Canine Degenerative Myelopathy

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Canine degenerative myelopathy (DM) was first described in 1973 by Averill as an insidious, progressive, general proprioceptive (GP) ataxia and upper motor neuron (UMN) spastic paresis of the pelvic limbs beginning in late adulthood, ultimately leading to paraplegia and necessitating euthanasia.[1] Until recently, presence of primary axonal degeneration and nerve fiber loss that was restricted to spinal cord white matter and most severe in the mid to caudal thoracic region was compatible with a diagnosis of DM. The disease was termed "degenerative myelopathy" because of its histopathologic nature as a nonspecific degeneration of spinal cord tissue of undetermined cause. In 1975, Griffiths and Duncan published a series of cases with similar clinical signs and histologic changes in the white matter. They also reported hyporeflexia and nerve root involvement, and they termed the condition chronic degenerative radiculomyelopathy.[2] Though most of the dogs in these initial reports were German Shepherd Dogs (GSD), other breeds were represented. Nonetheless, for many years, DM was considered an UMN and GP disease in the GSD.[3] More recently DM has been recognized as a common problem in a number of breeds with an overall prevalence of 0.19%.[4] Additionally, the clinical spectrum of DM has been broadened to involve both the UMN and lower motor neuron (LMN) systems.[5] A recent advance in the molecular genetics of DM indicates that this canine disease may share pathogenic mechanisms with some forms of human amyotrophic lateral sclerosis (ALS – Lou Gehrig's disease).[5]

Signalment

There is no sex predilection. Age of onset of neurologic signs is usually 5 years or older with a mean age of 9 years in large dog breeds with DM.[1;2;6;7] Most dogs are at least 8 years of age at onset of clinical signs. A study in Pembroke Welsh Corgis (PWC) reported a mean age of onset of 11 years.[4] Histopathologically confirmed cases of DM have been reported in the following dog breeds: GSD,[1-3;5;6] Siberian Husky,[8] Miniature Poodle,[9] Boxer,[5;10] PWC,[4;11] Chesapeake Bay Retriever,[5;12] Rhodesian Ridgeback,[5] and mixed breed.[1] Other previously reported breeds presumptively diagnosed without histopathologic confirmation include the Irish Terrier,[2] Kerry Blue Terrier,[2] Labrador Retriever,[7] Bernese Mountain Dog,[7] Hovawart,[7] Kuvasz,[7] Collie,[7] Belgian Shepherd,[7] Giant Schnauzer,[7] Soft-coated Wheaten Terrier,[7] Mastiff,[7] Borzoi[7]and Great Dane.[13] Recently, we have been able to histopathologically confirm DM in the Bernese Mountain Dog, Standard Poodle, Kerry Blue Terrier, Cardigan Welsh Corgi, Golden Retriever, Wire Fox Terrier, American Eskimo Dog, Soft-coated Wheaten Terrier and Pug (Zeng – publication pending).

Clinical Spectrum

The original clinical descriptions of DM were from the GSD and other large dog breeds that are euthanized early in the course of the disease.[1-3] Progressive, asymmetric UMN paraparesis, pelvic limb general proprioceptive ataxia and lack of paraspinal hyperesthesia are key clinical features of DM. Neurologic localization is to the T3 to L3 spinal cord segments. With longer disease duration, clinical signs will progress to LMN paralysis in the pelvic limbs and eventually affect the thoracic limbs.[1;4;5;7;9]

The clinical course of DM can vary after the presumptive diagnosis with a mean time for disease duration of 6 months in larger dog breeds.[1;3;6] Most large dogs progress to nonambulatory paraparesis within 6 to 9 months from onset of clinical signs. Pet owners usually elect euthanasia when the dogs can no longer support weight in their pelvic limbs and need walking assistance. Smaller dog breeds can be cared for by the pet owner over a longer time.[4;9] The median disease duration in the PWC was 19 months.[4] The PWCs often have signs of thoracic limb paresis at the time of euthanasia.

Early Disease

The earliest clinical signs of DM are GP ataxia and mild spastic paresis in the pelvic limbs. Worn nails and asymmetric pelvic limb lameness are apparent upon physical examination. Asymmetry of signs at disease onset is frequently reported.[1;4;7;9] At disease onset, spinal reflex abnormalities are consistent with UMN paresis localized in the T3 to L3 spinal cord segments.[1] Patellar reflexes may be normal or exaggerated to clonic; however, hyporeflexia of the patellar reflex has also been described in dogs at similar disease stage.[2] Flexor (withdrawal) reflexes may also be normal or show crossed extension (suggestive of chronic UMN dysfunction). Often dogs progress to nonambulatory paraparesis and are euthanized during this disease stage.

Late Disease

If the dog is not euthanized early, clinical signs will progress to LMN paraplegia and ascend to affect the thoracic limbs.[1;4;7;9] Flaccid tetraplegia occurs in dogs with advanced disease.[4;5;9] The paresis becomes more symmetrical as the disease progresses. Lower motor neuron signs emerge as hyporeflexia of the patellar and withdrawal reflexes, flaccid paralysis, and widespread muscle atrophy beginning in the pelvic limbs as the dogs become nonambulatory.[5;95;9] Widespread and severe loss of muscle mass occurs in the appendicular muscles in the late stage of DM. Most reports attributed loss of muscle mass to disuse[1;2;4;8;9] but flaccidity in dogs with protracted disease suggests denevation.[5;8;9] Cranial nerve signs include swallowing difficulties and inability to bark.[4;5;9] Urinary and fecal continence usually are spared also until the latter disease stage with paraplegia.[1;4;7;7;8]

Differential Diagnosis

Definitive diagnosis of DM is determined postmortem by histopathologic examination of the spinal cord. The diagnosis of DM can be challenging because the clinical presentation can mimic many acquired spinal cord diseases. Older dogs often have concurrent or overlapping orthopedic and neurologic disease that can confound the interpretation of the neurologic examination.[14] Disorders that often mimic and coexist with DM include degenerative lumbosacral syndrome, intervertebral disc disease, spinal cord neoplasia and degenerative joint diseases such as hip dysplasia or cranial cruciate ligament rupture.[15] The PWC is a chondrodystrophic breed and prone to Hansen type I intervertebral disk disease. Hansen type II intervertebral disk disease can be an incidental or clinically significant finding more common in the older large, nonchondrodystrophic breeds.[16] Pelvic limb dysfunction can present prior to thoracic limb paresis in cervical spinal cord disease (e.g. caudal cervical spondylomyelopathy), and in generalized neuromuscular diseases. Paw replacement (proprioceptive positioning) is a very useful test that distinguishes between orthopedic and neurologic diseases because it does not require weight-bearing. Animals with orthopedic disease will not have paw replacement deficits.

Diagnostic Approach

Accurate antemortem diagnosis is based on pattern recognition of the progression of clinical signs followed by the completion of a series of diagnostic steps to exclude other disorders.[14;15] Neurodiagnostic techniques for evaluation of spinal cord disease include CSF analysis, electrodiagnostic testing and spinal cord imaging procedures. A presumptive diagnosis of DM often is made based on lack of clinically relevant compressive myelopathy as determined by computed tomography/myelography or magnetic resonance imaging (MRI). Magnetic resonance imaging is especially useful for identifying early intramedullary spinal cord neoplasia and evidence of extradural compressive myelopathy. Imaging often reveals disk protrusions which can confound a diagnosis of DM. The clinician must be guided by clinical experience to evaluate for rapidity of disease progression, presence of paraspinal hyperesthesia and amount of spinal cord compression to account for the severity of the myelopathy. Cerebrospinal fluid analysis can help rule out meningitis but also may be a potential source for biomarker identification. Abnormalities in electrodiagnostic testing have been reported but still need characterization at various disease stages.[2;4;5;7] Early in the progression of DM, no spontaneous activity is detected by electromyography (EMG) and nerve conduction velocities are within normal limits.[5] Later in the disease, EMG reveals multifocal spontaneous activity in the distal appendicular musculature. Fibrillation potentials and sharp waves are the more common waveforms recorded. Recordings of compound muscle action potentials (M waves) from stimulation of the tibial and ulnar nerves have shown temporal dispersion and decreases in amplitudes. The proximal and distal motor nerve conduction velocities were decreased when compared to the normal reference range.[5]

Summary of Histopathology

Definitive diagnosis of DM is based on histopathologic examination. Histopathologic changes include degeneration and nerve fiber loss of ascending sensory and descending motor pathways that are most severe in the mid- to caudal thoracic spinal cord. The spinal cord pathology of DM is consistent with a noninflammatory axonal degeneration.[1-3] In dogs with advanced DM, nerve specimens show fiber loss resulting from axonal degeneration and secondary demyelination. Muscle specimens have changes typical of denervation atrophy. Dogs with DM have characteristic patterns of axon cylinder vacuolization and drop out. Absence of any evidence of neuronal cell body degeneration or loss in the ventral horn of the spinal cord is not a prominent histopathologic finding. Canine DM is most accurately classified as a *multisystem central and peripheral axonopathy.*

Mutation in Superoxide Dismutase-1 (*SOD1*) as a Cause of Degenerative Myelopathy

The uniformity of clinical signs, histopathology, age and breed predilections suggest an inherited basis for DM; however, the late onset of disease has made it difficult to collect data from parents and siblings to substantiate this theory. Segregation of DM in families has been reported in the Siberian Husky,[8] PWC[4] and Chesapeake Bay Retriever.[12] Familial DM also occurs in the Rhodesian Ridgeback and Boxer (Coates – unpublished data). Awano et al.[5] used genome-wide association and DNA from PWCs to map the DM. Genome-wide association mapping of DM produced strongest associations with markers on CFA31 in a region containing the candidate gene *SOD1*. Resequencing of *SOD1* in DNA from normal and DM affected dogs revealed a missense mutation in exon 2. Additionally, spinal cords from DM affected dogs contain cytoplasmic aggregates that stain with anti-SOD1 antibodies. Homozygosity for the SOD1:c.118G>A allele is a major risk factor for canine DM. However, many dogs homozygous

for this mutation do not develop clinical signs which suggest an age-related incomplete penetrance. Mutations in *SOD1* are an underlying cause for some forms of human ALS (Lou Gehrig's disease), an adult onset fatal paralytic neurodegenerative disease. Canine DM associated with this *SOD1* mutation resembles an upper motor neuron onset form of human ALS.

Genetic Testing

A DNA test based on the *SOD1* mutation is commercially available (www.caninegeneticdiseases.net or www.offa.org/dnatesting/). The dogs homozygous for the mutation are *at-risk* for developing DM and will contribute one chromosome with the mutant allele to all of their offspring. The heterozygotes are DM carriers that are unlikely to or rarely will develop clinical DM but could pass on a chromosome with the mutant allele to half of their offspring. The normal homozygotes are unlikely to develop DM and will provide all of their offspring with a protective normal allele. The DM-associated SOD1:c.118A allele has been detected in at least 100 different dog breeds (manuscript in preparation). It remains to be seen whether or not mutant homozygotes are at risk of developing DM on all of these different genetic backgrounds. Additionally, it will be important to continue the histopathologic examination of spinal cords from DM suspects of various breeds to confirm the diagnosis and identify breeds that are susceptible to DM.

The *SOD1* DNA test is of potential use to dog breeders wishing to reduce the incidence of DM in the breed or line. The mutant allele appears to be very common in some breeds. Overly aggressive breeding programs to remove the mutant allele may further create a 'bottle neck' effect possibly selecting for other diseases and eliminating other desirable qualities of the breed. A realistic approach when considering which dogs to select for breeding would be to treat the test results as one would treat any other undesirable trait or fault. Dogs testing *at-risk* should be considered to have a more serious fault than those testing as carriers. Using this approach and factoring the DM test results into the breeding decisions should reduce the prevalence of DM in the subsequent generations while continuing to maintain and improve upon positive, sought after traits.

Management Strategies for Canine Degenerative Myelopathy

Treatment regimens have been empiric with lack of evidence-based medicine approaches. Although it is hypothesized that DM is an immune-mediated neurodegenerative disease, immunosuppressive therapies using corticosteroids have shown no long-term benefits in halting the progression of DM.[13;17] Kathmann *et al.*[7] reported survival data from 22 DM affected dogs that received varying degrees of physiotherapy. Dogs that received intensive physiotherapy had significantly longer survival times compared to dogs that received moderate or no physiotherapy. Physiotherapy and principles of physical rehabilitation may improve the quality of life for the DM affected pet and pet owner.[18] Overall, the long term prognosis of DM is poor.

Degenerative myelopathy is a spontaneous disease with uniformity in onset of clinical signs and disease progression. Dogs affected with DM could be used to investigate processes underlying motor neuron degeneration, evaluate potential therapeutic interventions, and map modifier loci.

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