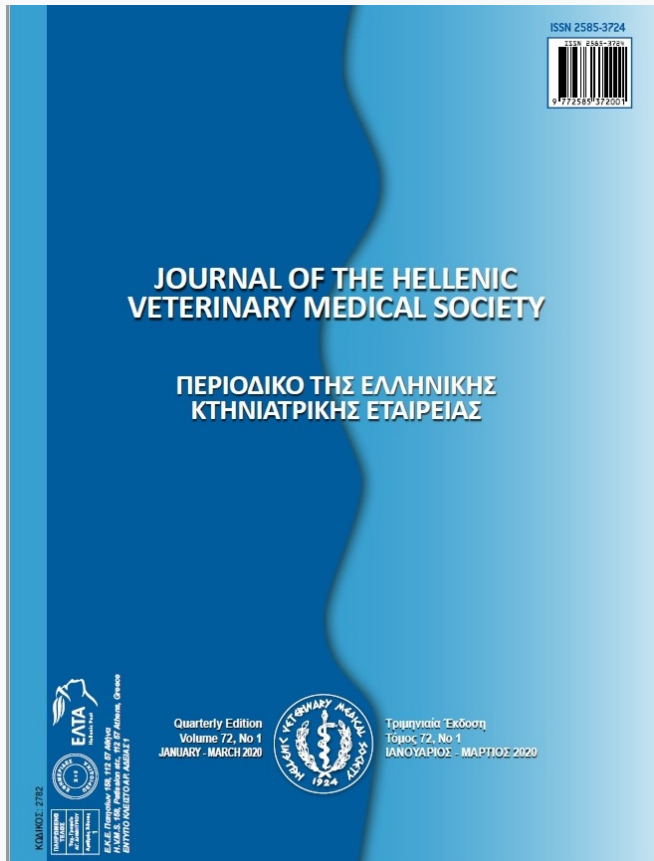


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Hereditary myelopathies in dogs

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ABSTRACT: The purpose of the current review is to summarize data regarding hereditary myelopathies in dogs. Canine degenerative myelopathy (DM) is a progressive disease prevalent in senior (≥ 8 years old), large breed-dogs, predominating in German shepherd dog. Neurolocalization indicates a thoracolumbar, upper motor neuron, lesion; it can progress to the thoracic limbs and later to lower motor neurons of all limbs resembling human amyotrophic lateral sclerosis (ALS). Tentative diagnosis is based on ruling out other progressive myelopathies. Clinical similarities between ALS and DM made superoxide dismutase 1 gene (SOD1) a viable candidate gene as an etiopathogenic factor. A E40K missense mutation of the SOD1 has been linked to DM. A genetic test for DM exists, which will aid breeding programs to eliminate the disease. Exercise and physiotherapy are important to slow the progression of DM. Long-term prognosis is poor as dogs become non-ambulatory within 4-6 months from the time of diagnosis. Dystrophic myelopathies include Afgan hound myelopathy/hereditary necrotizing myelopathy in Kooikerhondje dogs, leukoencephalomyelopathy and neuroaxonal dystrophy in Rottweilers and spongiform leukoencephalomyelopathy. A similar myelopathy is Jack Russell and Fox terrier hereditary ataxia. Their etiology is suspected to be hereditary and they appear at a young age. They are diagnosed solely postmortem with histopathological examination. There is no etiologic treatment and the prognosis is poor except for Rottweiler neuroaxonal dystrophy and Jack Russel ataxia due to the extremely slow progression of symptoms. Syringomyelia is characterized by the formation of fluid filled cavities within the spinal cord and outside the central canal that may communicate with the central canal and it is caused mainly due to Chari-like malformation (CLM). The most important clinical sign is neuropathic pain and is localized in the cervical region of the spinal cord. Progression of the disease varies, there are severe disabilities due to pain or it can be an incidental finding. CT and MRI are the preferable ways to detect the lesions. For CLM, therapy includes surgical and medical management. Drugs can be divided into analgesics (non-steroidal anti-inflammatory, gabapentin, pregabalin, tramadol), drugs reducing cerebrospinal fluid (CSF) production (omeprazole, acetazolamide, furosemide) and corticosteroids. Medical therapy diminishes the severity of clinical signs but never succeeds full resolution.

Keywords: *degenerative disease, myelodystrophy, myelopathy*

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INTRODUCTION

The etiology of myelopathies is multifactorial. Clinical signs depend on the location, size, and the rate of lesion development (Dewey and da Costa,

2016). The current review focuses on the most important hereditary myelopathies in dogs. Summarized data of the hereditary myelopathies are found in Tables 1 and 2.

Table 1. Summarizing data regarding hereditary myelopathies

Hereditary myelopathies	Etiology	Affected breeds	Lesion localization	Therapy	Prognosis
Degenerative myelopathy	Proteins generated from the mutation of SOD1 gene (E40K)	GSD, PWC, other large- and mixed-breed	T3-L3 spinal cord segments	Physiotherapy	Poor
Dystrophic myelopathies					
<i>Afgan hound myelopathy</i>	Autosomal recessive mode of inheritance	Afgan hound, Kooikerhondje	C6-T2 or T3-L3 spinal cord	None	Poor
<i>Rottweiler leukoencephalopathy</i>	Suspected inherited disorder	Rottweiler, Rottweiler crossbreed	Cervical spinal cord, brainstem, cerebellum	None	Poor
<i>Rottweiler neuroaxonal dystrophy</i>	Inherited disorder	Rottweiler	Cervical spinal cord	None	Guarded
<i>Spongiform leukoencephalopathy</i>	Suspected genetically inherited enzyme deficiency	Dalmatian, Miniature, Poodle, Border Terriers	Cervical spinal cord, brain	None	Poor
Jack Russel/Fox-terrier ataxia	Autosomal recessive mode of inheritance (CAPN1 gene, KCNJ10 gene)	Jack Russell terrier, Smooth-coated Fox terriers Ibizan hound, Parson Russell terriers	Cervical spinal cord, brainstem	None	Guarded to poor
Syringomyelia (Hydromyelia)	CLM, spinal cord/brain malformation, spinal cord trauma, obstructive inflammatory/neoplastic lesions	CKCS, any breed	Cervical spinal cord	Surgical Medical	Good to poor (depends on syrinx size)

CKCS, Cavalier King Charles Spaniel; CLM, Chiari-like malformation; GSD, German Shepherd; PWC, Pembroke Welsh Corgi; SOD1, Superoxidase dismutase 1

Table 2. Major clinicopathological findings of the hereditary myelopathies

Hereditary myelopathies	Anatomical region affected	Clinicopathological findings
Degenerative myelopathy	T3-L3 spinal cord segments	Dorsal portion of lateral and dorsal funiculi of the white matter: axon degeneration, myelin loss
Dystrophic myelopathies		
Afgan hound myelopathy	C6-T2, T3-L3 spinal cord	Dorsal and ventro-medial white matter: myelin loss, vessel proliferation
Rottweiler leukoencephalopathy	Cervical spinal cord Brainstem/Cerebellar	Dorsolateral funiculi of the white matter: demyelinating lesions Demyelinating lesions
Rottweiler neuroaxonal dystrophy	Cervical spinal cord	Dorsal horn grey matter: dystrophic axons
Spongiform leukoencephalopathy	Cervical spinal cord, brain	Spongiform change of the white matter, diminished myelin content, absence of microgliosis, Rosenthal fibers (astrocytic inclusion bodies)
Jack Russel/Fox-terrier ataxia	Cervical spinal cord	Dorsal and ventral funiculi
Syringomyelia (Hydromyelia)	Cervical spinal cord	Fluid-filled dilatation +/- communication with spinal canal

DEGENERATIVE MYELOPATHY (DM)

Degenerative myelopathy (DM) in dogs was first described by Averill in 1973 as a specific degenerative spinal cord disease (Kathmann et al 2006; Granger and Neeves, 2015).

Canine degenerative myelopathy is a slow, progressive neurodegenerative disease prevalent in several dog breeds (Griffiths and Duncan, 1975; Barclay and Haines, 1994; Coates et al. 2007; Awano et al. 2009; Holder et al. 2014; March et al. 2009; Miller et al. 2009). It has been recognized for > 35 years as a spontaneously occurring, adult-onset spinal cord disorder (Awano et al. 2009). Early neuroanatomical localization indicates a lesion between the 3rd thoracic (T3) and the 3rd lumbar (L3) spinal cord segments (Kathmann et al. 2006; Coates et al. 2007; Awano et al. 2009; Miller et al. 2009) and in lumbosacral spinal cord (Kathmann et al. 2006). Initially the disease is thought to be breed-specific to German Shepherds (GSD), thus named German shepherd myelopathy (Braund and Vandeveld, 1978; Longhofer et al. 1990; Barclay and Haines, 1994; Coates et al. 2007; Awano et al. 2009; March et al. 2009; Holder et al. 2014). However, other large breeds, including Old English sheepdog, Belgian shepherd, Collie, Giant Schnauzer, Labrador retriever, Borzoi, Soft-coated Wheaten terrier, Mastiff (Kathmann et al. 2006), Rhodesian Ridgeback, Boxer, Chesapeake Bay Retriever (Long et al. 2009; Granger and Neeves, 2015), Hovawart, Bernese Mountain dog, Kuvasz (Kathmann et al. 2006), Pug and Cavalier King Charles spaniel (Granger and Neeves, 2015), along with mixed-breed dogs have been reported to develop the disease. Pembroke Welsh Corgi (PWC) is a breed commonly affected by DM (Coates et al. 2007; Long et al. 2009; Miller et al. 2009; Granger and Neeves, 2015). DM is confirmed histologically in 3 closely related Siberian husky dogs, suggesting that hereditary factors may be involved in the pathogenesis (Bichsel et al. 1983). Interestingly, there is a feline case report with a presumed histopathological diagnosis of degenerative myelopathy due to the histopathological similarities identified in the thoracolumbar segments and the cause of the lesion that is not apparent (Mesfin et al. 1980).

There is no sex predilection in DM (Kathmann et al. 2006; Awano et al. 2009; Granger and Neeves, 2015), although in affecting PWC there is a predominance of females (Coates et al. 2007). Most dogs are at least 8 years of age before the onset of clinical

signs (Griffiths and Duncan, 1975; Kathmann et al. 2006; Awano et al. 2009; Crisp et al. 2014; Holder et al. 2014; Granger and Neeves, 2015), but young dogs can be affected as well (Coates et al. 2007; Polizopoulou et al. 2008). Interestingly, there are reported cases in 2 juvenile German Shepherds (6 and 7 months old) that present symptoms compatible to DM, which is confirmed histologically (Longhofer et al. 1990). On the contrary, in DM-affected PWC, there is a slightly older age distribution (median age 11 years) compared with previous studies (Coates et al. 2007; March et al. 2009). The initial clinical sign is a spastic and general proprioceptive ataxia and paresis of the pelvic limbs (Longhofer et al. 1990; Barclay and Haines, 1994; Kathmann et al. 2006; Awano et al. 2009; March et al. 2009; Crisp et al. 2014; Granger and Neeves, 2015). The asymmetric/symmetric weakness frequently progresses to paraplegia (Polizopoulou et al. 2008; Awano et al. 2009). At this stage of the disease, the preservation of spinal reflexes indicate an upper motor neuron paresis (Kathmann et al. 2006; Awano et al. 2009) although the patellar reflex can be decreased or abolished because of lesions in the dorsal nerve root ganglia (Miller et al. 2009). Pain sensation, bladder control and the panniculus reflex are normal (Griffiths and Duncan, 1975). Hyporeflexia of the myotatic and withdrawal reflexes occur in the advanced disease stage (Kathmann et al. 2006; Awano et al. 2009). In dogs that are not euthanized, the disease progresses and thoracic limbs may be affected (Barclay and Haines, 1994; Awano et al. 2009; Miller et al. 2009; Crisp et al. 2014). In advanced DM cases, dogs may also exhibit signs of lower motor neuron disease, including flaccid tetraparesis, generalized muscle atrophy and hyporeflexia of all limbs (Kathmann et al. 2006; Awano et al. 2009; Miller et al. 2009). The disease duration can exceed 3 years however; most dog owners elect euthanasia within 6 months to a year of diagnosis and after they become paraplegic (Awano et al. 2009). Clinical progression of DM in PWC is similar to that of DM in GSD and other described breeds, however, it is characterized by a longer duration (19 months versus 6 months) (Coates et al. 2007). Many affected dogs may survive with supportive nursing care until respiratory failure develops, which has been reported to occur 3 years or later after the disease onset (Nakamae et al. 2015).

Tentative antemortem diagnosis is based upon ruling out other diseases causing progressive myelopathy (Coates et al. 2007; Granger and Neeves, 2015). Common differentials include spinal cord compres-

sion, inflammatory disease and neoplasia (Griffiths and Duncan, 1975; Jones et al. 2005; Coates et al. 2007). Hip dysplasia and lumbosacral stenosis can often be confused with DM, but the neurologic deficits are different if a careful examination is performed (Griffiths and Duncan, 1975; Coates et al. 2007). It is worth remembering that hip dysplasia can often co-exist with DM and exaggerate the signs seen in the latter disease (Griffiths and Duncan, 1975). Initial tentative diagnosis is based on signalment (older large-breed dogs) and onset of clinical signs (slow progression) (Kathmann et al. 2006). The proposed diagnostic investigation includes advanced diagnostic imaging techniques (computed tomography-CT, magnetic resonance imaging-MRI), along with cerebrospinal fluid (CSF) analysis (Jones et al. 2005; Kathmann et al. 2006; Coates et al. 2007). Results of CSF analysis are usually unremarkable although occasionally increased protein concentration is noted, especially when samples are collected via a lumbar tap (Kathmann et al. 2006). Morphologic characteristics such as spinal stenosis, focal attenuation of the subarachnoid space, spinal cord deformity, small spinal cord and paraspinal muscle atrophy are common in DM dogs detected via computed tomography combined with myelography (Jones et al. 2005).

Clinical similarities between amyotrophic lateral sclerosis (ALS) and DM lead to the investigation of superoxide dismutase 1 (SOD1), a gene potentially involved in DM pathogenesis (Awano et al. 2009; Holder et al. 2014; Ivansson et al. 2016). In humans, ALS is a disease typically seen between the ages of 45 and 60, where degeneration of upper and lower motor neurons culminates in paralysis and death (Holder et al. 2014). Studies suggest SOD1 activity is unaffected by the presence of SOD1 mutations. Instead, proteins encoded by the mutation version of the gene demonstrate an increased propensity to form aggregates. The relationship of this finding to the pathogenesis of neuronal dysfunction seen in ALS and DM is to be elucidated (Holder et al. 2014). However, while SOD1 mutation homozygosity is a predisposing risk factor, some affected animals do not have the mutation (Awano et al. 2009; Chang et al. 2013). Furthermore, carrier dogs might not develop the disease (Awano et al. 2009; Chang et al. 2013).

There is a study including at risk-PWC dogs homozygous for the SOD1 risk allele, detecting genetic modifier loci that are differentiated between dogs that developed the disease early and dogs that did not de-

velop the disease even at an advanced age (Ivansson et al. 2016). The study results suggest that the mutant SOD1 proteins accumulate in reactive astrocytes during the early phase of DM pathology, which may contribute to subclinical neurodegeneration (Kobatake et al. 2016).

Recently, a novel missense mutation, associated with DM, has been described in the Bernese mountain dog (T18S) (Capucchio et al. 2014; Crisp et al. 2014). Both E40K and T18S mutations in cSOD1 are not loss of function mutations, but form enzymatically active dimers that are prone to aggregation *in vitro* (Crisp et al. 2014). A genetic test for DM has been developed and is expected to aid in planning breeding programs designed to slowly eliminate DM (Long et al. 2009; Holder et al. 2014). Dogs showing consistent clinical signs and being homozygous for the mutation, are raising the index of suspicion of DM whereas those with heterozygous or homozygous wild-type genotypes are considered more likely to be affected by other disease processes (Holder et al. 2014).

A polyclonal antibody against cSOD1 is generated to further characterize the mutant SOD1 protein and its involvement in DM pathogenesis (Nakamae et al. 2015). Definite diagnosis of DM is determined post-mortem by histopathological examination of the spinal cord (Coates et al. 2007; March et al. 2009). Neuromuscular histopathological findings include axon loss, which begins in the thoracolumbar spinal cord and later may involve the cervical and lumbar segments (Barclay and Haines, 1994; Coates et al. 2007; March et al. 2009). Lesions are restricted to the white matter (Barclay and Haines, 1994) and described as discontinuous, bilateral and asymmetric (Longhofer et al. 1990; Coates et al. 2007; March et al. 2009). All white matter funiculi are affected but a predominance of lesions in the dorsal portion of the lateral funiculus and dorsal funiculus have been reported (March et al. 2009; Miller et al. 2009). The degenerative changes involve both the axons and the myelin sheaths (Griffiths and Duncan, 1975; March et al. 2009) with dilation of the myelin sheath, axonal swelling and concurrent fragmentation and phagocytosis of axonal and myelin debris (March et al. 2009). Both motor and sensory tracks are affected (Johnston et al. 2000). They occur at the distal portions of the fiber tracks (Griffiths and Duncan, 1975; Johnston et al. 2000). In the dorsal columns, the rostral portion is affected (Griffiths and Duncan, 1975). Histologically, there are vacuolar spaces which represent lost myelin and axonal degen-

eration which appears as large eosinophilic circular granular bodies in sections stained with hematoxylin and eosin (Barclay and Haines, 1994). Together, these result in a spongy appearance of the white matter histologically (Barclay and Haines, 1994).

Studying the brain of DM-affected dogs reveals neuronal degeneration and loss in the red, lateral vestibular and dentate nuclei, changes that may be related to the origin of the damage and subsequent Wallerian degeneration (Kathmann et al. 2006).

Affected dogs present lesions in the posterior and lateral columns (Awano et al. 2009). In all DM affected dogs, the surviving spinal cord neurons contain cytoplasmic inclusions which are stained with anti-SOD1 antibodies, appearing as well-defined dark clumps immunohistologically (Awano et al. 2009; Granger and Neeves, 2015). Homozygosity for the A allele is associated with DM in 5 dog breeds: Pembroke Welsh Corgi, Boxer, Rhodesian ridgeback, German shepherd and Chesapeake Bay retriever (Awano et al. 2009). In contrast, homozygosity for G allele and heterozygotes, no staining or diffuse light staining similar to the background staining is found in cells of the spinal cords (Awano et al. 2009).

Several authors suggest that exercise and physiotherapy are important to slow the progression of DM (Kathmann et al. 2006; Granger and Neeves, 2015) by virtue of optimizing muscular tone and blood circulation. Walking or swimming should be done on a daily or every other day schedule (Polizopoulou et al. 2008). In a study performed in DM-affected dogs, daily, controlled physiotherapy prolongs survival time to an average of 255 days (Kathmann et al. 2006). A physiotherapy protocol can include daily gait exercise, massage, passive joint movement and hydrotherapy and it seems to be the most important factor in preserving ambulatory status in dogs with DM (Kathmann et al. 2006). Thus, even in dogs with severe neurological deficits at the time of diagnosis, physiotherapy may result in longer survival time even in comparison with dogs with minor neurological deficits that do not receive physiotherapy (Kathmann et al. 2006). When the affected animals are left untreated, non-ambulatory paraplegia is usually established within 6 months after the initial diagnosis (Kathmann et al. 2006; Polizopoulou et al. 2008).

Long-term prognosis is poor (Coates et al. 2007). Dogs lose the ability to ambulate within 4-6 months from the time of diagnosis (Coates et al. 2007). Tho-

racic limb function and urinary and fecal continence usually are spared until end-stage disease (Coates et al. 2007).

DYSTROPHIC MYELOPATHIES

Afgan hound myelopathy/ Hereditary necrotizing myelopathy in Kooikerhondje dogs

This is a rapidly progressive myelopathy with an autosomal recessive mode of inheritance (Averill and Bronson, 1977). It appears in young (3-13 months old) Afgan hounds (Averill and Bronson, 1977; Dewey and da Costa, 2016). Neuroanatomically, it is a C6-T2 or a T3-L3 myelopathy (Dewey and da Costa, 2016). Affected dogs present symmetrical paraparesis and become paraplegic or even tetraparetic/tetraplegic within 1-3 weeks (Dewey and da Costa, 2016). It can affect the respiratory function lethally (Dewey and da Costa, 2016). Diagnostic tests are normal except for CSF analysis that may reveal increased total protein concentration in some cases (Dewey and da Costa, 2016). Diagnosis is established postmortem with the histopathological examination of the spinal cord. Lesions include symmetrical vacuolization with extensive myelin loss and vessel proliferation in the dorsal and ventro-medial spinal cord of the white matter from caudal cervical to lower lumbar segments, bilaterally (Averill and Bronson, 1977; Cummings and de Lahunta, 1978). There is no treatment and the prognosis is poor (Dewey and da Costa, 2016). A similar disorder, which is called, hereditary necrotizing myelopathy is reported in Kooikerhondje dogs (Mandigers et al. 1993).

Rottweiler leukoencephalomyelopathy

Leukoencephalopathy (LEM) is a progressive, non-painful, central nervous system (CNS) white matter disorder characterized by abnormal myelin synthesis and/or maintenance (Dewey and da Costa, 2016). Its etiology remains unknown although it is suspected to be an inherited disease (Wouda and van Nes, 1986; Dewey and da Costa, 2016). Leukoencephalopathy with brain stem and spinal cord involvement is a neurodegenerative disease in humans with clinical features and MRI findings similar to the histopathological lesions of LEM in Rottweiler dogs (Hirschvogel et al. 2013). Leukoencephalopathy in humans is caused by mutations in the *DARS2* gene, which encodes a mitochondrial aspartyl-tRNA synthetase (Hirschvogel et al. 2013). Due to the phenotypic similarities between human leukoencephalomyelopathy with brain stem and cervical involvement and lactate elevation

(LBSL) patients and LEM-affected Rottweiler dogs, the *DARS2* gene is investigated as a candidate for canine LEM in a case, but no mutation in the gene is found (Hirschvogel et al. 2013). More advanced DNA sequencing, such as the use of next-generation technologies for whole-exome or whole-genome resequencing, may enable the identification of the causative mutation of Rottweiler LEM (Hirschvogel et al. 2013). Young adult Rottweiler and Rottweiler crossbred dogs are most commonly affected (Gamble and Chrisman, 1984; Dewey and da Costa, 2016). The neuroanatomical localization of the disease is the cervical spinal cord (Dewey and da Costa, 2016). Clinical signs include progressive ataxia, proprioceptive deficits which are more prominent in the pelvic limbs while hypermetria is more pronounced in the thoracic limbs (Dewey and da Costa, 2016; Hirschvogel et al. 2013). Tetraparesis worsens slowly over maximum a year (Dewey and da Costa, 2016).

Diagnostic investigation involves signalment, history, clinical signs and MRI (Dewey and da Costa, 2016). CSF analysis, including measurement of proteins and total nucleated cells count (TNCC), CSF cytology and measurement of lactate concentrations in the CSF and serum are unremarkable (Yin et al. 2001; Löbert, 2003). Radiological examination of the cervical region of the spinal cord is normal (Dewey and da Costa, 2016). MRI findings are extremely rare, they have been described in only one case, showing bilateral symmetrical hyper intensities in the region of both lateral funiculi on transverse T2-weighted images and isointense on T1-weighted plain images (Hirschvogel et al. 2013). Due to the lack of a genetic test for this disorder, postmortem histopathological examination is required to confirm the diagnosis (Hirschvogel et al. 2013). Symmetrical demyelinating lesions are seen in the spinal cord, especially in the cervical region, brain stem and cerebellum. Demyelination is more prominent in the dorsolateral funiculi of the cervical spinal cord and explains both paresis and ataxia, as the ascending proprioceptive tracts and descending upper motor neuron (UMN) tracts traverse this region (Wouda and van Nes, 1986; Slocombe et al. 1989; Christman, 1991). Despite the cerebellar involvement, these dogs typically do not exhibit symptoms of cerebellar dysfunction (Davies and Irwin, 2003; Dewey and da Costa, 2016). There is no effective treatment against leukoencephalomyelopathy and prognosis is poor (Dewey and da Costa, 2016). There have been no reports of LEM in the literature since 1989 (Slocombe et al. 1989), which

could suggest a true decrease in incidence, a lack of information about the disease or exclusion of carrier animals from breeding (Davies and Irwin, 2003).

Rottweiler neuroaxonal dystrophy

Neuroaxonal dystrophy is a degenerative, inherited UMN disease that affects young adult Rottweiler dogs (Davies and Irwin, 2003). Clinical signs appear at a young age (<12 months old), earlier than in leukoencephalomyelopathy (Christman, 1992; Boersma et al. 1995). They include forelimb hypermetria, progressive sensory ataxia, proprioceptive dysfunction (Cork et al. 1983; Evans et al. 1988; Boersma et al. 1995; Davies and Irwin, 2003). Cerebellovestibular signs (head tremor, nystagmus) develop later in the course of the disease however strength is maintained (Christman, 1992; Davies and Irwin, 2003). Neuroanatomically, neuroaxonal dystrophy affects the cervical region of the spinal cord as in leukoencephalomyelopathy, however, the cerebellovestibular signs (frequent in the former disease) are lacking (Cork et al. 1983). Cerebellar atrophy was observed in the autopsy of two cases (Cork et al. 1983).

Definite diagnosis is based on postmortem histopathological examination of the spinal cord. Dystrophic axons appear swollen, eosinophilic, homogeneous or granular and contain variable amount of ubiquitin-immunoreactive deposits (Moretto et al. 1993). Characteristic axonal spheroids are most prominent in the dorsal horn grey matter, the nucleus of the dorsal spinocerebellar tract, the vestibular nucleus, and the nucleus gracilis, the lateral cuneate and cuneate nuclei (Cork et al. 1983; Chrisman, 1992). This distribution of lesions explains the predominance of sensory abnormalities observed clinically. Ultrastructurally, spheroids appear to be swellings of distal axons which are filled with accumulations of smooth membrane-bound vesicles, membranous lamellae, dense bodies, and other organelles (Cork et al. 1983). An inherited disorder of axonal transport is suspected as the underlying defect in this disorder (Cork et al. 1983; Siso et al. 2001). Siso et al. (2001) mention the presence of abnormal expression and accumulation of proteins, which participate in the trafficking, docking and fusion of the synaptic vesicle to the plasma membrane. Similar findings have been observed in isolated dystrophic axons of aged dogs, indicating severe disruption of axonal transport in dystrophic axons in canine neuroaxonal dystrophy (Siso et al. 2001). Neuropathological changes are similar to those identified in human neuroaxonal dystrophy (Cork et al. 1983).

There is no therapy for neuroaxonal dystrophy (Boersma et al. 1995). The short term prognosis is not as poor as in leukoencephalomyelopathy because the progression of the disease is very slow and the affected dogs can be acceptable pets for several years (Christman 1992; Boersma et al. 1995).

Spongiform leukoencephalomyelopathy

It has been reported in young Dalmatians, Miniature Poodles and Border Terriers (Martin-Vaquero et al. 2012). It is a rare disorder called fibrinoid leukodystrophy, and is characterized by lesions in both the brain and the spinal cord. Even though the spinal cord is affected, the predominant clinical signs are generalized tremors (Martin-Vaquero et al. 2012). Histopathological findings include a spongiform change affecting the white matter of the brain and spinal cord with diminished myelin content and absence of microgliosis (Martin-Vaquero et al. 2012). This diminished myelin staining can indicate disruption of normal function or diminished formation (Martin-Vaquero et al. 2012). A prominent histopathological finding is the detection of Rosenthal fibers, which are astrocytic inclusion bodies, located in the white matter of the brain and the cervical region of the spinal cord (Richardson et al. 1991). Their origin is not clear, but it is believed that they represent a primary astrocytic abnormality (Borrett and Becker, 1985). It is not yet known whether the astrocytic abnormality is due to a genetically inherited enzyme deficiency (Richardson et al. 1991).

There is no curative treatment, the disease progresses and the prognosis is poor (Dewey and da Costa, 2016).

JACK RUSSELL AND FOX-TERRIER ATAXIA

It is a rare, presumably inherited, progressively degenerative axonopathy that was first diagnosed in Jack Russell terriers and Smooth-coated Fox terriers in Sweden and England (Björck et al. 1957; Hartley, 1973). As these dogs have common ancestry, affected dogs are suspected to have the same disease (Rohdin et al. 2015). However, segregation analysis indicated different mode of inheritance in the two dog breeds despite the similarities between the diseases (Björck et al. 1957; Hartley, 1973; Wessmann et al. 2004). It has also been described in Ibizan hounds and Parson Russell terriers. In the latter, a missense mutation in the CAPN1 gene is found and is strongly associated with a phenotypically similar inherited ataxia (Forman et al. 2013). Additionally, another missense mu-

tation in the KCNJ10 gene is significantly associated with a similar ataxic neurological disease in 14 dogs belonging in the Russell group of terriers (Gilliam et al. 2014) and in ataxic Smooth-haired Fox Terriers and Toy Fox Terriers (Rodhin et al. 2015). Identification of this gene in a homozygous state in ataxic dogs of different, albeit related, breeds support an earlier assertion that this mutation is causal for a neurodegenerative disease that is inherited in an autosomal recessive mode (Gilliam et al. 2014).

Clinical signs appear at a young age (2-9 months), and worsen progressively (Wessmann et al. 2004). They include symptoms of cervical myelopathy; pelvic limb ataxia that progresses to all four limbs ataxia, dysmetric gait and occasional intention tremor suggesting cerebellar dysfunction than myelopathy. However the involvement of the spinocerebellar tract of the cervical spinal cord is a possible explanation for these clinical signs (dysmetric spastic gait and intention tremor). Rodhin et al. (2010) mention clinical evidence of brain stem involvement (behavioral changes, bilateral decreased menace response), that is confirmed histopathologically. Wessmann et al. (2004) report seizures occurring simultaneously with ataxia while others develop respiratory distress. Additionally, they find that the brain lesions are detected only in Jack Russell Terriers and not in Fox Terriers (Wessmann et al. 2004).

The disease can be clinically diagnosed with a high certainty because of the breed, the age of clinical onset and the nature of the typical clinical signs (Wessmann et al. 2004). Routine laboratory tests in blood and CSF in addition to radiological examination of the spinal cord are normal (Wessmann et al. 2004). Abnormal brain stem auditory-evoked potentials (BAEPs) are recorded in affected dogs and can support clinical diagnosis. Diagnosis is confirmed postmortem with histopathological examination of the affected region (Hartley, 1973). Lesions are characterized by bilateral myelopathy (Hartley, 1973; Summers et al. 1995), and more precisely in the dorsal and ventral funiculi of the cervical region of the spinal cord (Summers et al. 1995). Regarding the lesions, they are located in the central auditory pathways, the dorsal part of the lateral lemniscus, the ventromedial sulcus of the ventral funiculus and the trapezoid body (Hartley, 1973; Summers et al. 1995). Rarely, lesions are found in the spinal ganglia of the lumbar region or the cauda equina (Hartley, 1973).

There is no curative therapy for this disease. Al-

though it is not lethal, most dogs are euthanized after their owner's request in their 1st year of life (Hartley, 1973). However some cases with mild gait abnormalities have survived for years (Wessmann et al. 2004).

SYRINGOMYELIA (HYDROMYELIA)

Syringomyelia is a fluid-filled dilatation within the spinal cord that can or cannot communicate with the central canal and is usually not lined by ependymal cells (Lee et al. 1985; Norman, 1987; Wisoff and Epstein, 1989; McClarty et al. 1990; Kirberger et al. 1997; Churcher and Child, 2000). In the vast majority of cases, syringomyelia is the result of Chiari-like malformation (CLM) (Oldfield et al. 1994; Rusbridge et al. 2000). A lot of breeds have been identified to be at risk for Chiari-like malformation, however, the Cavalier King Charles Spaniel (CKCS) is the predominantly affected breed (McGrath, 1960; Geib and Bistner, 1967; Churcher and Child, 2000; Rusbridge and Knowler, 2004). Furthermore, syringomyelia can be caused by other spinal cord or brain malformation, spinal cord trauma, inflammatory or neoplastic processes that obstructs the normal flow of CSF, or idiopathic with no underlying etiology (Schmahl and Kaiser, 1984; Child et al. 1986; Cauzinille and Kornegay, 1992; Kirberger et al. 1997; Rusbridge and Knowler, 2004).

Clinical signs in CKCS with CLM may appear between 6 months and 3 years of age (Rusbridge et al. 2006). Depending on the underlying etiology dogs may be presented at any age but those with more severely clinical signs tend to be younger than 2 years old (Rusbridge and Knowler, 2004). The most important clinical sign in syringomyelia is neuropathic pain (Rusbridge et al. 2000; Todor et al. 2000; Nakamura et al. 2004). Although lesion localization may be difficult, it usually involves the cervical spinal cord (Rusbridge et al. 2006). In CLM, there is cervical hyperesthesia appearing clinically with persistent scratching of the neck and shoulder without skin contact (phantom scratching) (Churcher and Child, 2000; Rusbridge et al. 2000). Scoliosis associated with syringomyelia has also been identified mostly in young animals (Fourneaux et al. 1973; Child et al. 1986; Chuma et al. 1997; Rusbridge et al. 2000). Scoliosis secondary to syringomyelia is the result of muscular imbalance due to paraspinal muscle atrophy (Tagaki et al. 2005). Progression of the disease varies (Rusbridge et al. 2006). In some dogs, there is only scratching with mild pain, and other neurological disorders (ataxia, paresis) appear slowly and

progressively or never (Rusbridge et al. 2006). However other dogs are severely disabled due to pain that progressed within 6 months from the first symptom observed (Rusbridge et al. 2006). In others, syringomyelia is an incidental finding (Lu et al. 2003).

The age of clinical onset varies, depending on the etiology of the disease, the different rate of fluid accumulation and the ensuing spinal cord damage and dysfunction (Rusbridge et al. 2006). However, signs of pain are not well correlated with the size of the syrinx, ie, humans or animals with wider or longer syringes are not necessarily in more pain than those with smaller syringes (Lu et al. 2003; Nakamura et al. 2004). On the other hand, there are other reports showing a relationship between the degree of pain and the width of the syrinx; dogs with larger syringes are in pain and dogs with smaller syringes are not in pain (Rusbridge et al. 2007). Furthermore, Rusbridge et al. (2007) examined not only the width of the syrinx but also the localized damage in the spinal cord, indicating that the asymmetry of the syrinx, is important in the pathogenesis of neuropathic pain. There have reported other neurological disorders such as thoracic limb weakness, muscle atrophy (ventral horn cell damage), pelvic limb ataxia and weakness, white matter damage with involvement of the lumbar spinal cord by the syrinx (Rusbridge et al. 2000). Hydrocephalus has also been reported in syringomyelia cases (Schmahl and Kaiser, 1984; Itoh et al. 1996).

Diagnostic imaging and especially CT and MRI are the preferable way to detect the cavitory lesions (Kirberger et al. 1997; Churcher and Child, 2000; Rusbridge et al. 2000). Mid-sagittal images provide excellent definition of intramedullary cavitation and allow quantitative investigation of the malformation (Churcher and Child, 2000). Sometimes, myelography can be helpful, when the contrast medium enters the cavity within the spinal cord (Kirberger et al. 1997). CSF analysis is usually normal however sometimes it reveals mild inflammation. It is important to perform CSF analysis in order to rule out other diseases (Kirberger et al. 1997).

For Chiari-like malformation (CLM), therapy can be either surgical and/or medical. However, therapy of CLM is beyond the scope of this review and thus only therapy reflecting the elimination of symptoms due to syringomyelia is going to be discussed.

Medical treatment includes analgesics, drugs that reduce CSF production and corticosteroids (Rus-

bridge et al. 2006). In mild cases, pain can be controlled with nonsteroidal anti-inflammatory drugs (Rusbridge et al. 2000). For the relief of scratching, or more severe cases, gabapentin (10 mg/kg b.w., orally, TID) is useful in order to eliminate the neuropathic pain (Levendoglu et al. 2004). Pregabalin (2 mg/kg b.w., orally, BID), which is considered more effective than gabapentin, and tramadol (2-4 mg/kg b.w., orally, TID/QID) may also be administered. There are some reports on medications that decrease CSF flow and include omeprazole, acetazolamide, furosemide but, clinical data on their use and effectiveness are lacking (Lindvall-Axelsson et al. 1992; Itoh et al. 1996; Javaheri et al. 1997; Churcher and Child, 2000). Regarding acetazolamide, long-term treatment has adverse effects like abdominal pain, weakness, lethargy and thus it is contradicted for long-term use (Vogh, 1980; Shinnar et al. 1985; Carrion et al. 2001). Corticosteroids are administered (0.5 mg/kg b.w., orally, BID), to decrease CSF production (Rusbridge et al. 2000). Although corticosteroids may be effective in limiting signs and progression, most dogs require continuous therapy and develop adverse effects such as immunosuppression, weight gain and skin changes (Rusbridge et al. 2000). Medical therapy can diminish the severity of clinical signs but they never succeed full resolution (Rusbridge et al. 2000). Regarding surgical therapy, syringotomy can improve clinical signs (Cauzinille and Kornegay, 1992; Churcher and Child, 2000). In another report, they performed laminectomy combining with acetazolamide and the dog partially ameliorated, without deteriorating 12 months post surgically (Itoh et al. 1996).

Syringomyelia is usually presented with pain. The degree of pain is evaluated clinically and is not necessarily compatible with the severity of the lesions. Pain

management can be sufficient to improve pet's quality of life in most of the cases.

CONCLUSIONS

- Degenerative myelopathy is a progressive myelopathy of the thoraco-lumbar spinal cord segments, commonly seen in old German shepherd dogs.
- Physiotherapy can prolong the ambulatory status of the DM-affected dogs.
- Afgan hound myelopathy, Rottweiler leukoencephalopathy, Rottweiler neuroaxonal dystrophy, Spongiform leukoencephalopathy and Jack-Russel/ Fox-terrier ataxia are non-painful, hereditary myelopathies affecting the cervical region of the spinal cord.
- Syringomyelia is commonly caused by Chiari-like malformation (CLM).
- Syringomyelia can become painful depending on the length and the size of the intramedullary fluid-filled syrinx.
- Therapy for syringomyelia caused by CLM includes surgical and medical management.

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