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CHAPTER 32

Neurologic Disorders in Cheetahs and Snow Leopards

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Worldwide, cheetahs *(Acinonyx jubatus)* in captivity develop a number of health problems rarely observed in free-ranging cheetahs and unusual in other species, especially felids. These include diseases of the central nervous system (CNS) as well as non-CNS diseases. Among the neurologic diseases, cheetah ataxia, caused by a degenerative spinal cord disorder affecting young and adult cheetahs, represents a serious threat to a sustainable captive cheetah population in Europe. Furthermore, several cases of feline spongiform encephalopathy have been diagnosed in European cheetahs. Although the disease has been reported in several large cat species, the relatively high incidence in cheetahs suggests that they may be more susceptible than other zoo felids. In North America, leukoencephalopathy is an emerging neurologic disease of unknown cause and has had a major impact on the Species Survival Plan (SSP) captive breeding program through loss of important founders.

In snow leopards (*Uncia uncia,* formerly *Panthera uncia*), two neurodegenerative diseases characterized by spinal cord white matter degeneration and neuronal chromatolysis, respectively, have been observed in cubs born in European zoologic institutions. Although somewhat similar to the cheetah myelopathy, these disorders appear to occur only sporadically and do not seriously impact the captive breeding population.

This chapter is restricted to the neurologic disorders that have been observed specifically in cheetahs and snow leopards. However, further classic causes of neurologic diseases, such as canine distemper virus infection, tumors, and degenerative spinal diseases involving intervertebral disc diseases and spondylosis, must be considered as possible differential diagnoses, as in any species.

NEUROLOGIC DISEASES IN CHEETAHS

Cheetah Myelopathy

The cheetah myelopathy is a new and unusual neurologic disease characterized by degenerative lesions of the spinal cord and causing ataxia and paresis. It has emerged in the past 20 years in the European Endangered Species Program (EEP) cheetah population and represents a serious threat to a sustainable captive European cheetah population.[28] To date, more than 60 cases have been registered in at least 16 different locations in Europe and in Dubai (United Arab Emirates), resulting in the euthanasia of numerous cheetahs that were part of the EEP breeding program. This disease accounts for 25% of all deaths in the European cheetah population and represents a limiting factor in the growth of the European captive population. Cheetahs of every age group are affected, and often several or all cheetahs of the same litter will eventually develop the disease, either simultaneously or successively over several months or years.

The onset of the myelopathy may be peracute, in many cases subsequent to a stressful event (e.g., hand capture of cubs for deworming or vaccination), and is often temporally associated with clinical herpesvirus infection in dams and littermates. The course of the disease is variable, from rapidly progressive ataxia to a slower development that may include stabilization and acute relapsing episodes.

The etiology of the cheetah myelopathy is still unknown, and several causes have been considered, including genetic, environmental, toxic, nutritional (especially copper), and viral factors. Further characterization

of the lesion using molecular biologic techniques, as well analytic and epidemiologic investigations of the environmental status of captive cheetahs (e.g., nutrition, standard medication) are in process and may provide clues to the pathogenesis of this unique disease entity.

Clinical Signs

In cheetah cubs and adults, onset of ataxia or paresis is usually peracute to acute and may occur spontaneously or after a stressful event for the individual or the litter. Events that have been described include hand capture, restraint, and transport for examination or treatment and translocation to a new enclosure. In cubs, clinical signs are often preceded by sneezing and ocular discharge typical of feline herpesvirus type 1 (FHV-1) infection in the dam or littermates.

Whereas clinical onset always starts with pelvic limb ataxia/paresis, disease progression and severity of the symptoms vary considerably among individuals. The clinical neurologic signs indicate an upper-motor-neuron lesion and proprioceptive deficits, with involvement of the long-tract sensory pathways in all cases. After onset of hind limb ataxia, sometimes with involvement of the forelimbs, simultaneous and subsequent recorded symptoms include paresis, staggering, knuckling, swaying high-stepping gait (hypermetria), falling over while turning, dragging of the paws or hind limbs, difficulty rising to a standing position, and finally, in the most severe cases, recumbency. In most cases these clinical symptoms are accompanied by slowly developing wasting (disuse atrophy) of the hind limb muscles. In the standing position the hind legs are typically placed more laterally than normal (abducted) in a base-wide stance, and support of the tail is reduced. In some cases, urinary incontinence was indicated by urine soiling of the perineum. Tremor of the head was observed in some advanced cases.

As previously stated, the course of the disease is variable; the initial ataxia and paresis may develop rapidly to hind limb paralysis and recumbency or may progress slowly and stabilize with mild symptoms for several months or years. Although clinical improvement after tentative treatment was observed in a few cases, relapsing bouts of ataxia or paresis eventually reappeared in most cases. Throughout the disease progression, the affected cheetahs had a normal appetite, did not seem to experience pain, remained alert, and responded to visual and auditory stimuli.[14,26,27,29]

Epidemiology

To date, more than 60 cases have been recognized in at least 16 different institutions, including zoologic parks and private owners. The first cases of cheetah ataxia were described in South Africa in 1981,[3] but since then, the syndrome has been reported only in Europe and the United Arab Emirates. Some anecdotal evidence from wild-caught cubs in Namibia has been reported.[9] All affected cheetahs have been captive-bred in a European, Middle Eastern, or South African institutions from captive-borne or wild-caught parents, belonging to the South African subspecies *(Acinonyx jubatus jubatus)* or East African subspecies *(Acinonyx jubatus soemmeringii).* All affected cheetahs were born from parents without prior clinical neurologic signs. Some of the parents were known to have produced other healthy litters before or after the ataxic litters, and individual parents developed ataxia themselves at a later stage. Often, several or all cubs or siblings from a same litter were affected, with symptoms starting simultaneously in all individuals or developing successively over several months or years. There is no apparent gender predilection, and the age of onset of the ataxia ranges from 2.5 months to 12 years.

The captive management and holding conditions vary among institutions that have reported ataxic cheetahs, and no "common denominator" could be identified to date. At most facilities, the cheetahs live in enclosures of varying size with natural soil, usually grassy areas, and heated indoor pens. Ataxia has been recorded at institutions keeping only one pair of animals, as well as institutions holding several cheetahs together or in separated paddocks, usually adjacent to each other. In most institutions the cheetahs are housed in visual or auditory range of unrelated cheetahs or other species. Feeding regimen is mostly composed of a daily meat ration (rabbit, goat, chicken, calf), usually supplemented with a vitamin-mineral additive. In a few institutions the meat is attached to a ski lift–like mechanism that provides a simulated hunting situation, encouraging frequent physical exercise.

Vaccination and deworming of the young and adult cheetahs are routine in all institutions that have reported ataxic animals. A few cubs developed clinical signs before vaccination, but most of the affected cheetahs were routinely vaccinated against feline parvovirus (FPV), FHV-1, and feline coronavirus (FCV) using inactivated or modified live vaccines.[14,26,29] Some individuals were also vaccinated against feline leukemia virus (FeLV). Known products used for deworming include ivermectin, mebendazole, fenbendazole, febantel, pyrantel pamoate for cubs, pyrantel tartrate, and fipronil.

Clinical Pathology and Ancillary Procedures

Thorough clinical investigations have been carried out in most reported ataxia cases. Although the cheetah

myelopathy has often been temporally associated with clinical herpesvirus infection in cubs, no definitive etiologic factor could be determined.[14,26,27,29] Plain radiographs, contrast myelography, and magnetic resonance imaging (MRI) were normal. No abnormalities were detected in the cerebrospinal fluid (CSF) or in the urine.

Hematology and blood chemistry values were always within the normal range. Serum copper values (6-22 μmol/L) revealed no significant difference between ataxic cheetahs and domestic dogs and cats. Furthermore, there was no significant difference in liver copper levels between ataxic cheetahs (4.6 ± 3 ppm) and cheetahs without CNS disease (4.3 ± 1.5 ppm). However, a significant difference in liver copper has been shown between cheetahs and dogs and cats, but not a wild lynx.[29] This difference might be explained by the domestic animals being mostly fed with supplemented commercial food.

Serologic examinations revealed negative or low titers against feline infectious peritonitis (FIP), canine distemper virus (CDV), FPV, FCV, FeLV, feline immunodeficiency virus (FIV), Borna disease virus (BDV), encephalomyocarditis virus, tick-borne encephalitis virus, mucosal disease complex virus, Teschen-Talfan disease virus, *Listeria monocytogenes,* and *Chlamydophila psittaci.* Antibody titers against FHV-1 and *Toxoplasma gondii* were elevated in several cases but negative in another institution, although the cubs had shown ocular discharge and mucopurulent conjunctivitis.[14] The tests for FIP were also negative.[26]

A herpesvirus was isolated from the eyes and nose of one cub with ocular discharge, and the gene sequence showed 99% overlap with FHV-1.[29]

At necropsy, ataxic cheetahs are frequently diagnosed with mostly mild or moderate lesions in non-CNS organs. Most of these non-CNS diseases are "classic" diseases frequently observed in captive cheetahs, such as gastritis, enterocolitis, glomerulosclerosis or glomerulonephritis, hepatic or renal amyloidosis, and myelolipoma. However, no correlation could be made with the myelopathy.

Pathology

Gross pathologic lesions in the spinal cord are rarely seen and consist of multifocal, segmental, bilateral, symmetric, grayish white discoloration of the spinal cord white matter.

Histologically, almost exclusively the white matter of the spinal cord is affected in all animals, consisting of continuous columns of white matter degeneration with only occasional presence of chromatolytic neurons in the gray matter. The lesions of the spinocerebellar tracts (laterodorsal funiculi) may extend into the medulla oblongata up the cerebellar peduncles. Discrete perivascular lymphocytic infiltration may be observed in the brainstem and the spinal cord meninges. In the ventral roots, dorsal roots, and peripheral nerves, rare wallerian degeneration with typical digesting chambers has been noted, as well as occasional chromatolytic neurons in the dorsal root ganglia. Neuronal lipofuscinosis is regularly seen in the brain and spinal cord gray matter in animals older than 6 years. No other lesions are observed in the white and gray matter of the brain.

The pattern, distribution, and severity of histologic lesions vary among individuals. Lesions are most prominent from the distal cervical to midthoracic segments, gradually decreasing in severity toward the craniocaudal direction. The degenerative changes are always bilaterally symmetric and often affect the entire circumferential length of lateral and ventral spinal cord funiculi, involving both ascending and descending tracts. The proper fascicle usually is largely spared, and the dorsal tracts are affected only in a few cases, generally older animals. The degenerative lesions are characterized by ballooning of myelin sheaths, either devoid of axons or containing intact or fragmented axons or macrophages (gitter cells, myelinophages). On the longitudinal sections, intact or slightly swollen axons are often seen within dilated myelin sheaths. Spheroids are observed rarely. Depending on the severity and duration of the lesions, myelin sheath vacuolation is associated with varying degrees of astrogliosis, characterized by gemistocytes and proliferation of fibrous processes. Considering the presence of intact axons within dilated myelin sheaths, the lack of features typical for early axonal degeneration, and the excess of myelin loss compared with axonal degeneration, the white matter lesion has been classified as a primary myelin disorder.[26,29] However, based on ultrastructural studies, other authors suggest that demyelination must be considered secondary to axonal degeneration.[14]

Therapeutic Trials

Because the etiology of the cheetah myelopathy is unknown, no treatment beside supportive care, as appropriate, may be recommended. Numerous treatment attempts have been reported. Products used include the nonsteroidal antiinflammatory drugs (NSAIDs) tolfenamine, flunixin meglumine, and carprofen; the steroids dexamethasone and prednisolone; various supplementary drugs such as vitamin B complex, α-tocopherol, and selenium, a paraimmunity inducer; and serum-neutralizing antibodies against FPV, FHV-1, and FCV.

In summary, it appears that the progression of the disease process was not influenced by drug therapy.[14,26,27] In few cases, temporary improvement of the ataxia after therapy with acyclovir and prednisolone could be noted, but resurgence of ataxia/paresis reappeared in most cases.[29] With oral and intravenous cupric sulfate ($CuSO_4$) treatment in 4-month-old cubs with ataxia, serum copper could be raised from 2.5-7 µmol/L to 15-70 µmol/L, but there was no improvement of the symptoms.[27] Similarly, copper supplementation had no effect in the cubs reported in Ireland,[14] and long-lasting, increased dietary copper intake did not prevent the appearance of the disease in several other zoos.

Etiology

Many hypotheses, including genetic, alimentary, toxic-environmental, and infectious factors, have been considered, but to date, no definitive conclusion could be drawn. Investigations to determine the cause of the cheetah myelopathy have been based on known causes of myelopathy in human and domestic animals. Numerous similar, but not identical, human and animal disorders of the spinal cord that feature white matter demyelination have been described, but the etiology is often unknown and the diseases are classified as "idiopathic." A presumed cause has only been determined in few cases, involving viral, genetic, autoimmune, nutritional-metabolic, toxic, and physical factors. Considering that the cheetah myelopathy has never been reported within the North American, South African, or Japanese populations, and in view of the similar genetic base of these cheetah populations, extrinsic factors, either related to the management or the environment, must be considered. Again, however, no common denominator has been identified to date.

A degenerative myelopathy of presumed inherited basis is known for several dog species, including the Afghan hound, miniature poodle, German shepherd, Siberian husky, Koiker, and Rottweiler.[23] Regarding the cheetah myelopathy, many different founder lines have been affected, suggesting that it is not a familial disease. Additionally, the pattern of incidence does not indicate a genetic basis for this disease. However, a genetic component to general disease predisposition and response cannot be ruled out, and anticipation of multifactorial inheritance might play a role.[2] In view of the phenotypic similarities of the diseases in the EEP cheetah population with human mitochondrial DNA–associated diseases, the cheetah mitochondrial genome was analyzed to investigate a possible extrachromosomal genetic basis for the myelopathy. One heteroplasmic and two homoplasmic single-nucleotide polymorphisms (SNPs) in the mitochondrial complex I of cheetahs with and without neurodegenerative diseases were identified. However, a correlation between these SNPs and the myelopathy could not be demonstrated.[4]

Known nutritional myelopathy entities include swayback and enzootic ataxia in sheep and goats caused by copper deficiency,[31] equine degenerative myelopathy due to a presumed vitamin E deficiency,[23] degenerative myelopathy related to vitamin B_{12} deficiency in humans[8,15] and cat,[20] and hound dog ataxia associated with possible methionine deficiency.[21] As noted earlier, the first cases of cheetah ataxia were described in South Africa in 1981,[3] then later in two litters in The Netherlands.[32] The disease was ascribed to copper deficiency, based on the copper measurement in the organs and because one cheetah completely recovered after copper supplementation. It is not clear from the description of the cases, however, whether pathologic lesions were similar to the later outbreaks. This copper deficiency hypothesis could not be confirmed by other authors or in my experience. Although a significant difference in liver copper level has been shown between cheetahs and dogs and cats, there was no significant difference in the serum copper level.[29] Again, this difference in the liver copper levels could be explained by the domestic animals mainly being fed with supplemented industrial food.

Infectious agents need to be considered as a potential etiology for the myelopathy. Viruses such as CDV or FeLV may cause degenerative lesions in the CNS white matter.[6,24] However, attempts to identify potential causative infectious agents in the cheetahs have been unsuccessful to date.[29] In a recent study, immunohistochemical (IHC) screening for FHV-1, BDV, canine parvovirus (CPV), and CDV antigen of paraffin-embedded and formalin-fixed brain and spinal cord tissues from 25 cheetahs with cheetah myelopathy was performed.[22] Despite FHV-1 positivity in serum samples and conjunctival swabs from two litters of cheetah cubs and one positive titer against BDV, as well as the presence of inflammatory lesions in several brain and spinal cord samples, no positive immunolabeling for FHV-1, BDV, CPV, or CDV was demonstrated. Additionally, IHC screening for FeLV antigen was negative, and no cheetah had a positive FeLV titer.

Cheetah Leukoencephalopathy

Leukoencephalopathy is a serious degenerative disease affecting North American cheetahs[12] but has never

been observed in the European (with one exception in the United Kingdom) and South African populations despite thorough investigations. The most distinctive clinical signs are blindness or visual abnormalities, lack of responsiveness to the environment, behavioral change, incoordination, or convulsions. However, some affected cheetahs may have no specific neurologic signs. The disease emerged in 1996, peaked between 1998 and 2001, and is now declining. About 70 animals have been affected to date at about 30 different facilities. Most affected animals are at least 10 years old. The pathologic lesions are restricted to the cerebral cortex and characterized by loss of white matter with associated, bizarre astrocytosis. The cause is unknown, but epidemiologic features suggest exposure to an exogenous agent through diet or medical management. For clinical diagnosis, MRI is the most sensitive method, but confirmation of the disease is based on histopathologic investigations. The cheetah leukoencephalopahy appears to be irreversible, and treatment is limited to supportive therapy.

Feline Spongiform Encephalopathy

Feline spongiform encephalopathy (FSE) affecting domestic and captive feline species is a prion disease considered to be related to bovine spongiform encephalopathy (BSE). FSE has been reported in several nondomestic cat species, including cheetah, puma, ocelot, tiger, lion, and cougar, but the relatively high prevalence in cheetahs suggests that they may be more susceptible than other zoo felids. To date, nine cases of FSE have been diagnosed in cheetahs.[1,10,11,17,25] All affected cheetahs were older than 5 years, and with the exception of two cheetahs born in France, all were either born in the United Kingdom or imported from there. Clinically, chronic progressive ataxia initially involves the hind limbs but later progresses to involve the forelimbs. Further clinical signs appear with variable frequency and include postural difficulties, hypermetria, muscle tremors (particularly affecting the head), changes in behavior (e.g., increased aggressiveness, anxiety), hyperesthesia and hyperreaction to sounds, ptyalism, prominent nictitating membranes, and blindness. The clinical signs usually develop over about 8 weeks. One affected female had a litter when the clinical signs appeared, but she continued to suckle the cubs throughout the disease period until she was humanely euthanized. One of the three cubs later developed the disease at age 6 years. The diagnosis of FSE requires histopathologic examination of the brain and the finding of characteristic vacuolation. It is broadly accepted that FSE is the result of BSE infection in felids, and the incubation period appears to be 4.5 to 8 years in cheetahs. However, the occurrence of FSE in the offspring of an affected cheetah in France raises the possibility of vertical transmission.

Other Neurologic Disease Observed in Cheetahs

Vitamin A deficiency has been investigated as a cause of a neurologic disease in two adult cheetahs. Pathologically, there was evidence of coning of the cerebellum and ischemic necrosis of the spinal cord.[13]

NEUROLOGIC DISEASE IN SNOW LEOPARDS

Two distinct neurologic disorders have been reported in young snow leopards in France, Switzerland, and Finland. The cause of these diseases remains uncertain. However, several similar diseases in domestic animals have a familial background, and considering the narrow genetic basis of captive snow leopards, a genetic cause is suspected. A preliminary pedigree analysis showed that all affected cubs have common ancestors. However, a pure genetic cause is unlikely because the same ancestors also appear frequently in the lineage of unaffected snow leopards in other institutions.[7,18,19]

The first spinal cord disorder was diagnosed in a snow leopard litter at a French zoo. At age 3 to 5 weeks, the three cubs of the litter showed clinical neurologic symptoms characterized by head and body tremors and swaying gait, followed by inability to stand and paresis of the hind limbs. Additional clinical findings were loss of body weight and a shaggy hair coat. Because of the progression of the neurologic signs, all three cubs were euthanized at age 9 to 11 weeks and submitted to necropsy. Histopathologic investigations of the nervous system revealed lesions characterized by chromatolytic neurons in the spinal cord, predominantly in the proprioceptive nucleus thoracicus in the proximal lumbar segments. Distinct myelin sheath dilation and axonal degeneration were observed in the corresponding thoracic and cervical ascending spinocerebellar tracts. No changes were seen in the brain, spinal ganglia, and peripheral nerves. The cause of this spinal disorder remains unknown, and no further ancillary procedures were performed. The litter was born from a breeding pair that had previously produced several normal litters.

The second disorder was diagnosed in snow leopard cubs born to three breeding pairs in one Swiss and two French zoologic institutions between 1997 and 2003. This spinal disorder was clinically and pathologically similar to a previously reported neurologic disorder in snow leopard cubs at the Helsinki Zoo in Finland. The disorders appeared in two, three, and respectively, four consecutive litters from each breeding pair, and all cubs born in the affected litters developed neurologic signs. Beginning at age 2 to 4 months, the cubs developed locomotion disorders characterized by swaying gait, hypermetria, and weakness of the hind limbs, associated with progressive muscle atrophy of the hind legs. Further clinical examination was performed, but the interpretation was difficult because the cubs were fearful. However, the spinal patellar and flexor reflexes were present. The only significant abnormalities revealed by ancillary investigations performed on two cubs were a borderline anemia and a low vitamin B_{12} level in the serum.

Because of the progressive course of the disease, most cubs were euthanized within 1 year of age. Necropsy was performed on five cubs and did not reveal any gross lesions. Histopathologic examination revealed degenerative lesions in all segments of the spinal cord. The lesions were confined to the lateral and ventral columns, with the dorsolateral and ventromedial aspects most severely affected. The changes were characterized by dilation of myelin sheath, containing preserved axons, myelinophages, or axonal debris, associated with astrocytosis and perivascular gitter cell cuffs. The loss of myelin was clearly visible in the Luxol–fast blue stain.

The etiology of this second spinal disorder remains unknown, but it seems important to note that the snow leopards in the Swiss zoo and in the two French institutions were fed with chicken only. Two of these institutions changed the diet to a variety of different meats, supplemented with vitamins and trace elements. The cubs born in these zoos after the diet change did not develop neurologic signs, whereas at the third zoo, which continued to feed chicken, the cubs born were again affected. This may be indicative of a vitamin B or other nutritional deficiency as the cause of the degeneration of the spinal cord in the snow leopard cubs in these facilities.

Besides these two degenerative disorders, we have diagnosed a spastic paralysis of the hind limbs in a 4-month-old snow leopard cub. The necropsy revealed a compression of the spinal cord by a mycotic abscess at the level of the fourth lumbar vertebra. Microbiologic culture performed on the abscess material revealed the growth of *Cladophialophora bantiana.* Neurologic diseases resulting from fungal infection are uncommon in human and domestic cats, but further cases of saprophytic infection involving the CNS have previously been reported in snow leopards. Extramedullary thoracolumbar fungal abscesses, caused by *Scopulariopsis brumptii*, were diagnosed in two young snow leopards,[5] and an *Aspergillus terreus* meningoencephalitis was reported in a neonatal cub.[16] It has been suggested that snow leopards may be more susceptible to infectious agents present in more temperate climates, because of a relative lack of exposure to infectious organisms in their natural habitat.[30]

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