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## Degenerative Disorders of the Central Nervous System (18-Mar-2003)

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The classification of degenerative disorders of the nervous system is difficult and somewhat arbitrary. Many of these conditions are familial or hereditary, breed-related, and involve degeneration of the nervous system within the first few months after birth. Premature degeneration of any component of the CNS, such as neurons, myelin sheaths or axons, can be considered under the broad panoply of abiotrophies which are disorders associated with an inherent lack of vital trophic or nutritive factor(s) [1]. Other degenerative conditions are yet to be classified and remain in the idiopathic grouping. Nevertheless, it is my intent to discuss the degenerative conditions and not necessarily fit them into tight classification schemes, which can vary from year to year, especially as new information becomes available. Despite this caveat, I have tended to follow a classification scheme used by Summers and colleagues in their veterinary neuropathology text [2], which includes leukodystrophies, hypomyelination, spongy degenerations, neuronal abiotrophies, motor neuron diseases, and several idiopathic degenerative disorders, including Lafora's disease, a degenerative condition usually seen in young adult dogs. Leukodystrophies may be viewed among the group of degenerative, abiotrophic disorders affecting dogs and cats [1]. These conditions are considered to be disorders of myelin synthesis and maintenance and involve CNS myelin with a typically bilaterally symmetrical, often regional, distribution [3]. While axonal necrosis and primary demyelination may be seen, lymphoplasmacytic inflammation is usually not a feature. In people, leukodystrophies are genetic diseases and are thought to represent an inborn error of metabolism due to a defective gene that produces an enzymatic abnormality and metabolic derangement that affects myelin [4]. Abnormalities of central myelinogenesis also occur with hypomyelinating disorders and spongy degenerations. Neuronal abiotrophies are disorders characterized by early or premature neuronal degeneration and death [1]. These disorders most commonly target cerebellar Purkinje cells but can also involve neurons more diffusely. Motor neuron diseases in dogs and cats are further examples of abiotrophic processes, are usually familial or hereditary affecting animals early in life, and typically involve the lower motor neuron, and as such, present with signs associated with a neuropathic syndrome.

The degenerative disorders reviewed in this chapter are presented in alphabetical order, based on the commonly used English names and terminology. The disorders are listed in the table below in relation to their classification within the categories of leukodystrophy, hypomyelination, spongy degeneration of the central nervous system, neuronal abiotrophy, motor neuron diseases, and idiopathic degenerative disorders. This listing also provides direct hyper-links to the sections for each individual disorder within the chapter. Commonly used abbreviations include the following: CT, computerized tomography; EMG, electromyogram; NCV, nerve conduction velocity test; PNS, peripheral nervous system.

### **Leukodystrophies**

Dalmatian Leukodystrophy  
Fibrinoid Leukodystrophy  
Afghan Hound Myelopathy  
Miniature Poodle Demyelination  
Rottweiler  
Leukoencephalomyelopathy

### **Hypomyelination**

Chows  
Lurcher Hounds  
Springer Spaniels  
Samoyeds  
Weimaraners  
Bernese Mountain Dogs  
Dalmatians  
Cats  
Miscellaneous

### **Spongy Degeneration of the CNS**

Spongy Degeneration in White Matter  
- Labrador Retrievers  
- Shetland Sheepdogs  
- Samoyeds  
- Silky Terriers  
- Egyptian Mau Kittens  
Spongy Degeneration in Gray Matter  
- Bull Mastiffs  
- Salukis  
- Cocker Spaniels  
- Malinois Shepherd Crosses  
- Rottweilers  
- Birman Kittens

### **Neuronal Abiotrophy**

Cerebellar Cortical Abiotrophies  
- Neonatal Cerebellar Cortical Abiotrophy  
- Kerry Blue Terriers  
- Gordon Setters  
- Rough Coated Collies  
- Border Collies  
- Australian Kelpies  
- Labrador Retrievers  
- Rhodesian Ridgebacks  
- Coton de Tuléar Dogs  
- Beagles  
- Miniature Poodles  
- Brittany Spaniels  
- Schnauzer-Beagle  
- Portuguese Podencos  
- Old English Sheepdogs  
- Bernese Mountain Dogs  
- American Staffordshire Terriers  
- English Bulldogs  
- Other Canine Breeds  
- Cats  
Multisystem Neuronal Abiotrophies  
- Swedish Lapland Dogs  
- Cocker Spaniels  
- Cairn Terriers  
- Miniature Poodles

### **Motor Neuron Diseases**

Giant-Breed Crosses  
Swedish Lapland Dogs  
English Pointers  
German Shepherds  
Doberman Pinchers  
Griffon Briquet Vendéens  
Salukis  
Other Canine Breeds

### **Motor Neuron Diseases with Neurofibrillary Accumulation**

Brittany Spaniels  
Rottweilers  
Collie  
Cats

### **Idiopathic Degenerative Disorders**

Alaskan Husky Encephalopathy  
Yorkshire Terrier Encephalopathy  
Central Axonopathy in Scottish Terriers  
Degenerative Myelopathy  
Encephalomyelopathy in Young Cats  
Encephalomyelopathy and Organic Acidopathies  
Hereditary Ataxia  
Hereditary Polioencephalomyelopathy of the Australian Cattle Dog  
Hound Ataxia  
Idiopathic Vascular Calcification  
Kooiker Dog Myelopathy  
Labrador Retriever Axonopathy  
Lafora's Disease  
Mitochondrial Encephalomyelopathy  
Nervous System Degeneration in Ibizan Hounds  
Neuroaxonal Dystrophy  
- Rottweilers  
- Collie Sheep Dogs  
- Chihuahuas  
- Papillons  
- Jack Russell Terrier  
- Cats

### **Afghan Hound Myelopathy**

This neurodegenerative disease (also called Afghan Hound hereditary myelopathy) occurs in Afghan Hounds, of either sex, and has an autosomal recessive mode of inheritance [5-9]. Clinical signs have been noted in dogs between 3 and 13 months of age. Pelvic limb paresis and ataxia often are the first signs observed and affected animals may have a synchronous (bunny hopping) pelvic limb gait. Within 1 to 3 weeks, these signs progress to paraplegia, thoracic limb paresis and/or tetraplegia. Spinal reflexes are usually intact or increased but may be depressed as a consequence of gray matter lesions, and breathing may be abdominal. Urinary incontinence is often seen especially in dogs with decreased pelvic limb sensation [6]. Fecal incontinence may also be present in paraplegic dogs [8]. Death frequently results from respiratory failure. Pelvic limbs and caudal thorax may be analgesic. CSF examination may reveal slight elevations in protein level (40 to 80 mg/dl) without increase in cell count [6]. Blood chemistry values, routine spinal radiography and myelography are usually normal. Grossly, grayish softenings of the white matter may be seen in formalin fixed tissue [8]. Histological lesions are limited to the CNS where they tend to be bilaterally symmetrical. Macro- and microcavitation and necrosis occur in white matter extending from mid-cervical to mid-lumbar segments and are especially severe in mid-thoracic cord segments where all funiculi are affected. Dorsal and lateral funicular damage tapers off in the caudal thoracic region, while ventral funicular lesions continue along the ventral median fissure to mid- or caudal lumbar segments. Rostrally, the dorsal and/or ventral funicular lesions extend to caudal or mid-cervical levels [5]. The fasciculus proprius is usually intact [5,6]. Myelin breakdown is characterized by swelling and fragmentation of myelin sheaths and macrophage infiltration, giving the white matter a vacuolar appearance. The largest cavities tend to occur in the dorsal funiculus and usually contain lipid-laden macrophages and proliferating vessels. Funicular axons remain intact. Gray matter involvement, when present, is confined to the dorsal nucleus of the trapezoid body and to the periphery of the spinal ventral gray columns. In the former, lesions are characterized by spongiform degeneration of the white matter, neovascularization, and hypertrophic astrocytes [5,6]. In areas of gray matter adjacent to affected white matter, variable increase in glial cells and mild central chromatolysis of neurons has been noted [8]. In one report, small foci of malacia were observed in the caudal brainstem and medial olivary nucleus [8]. Ultrastructurally, splitting of the myelin sheath occurs at the intraperiod line. Axonal spheroids are sometimes seen with pleiomorphic membranous

bodies and variable whorled neurofilaments.

The cause of these lesions has not been determined. Urine methyl malonic acid is negative and serum vitamin B12 levels are normal [6]. The disorder has been termed myelomalacia [7,8] and necrotizing myelopathy [6]. I have chosen to follow the lead of Summers and colleagues [10] in calling this condition a leukodystrophy because of the apparent preservation of axons, since malacia and necrotizing myelopathy connote destruction of all neuroectodermal elements [5]. This leukodystrophy has some clinical and pathological similarities to the degenerative myelopathy in Kooiker dogs [11]. Prognosis is poor to grave. There is no treatment.

### **Alaskan Husky Encephalopathy**

An episodic, incapacitating and ultimately fatal familial neurodegenerative disorder has been described in Alaskan Husky dogs [12,234]. Four dogs showed neurological signs before the age of 1 year (7 - 11 months) and one animal presented at 2.5 years old. Clinical signs in all dogs were acute in onset and included ataxia, seizures, behavioral abnormalities (including obtundation and propulsive pacing), blindness, facial hypalgesia and difficulties in prehension of food. In surviving dogs, the disease was static but with frequent recurrences of gait abnormalities and seizures. Pathological findings were limited to the CNS and bilateral and symmetrical soft gray cavitated foci were seen grossly in the thalamus and sometimes extended into the caudal brainstem. Microscopic lesions were characterized by neuronal loss, spongiosis, vascular hypertrophy and hyperplasia, gliosis, cavitation and mixed inflammatory infiltration. These lesions were seen as foci of bilateral and symmetrical degeneration in the basal nuclei (caudate nucleus, putamen, and claustrum), midbrain, pons and medulla, in addition to multifocal lesions at the base of sulci in the cerebral cortex and in the gray matter of cerebellar folia in the ventral vermis. The cerebellar changes varied from partial to widespread granule cell depletion and loss of Purkinje cells, but with isolated surviving Golgi neurons in the gliotic granule cell layer. Reactive gemistocytic astrocytes with prominent cytoplasmic vacuolation were observed in the thalamus. Spinal cord lesions were restricted to white matter and were characterized by Wallerian degeneration. In 2 dogs, the lesions were severe, bilaterally symmetrical, and involved the deep areas of the dorsolateral funiculus (corresponding to descending upper motor neurons running within the reticulorubrospinal tract) and the ventral funiculus flanking the ventral sulcus. These changes were most severe in the cervical cord. The nature and distribution of lesions were considered to resemble Leigh's disease (subacute necrotizing encephalomyelopathy) of man, in which several enzyme complexes involved in mitochondrial respiratory metabolism show defects, singly or in combination [13]. Neuronal sparing and astrocytic vacuolation suggested possible astrocytic dysfunction. Initial pedigree studies and test mating suggest an autosomal recessively inherited metabolic derangement of unknown nature as the cause of this breed-specific disorder.

### **Yorkshire Terrier Encephalopathy**

A severe subacute/chronic necrotizing encephalomyelopathy has been reported in young Yorkshire Terriers (onset of signs was between 4 months and 1 year of age) with signs and pathology (Fig. 1, Fig. 2, Fig. 3, Fig. 4 and Fig. 5) similar to those found in the above-mentioned encephalopathy of the Alaskan Huskies [221,238,240].



Figure 1. Bilaterally symmetrical thalamic cavitation (\*). Woelcke-Schroeder stain. Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 2. Intact nerve fiber (arrowhead) within cavitation. Bodian stain. Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

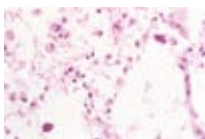


Figure 3. Gitter cells and intact neurons within cystic lesions. Hematoxylin & eosin (HE). Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 4. Spongy change and vascular proliferation, cerebral cortex. HE. Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 5. Severe depletion of Purkinje cells and granule cells, along with proliferation of Bergmann glia. HE. Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

CSF findings may include elevated protein concentration and a mononuclear pleocytosis. Multifocal, extensive areas of decreased opacity throughout the cerebral hemispheres, asymmetric ventriculomegaly, and lack of contrast enhancement were found on CT images of 3 affected dogs with multiple malacic cavitations within the brain [238]. In this report, the condition was termed a "necrotizing meningoencephalitis" which needs to be differentiated from the multifocal non-suppurative necrotizing encephalitis reported in Yorkshire Terriers in Switzerland [239], in which no malacic cavitations were described.

### **Central Axonopathy in Scottish Terriers**

A central axonopathy in 2 male and 1 female Scottish Terrier puppies from 3 different but related litters (sharing a common sire) has been reported [189]. Clinical signs consisting of severe whole-body tremors and ataxia were first detected at the age of 10 to 12 weeks. They worsened with activity and excitement and diminished during rest or sleep. Two dogs also had paraparesis. In one dog the neurological deficits progressed over several months. No abnormalities were seen on gross examination. Neuropathological examination revealed widespread axonal changes, vacuolation, and gliosis in the white matter of the CNS. Diffuse thickening or increased diameter was seen in many axons in the lateral and ventromedial funiculi and to a lesser extent in other white matter areas. Some axons appeared quite large, but with little fragmentation or dystrophic swellings. Myelin sheaths were thin or absent around these fibers. Myelin stains revealed decreasing staining intensity in the spinal cord. Similar, but less intense changes were present throughout white matter of the brainstem, cerebellum, and cerebrum. Status spongiosis and gliosis were seen in the white matter of the brain, brainstem, and spinal cord, and in gray matter of some nuclei of the brainstem, thalamus, and cerebellum. Occasional dystrophic axons were seen in nuclear areas of the brainstem and thalamus, in the granular layer of the cerebellum, and in the internal capsule, suggesting that the thickened axons might eventually progress to degeneration. Peripheral nerves were normal. The authors suggested that this may be an inherited condition with a poor prognosis, based on the progressive clinical course in one puppy.

### **Cerebellar Cortical Abiotrophies**

Cerebellar cortical abiotrophies are characterized by premature aging, with degeneration and death of various neuronal cell populations, and are the most common neuronal abiotrophies in small animals [1]. Clinical signs of cerebellar syndrome (e.g., ataxia-dysmetria, head tremor, broad-based stance, and loss of balance) occur most commonly in young animals that are clinically normal at birth, usually within a few weeks or months after birth. This "juvenile" onset encompasses most cases of cerebellar abiotrophy, although in some instances, there is an adult onset. Occasionally, a neonatal cerebellar abiotrophy is seen in which animals show cerebellar signs at birth (see below). The clinical course is typically progressive.

Antemortem diagnosis is suggested by clinical signs, age, breed, and by rule-out of acquired diseases. Examination of biopsy material from selected sites such as the cerebellum may confirm an antemortem diagnosis in some instances. Some cerebellar disorders are limited to Purkinje cells and to the anatomically- and developmentally-related granule cell layer. Reduction in numbers of granule cells might reflect degeneration or loss of Purkinje cells. Occasionally, retrograde degeneration occurs in other neuronal populations that project to the cerebellar cortex, such as olivary neurons that project to Purkinje neurons, and pontine neurons that project to granule cell neurons [1]. Regressive changes in neurons of cerebellar nuclei are regarded as transsynaptic degeneration following the Purkinje cell damage [14]. More recent reports indicate that some cerebellar disorders are accompanied by cerebral cortical neuronal degeneration (see multisystem neuronal abiotrophy in Miniature Poodles). In general, electrodiagnostic studies, serum biochemistry, and CSF analysis are of limited value in the diagnosis of degenerative cerebellar disorders, although imaging techniques might demonstrate cerebellar atrophy. Prognosis is guarded to poor. Presently, there is no treatment.

Cerebellar cortical abiotrophies have been reported in several breeds of dogs, as well as in cats, and each condition is discussed separately.

**Neonatal cerebellar cortical abiotrophy** has been identified in beagles [14,65] (see below), Samoyeds [65], and in Irish Setter puppies with hereditary quadriplegia and amblyopia (HQA), a condition associated with a fully penetrant, autosomal recessive gene [69]. Microscopic lesions included diffuse loss of Purkinje cells and variable loss of granule cells in the Beagles and Irish Setters, and swollen axons of Purkinje cells along with occasional myelin degeneration and axonal necrosis in the folia white matter of Beagles, Irish Setters, and Samoyeds [65,69]. Interestingly, microscopic lesions were not detected in the Irish Setters until around 3 months of age. A similar condition has been reported in Coton de Tuléar and Rhodesian Ridgeback puppies (see below).

#### **Cerebellar Cortical Abiotrophy in Kerry Blue Terriers**

This is an autosomal recessive disease that affects Kerry Blue Terriers [15]. Clinical signs of pelvic limb stiffness and head tremors reflect cerebellar disease and are seen between 9 and 16 weeks of age. Subsequent signs include dysmetria-hypermetria and often, an inability to stand by 1 year of age. The CNS lesions are progressive and tend to follow a relatively well-defined temporal course [16]. Degeneration of Purkinje cells in the cerebellar cortex is evident at the onset of clinical signs (approximately 2 to 4 months of age). After two weeks to one month of clinical illness, retrograde transsynaptic neuronal degeneration occurs in the olivary nucleus. Degeneration of both large and small neurons in the caudate nucleus begins approximately two to three months after the onset of clinical signs, and by seven to eight months of clinical illness, the caudate nucleus is reduced to numerous microcystic cavities and is almost devoid of neurons except for a narrow subependymal zone and the tail of the nucleus. Neuronal depletion in the pars reticularis of the substantia nigra, evident after five to seven months of clinical illness, is attributed to an anterograde transsynaptic mechanism of neuronal degeneration. Ultrastructural changes have been reported [17]. In the caudate nucleus, the initial lesion was mitochondrial hypertrophy in dendrites of intrinsic neurons. Degeneration of these neurons became widespread while axons of passage and terminal boutons were spared. During the final stages, there was severe disruption of the neuropil with loss of both neurons and glia. In the cerebellar cortex, the lesions involved principally Purkinje cells and progressed through a pattern of degeneration comparable to that involving intrinsic neurons of the caudate nucleus, with eventual astroglial scarring of the molecular layer. In contrast to the caudate nucleus, there was no disruption of the neuropil with loss of structure in the cerebellum. A disorder of glutamate metabolism with associated excitotoxic injury to Purkinje cells and neurons of the caudate nucleus has been proposed [16,17]. The condition is progressive and prognosis is poor.

#### **Cerebellar Cortical Abiotrophy in Gordon Setters**

This is believed to be an autosomal recessive, late-onset cerebellar disease affecting mature Gordon Setters between 6 and 30 months of age [18,19]. Dogs appear normal during the first 6 months of life, but between 9 and 18 months, they develop a mild thoracic limb stiffness, hypermetria, broad-based stance, and occasional stumbling. Nystagmus can occur late in the condition. These signs progress very slowly (e.g., over several years) or remain static after a short period of progression. Lesions are restricted to the cerebellum. There may be gross atrophy of the cerebellar cortex, particularly the pars intermedia. Microscopic changes are characterized by profound loss of Purkinje cells throughout most of the cerebellar cortex, although the vermis and paravermian regions of lobules IV, V, and VI were especially affected in one report [20]. The molecular layer is moderately thinned and the granule cell layer varies in thickness. Ultrastructural findings include a reduction in the size of Purkinje cells, axonal degeneration, and synaptic abnormalities in the cerebellar glomeruli and deep nuclei of the cerebellum, suggesting that the degenerative process begins in Purkinje cells and that granule cells may be secondarily affected [21]. Prognosis is guarded.

#### **Cerebellar Cortical Abiotrophy in Rough Coated Collies**

This is an autosomal recessive disease reported in Rough Coated Collie dogs in Australia [22]. Posterior incoordination occurs between 1 and 2 months of age. Subsequently, animals develop a broad based stance, hypermetria and head tremors and occasionally, a bunny-hopping gait. Affected animals frequently fall sideways or forwards with their legs in extension. Severely affected dogs typically spend most of their time lying down. Clinical signs may stabilize after 12 months of age. Pathologically, there is early and rapid degeneration of Purkinje cells and granule cells of the cerebellum. Other changes include neuron depletion in cerebellar roof nuclei, lateral vestibular nuclei, inferior olivary nuclei, and ventral horns of spinal cord. Additionally, Wallerian degeneration may be observed in the brainstem and in lateral and ventral funiculi of the spinal cord.

#### **Cerebellar Cortical Abiotrophy in Border Collies**

This condition appears to be very similar to that described in the Rough Coated Collie [23]. Clinical signs are first noted at 6 to 8 weeks of age and are characterized by ataxia, hypermetria and head tremor. There is loss of granule and Purkinje cells from the anterior folia of the cerebellar vermis, which is flattened grossly. The disease is believed to be familial. Prognosis is guarded to poor since clinical signs reportedly deteriorate with time. An unusual form of abiotrophy has been reported in two

sibling Border Collies in which there was extensive loss of the cerebellar granular cell layer with relative sparing of Purkinje cells [229].

### **Cerebellar Cortical Abiotrophy in Australian Kelpies**

This degenerative canine condition is thought to be genetically transmitted as an autosomal recessive trait [24]. Clinical signs usually begin around 6 weeks of age, but may be delayed until 12 weeks of age, and are characterized by ataxia, hypermetria, head tremor, truncal ataxia, and proprioceptive deficits. Menace response may be absent. There is regional loss of Purkinje cells and granule cells and mild spongiosis and Wallerian degeneration in white matter tracts of affected cerebellar folia. Changes are most severe in lingula, central and culmen lobules of the cerebellar vermis. Occasionally, necrotic Purkinje cells are present. White matter spongiform changes may be seen in cerebellar dentate nuclei and in vestibular nuclei. Prognosis is poor.

### **Cerebellar Cortical Abiotrophy in Labrador Retrievers**

This degenerative condition has been described in three Labrador Retriever puppies from a litter of twelve [25]. Clinical signs occur about 12 weeks of age and include pelvic limb ataxia, hypermetria, truncal ataxia, and wide-based stance. Within a week, signs progress rapidly to thoracic limb involvement, falling, and inability to walk without assistance. Positional nystagmus and reduced menace response may be noted. Results of laboratory diagnostic testing for toxoplasmosis, canine distemper virus, *Cryptococcus* capsular antigen, and electroencephalography were normal. The genetic status of this condition remains to be confirmed. Grossly, the cerebellum is smaller than normal. There is loss of Purkinje cells and granule cells, granule layer thinning, and folia white matter gliosis in all regions of the cerebellar cortices, especially in central and lingula lobules of the rostral vermis. The culmen and declive lobules are affected later in the disease. Retrograde degeneration of brainstem nuclei is not observed.

A similar disorder has been seen in a puppy of predominantly Labrador Retriever breeding (the mother was a purebred Labrador Retriever and the father was a Labrador-Chesapeake Retriever cross) [26]. The clinical signs were similar to those described above; however, the progression was very slow and the dog required no assistance to walk, even at one year of age. Also, abnormal nystagmus was not seen. This dog exhibited seizure-like episodes similar to those described for Gordon Setters (see above), characterized by progressing episodes of recumbency with opisthotonus and muscle rigidity. Gross and microscopic findings were similar to those seen in the Gordon Setters, although neuronal loss and/or axonal swelling was found in the olivary and vestibular nuclei, along with swollen axons in the vestibular nerve in the region of the cochlear nucleus. Axonal spheroids were seen in the cerebellar nuclei. These changes were considered to represent transynaptic degeneration as a consequence of Purkinje cell loss. Increased numbers of Bergmann's astrocytes were seen around Purkinje cells and there were increased numbers of astrocytes in the cerebellar white matter.

### **Cerebellar Cortical Abiotrophy in Rhodesian Ridgebacks**

An unusual syndrome of cerebellar Purkinje's cell degeneration and coat color dilution has been reported in a family of Rhodesian Ridgeback dogs [27]. Three puppies were presented for growth retardation, inability to ambulate, and progressive ataxia. Signs were usually seen by 2 weeks of age. By 4 weeks, ataxia was so severe that affected pups were unable to stand or maintain a sternal posture, and tended to lie on their sides making spasmodic limb movements when stimulated. At this time, affected puppies were one-half the size of their normal littermates. They often assumed an opisthotonic posture with rigid extension of forelimbs, and the hind limbs were flexed at the hip, bringing these limbs forward under the body. Intention tremor of the head was noted, especially during eating and playing. Horizontal nystagmus was also observed, particularly after stimulation of the retina with a light beam. All affected pups and none of the normal littermates had a dilute coat color at birth. The iris of affected pups was blue rather than the dark brown to light amber color normally seen in this breed. Results of routine laboratory tests, urine metabolic screenings, and karyotype analyses were normal. Grossly, the cerebellum was smaller than normal, including the vermis and hemispheres. Microscopic changes were limited to the cerebellum. Folia were small, with thinning of the granular and molecular layers, and there was marked reduction in Purkinje cell numbers (note that the microscopic changes were not detected until around 1 month of age). Occasional necrotic Purkinje cells had nuclear pyknosis and cytoplasmic eosinophilia. These changes were most prominent in the dorsal vermis and flocculus. Swollen, eosinophilic Purkinje cell dendrites were present in the molecular layer, associated with Purkinje cell necrosis and depletion. There were increased numbers of astrocytes with large nuclei throughout the molecular layer. The granule cell layer was hypocellular, particularly in areas of Purkinje cell loss. Histological examination of a skin sample revealed uneven distribution of macromelanosomes within hair shafts. Pedigree analysis suggested an autosomal recessive mode of inheritance. This is the first description of a genetic syndrome affecting the CNS and associated with coat color dilution in dogs. While the molecular basis for this condition is unknown at this time, present evidence supports the hypothesis of a single gene mutation with pleiotropic effects [27].

### **Cerebellar Cortical Abiotrophy in Coton de Tuléar Dogs**

A neonatal ataxia syndrome has been described in Coton de Tuléar puppies [225] with signs very similar to those seen in the Rhodesian Ridgeback puppies, with most of the affected pups being unable to stand and having a propulsive "swimming" form of gait. They frequently would fall to lateral recumbency with subsequent decerebellate posturing and paddling. Ocular motor abnormalities included fine vertical tremors at rest and saccadic dysmetria. The condition was nonprogressive at least until 4 months of age. No specific abnormalities were identified in blood, urine, CSF cellularity/protein (although a mild increase in protein concentration was observed in one dog), CSF organic and amino acid concentrations, brain imaging (MRI/CT), and electrodiagnostic testing (brain stem auditory-evoked potentials, EMG, nerve conduction studies). Microscopic lesions were not seen in the CNS or muscle/nerve using light microscopy or immunocytochemical techniques, although ultrastructural studies of the cerebellum showed synaptic abnormalities, including loss of presynaptic terminals and organelles associated with parallel fiber varicosities within the molecular layer and increased numbers of lamellar bodies in Purkinje cells. An autosomal recessive trait affecting development of the cerebellum is suspected. Remarkably, an unusual form of cerebellar granular degeneration has also been in three male Coton de Tuléar puppies between 12 and 14 weeks of age showing progressive cerebellar signs beginning at 8 weeks after birth. Signs included generalized ataxia with hypermetria, tendency to fall, intention tremor and abnormal menace response. Grossly, the cerebellum appeared shrunken. Histopathologically the granular cells were diminished or almost completely absent. However, with the exception of some swollen Purkinje cell axons ("torpedos") in the granular layer, Purkinje cells did not appear to be reduced in number and did not show degenerative changes. There was a marked gliosis in the molecular layer, and occasionally small inflammatory foci were present in the cerebellar cortex. A marked diffuse T cell infiltration (CD3(+) cells) occurred in the lesions (B cells were not seen). CD18 staining showed an upregulation of microglial cells at the lesion site. The lesions resembled some forms of paraneoplastic syndromes in people believed to be caused by an autoimmune mediated T cell reaction [227]. The authors state that this congenital condition in the Coton de Tuléar dog breed could be based on a genetically defined immune defect leading to autoimmune destruction of the granular cells.

### **Cerebellar Cortical Abiotrophy in Beagles**

A degenerative cerebellar disease has been reported in Japan involving three Beagle puppies from a litter of eight [14]. Clinical signs began at 3 weeks of age and were characterized by frequent falling. Signs were progressive. The cerebellum appeared smaller than normal. Lesions were confined to the cerebellum and were characterized by thin folia and widened sulci, extensive degeneration and loss of Purkinje cells, thinning of molecular and granule cell layers, and granule cell depletion. Axonal torpedoes (a non-specific sign of Purkinje cell degeneration) were seen in the granule layer. The cerebellar hemispheres were most severely involved followed by rostral parts of the culmen and declive of the vermis. The genetic status of this condition remains to be confirmed. A similar, early onset disorder reported in a Beagle puppy in the USA was considered to be inherited as an autosomal recessive trait [28].

### **Cerebellar Cortical Abiotrophy in Miniature Poodles**

This degenerative condition is described under multisystem neuronal abiotrophy.

### **Cerebellar Cortical Abiotrophy in Brittany Spaniels**

This late-onset cerebellar disorder has been observed in older, usually spayed, Brittany Spaniels [29,30]. Onset of signs occurs between 7 and 14 years of age. Clinical signs are slowly progressive, sometimes extending over a 4-year course. Subtle limb spasticity and hypermetria eventually leads to truncal ataxia, head tremor, "lurching" gait, "saluting" movements in the thoracic limbs, frequent falling, and inability to stand. Terminally, dogs crawl in a crouched thoracic posture with neck extension. Results of all diagnostic testing, including CSF analysis, are normal. The cerebellum is grossly normal. Microscopic lesions are confined to cerebellum, medulla oblongata and spinal cord. The most severe lesion is diffuse Purkinje cell loss (approximately 20%) throughout the cerebellar lobules, particularly in the vermis, with massive neurofilament accumulation in degenerating cells. Neurofilamentous accumulation in Purkinje cells and their processes appears to precede necrosis. Axonal spheroids are scattered in granular and deep molecular layers. There is some bilateral neuronal degeneration in the dorsal horns of the spinal cord and in the gracilis and cuneate nuclei. There is bilateral sporadic axonal degeneration in the dorsal columns and lateral and ventromedial areas of the spinal cord. The genetic status of this condition remains to be confirmed.

An unusual cerebellar abiotrophy characterized by granular cell loss has been reported in an intact, male Brittany Spaniel (3 years old), with a history of ataxia and head tremors of more than 6 months duration [31]. Grossly, the cerebellum was symmetrically smaller than normal and represented < 6% of the total brain weight (normal is 10%). Histological examination showed an unusual form of cerebellar abiotrophy characterized by marked and diffuse depletion of the granular and molecular layers of the cerebellum with normal morphology and numbers of Purkinje cells. The marked loss of neurons in the granular layer was thought to be due to an innate metabolic error of granule cells and that concomitant decreased

thickness of the molecular layer might be expected because of the decreased excitatory input from granule cell parallel fibers. It was reasoned that the slight changes in Purkinje cells was expected because the major excitatory input comes from brainstem nuclei, with only minor excitation evoked from granule neuron synapses.

#### **Cerebellar Cortical Abiotrophy in a Schnauzer-Beagle Dog**

Late-onset cerebellar degeneration has been reported in a 6 year old male Schnauzer-Beagle dog with clinical signs similar to those seen in Brittany Spaniels [32]. The condition progressed slowly over a 5-year period to a point where the dog was unable to walk, eat or drink without assistance. Cerebellar biopsy revealed reduction in size of the cerebellar hemispheres and vermis, loss of Purkinje cells and granule cells, Purkinje cell degeneration, and thinning of the molecular layer. Some Purkinje cells were displaced into the granule cell layer.

#### **Cerebellar Cortical Abiotrophy in Portuguese Podencos**

Cerebellar cortical abiotrophy has been reported in two Portuguese Podenco littermates [33]. Clinical signs had an early onset around 2 to 3 weeks of age and were characterized by progressive cerebellar ataxia. Lesions were confined to the cerebellar hemispheres and characterized by extensive loss, degeneration, and necrosis of Purkinje cells. An autosomal recessive pattern of inheritance was suspected.

#### **Cerebellar Cortical Abiotrophy in Old English Sheepdogs**

A slowly progressing, late-onset form of cerebellar degeneration characterized by progressive gait abnormality has been reported in Old English Sheepdogs, with an apparent autosomal recessive mode of inheritance [34]. Clinical signs began when dogs were from 6 to 40 months of age and were characterized by wide-based stance in hind limbs, hypermetric forelimb gait, and inconsistent menace deficit. As the disease progressed, truncal ataxia progressively worsened, often with dragging of the toes, and ambulation became increasingly difficult, with frequent falling and difficulty rising from a recumbent position. Some dogs developed a fine head tremor. The course of the disease developed slowly over many months to several years. The cerebellum appeared grossly normal. Microscopically, there was localized loss of Purkinje cells with gliosis, thinning of the granule cell layer, and increased cellularity of the molecular layer. These changes were restricted to the folia of the paravermal and vermal cerebellar cortex. There was also a marked increase in glial cell numbers in the cerebellar nuclei. Interestingly, 4 of 22 dogs in this study had no histological cerebellar changes but had clinical signs of cerebellar degeneration.

#### **Cerebellar Cortical Abiotrophy in Bernese Mountain Dogs**

An unusual disorder has been reported in Bernese Mountain Dogs characterized by progressive cerebellar and hepatic disease [35]. Clinically, stiffness in the hind limbs, mild incoordination, and a slight head tremor were first noticeable when pups were 4 to 6 weeks old. As the condition progressed, pups assume a wide-based stance. Other signs included head bobbing, spontaneous nystagmus, and, finally, paresis. Hematologic findings included leukocytosis with a left shift; normocytic, normochromic anemia; hypoproteinemia, low serum creatinine, and urea nitrogen concentrations; excessive fasting plasma ammonia concentration; and an increase in concentration of serum bile acids. Portal venography performed on 1 dog revealed a small liver and extensive extrahepatic varicosities. Necropsy revealed cerebellar hypoplasia, nodular liver, extensive abdominal varicosities, and ascites. Histologically, degeneration and depletion of Purkinje's cells and vacuolation, degeneration, and nodular regeneration of hepatic tissues were evident. Preliminary analysis of the pedigree suggested an autosomal recessive pattern of inheritance.

#### **Cerebellar Cortical Abiotrophy in American Staffordshire Terriers**

A disorder has been recently recognized in American Staffordshire Terriers in the United States (Dr. Natasha Olby, personal communication, 2001) and in Europe [217,220] with adult onset, slowly progressive cerebellar signs. Clinical signs develop between 2.5 and 6 years of age and include ataxia, spontaneous nystagmus and falling over. Neurological examination reveals ataxia in all limbs with normal conscious proprioception and, as the signs progress, worsening hypermetria and truncal ataxia. Strength is normal. Dogs ambulate well on flat straight surfaces, but tend to trip, stagger, or fall over as soon as they attempt to turn quickly, negotiate a door, or go down steps. Affected dogs often fall over when they shake their heads. In some instances, dogs assume an opisthotonic posture after falling. Spontaneous nystagmus (horizontal, rotary and vertical) is easily elicited by sudden movements. Menace reaction may be absent in severely affected dogs. To date, CSF analysis, and metabolic screening have been normal. Imaging studies have revealed asymmetrical lateral ventricular dilatation (CT scans) and symmetrical cerebellar atrophy (MRI scans) [220]. Histopathological findings include complete absence of Purkinje cells in cerebellar cortex, increased density of Bergmann glia in the Purkinje layer, and thinning of molecular and granular layers. Pedigree analysis is compatible with an autosomal recessive inheritance.



### **Cerebellar Cortical Abiotrophy in English Bulldogs**

Clinical signs characterized by wide-based stance, generalized intention tremors, hypermetria in all limbs, decreased menace response and slight proprioceptive deficits have been described in 3 young English Bulldogs (between 5 and 8 months of age) born from the same parents [223]. Onset of signs was around 2 months of age. A CT scan on one dog was normal. No gross abnormalities were noted in the CNS. Histopathology was limited to the cerebellum and included severe Purkinje cell loss and marked gliosis in Purkinje and granule cell layers. Occasional Purkinje cells were located in molecular and granule cell layers. The condition is believed to be inherited.

### **Cerebellar Cortical Abiotrophy in Other Canine Breeds**

Cerebellar degenerations, usually involving Purkinje cells, have been reported in families of Samoyeds (with swollen axons of Purkinje neurons in the granule cell layer), Airedale Terriers, Finnish Harriers, and Bern Running Dogs [36]. A genetic basis has been suggested. A similar disorder has been observed in single litters of Akitas, Clumber Spaniels, Golden Retrievers, Cocker Spaniels, Cairn Terriers, Fox Terriers, Great Danes, and mixed-breed dogs [36]. Cerebellar cortical abiotrophy has recently been reported in a Scottish terrier using magnetic resonance imaging [230]. At Auburn University, we have observed isolated cases of Purkinje cell degeneration and loss in German Shepherd, English Springer Spaniel, Miniature Poodle, and Pit Bull Terrier puppies aged between 6 and 16 weeks. Clinical signs are characterized by the typical cerebellar syndrome.

### **Cerebellar Cortical Abiotrophy in Cats**

Cerebellar cortical abiotrophy-degeneration is considered rare in cats [10]; however, late onset cerebellar degeneration was diagnosed in a one-and-a-half year old Siamese cat [37]. The cat presented with mild ataxia involving all four limbs. Over the following two years, the signs gradually progressed to severe incoordination, a frequent tendency to fall, and a head tremor. Profound and diffuse Purkinje cell loss and evidence of brainstem Wallerian degeneration were found on histopathological examination, but no etiological agent was detected. A similar clinical history was noted in a 4 year old male Domestic Shorthair cat with signs of symmetrical hypermetria and spasticity, whole body tremor, intention tremors of the head, positional vertical nystagmus, and loss of balance [191]. In addition, the cat had bilaterally absent menace response and widely dilated pupils with diminished pupillary light response. Fundoscopic exam revealed end-stage retinal degeneration, pale optic disks and retinal vessel attenuation. Grossly, the cerebellum was approximately two-thirds the normal size. Microscopic lesions were restricted to the cerebellum and included marked reduction/loss of Purkinje cells in all folia and 'empty baskets', along with diminished molecular layer and increased numbers of Bergmann's glia. Photoreceptor degeneration was observed in retinal sections associated with pronounced reduction in rod/cone numbers. This case was considered to be analogous to spinocerebellar ataxia type 7 (SCA7) in humans, an autosomal dominant form of cerebellar ataxia with retinal degeneration [192] associated with accumulation of expanded polyglutamine proteins resulting from an expanded CAG (cytosine-adenosine-guanine) sequence [193,194].

There have been recent reports of cats with hereditary cerebellar degeneration, transmitted as an autosomal recessive trait [38,39]. Cats developed cerebellar signs around 7 weeks of age characterized by intention tremor, especially of the head and neck, during eating and drinking, wide-based stance when standing, and ataxia-dysmetria with staggering gait and frequent falling. The clinical course was progressive. The cerebellum was atrophic. Microscopic findings included pronounced loss of Purkinje cells with an increase in Bergmann's glia in the cerebellar hemispheres, preservation of some Purkinje cells in the vermis and moderate neuronal depletion of the olivary nucleus. Cerebellar and pontine nuclei were normal, as were other areas of the brain, spinal cord and peripheral nerves. Electron microscopic examination revealed swelling of the distal dendrites of Purkinje cells in the less-affected nodule of the vermis, and clusters of presynaptic boutons without any synaptic contact in the severely affected folia. Presence of presynapses in the molecular and Purkinje cell layers was confirmed by positive immunoreactivity to anti-synaptophysin. Quantitative ultrastructural analysis revealed an increase in the density and mean size of presynapses in the molecular layer of the severely affected folia. These findings suggested that degeneration of Purkinje cells began at the most distal part of the dendrite, and that presynapses, axon terminals of the granular cells and basket cells may remain for a long time even after complete degeneration of the Purkinje cells [39]. These cats were considered to represent a novel animal model of human spinocerebellar degeneration.

Several other variants of this condition have been reported. An olivopontocerebellar atrophy has been observed in 2 adult feral cats with signs of head and limb dyssynergia and microscopic lesions characterized by loss of cerebellar cortical neurons (Purkinje cells, Golgi and basket cells and granule cells), loss of myelin in vermis and lobules, reduction in pontine nuclei and transverse fibers, and neuronal loss/gliosis in the inferior olivary complex [222]. Cerebellar degeneration involving only Purkinje cells (characterized by cell loss and degeneration including dendritic vacuolization and axonal spheroids) with normal inferior olive and pontine nuclei, has been described from Belgium in two 4 month old female kittens from the same litter with characteristic cerebellar signs [224]. MRI in one kitten was normal. The cerebellum was grossly normal. A similar condition has been reported from the U.K. in two domestic shorthair littermate kittens with signs occurring

around 7 - 8 weeks of age [228]. Cerebellar abiotrophy has also been reported in cats with neuraxonal dystrophy.

### **Dalmatian Leukodystrophy**

A progressive neurological disorder, transmitted by autosomal recessive inheritance, was described in male and female Dalmatian dogs [40]. Clinical signs were noted between 3 and 6 months of age and were characterized by visual deficiency and progressive ataxia, initially in the hind limbs, then involving all limbs, sometimes progressing to the point where the dog could no longer stand. Results of routine hematology, urinalysis, and CSF analysis were within normal limits. Gross pathological findings included brain atrophy, dilatation of lateral ventricles, and cavitation of the central white matter of the cerebral hemispheres, primarily involving the centrum semiovale. The subcortical arcuate fibers (U-fibers) of the cerebral white matter appeared to be spared. The occipital lobes were usually more severely involved than more rostral areas of the brain. Bilaterally symmetrical grayish and somewhat depressed areas, and occasional foci of softening, were also found in the corpus callosum. Microscopic lesions occurred in internal and external capsules, caudate nucleus and claustrum (sometimes with microscopic cavities in these basal ganglia), optic nerve, and less frequently, the spinal cord where lesions were mainly confined to the ventral horns and adjacent white matter in thoracic cord segments. A few cases had vacuoles within the spinal cord white matter adjacent to the gray matter and beneath the meninges. Within affected areas of white matter, there was a diffuse loss of myelin, widespread vacuolation, edema, presence of numerous, lipid-filled macrophages, and reactive astrocytosis. Axons appeared to remain intact, at least initially. Vacuolation was seen in myelin sheaths as a result of lamella splitting. Spinal roots and peripheral nerves were unaffected. Prognosis was poor. There is no treatment. To my knowledge, there have been no additional reports of this disease during the past 15 years; however, very similar clinicopathological findings have been reported in 2 related Labrador Retriever puppies [237].

### **Degenerative Myelopathy**

This degenerative disease may have an inherited basis in dogs [41] and it may represent an abiotrophy [1]. It is most often observed in German Shepherd dogs over 5 years of age; however, a similar clinical and pathological condition has been reported in young German Shepherd dogs [42], other breeds of dogs [43-46], and cats [47]. The onset of the disease is insidious. Initial signs include pelvic limb ataxia and paresis. Ataxia, in the form of hypermetria or excessive circumduction of the limb, crossing of the legs when walking with one limb catching behind the other, is greater than paresis, seen as dragging the toes and flexing the stifles when weight-bearing [45]. The signs progress slowly to truncal ataxia and severe pelvic limb paresis. Knuckling of paws of pelvic limbs is commonly observed, with wearing of the nails of the affected pelvic limb(s). The cutaneous trunci reflex is usually intact. Deep pain perception is unimpaired. Some dogs have a depressed patellar reflex. Sphincter function remains normal. The disease usually is slowly progressive over 6 to 36 months, although fluctuations in clinical signs may be seen [48].

Grossly, spinal ganglia, dorsal and ventral roots and rootlets are normal. Histopathologically, white matter changes are found throughout the length of the spinal cord, with the most severe lesions being present in the thoracic cord. Lesions are characterized by degeneration of white matter, especially in dorsolateral and ventromedial funiculi, along with degenerating dystrophic axons, swollen myelin sheaths, often with macrophages, astrocytosis, and gliosis. Axons may fragment and disappear. The lesions are bilateral but not necessarily symmetrical, are not restricted to particular fiber tracts, and on longitudinal studies, appear not to be continuous [41]. Lesions typically do not extend into the brainstem [46]. However, at variance with all previous reports, a recent study documented chromatolysis, gliosis and neuronal loss in various brain neurons, including the red nucleus, lateral vestibular nucleus and, occasionally, in the dentate nucleus [49]. The significance of these changes is uncertain, especially since the authors found similar lesions in dogs with spinal injuries. Leptomeningeal thickening and fibrosis has been noted [46]. Dorsal root involvement and loss of neurons in dorsal gray horns (Clarke's column) of spinal cord have been observed in some German Shepherds [45,46], although this may be an age-related effect [50]. Ventral roots are unaffected. Occasional dorsal root ganglion cells show minor central chromatolysis [45]. No significant changes are seen in brain, peripheral nerves or muscles, including end-plates and spindles [41,45,46].

The pathogenesis of this disease is unknown. It is unrelated to intervertebral disk degeneration, spondylosis deformans or osseous metaplasia of dura mater. Trauma and vascular disease have been suggested as possible causes [46], but have not been substantiated. Some affected dogs have an associated enteropathy characterized by biochemical changes in peroral jejunal biopsies and accompanied by overgrowth of bacteria in duodenal juice, and decreased serum levels of tocopherol (vitamin E) and cobalamin (vitamin B12) [51-53]. The significance of these findings remains unclear and a recent study refutes vitamin E involvement [49] (See vitamin E deficiency, in Nutritional Disorders). The clinical course of the disease in dogs with low levels of vitamin B12 has not been reversed by parenteral administration of cobalamin [52]. Morphologic and morphometric data [41] do not support the hypothesis that this disease represents a "dying back" neuropathy [45]; although this theory involving distal involvement of motor and sensory fibers is still favored by some [49]. Another theory is that degenerative myelopathy is an immune-mediated neurodegenerative disease [54]. Depression of cell-mediated immune responses (to concanavalin A, phytohemagglutinin P and pokeweed mitogens reportedly occurs secondary to a progressive

increase in the number of circulating suppressor cells [55,56]. Affected dogs have 3 to 10 times more circulating immune complexes than normal dogs, including a possible protein-specific antigen with a molecular weight of 85 kD, and plasma cell infiltrates are reportedly found in several organs, including kidneys and intestinal tracts [48]. Furthermore, an immunohistochemical study on German Shepherd dogs with degenerative myelopathy reports focal staining for immunoglobulin G (IgG) and the third component of complement (C3) in spinal nerve tracts characteristically affected in degenerative myelopathy [57]. Deposition of IgG and C3 is also found with large and small blood vessels and in other areas independent of visible lesions, suggesting that IgG and C3 deposition may precede histological evidence of spinal cord damage. Degenerative myelopathy may well be a genetic, late-onset neurodegenerative disease [45,49]. Griffiths and co-workers are searching for candidate genes [49]. A study aimed at characterizing the histopathology, antemortem diagnostics (myelography/MRI and electrophysiology), excitotoxicity/oxidative stress in CSF (glutamate, methionine, prostanoids) and genetic factors is currently being undertaken at Texas A and M University with Dr. Joan Coates as the senior investigator. Diagnosis is based on clinical syndrome, breed, and age. Hematology, blood chemistries, urinalysis, and CSF analysis are normal (although an elevation in protein in CSF samples from the lumbar cistern have been reported in some dogs [48]), as are spinal radiographic-myelographic studies, which help distinguish degenerative myelopathy from other degenerative conditions, such as pachymeningitis, disk protrusion, diskospondylitis, and spinal neoplasia. It has been reported that spinal cord evoked potentials recorded at the level of the cisterna magna, after stimulation of the sciatic nerve, are abnormal and that magnetic resonance imaging may reveal lesions throughout the spinal cord [58]. Despite the claims for immune-mediated disease (see above), repeated mitogen response assays in some dogs with confirmed degenerative myelopathy are negative [59]. Prognosis is guarded.

Recommended treatment involves a combination of exercise, vitamin supplementation, and administration of aminocaproic acid (EACA) (Amicar®, Lederle), at 500 mg, PO, tid [60]. This is the only drug that has been shown to alter the course of the disease, perhaps by blocking the final common pathway of tissue inflammation. It has been stated that EACA does not cure degenerative myelopathy but may slow its progression by as much as 50%, and that clinical improvement will usually be seen within 2 months of initiation of treatment [58]. Approximately 15 - 20% of affected dogs have no further deterioration, some improve, and others have survived for more than 4 years. The main disadvantage of this drug is its expense-it may cost from \$ 80 to \$100 per month. As an alternative, the generic injectable form of the drug (250 mg/ml) can be given as an oral solution by mixing 192 ml of EACA with 96 ml of a hematinic compound, e.g., Lixotinic. This combination provides 500 mg of EACA in 3 ml of the mixture. The dose of EACA in this form is 500 mg, tid. It is recommended that corticosteroids be reserved for acute exacerbations (e.g., prednisone, at 1 mg/kg/day, in three divided doses for 3 days before reducing to 0.33 mg/kg every 12 hours for 2 days, and continuing at maintenance levels of 0.5 mg/kg, every other day). High doses of vitamin E (2000 IU /day) and B complex vitamins (e.g., stress tablets, twice daily) can be given with the EACA. For pain, acetaminophen (i.e., Tylenol®) may be given at 5 mg/kg (not to exceed 20 mg/kg/day) [48]. Drugs that have no benefit include dimethyl sulfoxide, cobra venom, and immunosuppressive agents, such as cyclophosphamide and azathioprine. In conjunction with treatment, affected dogs should be placed on an increasing exercise program, including walking and swimming.

### **Encephalomyelopathy in Young Cats**

In a retrospective study, Palmer and Cavanagh have described a neurodegenerative disorder that primarily occurred in cat colonies (both conventional and specific pathogen-free) in the United Kingdom between 1969 and 1980 [61]. In some colonies, over 40 per cent of litters were affected. In this report, 19 cats aged 3 to 16 months developed neurological signs including hind limb ataxia that progressed to paraparesis, paraplegia, and in some instances, tetraparesis, along with urinary and fecal incontinence and muscle atrophy over the hindquarters. Other signs included visual deficits, dilated pupils, sluggish pupillary light reflexes, head shaking, head tremor, nystagmus, seizures ("fits"), and proprioceptive deficits. Spinal reflexes appeared intact, although the cutaneous trunci reflex was absent in some cats. Pain perception was also absent in one cat. Hematology and serum chemistries were normal. Serological testing for picorna virus, feline rhinotracheitis, feline pneumonitis, panleukopenia virus, and toxoplasmosis were negative. Transmission studies (animal and culture) were also negative. Plasma and red blood cell cobalamin levels were normal. Treatment of some cats with vitamin B12, at 0.25 mg/day for 6 weeks reportedly led to clinical improvement, although complete remission of signs did not occur. Histopathological changes were confined to the CNS and characterized by Wallerian degeneration (degeneration of axons and myelin with myelophages often seen within remnants of the fiber) affecting long tracts in the spinal cord and variously in the brainstem, cerebral white matter, and optic pathways. There was an accompanying mild status spongiosis, increased numbers of astrocytes and microglial cells, and occasionally, swollen axons. Inflammatory changes were not a feature. Most severe lesions occurred in the spinal cord, especially involving larger diameter fibers (e.g., spinocerebellar and ventral tracts). There was no evidence of a distal dying back distribution to the lesions. All areas of the spinal cord were affected except the dorsal columns. In the brainstem, Wallerian degeneration was noted in the external arcuate fibers and caudal cerebellar peduncles, and less commonly in middle and rostral cerebellar peduncles, medial lemniscus, pyramidal tracts, spinal

trigeminal tracts, pontine decussation, medial longitudinal fasciculus, and cerebral peduncles. In 7 cats there was loss of Purkinje cells in the cerebellum and in 8 there was neuronal degeneration-loss in the spinal cord, especially in the intermediate cell columns, either at the base of the dorsal columns or in the region of Clarke's column. Larger ventral horn cells and larger neurons in the brainstem were usually not affected. No changes were found in peripheral nerves, spinal ganglia, or skeletal muscle.

The cause of this condition remains unknown. Genetic studies were inconclusive and nutritional and dietary toxins were ruled out. Despite the absence of inflammatory changes and the fact that no viral agent was isolated, the authors suggested the condition might have an infectious cause. Purkinje cell loss as well as spinal cord myelin degeneration and neuronal degeneration have been reported in young cats with feline panleukopenia virus [62] and the condition has some similarities to idiopathic feline polioencephalomyelitis. Another degenerative myelopathy with changes similar to those seen in the colony cats has recently been reported as a complication of chronic feline leukemia virus infection [63].

### **Encephalomyelopathy and Organic Acidopathies**

Several inherited diseases in people involve abnormal metabolism of organic and amino acids leading to neurologic dysfunction [195]. These conditions are rarely recognized in dogs and cats; however, methylmalonic and malonic aciduria has been reported in a young dog with progressive encephalomyelopathy (see cobalamin deficiency).

Two distinct autosomal recessive encephalopathic disorders with elevated urinary excretion of 2-hydroxyglutaric acid are recognized in infants and children: L-2-hydroxyglutaric aciduria and D-2-hydroxyglutaric aciduria [203-205]. Recently, a third variant has been reported associated with both isomeric forms of 2-hydroxyglutaric acid [206]. L-2-hydroxyglutaric aciduria is characterized by moderate to severe mental deficiency, often with cerebellar dysfunction, and epilepsy [203,207]. Magnetic resonance imaging typically reveals subcortical leukoencephalopathy, cerebellar atrophy, and signal changes in the putamina and dentate nuclei [203,208]. Increased levels of L-2-hydroxyglutaric acid also occur in blood and CSF. Patients may also have hyperlysinemia in plasma and CSF [203,209]. Patients with D-2-hydroxyglutaric aciduria have somewhat different clinical features (severe and mild phenotypes have been recognized), including dysmorphic facies, developmental delay, generalized hypotonia, myoclonic seizures, cortical blindness, and dilated cardiomyopathy [205,210]. The most consistent MRI finding is enlargement of the lateral ventricles (especially occipital); early MRI may demonstrate subependymal cysts and signs of delayed cerebral maturation. Later MRI may reveal multifocal cerebral white-matter abnormalities [211]. In addition, there lesions have been reported in the substantia nigra, the periaqueductal area, the medial part of the thalamus, the hypothalamus, the caudate nucleus, putamen and globus pallidus [212]. Patients typically have elevated levels of D-2-hydroxyglutaric acid in plasma and CSF, along with increased CSF levels of gamma-aminobutyric acid [213].

L-2-hydroxyglutaric aciduria has recently been reported in six Staffordshire Bull Terriers from 4 months to 7 years of age with clinical signs of seizures, ataxia, or dementia [214]. Cerebral MRI findings revealed a diffuse polioencephalopathy with hyperintensity on T2-weighted images of the cerebral, cerebellar, thalamic and brainstem gray matter. L-2-hydroxyglutaric acid levels were increased in urine, plasma and CSF. In all dogs tested, CSF lysine levels were also increased. One dog had increased urinary excretion of methylmalonic acid. CSF cytology/protein content was normal. Electrodiagnostic testing on muscle and nerve was normal as were muscle biopsies. While serum total and free carnitine concentrations were within the normal range, the concentrations of muscle total and free carnitine were reportedly low. Histopathology of the CNS has yet to be reported in affected dogs. The authors state that treatment strategies, pedigree analysis, and studies aimed at identifying the underlying biochemical defect are underway.

D-2-hydroxyglutaric aciduria has also been reported in an adult dog with a 2-year history of progressive lethargy and muscle weakness [215]. A neuromuscular component to this disease was suggested by abnormal spontaneous activity, including myotonic discharges (on EMG studies) and observation of scattered atrophic angular myofibers with increased lipid content in a muscle biopsy. Interestingly, muscle biopsy in one human patient with D-2-hydroxyglutaric aciduria demonstrated excessive glycogen histochemically and subsarcolemmal cylindrical spirals with normal mitochondria ultrastructurally [210].

### **Fibrinoid Leukodystrophy**

Fibrinoid leukodystrophy (synonyms include Alexander's disease and fibrinoid encephalomyelopathy) is a rare degenerative disorder that has been reported in two 8 month old male littermate black Labrador Retriever dogs, a 9 month old male Scottish Terrier, a 6 month old female Miniature Poodle, and a 13 week old Bernese Mountain dog [64-68]. Clinical signs are noted from 2 to 6 months of age and include pelvic limb paresis, progressive ataxia, wide-based stance, generalized weakness, exercise intolerance, reluctance to go up and down stairs, and sometimes tremors, falling, and personality changes, ranging from depression, agitation, and growling. In the Scottish Terrier, head tilt, seizure-like activity characterized by thoracic limb extension and opisthotonus, abduction of all limbs, and progressive tetraparesis were seen. At 9 months of age, the elbow and stifle joints of this dog were maintained in a flexed position with abnormally short range of motion, and attempts to ambulate resulted in a "swimming" motion [69].

Hematology, blood chemistries, urinalysis, and CSF analysis are normal. In the Scottish Terrier, an abnormal electroencephalogram was recorded, consisting of 50 to 75  $\mu\text{V}$ , 2 to 5 Hz wave forms [69]. Gross changes include gray pallor of cerebral subcortical white matter and sometimes, enlargement of the lateral ventricles. Histopathological changes include diffuse pallor with vacuolation of subcortical white matter with increased vascularity in which vessels are accentuated by thick cuffs of Rosenthal fibers, and mild to moderate gemistocytic astrocytic gliosis. There may be considerable myelin loss in some affected dogs [67], and neuronal loss may be evident in the cerebral cortex and subcortical gray structures [65]. The Rosenthal fibers are round, club-shaped, or elongated eosinophilic refractile bodies (up to 50  $\mu\text{m}$  in diameter) that are also found in astrocytes located in subependymal and subpial areas of the brain and spinal cord. These bodies are common in pontine and midbrain regions. In one immunohistological report, the Rosenthal fibers were positive for glial fibrillary acidic protein and  $\alpha\beta$ -crystallin [67]. Ultrastructurally, the refractile bodies consist of non-membrane bound granular osmiophilic aggregates within the cytoplasm of astrocytic processes adjacent to vessels. The aggregates are surrounded by bundles of glial filaments ranging in diameter from 7 to 10-nm, a size and morphology similar to that of glial fibrillary acid protein [66]. Scattered peripheral nerve fiber degeneration and demyelination were reported in one affected dog [68]. In skeletal muscle from this dog, multiple subsarcolemmal masses were noted in many muscle fibers and were basophilic on hematoxylin and eosin staining, bright red with Modified Gomori's Trichrome, black with NADH-TR, weakly periodic acid-Schiff positive, and brown with osmium tetroxide.

The histological, immunohistochemical, and ultrastructural findings in affected dogs appear identical with those in human cases [67]. The cause of this disease is not known, although the bodies may represent an overproduction of astrocytic fibers, and genetic or congenital disease has been postulated. In people, the condition is thought to represent an inborn error in astrocyte metabolism that leads to global dysmyelination or demyelination of the CNS [4]. The origin of the myelin loss is also unclear, but may be due to secondary damage to oligodendrocytes. Prognosis is poor. There is no treatment.

### **Hereditary Ataxia**

Hereditary ataxia is an autosomal recessive disorder in Smooth-Haired Fox Terriers in Sweden that has been reported as a clinical entity since 1941 [70,71]. A similar condition has been described in Britain and in Germany in Jack Russell Terriers, a short-legged variety of the Smooth-Haired Terrier breed [72,73]. In the German study, certain families of Jack Russell Terriers were predisposed to the disease [73]. Clinical signs in both breeds occur between 2 and 6 months of age when pelvic limb swaying and incoordination are observed. The incoordination progresses to involve all limbs and a prancing or dancing type of gait is observed, especially affecting the hind limbs. There is over protraction of the forelimbs. Animals appear to be unable to gauge the extent of a movement, which is unpredictable in direction. Severely affected animals frequently fall and are unable to rise again to their feet. Animals have difficulty in climbing stairs and jumping. There is no skeletal muscle atrophy. The head may show a rotational intention tremor, while hearing appears unimpaired. Approximately one third of the German cases have seizures and some dogs develop respiratory distress (Dr. Andrea Tipold, personal communication, 2001). Clinical signs may stabilize after several months and some affected animals are able to carry on a relatively normal life, in spite of the abnormal movements. In no case has the disease, per se, proved to be fatal [71].

Pathologically, a symmetrical bilateral myelopathy is found in the dorsolateral and ventromedial white matter of cervical, thoracic, and lumbar spinal cord [70]. There is myelin pallor reflecting Wallerian degeneration of the white matter, which has a spongy vacuolar appearance, accompanied by a mild subpial astrocytosis [10]. The dorsolateral spinal cord lesions appear to involve the spinocerebellar pathways [70]. In the Jack Russell Terriers, similar lesions are seen in the spinal cord but tend to be most severe in cervical segments (Dr. Andrea Tipold, personal communication, 2001). In addition, moderate diffuse gliosis, marked loss of myelinated nerve fibers, and argyrophilic axonal spheroids are found in central auditory pathways, including superior olivary nuclei, cochlear nuclei, connecting nerve fibers between these nuclei and the trapezoid body, and the lateral lemniscus [72]. Massive ballooning of myelin sheaths, with an apparently intact axon, was found in dorsal and ventral nerve roots and sciatic nerves, often accompanied by endoneurial edema and fibrosis and axonal swelling. In addition, marked nerve fiber loss and variable numbers of macrophages are found in the sciatic nerves [72].

Routine hematology and blood chemistries, urinalysis, CSF analysis, radiography, myelography, and spinal computed tomography are normal [70,73]. An abnormal measurement of brainstem auditory-evoked potentials (only waves I and II being detected) has been found in some affected Jack Russell Terriers [73]. There is no treatment. Control measures should focus on preventing further breeding of affected animals or their parents. Preliminary pedigree studies suggest a polygenic model of inheritance in Jack Russell Terriers [216].

### **Hereditary Polioencephalomyelopathy of Australian Cattle Dogs**

A vacuolar degeneration affecting primarily the gray matter in the CNS of young Australian Cattle Dogs has been described [74]. Male and female dogs were affected and clinical signs were noted within the first year of life. An initial presentation of psychomotor seizures (episodes of running in circles, vocalizing and urinating) was followed within approximately 6 to 12 months by progressive fatigue and thoracic limb stiffness, and eventual spastic tetraparesis over an ensuing period of several

months. Dogs in lateral recumbency could move their neck and trunk but thoracic limbs were rigidly extended in a tetanic posture with persistent contraction of extensor muscles. Dogs remained bright and alert. Patellar reflexes were depressed or absent in 2 dogs, but nociception and withdrawal reflexes were normal. In thoracic limbs, dogs felt a noxious stimulus applied but were unable to withdraw these limbs. While normal vestibular nystagmus was difficult to elicit, a brief positional nystagmus could be induced. Remaining cranial nerve function was normal. Routine blood cell count and serum biochemistry were normal. CSF analysis was normal in one dog but a mild increase in protein (29 mg/dl) and mild mononuclear pleocytosis (13 cells/ml) comprising leukocytes and macrophages, a few of which contained myelin fragments, was found in another dog. EMG studies showed evidence of continual muscle fasciculations in proximal thoracic limb muscles, rhythmic contraction of carpal flexors, and denervation potentials in numerous thoracic limb muscles.

Bilateral and symmetrical foci of malacia were seen grossly in the nuclei of the cerebellum and brainstem (caudal colliculi, lateral vestibular nuclei, lateral cuneate nuclei, and lateral reticular nuclei) and the gray matter of the spinal cord associated with cervical and lumbosacral intumescences. Additional, focal lesions were noted in the interpositional nucleus of the cerebellum and spinal nuclei of the trigeminal nerve. Bilateral atrophy of thoracic limb muscles was also found, being most severe in the scapular musculature. Microscopically, vacuolation of glial cells, dilation of the myelin sheaths and reactive astrocytosis characterized mild CNS changes and were seen in oculomotor, abducent, lateral cerebellar and hypoglossal nuclei, and the reticular formation. Dissolution of the neuropil, prominent vacuolation of reactive astrocytes, numerous glial fibrillary acidic protein-positive coiled astrocytic processes, neuronal vacuolation and loss with relative sparing of large neurons were observed in more advanced lesions. This change was most severe in the C7 - T1 region where tissue loss involved up to 80% of the spinal cord with relative sparing of only the central canal and a thin subpial band of white matter and substantia gelatinosa. The innermost area of the affected cord segments was characterized by advanced rarefaction. The next zone was filled with macrophages followed by a cribriform vacuolar zone and finally, the outer unaffected zone of white matter. Ultrastructurally marked mitochondrial accumulation and swelling were seen in astrocytes. Scattered Wallerian degeneration was found in ventral roots and peripheral nerves. In the appendicular muscles, changes interpreted as long-term denervation atrophy accompanied by widespread expression of the neonatal isoform of myosin were observed. The character of the neurological signs and the nature and distribution of the lesions within the CNS appear to be novel in veterinary neurology. A biochemical defect, possibly mitochondrial, affecting several cell populations within the CNS was proposed, with a more pronounced effect on glial cells than neurons. Genetic analysis suggested an autosomal recessive mode of inheritance.

### **Hound Ataxia**

A degenerative myelopathy has been recognized in Britain and Ireland in adult Foxhounds, Harrier Hounds and Beagles, of either sex [75-78]. In some packs, up to 75% of animals have been affected [77]. Age of onset varies from 2 to 7 years. Initial signs are pelvic limb weakness, ataxia and exaggerated elevation of these limbs when retracted at a gallop. Occasionally the pelvic limbs are dragged. The cutaneous trunci reflex is usually absent at levels caudal to T13 - L2 vertebrae. Muscle atrophy is not observed and spinal reflexes are normal. Affected animals usually become unworkable due to increasing pelvic limb incoordination within 6 to 18 months from the onset of symptoms. Animals remain bright and alert and thoracic limb function and cranial nerves are normal. In some affected dogs, clinical signs are not progressive. In one report, consanguinity was not established between affected dogs [78].

No gross lesions are observed. Histologically, severe Wallerian degeneration is found in the spinal cord involving all tracts except dorsal columns. Lateral columns are also unaffected in the cervical cord region. The degeneration, characterized by severe myelin ballooning with intramyelinic macrophages, is diffusely distributed within funiculi, varying in intensity from slight to severe. Axonal spheroids are rarely seen. The pathological severity seems unrelated to clinical neurological deficiency. Degeneration in lumbar cord is not as marked as in more rostral levels. In some animals, changes are most severe in the thoracic cord region. Typically, changes are not seen in gray matter of the cord, although chromatolysis was seen in neurons of the thoracic cord segments in one 2.5 year-old female Foxhound accompanied by astrocytosis and gliosis [77]. Tract degeneration extends into the brainstem, including the external arcuate fibers, inferior cerebellar peduncles, spinothalamic tract, medial longitudinal fasciculus, and tectospinal tract. At midbrain level, Wallerian degeneration is seen in the medial lemniscus, medial longitudinal fasciculus, decussation of the superior cerebellar peduncles, and rarely, the lateral lemniscus. With the exception of chromatolysis affecting neurons of the lateral vestibular nucleus in one Foxhound, there is no evidence of nerve cell damage or loss. No lesions are found in skeletal muscles, nerve roots or dorsal root ganglia, but in occasional animals, degenerative changes (possibly sensory) are found in sciatic nerves [77]. In one ultrastructural report, degenerate fibers were accompanied by astrocytic proliferation, and changes suggestive of a primary myelinopathy included vacuolated myelin sheaths around apparently intact axons, degenerative changes in inner oligodendrocyte tongues, large numbers of remyelinated axons with disproportionately thin myelin sheaths, and the occurrence of myelin lamellae around glial cells [78].

The etiology of this condition remains unknown although a dietary factor may be involved, since outbreaks typically occur in

animals kept under hunt condition where they are fed a diet consisting of paunch or tripe (the four stomachs of cattle and sheep), which has questionable nutritive value. Sheahan and colleagues suggest that the condition is associated with methionine deficiency and altered methionine synthetase activity [78] (see cobalamin deficiency). One outbreak in Beagles was attributed to pitch poisoning (dogs were eating the pitched lining of the kennels) [79], however, it is likely that this is another condition since the onset of signs was rapid, one affected dog was only 3 months of age, and in at least 2 cases, there was gradual recovery. Furthermore, no dogs were available for necropsy studies.

Results of hematological, radiographic, myelographic, and CSF testing are within normal limits. Serum copper levels are normal. In one report, mean serum methionine levels were significantly lower and mean liver methionine synthetase levels were significantly greater in affected dogs restored to a balanced diet than in age-matched controls maintained on the balanced diet [78]. However, methionine synthetase levels in spinal cord from affected animals were normal, as were liver folate concentrations [78]. To date, there is no specific treatment; however, the condition has been eliminated in kennels after the diet is changed to one containing a high proportion of meat [78,80].

### **Hypomyelination**

Over the past two decades, CNS hypomyelination has been reported in several breeds of dogs, some of which are known to be inherited. The condition has also been reported in cats.

#### **Hypomyelination in Chow Chows**

Hypomyelination of the CNS in Chow Chow dogs is believed to be hereditary [81,82]. Animals show clinical signs at 2 to 4 weeks of age-wide-based stance, "rocking horse" motion of the entire body when attempting to walk, hypermetria, intention tremors of head and limbs, and often, a bunny-hopping gait. Tremors decrease or cease completely when affected animals lie quietly or are asleep. Menace response is depressed bilaterally, however, vision and pupillary reflexes are normal. Clinical signs plateau from 6 to 12 months, followed by gradual improvement to the point where only a slight intention tremor is noted in some dogs, with other dogs appearing normal [82].

In these dogs, a severe myelin deficiency is found throughout the CNS, especially in subcortical white matter and foliate white matter of the cerebellum, as seen with myelin stains (e.g., Luxol fast blue). The outer half of the lateral and ventral columns of the spinal cord, the ventral half of the cerebral peduncles, parts of the optic tracts and several brainstem tracts such as spinothalamic and vestibular fibers are virtually devoid of myelin, with only a few single, widely separated myelinated fibers seen [81]. Axons appear normal and have thin or uncompacted myelin sheaths. Most axons in poorly myelinated areas are naked. Cell processes in contact with these axons appear to be derived from fibrous astrocytes and from large cells with abundant granular electron-dense cytoplasm, typical of oligodendrocytes, and containing astrocytic-type fibrils, a few profiles of rough endoplasmic reticulum, mitochondria, and many free ribosomes. No lesions are found in the gray matter. Peripheral and cranial nerves are myelinated normally. The myelin deficiency in absence of degenerative changes indicates a disorder of myelin formation rather than breakdown. Follow-up studies on older Chows revealed that myelination progressed with age but was still deficient at the age of 3 years [82]. Axons had thin or uncompacted myelin sheaths, separated by massive astrocytosis, and bizarre myelin formations. Conventional numbers of morphologically normal oligodendrocytes were found in the myelin-deficient areas. These results suggested that the condition in Chows dogs involved retarded myelination possibly due to a dysfunction or delay in oligodendroglial maturation [82].

#### **Hypomyelination in Lurcher Hounds**

A similar tremor syndrome and hypomyelinogenesis has been reported in two 4 week old, male, crossbred Lurcher Hound puppies [83]. Signs were first seen at 2 weeks of age and were characterized by pelvic limb bouncing or dancing while standing, along with fine tremors of the limbs and trunk, which sometimes involved the head. Tremors became more pronounced with excitement, abated with rest, and disappeared during sleep. Hypermetria was seen in the forelimbs in one puppy. Cranial nerve function, spinal reflexes, and postural reactions were normal. Clinical signs regressed completely in one puppy by 16 weeks of age.

Hypomyelination (based on pallor of myelin staining and abnormal myelin sheath:axon relationships) was present in spinal cord sections with numerous axons surrounded by inappropriately thin myelin sheaths, especially in the peripheral areas of the lateral funiculi of the cervical spinal cord. Some axons were naked. Small myelin figures were found in axons within oligodendrocytic and astrocytic processes. Demyelination was not seen. Oligodendrocytes and astrocytes appeared normal and there was no evidence of demyelination, lipophages, or inflammatory cells. Nerve roots and peripheral nerves were normal.

#### **Hypomyelination in Springer Spaniels**

A myelin disorder that has an X-linked recessive mode of inheritance has been reported between 2 and 4 weeks of age in male Springer Spaniels [84,85]. Tremors in Springer Spaniels ("shaking pups") are much more severe than those in Chow

Chows or Lurcher Hounds. Animals have great difficulty standing, performing useful coordinated movements, and cannot feed without assistance. A pendular nystagmus may be seen. Affected dogs are approximately half the size and weight of normal littermates. Seizures may occur as dogs mature. Most animals are euthanized as a result of progressive morbidity. Some heterozygous female puppies have shown a tremor at 12 - 14 days of age, which is not as severe as the affected males and which may disappear by 1 month [85].

Hypomyelination occurs throughout the CNS and it is more marked in the cerebrum and optic nerves than in the spinal cord. There is marked pallor of the white matter on gross examination of the CNS. Axons are either naked or surrounded by a disproportionately thin layer of myelin. Myelinated internodes tend to be short and heminodes are frequent. Vacuoles are present adjacent to axons or within glia but there is no evidence of demyelination. At the light microscopic level, many oligodendroglial and astrocytic nuclei are seen. Peripheral, cranial and autonomic nerves are myelinated normally. A marked transition from normal Schwann cell myelin to the amyelinated-hypomyelinated area of oligodendroglial territory is seen in dorsal and ventral nerve root entry zones. Ultrastructurally, there is marked distension of the rough endoplasmic reticulum (suggesting an abnormality of protein synthesis or transport) and perinuclear envelope in oligodendrocytes. Myelinated and non-myelinated zones are often found on a single axon. Many myelin sheaths appear poorly compacted and often show paranodal or internodal abnormalities suggestive of immaturity. Abnormal inter-relationships of oligodendrocytes and astrocytes are present at many paranodes [86] suggesting that astrocytic processes may interfere with oligodendrocyte-axon interactions [87]. A morphometric study revealed a marked reduction of oligodendrocytes in the affected pups [88]. Oligodendrocyte death was not noticeable. Astrocyte numbers were similar in both normal and affected pups. Axonal diameters were not reduced in the affected pups and there was no apparent correlation between myelination and axonal size in these animals. Total myelin volume and thickness were greatly reduced in the "shaking pups". Myelination appears to increase with age. Impaired stem cell division together with metabolic disturbance of oligodendrocytes was considered to be the main causes of the hypomyelination in this mutant [88]. Freeze-fracture studies indicated some abnormal contacts between oligodendrocytes and axons [89]. Biochemical studies have shown a reduction in various myelin proteins (myelin basic protein, myelin-associated glycoprotein, and 2' 3'-cyclic nucleotide phosphodiesterase, as well as proteolipid protein and the related DM-20 protein) and an immature form of myelin (the amount of the 21 kDa MBP compared to the 18 kDa MBP was relatively increased) in affected dogs [90,91]. Affected Springer Spaniel puppies carry mutations in proteolipid protein and DM-20, the major protein constituents of CNS myelin. These mutations reportedly hinder oligodendrocyte differentiation [92]. It has been reported that Schwann cells in shaking pups may penetrate the glia limitans and invade spinal cord, brainstem, and cerebellum and that this process increases with age [93]. Female heterozygotes of the shaking pup show myelin mosaicism of the optic nerve and spinal cord that is characterized by patches of normal central myelination interspersed between areas of amyelination or hypomyelination [85]. Abnormal oligodendrocytes with distended rough endoplasmic reticulum are found in the abnormal patches and are a marker of the trait.

### **Hypomyelination in Samoyeds**

This possibly inherited condition has been seen in puppies around 3 weeks of age [94]. Signs included generalized tremors (involving the head, eyes, trunk, and limbs), inability to stand, nystagmus (rapid spontaneous vertical or horizontal), and absent menace response. Tremors disappeared at rest or during sleep. Postural reactions, spinal reflexes, and nociception were normal. There was severe lack of myelin throughout the CNS, usually associated with reactive astrocytosis and diffuse staining for glial fibrillary acidic protein. The glia limitans appeared dense and thick with coarse astrocytic processes, especially in subpial and peripheral areas of the spinal cord. Staining for myelin basic protein was markedly diminished in hypomyelinated areas. Ultrastructurally, most axons were devoid of myelin, but occasional fibers were encircled by several poorly compacted lamellae, sometimes with accompanying astrocytic processes. Many naked axons were abutted by multiple astrocytic processes containing microtubules and intermediate filament bundles. Oligodendrocytes were greatly reduced in number (representing 13% of all glia counted compared to 57% in control pups). Furthermore, the oligodendrocytes were of the immature light or medium type and contained distended cisternae of endoplasmic reticulum and nuclear envelopes, similar to that seen in the shaking Springer Spaniels [88]. Lack of mature dark cells (these cells were present in the shaking Spaniels) suggested disruption in oligodendrocyte differentiation and maturation, as has been reported in the shaking Spaniels [88,92]. There were increased numbers of astrocytes and microglial cells (type III glial cells). Peripheral nerves were myelinated normally.

### **Hypomyelination in Weimaraners**

American Weimaraner puppies of either sex affected by hypomyelination develop generalized body tremors and dysmetria about 3 weeks of age [95]. Mental status, gait, postural reactions, vision, and cranial nerve and spinal reflexes are normal. Signs appear to ameliorate with age, so that dogs may be clinically normal by one year of age. Many axons throughout the brain and spinal cord are either hypomyelinated or amyelinated relative to controls.



Hypomyelination is especially prominent in peripheral subpial regions of the spinal cord, particularly of the ventral and lateral funiculi. In contrast, dorsal columns appear normally myelinated. Myelin is normal in nerve roots and peripheral nerves. In hypomyelinated areas, astrocytes outnumbered oligodendrocytes that have features typical of medium or dark cell types. Ultrastructurally, some myelin sheaths are uncompacted while many axons are being actively myelinated. There is no evidence of oligodendrocyte necrosis. Neuronal cell bodies are normal. A reversible defect in glial differentiation is considered responsible for the hypomyelination.

A condition has been reported in the UK in an 8 week old Weimaraner puppy with signs of incoordination, pelvic limb weakness and ataxia, bunny-hopping gait when attempting to move quickly, and abnormal frog-like sitting posture [96]. A tremor was not seen. There was no muscle atrophy in the limbs. There was subpial depletion of myelin throughout the spinal cord, involving all funiculi. Pial thickening and vacuolated degeneration of the sensory neurons in the dorsal horns and of neurons in the lateral cuneate nucleus and in the lateral caudal part of the reticular formation in the medulla accompanied this change. Dystrophic axons were present in the spinal cord, granular layer of the cerebellar vermis, and internal capsule. While focal vacuolation was seen in the cerebellar white matter, there was no myelin depletion found in the brainstem, cerebellum or cerebral hemispheres. No abnormalities were seen in nerve roots, dorsal root ganglia or in peripheral nerves. Despite the clinical and pathological differences, the condition in this puppy may be a variant of the disorder described above in the American Weimaraners.

### **Hypomyelination in Bernese Mountain Dogs**

Clinical signs of central hypomyelination appear in Bernese Mountain Dog puppies of either sex from 2 to 8 weeks of age [97] and are manifested as a fine tremor of the limbs and head which becomes more intense with excitement or stress and which disappears with sleep. Other signs are weakness, imbalance, a high tail carriage, and a stiff action of the pelvic limbs. Signs appear to gradually diminish with age but tremors may reappear when animals are frightened or excited. Hypomyelination, characterized by presence of thinly myelinated axons, is observed throughout the spinal cord but not in the brain. There is astrocytosis and an increased number of astrocytic processes. Oligodendrocytes appeared normal, except for a small number (approximately 5%), which contained abnormal dilated membrane systems, membranous whorls and osmiophilic structures. Peripheral nerves are myelinated normally. Preliminary breeding data suggest an autosomal recessive mode of inheritance.

### **Hypomyelination in Dalmatians**

Cerebrospinal hypomyelinogenesis has been reported in a 5 week old Dalmatian puppy [98]. Generalized body tremors were present at birth. The puppy could not walk voluntarily and horizontal pendular nystagmus was observed. The tremors disappeared at rest and during sleep. Spinal reflexes were normal. Grossly, on frontal sectioning of the brain and spinal cord, poor demarcation between the gray and white matter was noted. Microscopically, myelin was not found anywhere in the CNS, although normal axons were demonstrated with silver stains. Disseminated spongy vacuolation was found in the white matter of the spinal cord. There was no evidence of active white matter degeneration. Ultrastructurally, there was prominent astrocytic gliosis throughout the white matter. Cells, with features typical of oligodendrocytes, appeared reduced in number. Most nerve fibers were entirely devoid of myelin, but occasional larger axons were covered by a thin irregular layer of 2 or 3 myelin lamellae. Abnormal myelin inclusion figures were noted in some oligodendrocytic processes. Limited axonal necrosis was found throughout the white matter. The peripheral nerves were myelinated normally. A failure of myelin synthesis was considered the primary cause of this disorder.

### **Hypomyelination in Cats**

Hypomyelination of the CNS has been reported in two Siamese kitten littermates [99]. Signs began at 4 weeks of age and were characterized by a history of progressively intensive whole body intention tremors accompanied by episodes of frenzied behavior with indiscriminate biting. The kittens assumed a quiet (normal) state at rest, but with activity, the above-mentioned signs returned. Microscopic examination of spinal cord revealed marked hypomyelination, as suggested by pallor of white matter of the lateral and ventral funiculi, without apparent rostrocaudal gradation in severity. The dorsal columns appeared normal, as did nerve roots and spinal ganglia. Silver staining showed morphologically normal axons. The brainstem, cerebellum, and cerebral cortex appeared normal. Glial fibrillary acidic protein staining confirmed a mild astrogliosis, including an increased prominence of the glia limitans in the hypomyelinated areas, with astroglial processes often assuming a radial orientation. Ultrastructurally, there was a preponderance of nonmyelinated axons and the few myelinated sheaths that were present appeared thin and frequently loosely compacted. Astrocytic processes often had condensed intermediate filaments. Immunocytochemically, the intensity of staining for myelin basic protein, myelin-associated glycoprotein, and proteolipid protein was decreased in the hypomyelinated areas, reflecting the increased numbers of hypo- or amyelinated axons.

Note that frenzied behavior and biting is unusual for hypomyelination and may represent paresthesia evoked by inappropriate

excitation of noninsulated portions of sensory pathways [99].

### **Miscellaneous Hypomyelination**

Note that various forms of CNS hypomyelination have been reported in several lysosomal storage diseases, including globoid leukodystrophy in dogs and mannosidosis in cats.

### **Idiopathic Vascular Calcification**

A novel degenerative disease has recently been reported in a 3 month old Labrador Retriever puppy [196]. Clinical signs included progressive lethargy, weakness, and reluctance to move over a three day period. Examination revealed generalized muscle atrophy and palpably hard muscles. Joints were enlarged and painful and there was restricted range of joint and spinal movement. The dog showed slight ventroflexion of the head, neck stiffness, and was tetraparetic with proprioceptive deficits in pelvic limbs. All spinal reflexes were diminished. Radiographic studies showed multifocal mineralization throughout the body including intervertebral disks, cartilage of spinous processes, intersternbral and costal cartilages, growth plates, articular/periarticular soft tissues (joint capsules, muscle/tendon insertions), menisci, and thyroid, cricoid and extrathoracic tracheal cartilages. In addition, mineralization was noted in the common carotid arteries, tongue and kidney vessels, and vessels in the popliteal region. Sonography confirmed mineralization of neck and kidney arteries. EMG studies indicated presence of fibrillation potentials in paraspinal and limb muscles while nerve conduction was slow in the peroneal nerve. Grossly, carotid and coronary arteries were extremely hard and thickened by mineral deposition. Microscopic changes included marked mineral deposition in the tunica intima and tunica media of blood vessels in several organs, as well as in carotid and coronary arteries. The mineralization in periarticular tissue and joint capsules was accompanied by a granulomatous reaction with numerous multinucleated giant cells. In cervical and thoracic spinal cord segments, a myelopathy characterized by fragmentation and loss of axons and myelin ballooning/macrophage phagocytosis was found in all white matter funiculi. Multifocal subdural calcifications were seen at all levels of the spinal cord. Swollen axons and partial myelin loss was found in the peroneal nerve while calcifications were noted in perineurial vessels of the radial nerve. Atrophy and hypertrophy were present in skeletal muscle. No histological abnormalities were observed in the brain. The cause of the calcifications was not determined. Additional diagnostic testing revealed that serum parathormone, vitamin A, 25-hydroxycholecalciferol (25-OH-VitD), and 1,25-dihydroxycholecalciferol (1,25-OH-VitD) were normal. In addition, screening for mucopolysaccharidoses did not indicate storage disease. The authors suggested that this unusual condition had similarities to idiopathic arterial calcification of infancy seen in children, a rare disorder characterized by extensive arterial calcification and stenoses of large and medium-sized arteries with complications including severe systemic hypertension and cardiomyopathy [197].

### **Kooiker Dog Myelopathy**

A degenerative myelopathy has been reported in young Kooiker dogs (Dutch decoy dogs), of either sex, with signs beginning from 3 to 12 months of age [11,100]. Clinical signs include mild to severe hind limb paresis and ataxia. In some dogs, forelimbs are similarly affected and there may be proprioceptive deficits, exaggerated spinal reflexes, and urinary incontinence. Many dogs are euthanized by 12 months of age. Routine hematology, blood chemistries, radiography, and myelography are normal. Grossly, lesions are found at all levels of the spinal cord, and are seen as transparent areas associated with malacia and loss of myelin and axons. Lesions appear most severe in the last cervical and first thoracic cord segments, being localized primarily in ventral and dorsal columns. The ventral malacic areas extend to involve lateral columns in some cervical and thoracic segments. In severely affected dogs, all white matter may be involved in some thoracic segments. There is reactive vascular proliferation, numerous macrophages, and variable numbers of gemistocytic astrocytes in the malacic areas. At the border of the necrotic areas, axons appear intact. Wallerian degeneration occurs in spinal cord segments caudal to the ventral and lateral malacic areas, and rostral to the dorsal areas of malacia. Spinal cord neurons and nerve roots are not affected. Wallerian degeneration in the dorsal funiculus sometimes extended to the gracile and cuneate nuclei. Severe neuronal degeneration may occur in trapezoid body, while vacuolation is sometimes seen in the olivary nuclei. Pedigree studies suggest this disease has a simple autosomal recessive mode of inheritance. This condition is quite similar clinically and pathologically to Afghan hound myelopathy except for the reported axonal involvement in the Kooiker dogs [2].

### **Labrador Retriever Axonopathy**

A degenerative disorder has been reported in Labrador Retriever puppies characterized by an ataxic-dysmetric gait when they first begin to walk [10]. The hind limbs move in a crouched, short-strided, adducted manner while the forelimbs are hypermetric. Animals may fall frequently. Forelimbs become progressively more spastic and abducted. By 3 to 5 months of age, most puppies are unable to stand or walk without assistance. Signs may remain static after this time. Head tremor occurs late in the course of the disease. Hematology, blood chemistries, and CSF analysis are normal.

Grossly, all affected puppies have aplasia or hypoplasia of the corpus callosum. Spina bifida at C7 has been found in two puppies. Microscopically, there is extensive bilaterally symmetrical degeneration of the spinal cord white matter, particularly in the superficial dorsal areas of the lateral funiculi, the fasciculus gracilis of each dorsal funiculus, and the ventral funiculus adjacent to the ventral median fissure. The degenerative changes are most severe in the thoracic cord segments, with decreasing intensity in the lumbar and cervical segments. Degenerative changes of partial or complete axonal and myelin loss and associated gliosis are found throughout the medulla oblongata, caudal cerebellar peduncles, and cerebellum. Ultrastructural studies indicate a more extensive loss of larger caliber axons with preservation of smaller processes. There is multifocal presence of swollen axonal spheroids that contain neurofilaments, vesicular structures, mitochondria, and Golgi apparatus. The spheroids appear most numerous in the dorsal funiculus of the cord at all spinal levels, on the lateral surface of the medulla, and in focal areas of the granular layer of the cerebellar cortex. They occur with less frequency in the foliate and central cerebellar white matter, transverse fibers of the pons and middle cerebellar peduncles, optic tracts, internal capsule, and corona radiata of the cerebrum. There is extensive neuronal loss in spinal ganglia and spinal cord gray matter. Degenerative changes are found in each olivary nucleus characterized by neuronal chromatolysis and scattered large spheroids. In some dogs, there is complete loss of cell bodies in these nuclei with astrocytic replacement. This degenerative disorder is presumed to have an inherited recessive mode of inheritance [10].

### **Lafora's Disease**

A progressive, degenerative neurological disorder associated with a complex glycoprotein accumulating within neurons and glial cells or lying free in the neuropil has been recognized sporadically in dogs for several decades. The condition is considered analogous to Lafora's disease in people in whom it is clinically characterized by progressive myoclonic epilepsy. Most reports involve older Beagles and Basset Hounds. Clinical signs are variable, including depression and somnolence [101]; however, seizures (e.g., myoclonic epilepsy, see Epilepsy) are often reported in advanced stages of the disease, and have been noted in affected dogs from 5 months to 7 years of age [102-107].

Seizures can be precipitated by external stimuli, especially a change in noise or light in the surroundings [103,107]. Electroencephalographic studies may reveal slow, rhythmic activity with showers of myoclonic type seizure patterns [107]. In a 10 year old female Corgi, clinical signs progressed from abnormal, jerky head movements to generalized muscle fasciculations with severe myoclonic contractions of the head and neck muscles [102]. Almost identical signs (body tremors, twitching, and/or abnormal jerky head movements) have been observed in Miniature Wirehaired Dachshunds in the United Kingdom [198] and in South Africa [199]. The myoclonic jerks occurred spontaneously or in response to visual or auditory stimuli, or sudden movement, but did not appear to affect consciousness. In one study, generalized seizures and hypnic jerks were also reported [198]. Apart from these signs, neurological examination was normal in these dogs, as were hematology and serum chemistries (except for mild increase in CK and lactate dehydrogenase levels in some instances), CSF analysis, and cranial magnetic resonance imaging. EMG studies may be normal [198] or show evidence of moderate amounts of fibrillation potentials and positive sharp wave activity [199]. Muscle biopsy may reveal presence of an amorphous bubbly subsarcolemmal material consisting of periodic acid-Schiff positive, diastase resistant inclusions (polyglucosan bodies) [105,198,199]. The inclusions also stain positively with Grocott's methenamine silver nitrate. Similar inclusions may be found in peripheral nerves [198]. The ultrastructural characteristics are similar to those inclusions found in the CNS (see below).

In most reports to date, variably sized, basophilic inclusions have been observed in perikarya and processes of neurons throughout the brain and spinal cord, and are often especially numerous in neurons within the cerebrum, cerebellum, thalamus, and midbrain [101-104,106,107]. The inclusions are strongly positive for carbohydrate stains, weakly metachromatic, and lipid negative [101,103]. The histological, immunohistochemical, and ultrastructural features of polyglucosan bodies in humans and Lafora bodies in dogs are similar [108]. Lafora bodies in dogs stain with concanavalin A indicating they contain mannose and glucose residues and suggest a derivation from rough endoplasmic reticulum and Golgi [109]. Occasionally, they are also seen in retina, peripheral nerves, liver, spleen, and lymph nodes. In skeletal muscle, inclusions that stain dark blue with hematoxylin and eosin, and red with periodic acid-Schiff (PAS), may be seen lying between myofibers or beneath the sarcolemma [103,105]. Based on differences in internal structure and staining characteristics, three types of Lafora bodies are recognized [104]:

1. Type I - Small (3 to 10  $\mu\text{m}$  in diameter), fine, evenly stained granules. This is the most common type and is usually found in middle and deep layers of the cerebral cortex and in glial cells of the cerebellum. Ultrastructurally, these bodies consist of branching fibrillar structures without a limiting membrane. The branching filaments measure about 8 - 10-nm in diameter [110].
2. Type II - These larger bodies (13 to 30  $\mu\text{m}$  in diameter) have a strongly PAS-positive homogeneous core with a more faintly staining radiating periphery. This form is commonly found in Purkinje cells of the cerebellum and in the midbrain. Electron microscopy reveals osmiophilic granules in a central core surrounded by fibrillar material. Rough

endoplasmic reticulum in affected neurons may be dilated with increased numbers of coarse ribosomes free in the cytoplasm. Such changes suggest abnormalities in protein synthesis.

3. Type III - These bodies range from 5 to 20  $\mu\text{m}$  in diameter and are occasionally found in the midbrain. These structures exhibit a dense peripheral ring of PAS-positive material.

The relationship between seizures and these Lafora bodies is enigmatic since similar inclusions have been observed in the CNS of older dogs (e.g., over 8 years of age) of various breeds with no signs of seizures [101,110-112]. These bodies may also be found in the retina of clinically normal dogs and cats [113]. Furthermore, in a recent study of epilepsy-prone beagles only 6 of 68 dogs (8.8%) had Lafora-like inclusion bodies [114].

Lafora bodies have also been found in cats. In a recent report, Lafora bodies were identified in the brain of a young adult cat with neurological signs characterized by intermittent but progressively worsening head and body tremors [115]. The cerebellar cortex was the most severely affected area of the brain and the deposits were identified within Purkinje cell bodies and processes and throughout the neuropil. More commonly, Lafora bodies occur in the CNS of aging cats, without signs of seizures, as incidental lesions [116]. In one feline study, most of the bodies were situated in the neuronal processes and disseminated throughout the brain, especially in the cerebral cortex, midbrain, cerebellum and medulla oblongata [117]. In the spinal cord of older cats and dogs, caudal lumbar and the coccygeal regions are reportedly predilection sites for Lafora bodies, being prominent in the ventral column and intermediate substance and preferentially located in neuronal processes, but only rarely in astrocytes. [118].

Prognosis is somewhat guarded in animals with Lafora's disease because of the tendency for signs to become progressively worse; however, this may not be the case for at least some affected Miniature Wirehaired Dachshunds [198]. In people, Lafora's disease is an autosomal recessive, progressive myoclonus epilepsy with characteristic inclusions (polyglucosan bodies) caused by mutations in the EPM2A gene, which codes for laforin, a cell membrane and endoplasmic reticulum-associated protein, tyrosine phosphatase, that may play a role in the prevention of polyglucosan accumulation in healthy neurons [200,201].

### **Miniature Poodle Demyelination**

A rare, possibly inherited, neurodegenerative disorder has been reported in Miniature Poodles [119-121]. Clinical signs first appear between 2 and 4 months of age with some puppies showing signs of ataxia-dysmetria with constant shifting of the hind limbs and difficulty standing. Puppies may fall frequently trying to reach their food bowl. Within 1 to 2 weeks, puppies develop a spastic paraplegia followed rapidly by a tetraplegia [119,120] and tend to lay on their sides with all limbs extended, sometimes with the forelimbs held in a clasped position [120]. Placing and hopping reactions are absent, while spinal reflexes are usually intact, cranial nerve function is normal, and puppies remain alert. Hand feeding may be necessary and some puppies appear to have impaired tongue function. In one report, grinding of the teeth was a constant sign [121]. Loss of sensation to pinprick caudal to the scapula was noted in another affected dog [119]. Hematology, blood chemistries, urinalysis, and radiography are within normal limits. CSF analysis is usually normal, although a mild protein increase was noted in one dog [121].

Microscopically, large areas of malacia occur in the midbrain and the cervical cord [119]. In the midbrain, there is a symmetrical loss of myelin in the tegmentum. Areas of malacia also occur bilaterally in medial and lateral lemniscus, inferior colliculus, cerebral peduncles, posterior commissure, corpus callosum, middle cerebellar peduncle, roof of the cerebellum, descending vestibular tract, and pyramids [119]. In the cord, the most severe lesions occur in dorsal and ventral white columns of cervical and thoracic segments [121]. Loss of myelin may be almost complete at C7 with only the fasciculus proprius being spared, while there is some preservation at C2 and T5, and only slight loss at the lumbar intumescence [119]. The dominant lesion appears to be distinct myelin degeneration and loss. In the center of the malacic lesions, nerve cells are preserved, although some show evidence of chromatolysis. There is some hyperplasia of small vessels with endothelial swelling, a microglial reaction, and variable astrocytosis. In some areas, lipid macrophages are common. A status spongiosis is found at the periphery of the malacic lesions with myelin ballooning. Silver stains reveal loss and degeneration of axons in some areas, but with some degree of axonal integrity in others [121]. Gray matter in the spinal cord is preserved, as are dorsal and ventral nerve roots. Prognosis is poor. There is no treatment. To my knowledge, there have been no additional reports of this disease during the past 20 years. Summers and colleagues reported that 2 cases had been seen at Cornell over the course of 30 years [3].

### **Mitochondrial Encephalomyelopathy**

A progressive encephalomyelopathy of insidious onset has been reported in a 16-month-old female English Springer Spaniel [122]. Clinically, the dog showed evidence of ataxia-dysmetria that was exacerbated by excitement, occasionally stumbled into objects, and had mild behavioral abnormalities, including moments of disorientation and being easily excitable. A vertical positional nystagmus could be elicited and postural reactions were delayed and spastic in all limbs. Patellar reflexes

were brisk and there was no evidence of muscle atrophy. Routine laboratory findings, including CSF analysis, were normal. Grossly, bilateral and symmetrical depressed gray foci were observed in the dorsal accessory olivary nuclei. Light microscopic findings included profound Wallerian degeneration (diffuse axonal and myelin loss) and astrogliosis of the optic pathways (bilaterally), loss of Purkinje neurons along with Bergmann's gliosis, granular cell layer torpedoes, and axonal spheroids and gliosis in cerebellar nuclei (bilaterally), focal bilateral and symmetrical brainstem spongiosis (olivary nuclei and substantia nigra) and diffuse neuraxial astrogliosis with swollen and abnormally shaped nuclei in the above-mentioned sites as well as in the lateral geniculate nuclei. The majority of neurons in the brain and spinal cord appeared normal. Variable, scattered Wallerian degeneration was found in all white matter funiculi of the spinal cord and peripheral nerves, especially the sciatic. Ultrastructurally, there were giant (up to 10 times normal size) and bizarre mitochondria (e.g., increase or loss of mitochondrial cristae, membrane blebbing, and internal compartments) within neuronal perikarya and axons as well as diffuse loosening of the cerebral and cerebellar neuropil associated with myelin sheath ballooning and/or astrocytic intracellular edema. It was suggested that the neuropathological findings in this dog resembled the mitochondrial encephalomyopathies of man.

### **Motor Neuron Diseases**

Motor neuron diseases are neurodegenerative disorders in which there is premature degeneration and death of various neuronal cell populations in the spinal cord and/or brainstem, and as such, can be classified among the degenerative abiotrophies [1]. In small animals, most of the conditions involve the spinal cord lower motor neurons and, based on comparative studies, have also been termed spinal muscular atrophies. Most of these degenerative conditions occur within the first 3 to 6 months of life. Motor neuron diseases have been reported in several breeds of dogs, in which they have a familial or genetic basis, but are only rarely seen in cats. Clinical signs usually are progressive and tend to be dominated by neuropathies in pelvic and thoracic limbs as a consequence of lower motor neuron (LMN) involvement. Prognosis is guarded to poor, and there is no treatment.

### **Motor Neuron Disease in Giant-Breed Crosses**

This rare degenerative condition, also known as Stockard's paralysis, was produced in 1936 by crossbreeding Great Danes with Bloodhounds and St. Bernards [123]. Clinical signs occur around 3 months of age and are characterized by sudden onset of paresis and posterior paralysis, priapism, and atrophy of pelvic limb appendicular muscles. There is no involvement of head, neck, or trunk. No additional reports have appeared in the literature since 1936. Pathological findings include chromatolysis, degeneration, and depletion of motor and preganglionic sympathetic neurons in ventral and intermediolateral horns of lumbar spinal cord. The disease is transmitted through an inheritable, multiple factor involving at least three dominant genes.

### **Motor Neuron Disease in Swedish Lapland Dogs**

An autosomal recessive disease has been reported in Swedish Lapland dogs [124] that has been compared to infantile spinal muscular atrophy (Werdnig-Hoffman disease) in children [124]. I have listed this condition with the multisystem neuronal abiotrophies.

### **Motor Neuron Disease in English Pointers**

A LMN degenerative disorder has been described in young English Pointer dogs in Japan [125] that appears to have an autosomal recessive mode of inheritance [126]. Clinical signs of pelvic limb trembling (an initial sign), weakness, dysphonia, and diminished tendon reflexes are observed in affected dogs at about 5 months of age. Progressive muscular atrophy occurs in all limbs and trunk, particularly in the shoulder region. Animals eventually become tetraplegic, with superficial muscle fasciculations seen and eventually, joint contractures. Electromyographically, fibrillation potentials and positive sharp waves are noted in epaxial, proximal, and distal appendicular muscles, but are first seen in distal muscles [127]. The clinical course of this progressive disease is 3 to 4 months. Routine hematology and radiography are normal.

Axonal degeneration is found in peripheral nerves and chronic neurogenic atrophy and endomysial fibrosis occur in skeletal muscle. While the number of ventral horn cells in the spinal cord seem to be normal, numerous accumulated lipid-like granules, 1 to 3  $\mu\text{m}$  in diameter, are present in ventral horn cells and in hypoglossal and spinal accessory nuclei of the brainstem. These granules stain with Nile blue sulfate, Sudan black B, Luxol fast blue, Alcian blue, and periodic acid-Schiff on paraffin sections, suggesting the granules are composed of a compound lipid. The granules have no autofluorescence. Ultrastructurally, granules appear as multi-lamellar structures, arranged concentrically or in parallel, resembling membranous cytoplasmic bodies or zebra bodies. This finding suggests that a hereditary abnormality of lipid metabolism may underlie the LMN disease in these dogs [125].

### **Motor Neuron Disease in German Shepherds**

A focal form of spinal muscular atrophy has been reported in two German Shepherd puppies [128]. Signs were seen 2 weeks after birth and were characterized by unilateral or bilateral thoracic limb weakness and atrophy, carpal valgus deformity, and carpal flexion due to contracted, atrophic flexor muscles. In one puppy, signs progressed rapidly over the ensuing 5 weeks to the point he was unable to stand or walk using the thoracic limbs. Electromyographic studies revealed fibrillation potentials and complex high frequency activity in shoulder, forearm and interosseous muscles, bilaterally. Microscopic changes included asymmetric loss and degeneration of motor neurons in the cervical spinal cord intumescence (from C5 to T1), especially in the lateral region of the ventral horn of C7 - 8. Degenerating neurons appeared vacuolated or chromatolytic. Glial nodules, neuronophagia, and axonal spheroids were seen occasionally. Degenerative changes, including axonal loss and multifocal presence of Bungner's bands (denervated Schwann cells), were observed in ventral rootlets and in thoracic limb peripheral nerves, and neurogenic atrophy was seen in muscle. Ultrastructurally, numerous denervated Schwann cells were seen together with dispersion and loss of ribosomes, and variable cisternal dilation in some degenerating neurons. The peripheral chromatolysis resulted from dispersion and loss of the free and attached ribosomes that normally form Nissl bodies. Prognosis is guarded. Surgical tenotomy and carpal splinting were effective in the second dog, which was clinically less affected. At 15 months of age, thoracic limb atrophy was not seen in this dog, although slight weakness was sometimes observed. This canine condition is thought to resemble the asymmetric and unilateral, benign spinal muscular atrophies found in people.

### **Motor Neuron Disease in Doberman Pinchers**

Motor neuron degeneration has been documented in 2 male Doberman puppies from a litter of eight [10]. Signs of pelvic limb weakness were seen around 4 weeks of age and progressed to tetraparesis and muscle atrophy in all limbs. Microscopic changes showed degeneration of neurons in spinal cord and various brainstem nuclei, including vestibular and reticular nuclei. The neurons were chromatolytic or vacuolar, the latter change apparently being derived from rough endoplasmic reticulum.

### **Motor Neuron Disease in Griffon Briquet Vendéens**

Motor neuron disease characterized by progressive weakness, hind limb paresis and eventually tetraparesis (extensor paralysis in hind limbs, flexor paralysis in forelimbs) was documented in two 2 month old Griffon Briquet Vendéen dogs from a litter of six [202]. Muscle atrophy was prominent in all limbs, with diminished spinal reflexes and loss of superficial and deep pain sensation. Mental status and cranial nerve function were normal. Microscopic lesions included marked neuronal loss in ventral horns cells of the spinal cord, Wallerian degeneration of ventral spinal roots and peripheral nerves, and neurogenic muscle atrophy. Axonal swelling was noted adjacent to neuronal cell bodies. In addition, a severe loss of motor neurons was observed in the red nuclei and in lateral and medial vestibular nuclei accompanied by astrogliosis.

### **Motor Neuron Disease in Salukis**

A motor neuron abiotrophy was reported in a 9 week old Saluki puppy presented for progressive generalized weakness and bilaterally symmetrical deformities of the carpi associated with limb contracture [236]. Histological lesions included diffuse, symmetrical, degenerative lower motor neuronopathy of the ventral horn of the spinal cord characterized by neuronal swelling, chromatolysis, swollen dendritic processes and enlarged axons. Degenerative changes were present in ventral nerve roots. No lesions were seen in spinal ganglia or brainstem nuclei. Similar clinical signs were noted in a sibling.

### **Motor Neuron Disease in Other Canine Breeds**

A LMN disease has been reported in New Zealand in 9 dogs (6 rural collie sheep dogs, a Pug, a Dachshund, and a Fox Terrier. Seven of the dogs were 3 to 9 months of age) [129]. Clinical signs included acute onset of posterior paresis that typically progressed rapidly (over 2 to 4 weeks) to posterior flaccid paralysis and, in 3 dogs, to tetraplegia. Severe muscular atrophy occurred in pelvic limbs and, in a few animals, in all four limbs. Microscopic lesions were found in thoracic and lumbar cord segments in dogs with pelvic limb signs and were also present in cervical cord segments in tetraplegic dogs. Lesions were characterized by mild to marked loss of motor neurons in lateral and ventrolateral regions of the ventral horn of the spinal cord (often seen as empty spaces), and often accompanied by diffuse microgliosis and several small glial scars in areas of missing motor neurons, and presence of Wallerian degeneration in ventral spinal roots and spinal nerves. The peripheral nerve changes appeared more severe in distal levels. Minimal changes were seen in dorsal roots or dorsal root ganglia. The cause of the LMN disease was not established.

### **Motor Neuron Diseases with Neurofibrillary Accumulation**

Several motor neuron disorders have been described in which there is accumulation of neurofilaments in neurons. The best studied is hereditary canine spinal muscular atrophy (HCSMA), a dominantly inherited, LMN disease in **Brittany Spaniels** that does not appear to be sex linked [130-132] and which has certain clinical and pathological features in common with familial amyotrophic lateral sclerosis in people [133]. Three forms of the disease have been recognized-accelerated, intermediate, and chronic [134]. The accelerated disease appears in puppies that are homozygous for the trait; whereas, heterozygous animals express intermediate and chronic phenotypes [132].

- a. Early Onset or Accelerated Disease - This form of the disease is similar to spinal muscular atrophy of infants (spinal muscular atrophy type I or Werdnig-Hoffman disease [135]). Puppies first show clinical signs by 6 to 8 weeks of age. Affected puppies are usually thinner than littermates, develop weakness associated with paraspinal and proximal pelvic limb muscular atrophy, and often have a slow tremor of the head. There is weakness of muscles of mastication and the tongue, which makes feeding difficult, and the gag reflex may be depressed. Affected dogs become tetraparetic or tetraplegic and are unable to lift their heads by 3 to 4 months of age. They lose about 30% of their body weight due to neurogenic muscle atrophy. Pathological findings occur in motor neurons of the ventral horns of the spinal cord and certain brainstem nuclei, especially the hypoglossal, and include chromatolysis, variable dendritic enlargement, and swollen axons in gray matter of spinal cord, and sometimes, in proximal portions of the ventral root exit zone or proximal ventral roots. Proximal axons are filled with massive accumulations of 10-nm maloriented intermediate neurofilaments, an abnormality similar to that which occurs early in the course of human amyotrophic lateral sclerosis [130,133]. Many myelin sheaths around distended axons are attenuated.
- b. Intermediate Disease - This is the most common form of the disease [2] and is similar to juvenile spinal muscular atrophy of children (spinal muscular atrophy type III or Kugelberg-Welander syndrome [135]). Clinical signs develop by 6 to 12 months of age, and are characterized by weakness in proximal muscles of limb girdles and trunk. Animals walk in a waddling fashion. Progressive atrophy ensues in proximal muscles of pelvic limbs and lumbar paraspinal muscles. Intercostal muscle involvement may lead to respiratory distress. Affected dogs are usually unable to walk by 2 to 3 years of age. Microscopic findings reveal loss of motor neurons late in the disease, fewer axonal swellings than those seen in the accelerated disease, and neuronophagia in ventral horn neurons. Ultrastructurally, there may be electron-dense, membrane-bound, intracytoplasmic vacuoles in both dendrites and neurons. Occasional neurons contain tubulo-fibrillar material. Wallerian-like degeneration may be present in ventral horn, intramedullary ventral root exit zone, and proximal ventral roots. Distal axons are atrophic.
- c. Chronic Disease - This form is characterized by slowly progressive disease, with dogs surviving well into adult life. Clinical signs are usually mild, except for overall thinness. One dog has reportedly survived for more than 7 years without marked motor involvement. Microscopically, motor neurons tend to be intact and only few axonal swellings are observed.

Electromyography reveals sporadic fibrillation potentials and positive sharp waves. Nerve conduction studies are normal. Degenerative changes in peripheral nerves result in neurogenic atrophy, particularly in more proximal appendicular and paraspinal muscles.

The pathogenesis of HCSMA remains unclear. The neurofilamentous swellings of proximal axons, atrophy of distal axons, and degeneration of motor neurons are believed to be associated with impaired axonal transport of the neurofilament triplet proteins and a maldistribution of phosphorylated neurofilaments [133]. Cyclin-dependent kinase 5, an enzyme that phosphorylates neurofilaments and regulates neurofilament dynamics, is markedly increased in young HCSMA homozygotes prior to the development of significant neurofilament pathology [136]. In the accelerated and intermediate phenotypes, there is a reduction in axonal size in ventral roots, primarily in large axons, and the frequency of small-caliber axons is increased; however, the density of fibers in motor nerves is increased, suggesting that the changes in axonal size in motor nerves are associated with both growth arrest and axonal atrophy [137]. Results of recent studies suggest that motor unit failure is due to failure of neuromuscular synaptic transmission that precedes nerve or muscle degeneration [231]. Immunocytochemical and morphometric studies on dogs with intermediate and chronic phenotypes indicate that HCSMA cholinergic motor neurons are smaller, with fewer neurons expressing choline acetyltransferase, compared with controls [138]. Acidic excitatory amino acids may also play a role in the pathogenesis. There are significant reductions in the levels of endogenous aspartate, glutamate, N-acetylaspartate (NAA), and the neuropeptide N-acetyl-aspartyl-glutamate (NAAG) in the spinal cord in homozygous but not heterozygous HCSMA [139]. In contrast, the activity of N-acetylated-alpha-linked-amino dipeptidase, an enzyme that cleaves NAAG into NAA and glutamate, is significantly increased. None of these parameters is affected in the motor cortex or occipital cortex. Other studies on colony dogs have revealed low serum vitamin E concentrations in affected dogs, especially puppies, but no mutations in a major cytosolic antioxidant enzyme, Cu/Zn superoxide dismutase (SOD1) [232,233].

Prognosis is favorable only for Brittany Spaniels with the chronic form of the disease. At this time, there is no treatment. A LMN disease associated with spinal muscular atrophy has been reported in young **Rottweiler puppies** [140-142]. Signs were seen at 4 weeks of age and included pelvic limb ataxia that rapidly progressed to tetraparesis and tetraplegia over the ensuing 2 to 4 weeks. Additionally, spinal reflexes were diminished or absent (except for flexor and perineal reflexes), and there was slight intention tremor, limb tremor after exercise, depressed postural reactions, megaesophagus with regurgitation, inability to hold up the head, generalized muscle atrophy, and development of pelvic limb extensor rigidity. Analysis of CSF was normal. Microscopic findings were characterized by central chromatolysis and swelling of many neurons in ventral horns of the spinal cord and in several brainstem nuclei, including red, oculomotor, trigeminal motor, and ambiguus nuclei. Wallerian-like degeneration was prominent in neuropil of spinal cord and in peripheral nerve. Affected neurons contained prominent Golgi complexes and numerous neurofilaments.

De Lahunta has described a young Rottweiler puppy with some clinical and pathological variations [1]. Tetraparesis was evident without significant muscle atrophy. The swollen chromatolytic motor neurons contained widely dispersed endoplasmic reticulum but few neurofilaments, and degenerative changes were found (in addition to those neuronal populations described in the Rottweilers above) in neurons of the spinal ganglia and various medullary sensory neurons, including vestibular, cochlear and cerebellar nuclei.

Neurofibrillary accumulation has also been reported in a 12 week old **Collie** puppy with signs of progressive neurological disease [143]. The puppy was weak, had difficulty rising from a sitting position, and would frequently collapse when walking. Patellar reflexes were diminished. Cranial nerve function appeared normal except for absence of menace response and presence of widely dilated and unresponsive pupils. A diffuse neuronal abnormality was observed microscopically. An intracytoplasmic slate-gray material that appeared fibrillar and often arranged in whorls distended the cell body and displaced the nucleus and Nissl substance peripherally. Lower motor neurons of the ventral gray column were affected in the first cervical spinal cord segment, as well as neurons in various brainstem nuclei, including vestibular nuclei, spinal nucleus of the trigeminal nerve, ventral nucleus of the trapezoid body, central tegmental nucleus, oculomotor nuclei, mesencephalic nucleus of the trigeminal nerve, a few neurons in the rostral colliculi, and many thalamic and hypothalamic neurons. A few Purkinje cells were affected as were occasional large pyramidal neuron in layer V of the cerebral cortex. Ultrastructurally, there was abnormal proliferation of 12-nm neurofilaments arranged in whorls and linear arrays.

There are only a few reports of **cats** with motor neuron disease. A LMN disease with accumulation of neurofilaments has been described in a 10 week old female, Domestic Shorthair cat with clinical signs of tetraparesis that progressed to tetraplegia within a few weeks [144]. There was diffuse atrophy of appendicular musculature. Spinal reflexes were absent. Mentation and cranial nerve function were normal. Abnormal spontaneous fibrillation potentials were detected in limb muscles with EMG. CSF analysis was normal. Microscopically, widespread degeneration was seen in the large motor neurons of the lateral parts of the ventral horns in the cervical and lumbar intumescences of the spinal cord. Nissl substance was missing in some cells, while nuclear destruction accompanied by advanced chromatolysis resulted in formation of ghost cells. Glial nodules were seen in areas of lost neurons. A diffuse argentophilia with indistinct whorls was seen after silver impregnation of the affected neurons. Wallerian degeneration was found in ventral spinal nerve roots and peripheral nerves of the affected spinal cord segments. No other lesions were found in the spinal cord, brainstem, cerebellum, or cerebrum. Ultrastructurally, the degeneration of nerve cells was characterized by abnormal proliferation of neurofilaments, which were also seen in dendritic spines but not in axons. The fibrillary material had a diameter of about 10-nm.

Summers and colleagues described a LMN disorder in 2 older cats with signs of crouched gait, severe muscle atrophy, and tongue fasciculations [10]. Signs were present in one cat for 3 years and for 1 year in the second cat. Profound loss of motor neurons in the ventral horns were observed in cervical, thoracic and lumbar cord segments, accompanied by mild astrocytosis and numerous macrophages in the ventral horns. Extensive loss of axons was noted in the ventral roots. While very few motor neurons were available for study, occasional swollen axons distended with filamentous accumulations were found in the ventral horns. In the brainstem, vacuolated neurons or occasional ghost cell were found in oculomotor and facial nuclei. The authors make the caveat that they were unsure if the cats had the same disorder or if the condition was inherited or acquired.

### **Multisystem Neuronal Abiotrophies**

Several familial neurodegenerative disorders occur in young dogs that are characterized by progressive degeneration and loss of neurons in multiple neuronal systems. These entities are considered to represent system degenerations and have been termed multisystem neuronal abiotrophies [1,10].

### **Multisystem Neuronal Abiotrophy in Swedish Lapland Dogs**

An autosomal recessive neurodegenerative disease has been reported in Swedish Lapland dogs [145] that has been compared to infantile spinal muscular atrophy (Werdnig-Hoffman disease) [124]. Signs appear in affected puppies at 5 to 7 weeks of age. The onset is marked by thoracic or pelvic limb weakness that progresses rapidly to tetraparesis and tetraplegia. In 7 to 14



days after onset, puppies are in sternal recumbency and unable to stand. The carpi become fixed in a flexed position and pelvic limbs become extended with extreme flexion of the stifles. Subsequent muscle wasting and deformity are most pronounced in distal portions of the limbs. Spinal reflexes are reduced or absent, and electromyographic examination reveals denervation potentials. Microscopically, central and peripheral neuronal chromatolysis along with neuronal degeneration and loss are observed in the lateral parts of the ventral horns in cervical and lumbar intumescences, and in dorsal root ganglia. While no degenerative changes are found in any of the motor nuclei of the brainstem, other affected neurons include those in the dorsal gray column of the spinal cord, trigeminal ganglia, and the trigeminal mesencephalic nucleus. Degeneration of Purkinje cells is pronounced and associated with chromatolysis and ischemic cell change, with prominent axonal degeneration in the cerebellar foliate white matter and cerebellar roof nuclei. The neuronal changes are accompanied by diffuse axonal degeneration in the dorsal roots, dorsal funiculus of the spinal cord, and spinocerebellar tracts, as well as in the trigeminal, optic, and vestibulocochlear nerves. It is suggested that the pathologic process is initially manifest as degeneration in the terminal portion of the axon and then proceeds toward the cell body as a "dying back" phenomenon. Prognosis is poor and there is no treatment.

### **Multisystem Neuronal Abiotrophy in Cocker Spaniels**

This is a slowly progressive neurological disease that has been reported in 4 red-haired Cocker Spaniels (1 female and 3 males), aged between 10 and 14 months [146]. The dogs had a common male ancestor. Clinical signs began in all dogs several months before presentation and included behavioral changes such as apathy, loss of house training, loss of recognition of persons and objects, hyperactivity, hypersexuality, and aggression. All dogs appeared excessively anxious and were easily startled. Menace response was absent in all dogs. One dog had a slight head tilt, and another had fixed miotic pupils. Hypermetria, intention tremors, ataxia, and wide-based stance were noted in three dogs. Other variable signs included periodic falling, bumping into objects, pacing, and circling. Delayed knuckling reactions occurred in one dog. Spinal reflexes were normal. CSF analysis and skull radiography were unremarkable. Pathological findings included bilaterally symmetrical lesions in gray and white matter. There was diffuse nerve cell loss, gliosis, and occasional dystrophic axons throughout subcortical and brainstem nuclei, including septal nuclei, globus pallidus, subthalamic nuclei, substantia nigra, tectum, medial geniculate bodies, and cerebellar and vestibular nuclei. White matter changes, which were considered to be secondary to the neuronal loss, included gliosis, moderate numbers of axonal spheroids, perivascular macrophages, and myelin loss. The white matter changes were most pronounced in central cerebellar areas, corpus callosum, thalamic striae, subcortical white matter, and in fimbriae of the fornix. No lesions were noted in the one spinal cord examined.

The etiopathogenesis of this unique condition is presently unknown. Pedigree studies suggest a possible autosomal recessive mode of inheritance. Prognosis appears to be poor. Corticosteroid therapy in two dogs was ineffective.

### **Multisystem Neuronal Abiotrophy in Cairn Terriers**

This neurodegenerative condition in young Cairn Terriers of either sex has been termed "progressive neuronopathy" [147] and "multisystemic chromatolytic neuronal degeneration" [148]. It has been seen in the USA, Australia, Holland, and the UK [148-150]. Clinical signs begin around 5 months of age and are characterized by pelvic limb weakness that progresses to tetraparesis, depressed spinal reflexes and diminished proprioception, incoordination, hypermetria, and head tremor.

Microscopic findings include central and/or peripheral chromatolysis in medial aspects of dorsal and ventral horns (including Clarke's column) of the spinal cord as well as various brainstem nuclear groups-cuneate nucleus, glossopharyngeal and vagus nuclei, lateral vestibular nucleus, reticular nuclei of the medulla, cerebellar roof nuclei, red nucleus, and mesencephalic nucleus of the trigeminal nerve. Typically, neuronal loss is not a feature of this disorder. Moderate white matter changes (including axonal degeneration and considered to be secondary to the neuronal changes) are seen in lateral and ventral columns of the spinal cord, brainstem, dorsal and ventral nerve roots, and in peripheral nerves.

A range of clinical and pathological variations may occur in this condition. In one report of a 4 month old female Cairn Terrier with mild episodic paraparesis, clinical signs were apparent at 4 months of age and were confined to the pelvic limbs [148]. In addition, chromatolytic degeneration of varying pattern (e.g., central, peripheral, or patchy) was observed in neurons of the cerebral cortex, in spinal, autonomic and myenteric ganglia, as well as in brainstem and spinal cord neuronal populations mentioned above. In another case report involving an 11 week old Cairn Terrier [151], pelvic limb weakness was noted initially. Signs rapidly progressed to include head tremors, inability to stand, uncoordinated movements involving the head, trunk and limbs, positional nystagmus, absent patellar reflexes, and absent menace response. Muscle atrophy was not evident. This dog also manifested episodic cataplectic attacks, characterized by generalized hypotonia or atonia that were responsive to imipramine (see narcolepsy). In this dog, a symmetrical thoracolumbar myelomalacia was found in dorsal horns and adjacent funicular white matter. Ultrastructural studies in these two case reports revealed dispersion and loss of ribosomes in chromatolytic neurons, often accompanied by numerous mitochondria [148,151]. More recently, the condition has been reported in two older Cairn Terrier littermates, an 18 months old male and an 11 month old female [150]. The initial clinical signs were characterized by hind limb weakness and ataxia, which deteriorated with exercise. These signs progressed

over several months to tetraparesis.

### **Multisystem Neuronal Abiotrophy in Miniature Poodles**

This degenerative condition has been described in two male puppies from a litter of three [152]. Clinical signs appear at 3 to 4 weeks of age and were characterized by rolling from side to side, inability to stand or right into sternal position, periodic opisthotonus, intention tremors involving head and sometimes, trunk and limbs, and absent menace response. Abnormal vertical nystagmus could be elicited. Microscopically, degeneration was present in the cerebral cortex and cerebellum. Cerebellar cortical atrophy was characterized by extreme loss and degeneration of Purkinje cells which appeared either pale, swollen and vacuolated or shrunken and hyperchromatic associated with eosinophilia and nuclear pyknosis [2]. In addition, there was granule cell loss, gliosis in the molecular layer, and axonal degeneration in foliate white matter. Vacuolar degeneration was present in the lateral (dentate) cerebellar nuclei. Diffuse degenerative (hyperchromatic) and vacuolar changes were also present in neurons throughout the cerebral cortex. Ultrastructural studies indicate that vacuolar neuronal degeneration was associated with marked dilation of endoplasmic reticulum and loss of ribosomes. Shrunken Purkinje cells had decreased numbers of Nissl bodies and there were accumulations of mitochondria and lamellar bodies. The latter, stacked derivatives of endoplasmic reticulum, were not seen in shrunken cerebral perikarya. Lamellar bodies reached giant proportions in the dendritic stems of degenerating Purkinje neurons. In Purkinje axons, however, honeycombed aggregates of axoplasmic tubules usually predominated. The cytological changes in these Poodle pups were notably different from those reported in ultrastructural studies of canine inherited cerebellar degenerations. The genetic status of this condition remains to be confirmed.

### **Nervous System Degeneration in Ibizan Hounds**

A neurodegenerative condition has been described in Ibizan Hounds characterized by a gait abnormality that occurs around the time puppies first begin to walk [10]. Puppies manifest an ataxic-dysmetric gait that affects the hind limbs initially and then progresses to the forelimbs. The gait has a bouncy, dancing character associated with awkward strides, truncal swaying, and frequent falling. Patellar reflexes are absent, but without evidence of muscle atrophy. No gross lesions are seen in the CNS. Microscopic changes include bilaterally symmetrical degeneration of ascending and descending white matter tracts throughout all levels of the spinal cord and involving all funiculi. Changes appear more severe in the thoracic cord, and especially involve the lateral areas of the dorsal funiculus, the superficial and dorsal portion of the lateral funiculus, and superficial regions of the ventral funiculus. Numerous large spheroids are found in the cochlear neurons of the trapezoid body. The dorsal nucleus of the trapezoid body appears gliotic. Degenerative changes, including myelin and axonal degeneration and macrophage infiltration are seen in spinal roots, especially ventral roots, and in peripheral nerves. An autosomal recessive mode of inheritance is suggested by pedigree analysis. The condition is considered to have clinical and pathological similarities to hereditary ataxia in Smooth-haired Fox Terriers and Jack Russell Terriers.

### **Neuroaxonal Dystrophy**

Neuroaxonal dystrophy (NAD) is a degenerative neurological disease that has been reported in cats and dogs. NAD is transmitted as an autosomal recessive trait in Tri-Colored cats and is familial or believed to be inherited in a similar fashion in dogs. The disease is characterized by membrane-filled swellings ("spheroids") of preterminal regions of axons and in synaptic terminals within the CNS [10]. The pathogenic mechanisms underlying the development of this type of axonal abnormality are not well understood, although it is believed that the degeneration starts in the distal axon and progresses proximally, resulting in eventual death of the neuronal cell body [153]. Neuroaxonal dystrophies are considered further examples of abiotrophic processes in animals [1]. In humans, NAD can be separated into 3 types [153]:

- a. physiological NAD: a normal part of brain aging;
- b. primary NAD: diseases in which the main pathology is neuroaxonal dystrophy; and
- c. secondary NAD, occurring as a "reactive" process in another condition.

A similar morphological classification seems to exist in animals. In general, clinical signs of cerebellar-like disease develop in young animals with primary NAD and signs are typically progressive. Ancillary laboratory tests, such as CSF analysis and electrodiagnostics are usually normal. There is no treatment. Prognosis is guarded due to the progressive nature of the disease.

### **Neuroaxonal Dystrophy in Rottweilers**

A recessive mode of inheritance is suspected in Rottweiler dogs with NAD [154-156]. Clinical signs are characterized by slowly progressive ataxia, hypermetria, and wide-based stance beginning in the first year of life, and in some cases, as early

as 10 weeks of age [157], although in one report, 3 dogs were normal in the first year of life, while a fourth dog only showed poor coordination and clumsiness during the first year [158]. Some dogs stand with legs crossed or on three legs with one elevated. Mild proprioceptive deficits have been reported [157]. As the neurological deficit progresses, sometimes over several years [155], head intention tremors, postural and spontaneous nystagmus (positional and then continuous), and menace deficit with preservation of vision and pupillary light reflexes, may be noted. In advanced cases, dogs are unable to climb or ascend stairs. Some Rottweilers have been observed with the disorder for more than 6 years. Muscle bulk, tone and strength appear to be preserved [154]. Hematology and blood chemistries are normal, as are plasma and urine amino acid levels and serum vitamin E levels. Analysis of CSF is usually normal, although a mild protein increase has been reported in one affected dog [158]. Nerve conduction studies are normal, while EMG studies may reveal the presence of fibrillation potentials and positive sharp waves in interosseous muscles [154,158].

Histological changes are progressive and tend to mirror the clinical signs [10]. Grossly, the cerebellum is normal or mildly atrophic [158]. Microscopic studies reveal the presence of massive numbers of axonal spheroids in gray matter of many regions of the neuraxis, especially in sensory axon terminals, e.g., the dorsal horn of the spinal cord, nuclei gracilis and cuneatus, accessory cuneate nucleus, sensory nucleus of the trigeminal nerve, nucleus of the dorsal spinocerebellar tract, granular layer of the cerebellum, vestibular nucleus, and lateral and medial geniculate bodies. The spheroids (up to 100  $\mu\text{m}$  in diameter) are often eosinophilic and either smooth or granular. Some may be palely vacuolated with central cores of swirling filaments or granules that are often argyrophilic. The central cores may stain with Luxol fast blue and periodic acid-Schiff. Some spheroids retain portions of the myelin sheath, while in others, the sheath is attenuated and frequently absent. In some dogs, a marked loss of cerebellar Purkinje cells has been reported, especially in the vermal lobules and floccules [154]. Ultrastructurally, spheroids are filled with accumulations of smooth membrane-bound vesicles, membranous lamellae, dense bodies, tubulovesicular arrays, and neurofilaments [158]. The pathogenesis of this condition remains uncertain, although perturbations of axonal transport have been suggested [158], a theory supported by findings of accumulated synaptic proteins (including synaptophysin, synapsin-I, synaptosomal-associated protein of 25 kDa (SNAP-25), Rab 3a, and alpha-synuclein) in dystrophic axons [235]. Prognosis is poor because of the slow progression of the disease although affected dogs may be acceptable pets for a long time.

An unusual case of neuroaxonal dystrophy has been described in Australia in a 15 week old female Rottweiler puppy presenting with an acute onset of coughing and severe inspiratory stridor [159]. The dog was surgically treated for vocal cord paralysis. A few weeks post-surgery, the dog developed a bunny-hopping hind limb gait when running. Soon after, the owners reported that the dog collapsed while exercising and at rest. On reexamination, the dog had a severe inspiratory dyspnea, pronounced inspiratory stridor, was cyanotic and weak. Proprioceptive deficits developed soon after. Microscopic findings included vacuolation, hemorrhage, and chromatolysis of neurons in the medial vestibular nuclei. Additionally, there was vacuolation of the inferior cerebellar peduncle, and vacuolation and axonal swelling with macrophage infiltration in the spinothalamic tract at the same level. In the midbrain, there was vacuolation of the corticospinal tracts, the medial longitudinal fasciculus and gliosis of the rostral colliculus. Gliosis and neuronal vacuolation was found in the nodular lobule of the cerebellar vermis and inferior olivary nucleus. In the spinal cord, axonal swelling and vacuolation were present in various white matter tracts, including the ventral and dorsal spinocerebellar pathways, the fasciculus cuneatus, and the ventral corticospinal tract. Focal hemorrhages were present in the gray columns. This atypical neuroaxonal dystrophic condition has clinical and histopathological similarities to progressive tetraparesis and laryngeal paralysis in young Rottweilers with neuronal vacuolation and axonal degeneration [160] (see spongy degeneration in gray matter).

### **Neuroaxonal Dystrophy in Collie Sheep Dogs**

A cerebellar neuroaxonal dystrophy in Collie Sheep dogs has been reported in New Zealand and Australia [161]. Clinical signs developed from 2 to 4 months of age and gradually increased in severity. Signs included hypermetria, wide-based stance, difficulty in maintaining balance, intention tremor, and ataxia. Body growth, learning ability and social behavior with other dogs were normal. Microscopically, numerous spheroids, appearing as round or oval eosinophilic and moderately argyrophilic bodies ranging from 4 to 36  $\mu\text{m}$  in diameter, were found in cerebellar roof nuclei and lateral vestibular nuclei, and in the central cerebellar, adjacent peduncular, and folia white matter, where they were associated with mild Wallerian degeneration. Purkinje cells were normal. Spheroids were also seen in molecular layer of the cerebellum, nucleus gracilis, substantia nigra nuclei, rostral colliculus, cerebral cortex, and gray matter of the spinal cord. The spheroids were accompanied by moderate diffuse gliosis. The history of several affected puppies in litters from successive mating of the same sire and dam suggested an autosomal recessive mode of inheritance.

### **Neuroaxonal Dystrophy in Chihuahuas**

A degenerative neuroaxonal dystrophy has been reported in 2 female Chihuahua littermates [162]. At 7 weeks of age, there was sudden onset of tremor and exaggerated gait. Grossly, a moderate dilatation of the lateral ventricles was noted. The main histopathological change was presence of spheroids throughout the white matter of the brain and were especially prominent

in internal capsule, cerebellum, lateral geniculate body, anterodorsal nucleus of the thalamus, acoustic tubercle, superior and inferior olives, and corticospinal and spinothalamic tracts. Spheroids were also present in the lateral cuneate nucleus, and gray matter of the thalamus, but infrequently in the cerebral cortex. Minimal changes were found in the spinal cord. Ultrastructurally, the major accumulated organelle was a membrane-bound body with containing numerous mitochondria and dense bodies. In the gray matter many of the spheroids had synaptic clefts indicating that in these sites the spheroids were presynaptic.

### **Neuroaxonal Dystrophy in Papillons**

Neuroaxonal dystrophy has been reported in a litter of five 14 week old Papillon puppies [163]. Clinical examination revealed signs of ataxia, hypermetria and depressed postural reflexes affecting all four limbs. The severity of these signs varied between members of the litter. The condition became progressively worse and by 19 weeks of age all but the least severely affected pup (the single male of the litter) had deteriorated to the point that euthanasia was indicated on humane grounds. Pathological examination revealed widespread changes in both white and gray matter of the neuraxis caudal to the forebrain, particularly involving the dorsolateral white matter of the spinal cord, characterized by axonal swellings typical of neuroaxonal dystrophy.

### **Neuroaxonal Dystrophy in a Jack Russell Terrier**

A 9 week old Jack Russell terrier with progressive ataxia had histopathological lesions consistent with neuroaxonal dystrophy [164]. Gross observation revealed absence of the septum pellucidum, hypoplasia of the corpus callosum and marked bilateral hydrocephalus. Light microscopy of the CNS showed extensive axonal swellings principally in the gray matter of the brainstem where the sensory nuclei were most affected, especially medullary proprioceptive and vestibular nuclei, and in diencephalic nuclei [2]. Spheroids were also seen throughout the spinal cord gray matter with a few also present in the dorsal funiculi. Ultrastructurally, spheroids were identified as axonal terminals and dystrophic boutons and characterized by accumulations of membrane bound bodies. Clinical and morphological findings were similar to those identified in human infantile neuroaxonal dystrophy (Seitelberger's disease).

### **Feline Neuroaxonal Dystrophy**

Neuroaxonal dystrophy has been reported in Domestic Tri-Colored cats as an autosomal recessive condition [165] and has been termed feline hereditary neuroaxonal dystrophy (FHND). Clinical signs occurred in kittens around 5 - 6 weeks of age, at which time head tremors and head shaking were observed. Signs progressed to marked incoordination of gait and hypermetria. Affected kittens had a lilac color that darkened with age. Unaffected littermates were black. There was gross atrophy of the cerebellar vermis. Microscopically, axonal spheroids were found principally in the inferior olivary nucleus and lateral cuneate nucleus. Spheroids were noted also in the brainstem tegmentum, nucleus ventralis and ventralis anterior of the thalamus, and the cerebellar vermis. The spheroids had a finely granular homogenous quality, sometimes with a periodic acid-Schiff-positive central dark core. The spheroids were seen with and without ballooned cell processes. The latter type was found in the previously mentioned areas but also in medial lemniscus, medial longitudinal fasciculus, region of the central tegmental tract, and in dorsal roots of the spinal cord. These changes were accompanied by loss of neurons, including Purkinje and granule cells of the cerebellar vermis, and glial proliferation that was prominent in the molecular layers of the cerebellar vermis. Spheroids were present in the spiral ganglia of the inner ear, along with neuronal depletion. Ultrastructurally, most spheroids had a myelin sheath. Spheroidal morphology was variable and included large membrane-bound vacuoles with a homogeneous electron-opaque interior, numerous small mitochondria and osmiophilic dense bodies, sometimes within membrane-bound vesicles, and variable neurofilaments that were often separated by multilaminated membranous structures.

Neuroaxonal dystrophy (multifocal swollen axons in brainstem, medulla, and spinal cord; swollen myelin sheaths in spinal cord) with cerebellar abiotrophy (characterized by multifocal Purkinje cell loss and displacement of remaining Purkinje cells into the granular layer of the cerebellum with molecular layer gliosis) has recently been reported in 2 littermate Domestic Shorthair cats with dilute gray coat color [218]. Progressive cerebellar signs, stunted growth, muscle atrophy, and apparent blindness (absent menace response, miotic pupils and unusual green irises) began a few weeks after birth.

A syndrome resembling (FHND) has been studied in siblings from several litters of Domestic Shorthair cats born to the same queen [166]. The disorder was characterized by a sudden onset of hind limb ataxia, from 6 to 9 months of age, that slowly progressed to hind limb paresis with crouched standing or dragging-rolling gait, and eventual paralysis. Hematology, biochemistries, urinalysis, and electrodiagnostic testing were normal. Histologically, there was marked ballooning of axonal processes, with spheroid formation and vacuolation in specific regions of the brain and spinal cord. Some dystrophic axons contained a central periodic acid-Schiff positive core. Neuronal loss and gliosis were seen in certain brainstem nuclei (most severe in the lateral and medial cuneate nuclei and nucleus gracilis), the thoracic nucleus (dorsal nucleus or Clarke's column)

in the gray matter of the spinal cord, and the cerebellum (especially in the cerebellar nuclei and granular layer of the cerebellar vermis, with associated degeneration and loss of Purkinje cells). Degenerative changes in white matter were seen in ascending and descending tracts of the spinal cord and were most severe in the fasciculus gracilis in the cervical cord. The spheroids ranged in size from 25 to 100  $\mu\text{m}$  with similar microscopic and ultrastructural features to those described above in FHND. The syndrome in this report differed from FHND in Domestic Tri-Colored cats in that no inner ear involvement was seen, onset of clinical signs occurred at a later age, and there was involvement of cerebellar nuclei and spinal cord. In addition, although some of the affected cats did have diluted coat colors, abnormal coat color was not always associated with clinical disease.

Neuroaxonal dystrophy has also been reported in two 5 week old (male and female) Siamese kittens with progressive neurological signs including head tremor, hypermetria, proprioceptive deficits (all limbs), hind leg ataxia and paralysis. Signs were initially noted at 2 weeks of age [167]. The kittens had heightened responsiveness to touch and noise. Coat color in the kittens was normal. Grossly, the cerebellum was slightly smaller than normal in both cats. Microscopically, the most prominent changes were found in the brainstem and characterized by ballooning of cell processes, axonal spheroids, and neuronal depletion, principally in the lateral cuneate nucleus. Many spheroids had a dense, central eosinophilic core. Degeneration and loss of Purkinje cells were also observed, especially in the cerebellar vermis. In addition, vacuolation was seen locally around Purkinje cells and in the granular layer, as well as in the white matter of the cerebellum and spinal cord. The condition was believed to be hereditary.

### **Rottweiler Leukoencephalomyelopathy**

This neurodegenerative disorder has been recognized in the USA, Netherlands, UK, and Australia affecting young Rottweiler dogs of either sex from about 1.5 to 4 years of age [168-171]. The etiopathogenesis is unknown, although the disease is considered to be inherited and transmitted as an autosomal recessive trait [171]. Clinical signs include ataxia, tetraparesis, hypermetria, proprioceptive loss, and normal or exaggerated spinal reflexes with increased muscle tone. Signs are often first seen in thoracic limbs [169-171]. The disease progresses over a 6 to 12 month period to the point where animals have difficulty in rising and standing, and there is frequent stumbling, scuffing of the paws, and falling [170]. There is no muscle atrophy, extensor tone is often increased, and pain sensation may be decreased [171]. Cranial nerves, vision, pupillary reflexes, and menace responses are unaffected. All diagnostic studies including hematology, blood chemistries, CSF analysis, electrodiagnostics (EMG and NCVs), plain radiography, and myelography are normal.

Bilateral, symmetrical lesions may be seen throughout the spinal cord, but are most severe in dorsal and lateral funiculi of the cervical cord segments. In transverse sections of fixed specimens, these lesions appear grossly as areas of increased pallor and opacity. In the brainstem, lesions tend to be bilaterally symmetrical and may be found in the spinal tracts of the trigeminal nerve, caudal cerebellar peduncles, deep cerebellar white matter, subventricular rostral medullary tracts, pyramidal tracts, and the medial lemniscus. Optic nerves and tracts may also be affected (but not to the point of causing visual deficits) [171]. Occasionally, diffuse or patchy lesions occur in the corona radiata [171]. Cranial nerves and autonomic ganglia are normal. Histopathological changes include rarefaction and polymicrocavitation of the white matter associated with demyelination, edema, diminished myelin staining, dissociation of myelin sheaths, gemistocytic astrocytosis, fibrillary gliosis, and macrophage infiltration [170]. In the severe cervical cord lesions, a narrow rim of normal white matter is seen between the edge of the lesion and the pial surface [169]. Wallerian degeneration is not a feature of this condition [171], and therefore, not surprisingly, axonal degeneration is mild, although a few swollen degenerating axons are seen occasionally. There is minimal inflammation or endothelial cell proliferation. Axonal spheroids are variably present, but in one dog, these structures were found in accessory cuneate nucleus, nucleus gracilis, nucleus cuneatus, and the nucleus of the dorsospinocerebellar tract, but were not associated with neuronal loss [169]. Ultrastructurally, myelin splitting, thinly myelinated axons and naked axon sheaths separated by broad astroglial processes, are seen [169,170]. There is little evidence of axonal swelling or neurofilament aggregation. Slocombe and colleagues found evidence of scattered swollen and vacuolated nerve sheaths within hind limb peripheral nerves in all of their affected dogs [170].

Possible storage disease has been ruled out in affected Rottweilers by the demonstration of a battery of normal lysosomal enzyme activities in peripheral blood leukocytes [170]. Presently, there is no treatment. Prognosis is poor.

This condition needs to be differentiated from neuroaxonal dystrophy in Rottweilers, which is often seen before 1 year of age, and is slowly progressive over several years. Clinical signs include hypermetria, head tremors, and nystagmus, but typically, there is no paresis [155,171]. Young adult Rottweilers (18 to 20 months of age) with cervical spondylomyelopathy and signs of progressive proprioceptive loss and ataxia may also be confused clinically with Rottweiler leukoencephalomyelopathy [168].

### **Spongy Degeneration of the CNS**

Spongy degeneration of the CNS in children has been termed Canavan's syndrome (van Bogaert-Bertrand type of spongy degeneration) and is characterized by accumulation of vacuoles in a variety of cells, particularly astrocytes [4], which also

contain abnormally structured elongated mitochondria [172]. The vacuoles result from excessive fluid accumulation, seemingly from metabolic disturbances that produce dysmyelination. Studies suggest biochemical heterogeneity in the pathogenesis of infantile spongy degeneration, including deficient activity of aspartoacylase (antemortem diagnosis can be made using cultured fibroblasts) and astrocytic mitochondria with reduced levels of adenosine triphosphate [4,173,174]. Increased amounts of N-acetylaspartic acid are found in urine and plasma [175]. In this condition, demyelination can be prominent but axons and oligodendroglia are not extensively affected [4]. Familial and hereditary forms of spongy degeneration have been recognized sporadically in young dogs and cats and the changes may be predominant in either white or gray matter.

### **Spongy Degeneration in White Matter**

Spongy degeneration has been observed in 2 young female **Labrador Retriever** littermates [176]. Clinical signs were noted between 4 and 6 months of age and were characterized by progressive ataxia-dysmetria of head, trunk, and limbs, wide-based stance, hyperreflexia with clonus, muscle atrophy, and episodes of exaggerated rigidity and opisthotonus. Excitement increased the frequency of the episodes. In one dog, signs included periodic extension of the forelimbs, dorsiflexion of the head, and falling over backwards. In the second dog, one spell of marked extensor rigidity and opisthotonus lasted for 2 hours. Cranial nerve function (apart from possible auditory deficits in one dog and a visual placing deficit in the second dog) and proprioception appeared normal, and dogs retained bowel and bladder control. At 11 months of age, one dog became very weak and dysmetric and all muscle groups were atrophic. This dog could take no more than 2 or 3 steps without falling or collapsing. Routine hematology, blood chemistries, urinalysis and CSF tests were all within normal limits. Distal tibial nerve conduction velocities were considered slow in the 11 month old dog and EEG studies revealed normal background activity with occasional spiking in the left frontal region. Microscopically, spongy degeneration of the white matter of the CNS and PNS was found, with most prominent lesions in cerebellar peduncles, deep cerebellar white matter, and in the subcortical and deep white matter of all lobes of the cerebrum [177]. Similar lesions were found in the tracts of some cranial nerves, in the thalamic area, midbrain and brainstem, and in the white matter of the spinal cord. These areas were associated with hypertrophied cell bodies, processes, and perivascular footplates of fibrous astrocytes. Myelin loss was described, but axons were normal and there was no evidence of myelin breakdown or inflammation. Ultrastructural studies indicated that the vacuolation was caused by myelin separation at intraperiod lines between major dense lines. The hypertrophic astrocytes had dilated cytocavitary systems, membrane-bound crystalline inclusions, abundant intermediate filaments, and degenerated mitochondria. The clinical, histological, and ultrastructural findings resembled those reported for the juvenile form of Canavan's disease (van Bogaert and Bertrand type) in children. The cause of this condition remains uncertain, but a biochemical lesion involving a membrane-associated adenosine triphosphatase ion transport system in astrocytes has been proposed [177]. Prognosis of dogs with this disorder appears to be poor. Treatment with acepromazine (0.25 mg/kg, IM) decreased the frequency of the episodes of extensor rigidity but resulted in marked weakness. Diazepam (15 mg, IV) did not improve the extensor rigidity-opisthotonus.

A progressive neurological disorder has been reported recently in several related litters of **Shetland Sheepdogs** [178]. Clinical signs, beginning at 7 days to 3 weeks of age, included seizures with increasingly frequency and severity, mental depression, inability to assume sternal recumbency from a lateral position, whole body hyperesthesia, intention tremors of head and neck, inability to ambulate, extensor and flexor rigidity and spasticity of all 4 limbs. Patellar and sciatic reflexes were hypertonic. Affected puppies tended to remain in an opisthotonic position at rest. Serum biochemistry profile, hematology, urinalysis, and CSF studies were normal. CT scans revealed diffuse hypomyelination of white matter in one affected pup, along with dilation of the lateral and 4th ventricles. Electrodiagnostic studies (EMG and NCVs) were normal. In puppies euthanized, no gross lesions were noted. Microscopic studies revealed severe, diffuse, patchy vacuolation of the white matter of the brain and spinal cord that did not appear to worsen with age. Spongiosis was most severe in the cerebellar medulla and folial white matter and the corona radiata. Vacuolation was moderate and patchy in the cerebral white matter and mild in the optic tracts and brainstem, although the caudal colliculi and ventrolateral pons were often involved. The corpus callosum was minimally affected. In the spinal cord, all white matter tracts were affected, especially those in the dorsal funiculi. The CNS vacuolation was not accompanied by glial cell response and there was no evidence of swollen, degenerating axons or axonal debris. In a few puppies, cerebellar Purkinje cells had subtle changes including intracytoplasmic vacuolation, swollen dendrites and axons, and some cells appeared to be undergoing degeneration. Ultrastructurally, the vacuoles were associated with interlamellar splitting of myelin sheaths. Cytoplasmic vacuolation of Purkinje cells corresponded to dilation of the endoplasmic reticulum. Vacuolation was seen occasionally in nerve roots, although peripheral nerves were normal. The disorder was compared to Canavan's disease, although diminished aspartoacylase enzyme activity in tissue or N-acetylaspartic aciduria was not found. In addition, biochemical screening for known human organic acid or aminoacid abnormalities (such as maple syrup urine disease, phenylketonuria, hyperglycinuria, and homocysteinuria) were negative. The mode of inheritance of this familial condition was not determined, although the authors considered an autosomal recessive inheritance unlikely due to the large number of puppies affected.

Spongy degeneration has also been described in **Samoyed** puppies [179]. Pelvic limb tremors were observed at 12 days of age, progressing to generalized tremors over the next 5 days. Microscopically, a generalized vacuolation of white matter was seen throughout the CNS. Changes were most severe in the cerebellum and spinal cord, and less severe in the cerebrum. No degenerative or inflammatory changes were found and dorsal and ventral spinal nerve roots were normal. There was no evidence of myelin breakdown. Axons appeared normal. Ultrastructurally, vacuolations arose from splitting and distension of the myelin sheaths, usually as a "blowout" to one side of the axon rather than encircling them. There was no evidence of astrocytic change or of expanded extracellular space. The cause was not determined.

A degenerative spongiform disorder has been reported in 3 **Silky Terrier** puppies from a litter of five [180]. Clinical signs were noted at birth and consisted of head nodding, approximately twice per second, and uncontrolled intermittent contractures of the vertebral column, especially muscles of the thoracolumbar region, at intervals of approximately 2 per second. Occasionally the pelvic limbs were lifted off the ground during these contractures. The episodes were intensified with excitement and decreased markedly after a period of enclosure in a confined space. Low intensity contractions continued during sleep. Signs did not appear to be progressive. A spongy state, along with pallor of myelin staining, was found throughout the cerebral white matter, especially in the corpus callosum, optic tracts, and subcortical cerebral and cerebellar white matter. A large number of Alzheimer type II protoplasmic astrocytes were found in severely affected areas. Axons were normal.

Spongy degeneration has been reported in two female littermate kittens of the **Egyptian Mau** breed of cat (a small breed derived from the Siamese cat) [181]. Clinical signs, first noticed in kittens at 7 weeks of age, were characterized by pelvic limb ataxia and hypermetria. At 4 months of age, signs included a fixed, vacant stare, slow deliberate movements, and intermittent periods of severe depression and reduced activity, with frequent flicking movements of distal pelvic limbs when at full flexion. Blink, righting, and withdrawal reflexes were severely reduced. The condition improved with age in one kitten, although occasional episodes occurred. At 20 months of age, this cat was well grown, could jump and run, but had slight residual posterior ataxia. Another littermate (a male) was reported with hind limb ataxia that was first noticed by the owner at 10 months of age. Microscopically, there was widespread vacuolation throughout the brain and spinal cord. The intensity of this vacuolation varied, but was most severe in cerebral subcortical and sub-ependymal white matter, cerebellar foliar white matter, and the midbrain and brainstem. No neuronal abnormalities were seen and axons appeared to be unaffected. A paucity of myelin occurred in the vacuolar areas. Cerebrocortical and spinal cord gray matter also contained vacuoles, but were much less severely affected than the white matter. Ultrastructural studies revealed intramyelinic vacuolation, resulting from splitting of the intra-period line of the myelin lamellae. There was no evidence of myelin breakdown, and no neuronal, axonal, or glial changes, although a few small myelin figures were noted in the cytoplasm of astrocytic foot processes.

### **Spongy Degeneration in Gray Matter**

There are several forms of spongy degeneration characterized by their predominant involvement of gray matter. One of these, believed to be an autosomal recessive disease, occurs in **Bull Mastiff** puppies [182,190], of either sex, usually between 6 and 9 weeks of age, although in one affected dog, signs were initially noted at 7 months of age [182]. Clinical signs included ataxia, most obvious in pelvic limbs, hypermetria, proprioceptive deficits, and head tremor that was accentuated as animals attempted to eat. To date, all affected animals have had visual deficits and slowed menace reflexes. Less constant signs included hysterical behavior, compulsive forward movements, backing compulsively when called, lifting a fore limb while eating, circling, and an intermittent nystagmus (seen in the oldest dog). Some dogs appeared dull, disinterested in their surroundings, and difficult to train. Ancillary aids such as hematology, blood biochemistry and CSF analysis were within normal limits. Venticulography revealed enlarged lateral ventricles, but unassociated with obstruction of CSF flow since the contrast passed from lateral ventricles to fourth ventricles and into the spinal subarachnoid space without hindrance. There was no evidence of megaesophagus and esophageal motility was normal. Magnetic resonance imaging in one report demonstrated symmetric hydrocephalus and two focal areas of increased signal intensity within the central nuclei of the cerebellum [190]. Macroscopic findings were characterized by moderate to severe communicating hydrocephalus with dilatation of all ventricles and the cerebral aqueduct. In addition, a yellow-brown discoloration of the cerebellar nuclei was seen. Microscopically, bilaterally symmetrical spongy lesions occurred in the three deep cerebellar nuclei (dentate, interpositus, and fastigial), where the lesions were most severe, in the lateral vestibular nucleus, and at the base of the inferior colliculus. The cerebellar lesions consisted of vacuolation, gliosis (increase in both microglia and astrocytes, many of which were hypertrophic), and frequent axonal spheroids. The neurons appeared normal but were often in close proximity to vacuoles and spheroids. No cerebellar cortical atrophy was observed despite the presence of occasional torpedoes in the granule cell layer. Many of the vacuoles were surrounded (partially or completely) by attenuated myelin. The vacuoles often contained myelin remnants and occasional axons. Degenerating axons were found within affected nuclei, the white matter of cerebellar folia, and the granule cell layer. Some swollen axons contained increased numbers of axoplasmic organelles, while others had dark, granular axoplasm. It was also reported that oligodendrocytes were degenerating. The basis for this vacuolar

change remains unclear. Prognosis is guarded. There is no treatment.

A similar spongiform disorder has been seen in young **Saluki** dogs with signs of seizures and behavioral changes, sleeping deeply, disinterest in their surroundings, aimless running, circling and back flips [2,183]. Skull radiography and CSF analysis were normal. EEG showed generalized low voltage activity in all leads. Microscopically, a pronounced spongiosis was present diffusely in the cerebrum (involving the deep laminae), brainstem and cerebellum. The spongiosis predominated in the gray matter, being especially severe in neuropil of olivary and cerebellar nuclei [2], but was also found in the thalamus, ventral internal capsule, tegmentum of the pons, nuclear areas of the medulla and optic nerve, usually accompanied by marked astrocytosis [183]. The lesions extended into white matter in some areas, such as at the junction of the lentiform nucleus with the internal capsule [2]. Lesions were not found in the spinal cord. A mild spongiform degeneration was noted in two clinically normal puppies. The condition was considered to be recessively inherited with variable expression. Familial spongy degeneration has recently been reported in three **Cocker Spaniel** puppies out of a litter of six, from a mating of the mother with her father [184]. Clinical signs began around 3 to 4 weeks of age and included episodic behavioral changes, aimless running, and autonomic signs (salivation, urination, and defecation) that may reflect psychomotor seizures [184]. Bilateral pelvic limb proprioceptive deficits, forelimb hypermetria, bunny hopping, and absent menace response have also been noted. Results of hematology, blood chemistry, urinalysis, thyroid function, serum bile acids, blood ammonia levels, CSF analysis, and CT scans were all normal. Microscopic changes were characterized by spongy degeneration and associated diffuse gliosis mainly found in the gray matter, and were especially evident in the pons and cerebellar nuclei. Lesion intensity was less severe in other brainstem nuclei such as the dorsal and ventral thalamic nuclei and dorsal nuclei of the lateral geniculate body, as well as in the cerebral cortex and cerebellar cortex. Lesions were multifocal and always bilaterally symmetrical. Many spheroids were found in spongy areas as well as in normal neuropil. Demyelination (based on Luxol-fast blue staining) was found in internal capsule, thalamic tracts, cerebellar peduncles, cerebellar rubrothalamic tract, facial tract, and the trigeminal spinal tract. Axonal changes were mild. Immunohistochemical staining for canine distemper virus was negative. No lesions were found in the spinal cord.

Spongy degeneration of the CNS has been reported in two **Malinois Shepherd** crossbreed puppies [185]. Coarse tremors involving the head, limbs and trunk were observed at 3 weeks of age. The tremors were accentuated by excitement or voluntary movement but disappeared at rest and sleep. Other signs included wide-based stance, difficulty in maintaining balance, a tendency to move backwards or to the side while attempting to walk, and stilted, hypermetric gait. A fine oscillating tremor was observed in the eyes. Oculocephalic reflexes were delayed and postural reactions were slightly hypermetric. Spinal reflexes were normal. Hematology and blood chemistries were normal. Microscopic findings were characterized by a bilaterally symmetrical spongy state throughout the brain and spinal cord, with predominant involvement of the gray matter. All layers of the cerebral cortex were affected. Gray matter lesions were noted in basal nuclei, brainstem nuclei, cerebellar nuclei, and in lumbar and cervical intumescences of the spinal cord gray matter. White matter was relatively uninvolved, except for a spongy state and myelin loss in the cerebellar folia and some vacuolation in the cerebral cortical U-fiber region. The neuropil vacuoles were located adjacent to neurons, blood vessels, and glial cells. Neurons were not involved. There was no sign of necrosis, demyelination, or hypomyelination. Gliosis and marked astrocytic hypertrophy (shown by glial fibrillary acid protein staining) were evident. Axons appeared normal. Prognosis was considered to be poor. A spongiform neurodegenerative disease has been recently reported in young **Rottweiler** dogs, of either sex, from North America, Europe, and Australia [160,186,187,219]. The condition is characterized by progressive signs of ataxia-dysmetria, especially apparent in the pelvic limbs, initially seen in puppies from 6 to 16 weeks of age, and progressing (sometimes over several months) to tetraparesis. Inspiratory stridor, associated with bilateral laryngeal paralysis, has been noted in several reports [160,186]. Absence of a gag reflex has also been reported [219]. Tendon reflexes are normal and there is no muscle atrophy in the limbs. In some affected dogs, ophthalmoscopy reveals persistent pupillary membranes on both irises and bilateral cataracts, and nystagmoid movements [160]. Behavioral changes, including aggression, absent-mindedness, and difficulty in training, have been noted in some dogs [186]. Analysis of CSF is normal, as are cervical radiography and myelography, ruling out vertebral malformation or injury. Thoracic radiographs show no evidence of megaesophagus. Electromyography may show abnormal spontaneous activity from the intrinsic musculature of the larynx, suggestive of denervation. At necropsy there is no gross abnormalities of the nervous system but atrophy of the dorsal cricoarytenoid muscles of the larynx has been noted in dogs with signs of laryngeal paralysis. Widespread histological abnormalities have been reported throughout the nervous system, including neuronal vacuolation (especially prominent in cerebellar roof nuclei and the nucleus of the spinal tract of the trigeminal nerve, but also in nuclei of the extrapyramidal system, thalamic nuclei, nucleus of the caudal colliculus, vestibular nuclei, medial cuneate nuclei, neurons of the spinal gray matter, dorsal root ganglia, and visceral ganglia), spongiform and microvesicular intra-axonal changes in the neuropil (in lateral vestibular nuclei, red nuclei, anterior colliculi, and dorsal root ganglia), and axonal degeneration which is most prominent in the spinal cord, especially severe in the thoracic segments, and most concentrated in the dorsolateral and ventromedial funiculi [160]. Wallerian degeneration in the spinocerebellar tracts may extend into the caudal brainstem, and in the central cerebellar gray and white matter. There is focally extensive degeneration and loss of Purkinje cells, Bergmann's gliosis, and presence of



axonal torpedoes in the granule cell layer. The dorsal cricoarytenoid muscles of the larynx show evidence of neurogenic atrophy, and nerve fascicles associated with this muscle (presumably from the recurrent laryngeal nerves) may have reduced numbers of axons. In one report, there was no sign of neuronal degeneration or loss in the nucleus ambiguus [160]. Wallerian-type degeneration has also been reported in sciatic nerves [186]. Ultrastructurally, the neuronal vacuoles are bound by a single membrane and are empty or contain granular material and sometimes membranous profiles [186,187,219]. Axosomatic and axodendritic synapses in affected neurons are intact both ultrastructurally and with synaptophysin immunostaining [187]. The cause of this condition remains unknown, although it is not considered to be a prion disease: immunoblotting and immunocytochemical staining of the brain for protease-resistant scrapie prion protein are negative [186,187,219]. A very similar (if not the same) condition has been described as an atypical form of neuroaxonal dystrophy in a 15 week old female Rottweiler with laryngeal paralysis [159].

A progressive spongiform neurodegenerative condition of the CNS has been reported in 5 related **Birman** kittens, of either sex [188]. All affected kittens were normal at birth. Clinical signs of progressive hind limb paresis and ataxia were first noted in animals from 2 to 6 months of age. The breeder noted that affected kittens had a very light coat color when born, were smaller in size than unaffected kittens, had smaller heads, and "closer-set" eyes, and a higher pitched meow. Kittens were bright and alert and 4 had bilateral cataracts. When walking, the hind limbs were excessively abducted with knuckling over on to the dorsal surface of the hind paws. Postural reactions were absent in the hind limbs and spinal reflexes were exaggerated. One cat had posterior paralysis and an absent menace response and gag reflex. Spinal reflexes and postural reactions were usually normal in the forelimbs, except in one cat with abnormal postural reactions on the right forelimb. This cat also had an inspiratory stridor and abnormal high-pitched meow. Hematology and blood chemistries were usually normal (2 cats had peripheral eosinophilia), as were CSF analysis (pressure, cell count, and protein levels), radiography, and motor nerve conduction velocity studies (performed in one cat). Microscopically, brains of all cats showed several large bilaterally symmetrical, disseminated foci of spongy change. These were often located in the gray matter of the cerebral cortex, and were especially marked in the piriform lobe where extensive vacuolation of the molecular layer extended into the pyramidal cell layer. Less severe foci were present in the inferior collicular nuclei of the midbrain. Vacuolation was also seen in the thalamus, cerebellar peduncles, oculomotor nucleus, and medulla oblongata. Vacuoles (from 10 to 50  $\mu\text{m}$ ) were spherical or ovoid and typically present in clusters in the neuropil. Wallerian degeneration was observed in sensory and motor white matter tracts in the spinal cord. Ultrastructurally, the spongy change was associated with intramyelinic edema. Vacuoles were bound by one or more lamellae. Most were empty but a few contained loose whorled myelin figures. Peripheral nerves were normal. All kittens were inbred and an inherited etiology was suspected [188].

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