replicates initially in the respiratory mucosa and spreads, perhaps carried intracellularly in pulmonary macrophages and other cells, to draining lymph nodes where further replication occurs. Virus then enters the bloodstream and from here dissemination of the virus throughout the reticuloendothelial system takes place. This results in a secondary viraemia that disseminates the infection to tissues throughout the body. The most striking feature of measles virus infection in vivo and in vitro is the formation of multinucleated giant cells which result from the fusion of infected cells with the adjacent cells.[75] In tissue culture these giant cells contain eosinophilic cytoplasmic inclusion bodies and their nuclei show condensation of chromatin at the nuclear membrane. The CNS of patients with SSPE shows inflammation of the meninges and perivascular cuffing in both grey and white matter. In the later stages of disease, demyelination and gliosis are observed. Although the mechanisms of myelin damage are unknown, it may be a result of either neural damage or the involvement of an autoimmune response, as T lymphocyte reactivity to the myelin constituent, myelin basic protein, has been observed.[76]

Diagnosis

Most measles infections are easily recognizable by the distinctive Koplik's spots, rash and catarrhal symptoms. Effective tests for laboratory diagnosis are available and include virus isolation in primary human or monkey cells and antibody determination by simple HI test and by ELISA.[77] Serological tests are effective in identifying cases of SSPE. Patients with this disease have increased serum antibody titres, which are 10–100 times higher than those seen in late convalescent-phase sera. There is also a pronounced

local production of oligoclonal measles virus antibodies in the CNS.[78] Viral antigen can be identified by immunofluorescence.

Prevention and control

No effective treatment is available, although in vitro measles virus replication is sensitive to interferon and ribavirin treatment. No treatment is presently available but pooled immunoglobulin can be administered for postexposure prophylaxis up to 5 days after exposure. Live attenuated vaccines are widely used and it is aimed to eradicate measles worldwide.[79] The rate of seroconversion after vaccination exceeds 90%. Vaccine complications are very rare. Encephalitis occurs at the same rate as in non-vaccinated individuals and the frequency of occurrence of SSPE is reduced by a factor of at least 10 in vaccinated persons. Recently, early administration with intrathecal high-dose interferon-α and intravenous ribavirin has been shown to be effective in the treatment of SSPE.

Canine distemper virus

Canine distemper virus (CDV) deserves mention in this chapter because of its relationship with measles virus and implication in the human neurological disease, multiple sclerosis. This virus gives rise to a chronic relapsing disease of dogs in which demyelination lesions are observed.[80] Furthermore, several studies have suggested associations between the incidence of multiple sclerosis and canine distemper in the dog population.[81]

Paramyxoviruses

Mumps

Mumps has been recognized from the fifth century BC when Hippocrates described the disease as one of swellings behind the ears accompanied by swelling of the testes. However, the first description of neurological involvement was that by Hamilton[82] in the eighteenth century. Transfer of disease from filtered secretions of an affected patient into experimental animals suggested the disease had a viral aetiology.

Epidemiology

Mumps infection increases in the winter months. Immunity to mumps is usually acquired between the ages of 5 and 14 years, with maximal humoral antibody occurring between 4 and 7 years of age.[83] Mortality from mumps is related primarily to the complications of meningitis/encephalitis and orchitis. These occur as age- and sex-specific hazards, with a peak risk in post-pubertal males. The incidence of CSF pleocytosis is reported in 30% of patients with mumps parotitis, whereas encephalitis occurs in as many as 35% of cases.[84]

Clinical features

The most characteristic feature of mumps is the swelling of the salivary glands which occurs in up to 95% of all symptomatic cases. The parotid glands are often involved. A moderate febrile response is present at the time of the disease onset. A wide variety of other organs have been involved and include the testes, CNS, epididymis, prostate, ovaries, liver, pancreas, spleen, thyroid, kidneys, eyes, thymus, heart and joints. The onset of mumps meningitis is marked by fever, with vomiting, neck stiffness, headache and lethargy. Seizures occur in 21–30% of patients with CNS symptoms. In cases of CNS involvement about one-third of all patients have evidence of intrathecal IgG synthesis and the presence of oligoclonal immunoglobulins during the first week of CNS symptoms. Examination of the CSF shows abnormalities in the vast majority of cases. The protein content in the CSF is markedly increased in 60–70% of all cases. This may be due to a damaged BBB, as indicated by high albumin indices that do not normalize for several weeks to months after the onset of the CNS symptoms. The CSF glucose content is depressed to 17–41% of the serum value in 6–29% of all cases.[85]

Pathogenesis and pathology

Natural infection is initiated by droplet spread with primary viral replication in nasal mucosa or upper respiratory mucosal epithelium and the time to first clinical symptoms is about 18 days. Virus is actively shed in saliva 6 days before symptoms, during which the virus multiplies in the upper respiratory mucosa and spreads to draining lymph nodes with subsequent transient plasma viraemia. Plasma viraemia is terminated by the developing humoral antibodies as early as 11 days after experimental infections of humans. Mumps virus has been shown to infect human lymphocytes in vitro and appears preferentially to infect activated cells of the T lymphocyte subset. This could imply that cell-associated viraemia may be another mode of virus dissemination. Viral replication in the parotid glands is accompanied by periductal interstitial oedema and a local inflammatory reaction involving lymphocytes and macrophages. Once within neurones, virus is able to distribute widely along neuronal pathways.

Viral invasion of the CNS occurs across the choroid plexus, although rarely is mumps meningoencephalitis fatal. CNS pathology is restricted to perivascular infiltration with mononuclear cells, scattered foci of neuronophagia and microglial proliferation.[86] Perivascular demyelination also occurs; this may be the result of an autoimmune attack on the brain tissue. Persistence of mumps virus has been suggested within the CNS of humans. Deafness is probably the result of direct damage to the cochlea and, to a lesser extent, cochlear neurones.[87] Most cases of mumps meningitis resolve without sequelae. However, ataxia and behavioural disturbances may be slow to resolve following mumps meningoencephalitis.[88,89]

Diagnosis

The clinical diagnosis of mumps is seldom problematic in the presence of parotitis. Laboratory diagnosis includes determination of virus-specific IgM and IgG levels. Mumps meningitis can be confirmed on the basis of a raised CSF serum antibody ratio.

Management and control

Hyperimmune γ-globulin to modify the course of mumps is used in selected cases. Two general types of vaccine have been used. Recently controversy over the links with autism and measles-mumps-rubella (MMR) vaccination has led to the idea of single vaccines. However, the most widely used are the live attenuated

mumps virus preparations given as the triple MMR vaccine; killed mumps virus antigens have a more restricted use.[90]

PARVOVIRIDAE

To date parvoviruses have rarely been implicated in human CNS disease[91] although infections of experimental animals with parvoviruses are well-known to induce cerebellar ataxia and affect the development of the cerebellum during the perinatal period.

PICORNAVIRIDAE

The Picornaviridae family consists of small RNA viruses and comprises nine genera: *Enterovirus*, *Rhinovirus*, *Hepatovirus*, *Aphthovirus* and *Cardiovirus*, *Parechovirus*, *Erbovirus*, *Kobuvirus* and *Teschovirus*. Those in which neurological disease has been reported are given in Table 48.6.

Enteroviruses

The enteroviruses multiply throughout the alimentary tract and tend to be resistant to known antibiotics and chemotherapeutic agents. The host range of the enteroviruses is varied and may be readily induced to yield variants, which has led to the development of attenuated polio vaccine strains. The enteroviruses which are important CNS pathogens of humans are polioviruses and coxsackie. For more detailed studies on enteroviruses, the reader is referred to *Fields Virology*.[2]

Poliovirus

The disease poliomyelitis (see also Chapter 16) has existed since ancient times, although the fact that the causative agent was a virus was first demonstrated only in 1909 by Landsteiner and Popper.[92] Studies in monkeys and the adaptation to tissue culture resulted in the development of methods of purification and the production of reliable vaccines through which infection can now be controlled. Poliomyelitis may be caused by one of three strains of virus: polio types 1, 2 or 3. Three forms of clinical disease have been recognized: paralysis, aseptic meningitis and minor febrile illness.

Epidemiology

Poliovirus was, until very recently, endemic worldwide, infecting susceptible infants and producing paralytic poliomyelitis in those who were not protected by maternal antibody. In 1916, 80% of cases were in those under 5 years of age. The changes in sanitation and hygiene in the late nineteenth century, with industrialization in the north of Britain, decreased the incidence in infants but resulted in a higher incidence of paralytic poliomyelitis in later childhood due to delay in exposure to the virus. In the epidemics of 1950 the peak age was 5–9 years, although about one-third of cases and two-thirds of deaths were in those over 15 years. Since 1985, most of the cases of polio worldwide have been in developing countries, although the number of deaths due to other diseases may mask the true incidence of infantile paralysis. Nevertheless, there are still outbreaks and the polio eradication programme aims to achieve its goal by the end of 2008.[93]

Pathogenesis

Following ingestion, poliovirus replicates in the pharynx and intestines, from which it is excreted. Transmission is by the faecal-oral route and thus the necessity for hygiene is paramount. After initial replication in the lymphoid tissue of the pharynx and gut, which leads to viraemia, the virus infects the CNS via the blood. Neural spread has been demonstrated in children following tonsillectomy.

Pathology

The anterior horn cells of the spinal cord are susceptible to infection with poliovirus and are damaged or, in severe cases, completely destroyed.[94] The lesions observed in the CNS may extend to the hypothalamus and thalamus. Neuronophagia is commonly observed, with inflammation being secondary to neuronal attack. In less severe cases oedema, which results in temporary disturbance of neural functions, subsides and the cells recover completely.

Clinical features

Following infection, approximately 1% of patients present with clinical disease. Abortive poliomyelitis is the most common form of the disease in which fever, malaise, drowsiness, headache and sore throat are experienced to varying degrees. The signs abate within a few days. Stiffness and pain in the back of the neck may also be experienced, in which case non-paralytic poliomyelitis, or aseptic meningitis, is diagnosed. The disease may become biphasic, whereby a minor illness is followed by a remission, but which subsequently develops into a major severe illness.

Diagnosis

Antibodies are usually present by the time paralysis occurs and a viraemia may be detected and used to determine the subtype using

Table 48.6 Picornaviruses implicated in human neurological disease

Genus	Virus	Disease
Enteroviruses	Human polio	Paralysis, aseptic meningitis, febrile illness
	Human coxsackie (groups A and B)	Aseptic meningitis, paralysis, meningoencephalomyelitis
	Echovirus	Aseptic meningitis, paralysis, encephalitis, ataxia or Guillain–Barré syndrome
	Enteroviruses (types 70, 71)	Paralysis, meningoencephalitis
Cardiovirus		Encephalomyocarditis

serological techniques. More recently, molecular biological techniques have been used to demonstrate poliovirus in CSF.

Prevention

In 1952, Salk developed an inactivated poliovirus vaccine[95] which became generally available in 1955, and by 1959, oral polio vaccines were developed using live attenuated virus which today consists of a mixture of three strains. The oral vaccine protects by producing both systemic antibody and local secretory IgA which would block virulent virus, preventing spread from the gut. These vaccines have the advantages over killed preparations of ease of administration and long-lasting immunity, although they have the 'disadvantage' of being excreted and thus have the potential to spread to non-vaccinated persons.[96]

Coxsackie and echoviruses

Of the non-polioenterovirus infections, echovirus 9 is the most frequent cause of enterovirus disease and the most common virus to be isolated in epidemics. The chief viruses implicated in CNS disease are coxsackie B1-6, A7 and A9, although many echoviruses have been associated with meningitis, as has enterovirus type 70. Of all the enteroviruses, Coxsackie B is responsible for more than half the cases of aseptic meningitis in children less than 3 months. Severe CNS disease has been observed in enterovirus 71 infections in the 1975 epidemic in Bulgaria, where antibodies to enterovirus 71 were detected in 72% of patients with paralysis and virus was isolated from the CNS. Of the seven reported epidemics with enterovirus 71, all reported evidence of CNS involvement.[97]

Other picornaviruses

Hepatitis A infection has also been linked with CNS involvement in which a child presented with seizures.[98] Also human parechovirus infections have been linked with transient paralysis and encephalitis.

More recently, a newly identified picornavirus, Ljungan virus, isolated from rodents, induces encephalitis in rodents, while a porcine teschovirus has been associated with encephalitis in pigs.

POXVIRIDAE

The family name is taken from the major clinical symptom of these viruses, namely pox – an elevated skin lesion – and includes variola and vaccinia. Neurological complications of poxvirus infections are generally associated with vaccination, namely post-vaccination encephalitis. The pathogenesis and pathology resemble other post-infectious encephalitides and include perivascular cuffing, mononuclear infiltration and demyelination.

REOVIRIDAE

The family REOviridae (*R*espiratory *E*nteric *O*rphan viruses) is comprised of 12 genera. The genus *Coltivirus* contains Colorado tick virus; *Orbivirus*, the Blue tongue virus that infects cattle and African horse sickness virus; the genus *Rotaviruses* contains viruses that cause diarrhoea. *Seadornavoiruses* are emerging pathogens from South-east Asia and contain *Banna* virus isolated from humans with encephalitis.[99] Rotaviruses have been rarely associated with encephalopathy in children and encephalitis was observed in four people as a result of accidental exposure to a vaccine of the Orbivirus, African horse sickness virus.

Coltiviruses

The genus Coltivirus are tick-borne viruses such as Colorado tick fever virus, associated with patients with flulike syndromes, meningitis, encephalitis, and other severe complications. Another coltivirus, Eyach virus, isolated from ticks in France and Germany, has been associated with febrile illnesses and neurological syndromes.[99]

Colorado tick fever

Colorado tick fever (CTF) was first described in the mid-nineteenth century in the Rocky Mountain States and associated with infections from the tick *Dermacentor andersoni*.[100]

Epidemiology

This disease is confined to the geographical distribution of the adult *Dermacentor andersoni* tick in the Rocky Mountain States and in parts of north-western Canada; it is a common infection in hikers and foresters during May and June.

Pathogenesis

Infection with CTF virus gives rise to little or no disease in the natural host and induces a prolonged or persistent viraemia in vertebrate hosts such as ground squirrels and chipmunks that serve as amplificatory rodents. CTF virus is involved in bone marrow precursor cells and its presence in erythrocyte precursors renders the host susceptible to haemorrhagic disorders. The onset of disease occurs 3–6 days after the tick bite.

Pathology

CTF virus infections do not generally result in death and thus pathological features are not well described. However, following experimental infections of mice, the cerebellum shows widespread necrosis and cellular infiltration.

Clinical features

A febrile illness develops, with headache and myalgia. A maculopapular rash is seen in about 50% of patients. Colorado tick fever is a benign disease but in very rare cases a bleeding diathesis may develop and, particularly in children, there may be a typical meningoencephalitic illness. Resolution of the acute phase may take 5–10 days. Infection in the CNS may be observed as a mild meningeal reaction to severe encephalitis. The frequency of CNS involvement ranges from 1 to 10%.[100]

Diagnosis

Abnormalities include leucopenia and thrombocytopenia; virus may be isolated from the blood owing to its persistence in the erythrocytes. Some time after disease onset, CF and neutralizing

antibodies may be detected in the blood[101] although PCR is more efficient and sensitive. CSF findings are typical of encephalitis.

Prevention and control

At present, there is no treatment for CTF, although health awareness when hiking in the affected areas may help to limit exposure to tick bites.

RETROVIRIDAE

Several features of retroviruses, such as their unique replication cycle, oncogenic ability and the wide variety of interactions with the host, including their ability to remain latent, have led to the intense scientific attention these viruses have received. Retroviruses are classified into the three subfamilies: Oncovirinae, Lentivirinae – lentiviruses (e.g. maedi-visna, which results in chronic inflammation of the CNS and human immunodeficiency viruses which result neurologically in AIDS dementia and demyelination) – and Spumavirinae.

Lentiviruses

In contrast to viruses that cause acute disease and where virus is finally eliminated, the lentiviruses include those that are able to escape such elimination and persist in the host. These include the maedi-visna of sheep, which give rise to chronic neurological disorders, and human immunodeficiency viruses in which neurological damage has been recognized.

Maedi-visna

Maedi-visna (*maedi* = laboured breathing, *visna* = wasting and paralysis – Icelandic translations) is the prototype lentivirus in which the slow onset of clinical disease results from prolonged incubation of the virus.

Epidemiology

The disease was first recognized in Iceland[101] but is observed in most countries with large sheep populations. Early transmission studies in Iceland showed that the disease could be transmitted from infected sheep to naive sheep by intracerebral inoculation. Many strains of visna have been obtained which vary in their ability to, for example, be propagated in tissue culture.

Pathogenesis

Virus is isolated from many tissues, particularly the lymphatics, spleen and peripheral blood leukocytes. Higher titres are isolated from the brain and lung. Conversion of the maedi illness to visna may occur as a result of infected peripheral blood leukocytes crossing the BBB and subsequently infecting the CNS.

Pathology

Following experimental infection, severe meningitis and encephalitis are observed, coinciding with perivascular lesions of inflammatory cells. The inflammatory cells observed in the CNS consist of monocytes/macrophages, plasma cells and T lymphocytes. Depending on the duration of the disease, the brain may show large areas of focal demyelination. Additionally, inflammatory lesions and/or demyelination may occur in the presence of areas of necrosis and gliosis.[102]

Clinical features

Clinical disease is observed as lymphadenopathy, pneumonia and CNS involvement. The sheep appear dyspnoeic with loss of flesh. The appearance of clinical disease is dependent on the strain of animal and dose of inoculation.[103]

Prevention and control

Due to the expense of developing vaccines for animals, very few studies on controlling infection have been attempted. However, sheep hyperimmunized with disrupted virus are known to develop neutralizing antibodies which are able to confer some protection against homologous virus infection.

Human immunodeficiency virus

The human immunodeficiency viruses (see also Chapter 20) consist of HIV-1 and HIV-2 and are typical lentiviruses. This chapter will concentrate only on the CNS diseases in HIV infections which are important because they are commonly seen during all stages of the disease and contribute to the outcome of the disease despite therapy.[104] The variations in clinical manifestation are dependent on both the stage of HIV disease and opportunistic infections, whether viral, such as JC infection giving rise to PML, or bacterial (e.g. *Listeria* monocytogenes meningitis).

The gross clinical features observed in neurological complications of HIV infections are classified by the neuroanatomical localization, i.e. whether the brain or cord is involved and whether the lesions are focal or non-focal. With regard to the neurological complications, these may be categorized depending on the stage of the disease: (1) during acute HIV infection of the CNS; (2) asymptomatic infection; (3) aseptic meningitis and headache; and (4) AIDS dementia complex (ADC). CNS syndromes of children give rise to a fifth syndrome resulting in abnormal neurological development and arrested intellectual and motor function.

HIV infection of the CNS

HIV may enter the brain across the BBB or by infecting monocytes (macrophages and microglia) which are productively infected by virtue of having surface CD4 molecules. Such macrophages may then cross the BBB, thus allowing the HIV access to the CNS. During the asymptomatic phase CNS involvement is common and at least 40% of all persons with HIV have abnormal CSF, with increased cell counts and protein levels. Anti-HIV antibodies are detectable in the CSF and in some patients oligoclonal bands are observed. It has been suggested that aseptic meningitis and headache, AIDS dementia complex and progressive encephalopathy of children are due to the direct effects of HIV infection.

The common neurological symptoms of early or primary HIV-1 infection are headaches and photophobia, which may be either acute or chronic. Although the cause of such clinical symptoms is not known in all patients, headaches have been related to systemic disease such as Pneumocystis carinii infection. Such features may

subside or progress to encephalitis, meningitis or ataxia. Aseptic meningitis affects 5–10% of HIV-infected patients; HIV may be diagnosed by positive virus culture or p24 antigen in the serum or CSF.

AIDS dementia complex

ADC is commonly observed in the later stages of HIV-1 infection in relation to major systemic infections, although in a small group of patients ADC occurs in the absence of opportunistic infections and may be related to HIV-1 infection of the brain. Infection and disease are not synonymous. ADC may be classified into five major stages ranging from stage 0, which encompasses normal mental and motor functions, to stage 4, in which the patient demonstrates rudimentary levels of intellectual and social comprehension and is paraparetic or paraplegic.

Epidemiology

The progression of HIV-1 infection to ADC is related, in general, to the level of immunosuppression in the patient. In early disease with opportunistic infections, approximately 10–30% of patients exhibit ADC stage 1, while 5–15% exhibit severe neurological disturbances (stage 2–3). In contrast, in the late stages of infection the majority of patients with AIDS show severe disability (stage 4).

Pathology

Pathological changes in the CNS of patients with ADC are most prominent in the subcortical regions, correlating with the observed subcortical clinical abnormalities. The most common changes include: (1) pallor of the white matter and demyelination; (2) gliosis, necrosis and mild neuronal loss; (3) multinucleated giant cells, which may be observed in the later stages of disease; and (4) spongiform changes, which are related to severity of dementia.[105]

Clinical features

Patients with ADC show distinct cognitive changes associated with subcortical, as opposed to cortical, changes. There is general mental slowing, including apathy, impaired concentration and features associated more with depression than CNS infection. Confusion, hallucinations, impaired memory and problem-solving deficiencies are common prior to obvious dementia. ADC may progress in steps or with sudden deterioration associated with systemic infection.

Diagnosis

In patients with ADC, computed tomography and magnetic resonance imaging show cerebral atrophy, although such a finding is non-specific. The CSF of ADC patients contains HIV-specific cytotoxic T cells, increased protein, oligoclonal bands and soluble intercellular adhesion molecule 1 (ICAM-1), which may serve as a marker for disease.[106]

Prevention and control

Zidovudine (formerly AZT) has been shown to improve neuropsychological performance and reduce the incidence of ADC, as has the antiinflammatory alkaloid cepharanthine.[107] Psychiatric disorders such as mania may be treated with lithium, as in non-infected patients.

CNS syndromes in children

Mother-to-child transmission accounts for 80% of HIV infections in children. Infected children present with encephalopathy, either progressive or static, that may be seen from the age of 2 months. The children with progressive encephalopathy become inactive and may develop paralysis and, if untreated, die within 1 year. The CSF may show an increased protein concentration and high levels of HIV-specific antibodies. Antibody levels in the serum (as a means of diagnosis) may be difficult to interpret owing to the presence of transplacental maternal antibodies. The brains of HIV-infected children are atrophic and contain perivascular inflammation, and the small vessels show calcification.

Opportunistic viral infections of the CNS

Although a variety of opportunistic CNS infections occur with HIV infection, only viral infections will be considered in this section. The major infections are observed with JC virus that gives rise to PML (see under Papovaviruses) and cytomegalovirus (CMV). PML occurs in 2–5% of patients with AIDS; its effects are observed as dementia and/or focal neurological signs. Herpesvirus infections, in the form of CMV, VZV and HSV-1 and -2, give rise to 'secondary viral encephalomeningitides'. CMV may result in encephalitis and retinal infiltration, which is observed in approximately 20% of patients with AIDS. As a result of immunosuppression VZV may be reactivated, giving rise to neurological syndromes such as hydrocephalus or ventriculitis. Like VZV, Human cytomegalovirus (HCMV) causes disease after both primary and recurrent infections. The former is more serious, particularly in pregnant women, who may transmit the virus to their offspring, with a high risk of intellectual impairment and deafness. Various experimental vaccines are in development, ranging from live, attenuated HCMV, subunit envelope glycoprotein, poxvirus vectors with CMV genes inserted, and plasmid DNA.

RHABDOVIRIDAE

The family Rhabdoviridae is divided into six genera, including *Lyssavirus*, which contains rabies virus, and *Vesiculovirus*, containing vesicular stomatitis virus (VSV). The name Rhabdoviridae is derived from the Greek 'rhabdos', meaning rod, reflecting the rod or bullet-shaped virus.

Vesiculovirus

While not commonly associated with neurological disorders, *Chandipura*, a vesiculovirus was associated with an outbreak of encephalitis in India in 2003 affecting 349 children with 55% mortality.[108]

Lyssaviruses

The name of this genus is derived from the Greek 'lyssa', meaning rage or frenzy, and includes rabies virus. The Duvenhage and Mokola viruses of this genus are also associated with human disease.

The rabies virus has a helical nucleocapsid with a lipid bilayer from which protrude 10-nm protein spikes. Of the five proteins identified, those designated G and N have been characterized most

extensively. The G protein is the only viral protein that induces virus-neutralizing antibody and is also a target for T helper and T cytotoxic lymphocyte reactivity. The importance of such antigenic determination offers an approach for the development of vaccines.

Rabies infections have been recorded since before 2000 BC and mentioned in historical documents of Democritis, Aristaeus and Artemis. Six important events in the history of rabies since the 1880s include the application of the human rabies vaccine (1885) and the finding of the pathognomonic Negri bodies for diagnosis (1903). In the 1940s a mass application of potent rabies vaccine for dogs was introduced, which greatly diminished the spread of disease. More recently the introduction of oral vaccination of foxes has resulted in the virtual elimination of rabies from Switzerland. Rabies hyperimmune antiserum was used in addition to the human vaccine regimen (1954) and the adaptation of rabies virus to cell culture and the development of a fluorescent antibody test for diagnosing infected animal brains (1958) have resulted in a dramatic improvement in the control of the disease.

Epidemiology

Rabies virus is capable of infecting all warm-blooded animals, but there is a hierarchy for susceptibility. Most susceptible are foxes, coyotes, jackals and wolves. The opossum is the least susceptible species. Moderately susceptible animals include dogs, the most frequent vector for transmission to humans, as well as cats, raccoons and skunks. An increasing source of rabies is observed in bat populations[109] and accounts for approximately 10% of rabies-infected animals in the USA. The epidemiology of human rabies parallels that in the animal population. The annual number of deaths worldwide caused by rabies is estimated at approximately 55 000 by the World Health Organization. A higher incidence is observed in areas where public health programmes are not implemented, such as in India and Mexico where the incidence is 3.3 cases per 100 000. Rabies has recently been reported following organ transplantation in four patients.[110]

Pathogenesis

The major route of infection is invariably via the bite from a rabid animal, although transmission by aerosols and as a result of corneal grafts must be taken into account. Once introduced, rabies virus is quickly sequestered. It was thought that the virus stayed in the nervous tissue close to the wound site, although later studies indicated that the virus replicates in muscle tissue before progressing to the peripheral nervous tissue via the neuromuscular connections. That rabies virus travels to the central nervous tissue via the nerves has been demonstrated experimentally: when the sciatic nerve was severed prior to injection of rabies virus in the foot of an animal, disease was prevented. The incubation period of the disease varies and may be as short as 2 weeks but is more commonly 1–3 months, and in a few cases more than 1 year.[111] Although it is widely accepted that the incubation period is related to the distance between the site of the bite and proximity to the CNS, a study by Dupont and Earle[112] did not support this view.

Pathology

Human rabies pathology, apart from the pathognomonic Negri body, consists of perivascular cuffing, some neuronophagia and limited neuronal necrosis. The limited pathology does not match the marked symptoms of hydrophobia, aerophobia, excitation and coma. There is pathology in other organs, and Negri bodies have been found in the cornea and adrenal glands.

Clinical features

Development of infection depends on the severity of the exposure, the site of the bite and possibly other factors. Neurological findings may be classified as either 'furious' or 'paralytic' and are not exclusive. Furious rabies is far more common and is characterized by spasms in response to tactile, auditory, visual and olfactory stimuli (e.g. aerophobia and hydrophobia). Such symptoms alternate with periods of lucidity, agitation, confusion and autonomic dysfunction. The alternative form of paralytic rabies ranges from paralysis of one limb to quadriplegia. Disease progresses to coma with neurological complications associated with abnormal hormonal homeostasis, alterations in temperature and inability to control blood pressure.

Diagnosis

Clinical diagnosis of rabies may be difficult in patients presenting with a paralytic or Guillain–Barré-like syndrome, and the World Health Organization (WHO) Committee on Rabies[113] has emphasized that rabies must be included in the differential diagnosis of all persons presenting with neurological involvement.

The laboratory diagnosis of rabies may be performed by fluorescent antibody techniques, on smears or frozen sections, and by the use of ELISA. A rapid rabies enzyme immunodiagnosis assay allows the antigen to be visualized by the naked eye and is thus a test that can be carried out in the field (with a special test kit). Molecular tests, such as the polymerized chain reaction, are available. Virus isolation can be performed using a murine neuroblastoma cell line (NAC1300), which reduces the time taken for diagnosis by 2 days.

Prevention and control

Rabies is 100% preventable and mortality can be reduced by preventing exposure to the virus, aborting infection and thereby preventing illness, or curing clinical disease. The WHO committee has stressed the importance of the adoption and establishment of international and regional surveillance systems in combination with dog control. In over 80 countries rabies is prevalent in dogs, the most dangerous reservoir. Each year approximately 4 million people in these areas receive treatment after exposure to rabies and in 99% of all human cases the virus is transmitted by dogs. Furthermore, 90% of people who receive postexposure treatment live in areas of canine rabies.[114]

Vaccination

The control of rabies is through oral immunization of domestic and, more recently, wild animals. Recombinant vaccines that make use of poxvirus, baculovirus and adenoviruses are possible. The vaccines available for human immunization are: (1) brain tissue vaccine (possible side-effects of autoreactivity to brain tissue); (2) purified duck embryo vaccine inactivated with b-propiolactone; and (3) tissue culture vaccines. For animal vaccination, nervous tissue-derived virus has been shown to be effective in mass vaccination of the canine population in North Africa. In contrast, cell culture-derived virus (either inactivated or

modified live virus) for canine rabies has been used in a combined vaccination programme with distemper, hepatitis, parvo and leptospirosis vaccines. Combined vaccines with foot and mouth vaccine are used for cattle, sheep and goats. For feline control, the rabies vaccine is combined with panleucopenia virus, feline calicivirus and feline parvovirus vaccines.

The vaccine virus is collected from infected human diploid cells (HDC), inactivated, and stored in a freeze-dried state. The vaccine (HDCV) contains no preservatives and must be used immediately once reconstituted.

Monoclonal antibodies

Post exposure treatment with murine monoclonal antibodies, and more recently murine–human chimeric antibodies and humanization of monoclonal antibodies, offers a more specific treatment regimen.

Interferon and interferon inducers

Administration of recombinant α-interferon with vaccines decreases rabies virus in subhuman primates. Exogenous interferon has already been shown to be effective in a patient given a corneal transplant from a patient with rabies.

TOGAVIRIDAE

The family Togaviridae comprises the genera alphaviruses and is based on various characteristics such as size, mode of replication and transmission by mosquitoes. The name togavirus is derived from the structure of the virus which consists of a ribonucleic acid within a lipid envelope (*Latin toga* = coat).

Alphaviruses

The knowledge of the structure and replication of alphaviruses has been based on the prototype virus Sindbis (SIN) as well as Semliki Forest viruses (SFV) which are discussed briefly in this section. Of the alphaviruses that are important encephalitogenic agents, eastern equine encephalitis (EEE), Venezuelan equine encephalitis (VEE) and western equine encephalitis (WEE) viruses are the most important. However, chikungunya virus (CHIK) infection is also known to induce neurological complications (Table 48.3). Other members such as Ross River Virus and O'nyong'nyong induce polyarthritis.

Chikungunya

The word chikungunya, meaning 'to contort or bend', was used by a tribe in Tanzania to describe the clinical manifestations (arthritis) of a virus epidemic of 1952–1953. Because this virus invariably results in crippling arthritis, CHIK infection was probably responsible for the epidemic in 1779 in Indonesia.

Epidemiology

CHIK is found in Africa, including Tanzania, Zimbabwe, Transvaal, Zambia and the Congo, and India, Sri Lanka and South-east Asia, including Vietnam and Thailand.[115] More recently, an outbreak in 2006 on Reunion Island led to over 200 deaths[116] and it has re-emerged in Malaysia in 2007.[117] The disease is transmissible by mosquitoes. *Ae. aegypti* and various *Culex* species are the vectors in urban epidemics in Asia. In Africa, the vector involved in forest areas is *Ae. africanus* and in Sudan *Ae. leuteocephalus*.

Clinical illness

The disease is biphasic. In the first phase, symptoms include fever and severe joint, limb, and spine pains. This phase can last 6–10 days. The second phase occurs after a febrile period of 2–3 days and is associated with an irritating maculopapular rash over the body, particularly on the extensor surface of the limbs. Joint pains may persist occasionally, without fever, for up to 4 months. In some cases myocarditis and peripheral circulatory failure have been seen. In this second phase, encephalitis and manifestations of neurological involvement are occasionally observed.[118] The mortality rate is estimated at 0.4%, but in patients under 1 year old it may be as high as 2.8% and similarly in those aged over 50 years the death rate may increase.

Diagnosis

Definitive diagnosis is by specific serological analysis such as HI, CF and ELISA and RT PCR[119] although the combination of febrile illness and rheumatic manifestations in a patient returning from sub-Saharan Africa or parts of Asia is a characteristic feature of CHIK infection.

Management and control

Supportive care for patients with CHIK infections is important with respect to the arthralgia. In severe cases, chloroquine phosphate may be administered. Inactivated virus vaccines have been shown to be effective but vaccination is restricted to laboratory workers, although a live attenuated virus is undergoing trials in experimental animals. The live CHIK vaccine TSI-GSD-218 has been reported to be promising in humans.[120]

Eastern equine encephalitis

Epidemiology

Eastern equine encephalitis (EEE) was first isolated in 1933[121] and retrospective studies of epidemics are suggestive of EEE as early as 1931 EEE virus is endemic along the eastern coast of the USA, Canada, Trinidad, Guyana, Mexico, Panama, Brazil, Peru, Columbia and Argentina. In most areas the virus is transmitted between marsh birds and Culiseta melanura mosquitoes, which do not feed on large vertebrates. With alterations in the conditions of the marshes or swamps, the virus is transmitted to other host mosquitoes that feed on small rodents, reptiles and amphibians. *Culex* species are considered to be the vectors for transmission of EEE virus in South America.[122] Human and equine cases are seen only when the spread becomes endemic.

Pathogenesis and pathology

Viraemia occurs soon after infection and may be accompanied by a febrile prodrome. Virus gains access to the nervous system and results in severe encephalitis. HI and neutralizing antibody are present in samples taken during the first 3–5 days of encephalitis.[123] However, this effective humoral immune response does not eradicate the virus from the brain, and neural destruction contin-

ues through direct cytopathic effect, inflammatory damage and vasculitis. The primary pathological features of EEE are confined to the CNS.[124] Lesions are scattered throughout the cortex and are particularly severe in basal ganglia and the brainstem; the cerebellum and spinal cord are minimally involved. Virions are present in oligodendrocytes and there is extensive neuronal damage as well as thrombosis of arterioles and venules. Inflammatory cells are widespread in lesions, perivascular areas and meninges. The cells are predominantly polymorphonuclear in the first week, but later mononuclear cells may predominate.

Clinical illness

Human infections are rare. In children the ratio is estimated to be from 2 : 1 to 8 : 1; in adults it is from 4 : 1 to 50 : 1. In severe cases the onset is abrupt, with high fever followed by all the features of meningitis, including coma, convulsions and neurological damage. Age is not a major factor in mortality but severe sequelae are more pronounced in children under 10 years of age.

Diagnosis and investigation

The abrupt onset of a severe febrile CNS illness is suggestive of this disease, and death in horses associated with hot, wet summers and the proximity of salt marshes give further credence to EEE infection.

The virus may be isolated from serum during the initial infection but most cases are diagnosed by testing paired sera in conventional HI or NT. Very high CF titres occur in most people convalescing from EEE. IgM antibodies are readily detected in acute sera by ELISA.[109] Virus may be isolated at autopsy.

Prevention and control

A vaccine inactivated by formalin treatment is available for use in laboratory workers or others at high risk of exposure. The same vaccine is used to protect endangered whooping cranes, which are susceptible to lethal visceral infection.[125]

Venezuelan equine encephalitis

This virus was first isolated by Beck and Wyckoff[126] from equine encephalitis epizootics in Venezuela. Viral strains belonging to the VEE group are pathogenic for horses and have been involved in human infections; the most important are designated subtype 1, variants A, B and C.

Epidemiology

VEE is endemic in Central and South America and parts of North America, and has occurred particularly in Venezuela, Colombia, Equador, Panama, Brazil, Mexico, Florida, Texas and Trinidad. Mosquitoes of both the *Aedes* and *Culex* genera are involved. *Cx. melanoconion* and *Deinocereites* species are the main vectors in rodent-to-rodent transmission. Horses are a major reservoir of infection and transmission of the virus can occur from horse to horse as well as transplacentally. More than 150 different animal species, including domestic and wild dogs and pigs, have been found to be infected with this virus. Birds have low viraemias but could infect mosquitoes, which may spread the disease and cause new epidemics.

Pathogenesis

Conventional serological methods show that the viruses grouped into the VEE complex are all closely related. The viruses in this group were further divided into subtypes and variants by Young et al.[127] using the HI test, and it seems that these minor distinctions are responsible for the fundamental differences in pathogenicity and biochemical significance.

The earliest humoral immune response appears around day 5 in hamsters and is directed to virion surface component. An epitope on E2 is shown to produce the most dominant protective neutralizing antibodies. In the mouse model, cell transfer experiments suggest that T helper lymphocyte activity is important in protection.

Clinical illness

The clinical disease in humans resembles an influenza-like syndrome, with fever lasting for 1–4 days. Occasionally this is complicated by shock and coma, in which case there appears to be widespread destruction of lymphoid tissues. Meningoencephalitis can occur, particularly in children, but is much less common in adults. Approximately 4% of patients develop CNS infections with convulsions, coma and paralysis. The overall mortality is <1% but in children with meningitis this may rise to 20% and is more frequent in undernourished populations and in the absence of medical care.

VEE should be suspected in any person suffering from febrile myalgic illness 6 days after being exposed to an enzootic biotope.

Prevention and control

Patients who develop CNS disease require anti-convulsants. Vaccinia virus recombinants containing genes encoding the VEE virus structural gene regions (C-E3-E2-6 K-E1) protect mice against virulent VEEV, but provide only partial protection against air-borne challenge. VV recombinants encoding the structural genes E3-E2-6 K-E1, E3-E2-6 K or 6 K-E1 also demonstrate the importance of E2 in protection. The experimental vaccine TC-83 is a live attenuated vaccine and the C-84 a formalin inactivated vaccine based on TC-83. Alpha interferon and the interferon producer PolyICLC have proved useful for postexposure prophylaxis.

Western equine encephalitis

Epidemiology

WEE virus is found in the USA but human infections are limited to the western two-thirds of the country. It is also found in Canada, particularly Manitoba, Saskatchewan, Alberta and British Columbia, and in South America. The disease is transmitted by various species of mosquito vectors. These include *Cx. tarsalis, Culiseta melanura* and other mosquitoes of these two genera. *Aedes* and *Anopheles* species may be slightly involved. The natural cycle is between *Cx. tarsalis* mosquitoes and wild birds. *Culex* mosquitoes readily feed on large vertebrates, so equine and human cases occur annually. The number of cases is dependent on rainfall because mosquito breeding is largely in ground pools.

Pathogenesis and pathology

The pathogenesis of WEE virus in humans resembles that of EEE. However, WEE is less neuroinvasive and neurovirulent, in both humans and laboratory animals. Infected cynomolgus macaques show multiple foci of necrosis, and cellular infiltrate,[128] found predominantly in areas such as the striatum, globus pallidus, cerebral cortex, thalamus and pons. In some areas polymorphonuclear infiltrates occur. There is widespread perivascular cuffing and meningeal reaction. The pathogenesis in rodents is similar to that of other alphaviruses.

Clinical illness

WEE is characterized by sudden onset of fever, headache and general symptoms of meningoencephalitis which can be clinically severe but rarely fatal. Neurological and psychological sequelae are seen primarily in children under 2 years of age. The ratio of inapparent to apparent clinical infection is estimated at 50 : 1–8 : 1 in children and more than 1000 : 1 in adults.

Prevention and control

Social activities such as screening of windows and doors and avoiding external pursuits are necessary to avoid infection. An inactivated vaccine is available for workers at risk from infection. More recently a DNA vaccine plasmius pVHX-6 has shown some efficacy in rodent infections.[115]

Semliki Forest virus

Although SFV has been assumed not to infect humans, the death of a scientist from whom SFV was isolated may suggest otherwise. More recently mild febrile illness has been reported in humans in Africa and was suggested to be due to SFV. The fact that SFV is known to induce neurological disease in experimental animals, with perivascular infiltrates and demyelination (Figure 48.4), warrants mention of this virus in this chapter. SFV was originally isolated in Uganda in 1944. Experimentally the virus induces encephalitis in a variety of laboratory rodents. Infection of mice with the A7 or M9 strains of SFV gives rise to lesions of demyelination in the CNS.

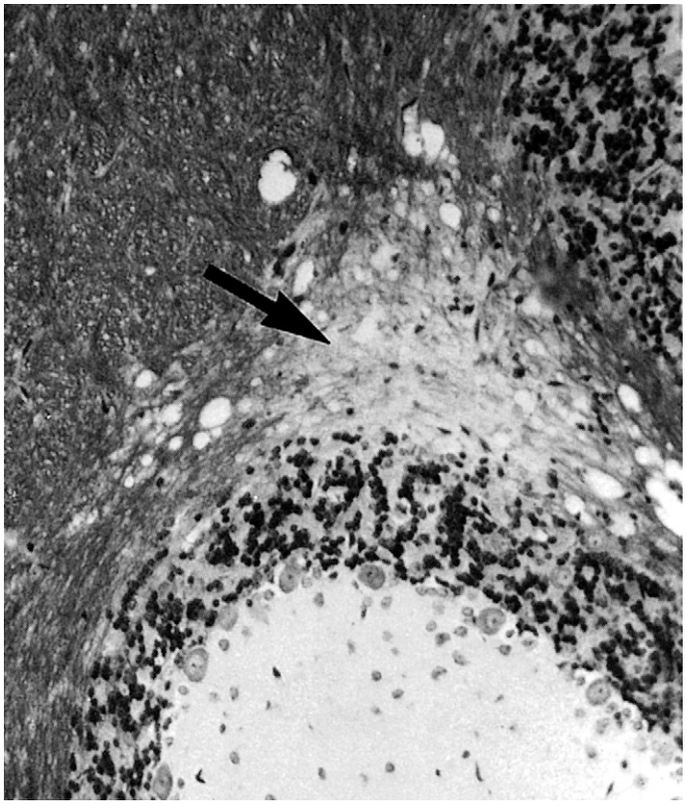

Figure 48.4 Demyelination (arrow) within the cerebellum of a mouse infected with Semliki Forest virus.

RUBIVIRUSES

History

The sole member of the rubivirus genus, rubella virus, was initially described in the early 1800s.[129] Although it is primarily a childhood illness, the disease is endemic worldwide and serious complications such as encephalomyelitis and post-infectious encephalopathy have been reported in adults and children. The large number of studies by German scientists have given rubella virus the synonym 'German measles', although the organism is unrelated to measles virus.

Epidemiology

Unlike most other togaviruses, rubella has no known vertebrate host and the only natural reservoir is humans. Rubella virus infections are found worldwide and in the temperate regions the epidemics occur in late winter and early spring. Periods of increased incidence every 6–9 years occur, with major epidemics every 10–30 years. Such epidemics are related to the susceptibility of individuals and factors that increase the transmission. Infection is generally acquired in childhood and approximately 60% of the population have antibodies by the age of 14 years. With the introduction of the rubella vaccine in 1969,[129] the incidence of rubella has decreased, although the seroprevalence rates approach 90–95%. The incidence of infection is higher in the tropics. Post-infectious encephalopathy or encephalomyelitis is estimated to occur in 1 in 6000 cases of natural rubella.

Pathogenesis and pathology

The pathology resulting from rubella infection is dependent on the mode of infection, i.e., whether it is due to maternal–fetal transmission or is acquired postnatally. The effect on the fetus depends on the gestation period. In the first trimester there is a high risk of infection and developmental growth is arrested, although the mechanism of damage is unknown. Maternal infection after the first trimester does not appear to damage the fetus, although the risk of congenital disease is known to increase before birth. Delayed neurological disease has been reported following late-onset rubella infection and may be associated with either congenital rubella or a rare complication of natural rubella acquired in childhood.

The pathological features of CNS involvement, particularly in the adult, include perivascular lesions of mononuclear cells and

demyelination. In childhood encephalopathy, neural degeneration is more apparent than in the adult, whereas perivascular infiltrates and demyelination are less common. The suggestion that autoreactivity may play a role in the pathology of late-onset rubella encephalitis, often referred to as progressive rubella panencephalitis, chronic progressive panencephalitis or non-congenital rubella, comes from studies in which lymphocytes proliferate in response to CNS proteins such as myelin basic protein.[130]

Clinical features

Rubella infection in early childhood or adult life is usually mild and asymptomatic. Symptoms of post-infectious rubella encephalopathy are observed shortly after the onset of the rash of typical rubella. The clinical features of encephalitis are similar to those of other forms of encephalitis, including headache, vomiting, stiff neck, fevers and convulsions, and altered levels of consciousness. The mortality rate is approximately 20%, with death occurring within a few days of the onset of symptoms. The late-onset rubella encephalitis is similar to other slow virus infections of the CNS. Following a prolonged asymptomatic period, neural degeneration is observed, usually in the second decade of life. Symptoms include behavioural changes, ataxia and seizures. Death usually results within 8 years of onset.

Diagnosis

The common symptoms of rubella, such as low-grade fever and maculopapular rash, should not be confused with other such infections. Confirmation of rubella may be made following isolation of the virus or by specific serological assays such as ELISA. The CSF cell count of patients with rubella encephalitis is high ($50/mm^3$); the majority of the cells are lymphocytes. The electroencephalogram is abnormal, oligoclonal bands are observed in the CSF[131] and rubella virus may be isolated.[132]

Management and prevention

Treatment of rubella encephalitis with corticosteroids has been reported.[133] Rubella vaccines, developed in the 1960s, have been used to vaccinate both school-aged children (USA) and women of child-bearing age (UK) in an attempt to decrease the incidence of congenital rubella infection. The attenuated viruses used are capable of infecting the fetus and thus vaccination of pregnant women is not recommended. More recently the policy of including the combined MMR vaccination procedure for all schoolchildren has been implemented in the UK. Future development of subviral vaccines may be necessary to counter the side-effects of vaccination using attenuated virus.

PRION DISEASES

Several so-called 'slow virus infections' of the CNS, although transmissible, are not conventional virus infections but rather classified as prion diseases or subacute spongiform encephalopathies (Table 48.7).

Prion diseases have a unique characteristic in being devoid of nucleic acid and yet able to transfer disease. Transmission of disease does not occur if the agents are treated with proteases.

Table 48.7 Prion disease of humans and animals

Host	Disease
Humans	Kuru
	Creutzfeldt–Jakob Disease, Classic (CJD)
	Variant Creutzfeldt–Jakob Disease (vCJD)
	Gerstmann–Sträussler–Scheinker Syndrome
	Fatal familial insomnia
Animals	Bovine spongiform encephalopathy (BSE)
	Chronic wasting disease of mule deer and elk
	Scrapie
	Transmissible mink encephalopathy
	Feline spongiform encephalopathy
	Ungulate spongiform encephalopathy

Additionally, attempts at molecular cloning are negative and nucleic acid antagonists have been shown to be ineffective. The term prion is derived from *pr*otein and *in*fection, meaning that the infectious agent is protein devoid of nucleic acid. This 'protein only' hypothesis is still under debate.

Of particular importance is the presence of a normal form of the protein found on all cells, particularly neurones. The two forms of prion proteins (PrP) (normal and infectious) are identical in terms of amino acid sequences but differ in their conformations. Furthermore, the normal protein is broken down by enzymes, whereas the abnormal prion protein (PrP^{sc}) is resistant to attack by enzymes and found in the CNS only during disease where the protein accumulates in the cell.

Kuru

Kuru was restricted to the population of villages in the highland of Papua New Guinea. The disease, which means shaking or shivering in the Fore language, is characterized by tremors that progress to lack of motor control and complete cerebellar ataxia. The clinical course of the disease generally results in death within 1 year of onset, although prolonged disease has been reported.[134] The disease was more common in children and females than in males, and was thought to be due to the practice of certain tribal rituals. The changes in ritual cannibalism and treatment of corpses have halted the contact of persons with infected brain tissue, resulting in a virtual cessation in the incidence of disease. In a recent review 11 patients were identified with Kuru between 1999 and 2004; the incubation times have been suggested to be as long as 56 years.[135]

The pathological picture is restricted to the CNS and is characterized by diffuse neuronal degeneration and astrocytic hypertrophy. The term 'spongiform encephalopathy' is derived from the large vacuolation of the large neurones of the striatum. In many cases amyloid-containing plaques are observed and electron microscopy reveals scrapie-associated fibrils common to other diseases in this group.

Creutzfeldt–Jakob disease and Gerstmann–Sträussler–Scheinker syndrome

Patients with Creutzfeldt–Jakob disease (CJD) present with rapidly progressive dementia and motor dysfunction; like Kuru, it is

usually fatal within 1–2 years following onset. The incidence of CJD is low (prevalence of 1 per million) and is generally sporadic, although there is evidence for a familial trait in 10% of all cases. Mutations in the natural PrP segregate with disease. The disease is transmissible experimentally, as shown in laboratory animals,[136] or as a result of 'accidental transmission' to humans following surgery.[137] Although the average age of CJD onset is in middle to late life, the disease has been described in young (4–19 years) patients undergoing growth hormone therapy. In these transmissions the disease resembled Kuru rather than typical CJD, suggesting that Kuru may have originated in New Guinea as a result of contamination of tissue from a patient with CJD.

Gerstmann–Sträussler–Scheinker syndrome (GSS) is a variant of CJD in which patients present with progressive cerebellar ataxia, giving rise to a longer period from onset to death compared with CJD. Again, several mutations in the PrP have been described and the disease is transmissible to laboratory animals.

Prevention and control

The resistance of the CJD/GSS prion to common sterilization procedures, such as boiling or the use of ultraviolet light, has resulted in a change in operating procedures and the use of hypochlorate and sodium hydroxide for sterilization.[138] To date, no treatment for the human diseases has been effective. Future therapeutic regimens will possibly include drugs that interfere with the PrP^{sc}, preventing it from accumulating in the cell, or gene therapy to switch off production of the protein.

More recently, studies directed towards blocking infective prion protein migration have been seen to be dependent on B-cells. In addition, therapeutic strategies using antibodies directed against the conformational forms of PrP are currently under investigation.

Animal prion diseases

Scrapie was observed in the 1930s following the use of louping ill virus vaccine produced in scrapie-contaminated brain tissue, although the disease has been recognized in sheep breeders for more than two centuries. The disease is a chronic disease in which affected animals present with progressive ataxia tremor and wasting. The name 'scrapie' is derived from the necessity of animals to rub or scrape as a result of the disease. Susceptibility to scrapie is dependent on the strain of sheep and is linked to polymorphisms in ovine PrP.

The disease, like the human prion infections, is characterized histologically by the presence of vacuolated neurones and spongiform changes, and may be induced experimentally in laboratory mice and guinea pigs. The use of transgenic mice, in which mutations in the PrP are deliberately introduced with resulting neurological defect, supports the role of this protein in initiating disease. Furthermore, transgenic mice lacking the gene that codes for the natural PrP are resistant to infection with the scrapie PrP.[139] The use of experimental prion disease has allowed the investigation of potential therapies and, although no effective treatment is available, the use of amphotericin B has been shown to reduce the concentration of scrapie PrP during the preclinical phase and to prolong the incubation period of the disease.[140]

Transmissible mink encephalopathy, which is very similar to scrapie, is spread through mink colonies as a result of fighting and cannibalism, and is thought to have originated from contaminated food derived from cattle. Infected tissue can transfer disease. Likewise bovine spongiform encephalopathy, first described in England in 1986, was possibly a result of feeding scrapie-contaminated food.[141]

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