Canine Degenerative Myelopathy - An Update for the MCOA

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Canine Degenerative Myelopathy, also referred to as CDM or DM, is a disease affecting the nervous system of many breeds both large and small. Classically affecting the spinal cord, the degeneration progresses causing loss of limb function from hind to front limbs (Averill 1973, Coates and Wininger 2010). Based on the SOD1 gene mutation the disease has many similarities to Amyotrophic Lateral Sclerosis, also known as Lou Gehring's Disease, a degenerative neurologic disease present in humans (Awano et al. 2009). Canine DM can serve as a model for ALS. With DM now being recognized as an important disease affecting dogs of many breeds, it is important to understand the cause to limit its genetic spread in future generations of dogs (Fiszdon et al. 2020).

There is no gender predisposition in DM, but age has a role as DM typically affects dogs in the later stages of their lives, around the age of 9 years in large dogs and 11 years in smaller breeds like the Pembroke Welsh Corgi (Coates et al. 2007). The earliest clinical signs include incoordination and hindlimb weakness (Averill 1973, Coates and Wininger 2010). General proprioceptive ataxia refers to a dog's inability to recognize limb position and posture, and this symptom is also characteristic of DM. As the disease progresses, the dog loses fecal and urination control, along with losing muscle mass and limb strength. If the dog becomes paraplegic and is not euthanized, the weakness ascends to the forelimbs and eventually the dog becomes tetraplegic (Coates and Wininger 2010). Once the disease reaches the dog's brain, the dog will struggle to even swallow or bark, and the condition is terminal with respiratory failure (Awano et al. 2009, Coates and Wininger 2010, Ogawa et al. 2013).

The main cause of DM is genetic with a mutation in the SOD1 gene (*SOD1*) (Awano et al. 2009). This stands for superoxide dismutase (SOD), and the 1 refers to the version of this enzyme found in the cytoplasm of the cell. When this gene is not copied correctly, or mutates, it can cause changes in the proteins that are coded by the gene, and these changes can in turn result in cell death, specifically of neurons and supporting cells (Fiszdon et al. 2020). For dogs with the mutated version of the gene, homozygous recessive individuals have the greatest risk of disease while heterozygous individuals have a decreased risk of DM. Homozygous refers to an organism having two copies of the mutated allele for the same version of a gene, while heterozygous refers to an organism having one mutated allele. While the presence of a mutated allele can indicate a likelihood of disease, there may be other genes or modifying genes that may also result in the disease phenotype or expressed trait. Additionally, not all homozygotes develop clinical disease, so the presence of the mutated allele indicates a risk for developing DM (Coates and Wininger 2010, Fiszdon et al. 2020).

In light of the genetic factors involved in DM, genetic testing has become a point of interest in its study. Genetic testing will complement other antemortem diagnostics for DM. Most DM-affected dogs are homozygous for the *mutant allele*. Thus, homozygosity for the *mutant SOD1* allele is a major risk factor for canine DM. However, many dogs homozygous for this mutation do not develop clinical signs. The age at onset for many dogs has exceeded the mean life expectancy of dogs indicating that DM has an age-related, incomplete penetrance mode of inheritance. DM has also been histopathologically confirmed in few heterozygous dogs of certain breeds (Zeng et al. 2014). The occurrence of DM in a heterozygote seems plausible since most human *SOD1* mutations cause dominant ALS.

A second SOD1 mutation that was homozygous in an affected Bernese Mountain dog was identified, and this mutant allele appears to be restricted to the Bernese Mountain Dog breed, where it is less common than the first mutant allele described. Affected homozygotes in other breeds have not yet been discovered. This finding serves as a reminder that direct DNA tests indicate the presence or absence of disease-causing alleles but cannot be used to rule-out a diagnosis because other sequence variants in the same gene or in a different gene might produce a similar disease phenotype (Wininger et al. 2012).

As a result of this ambiguity, the diagnosis of DM is generally one of exclusion, meaning that other diseases must be ruled out first before DM can be diagnosed with certainty. Generally, differential diagnoses include intervertebral disc herniation, cancer of the spine or spinal cord, and other mimicking compressive spinal cord diseases. These may be ruled out by imaging methods such as spinal cord magnetic resonance imaging (MRI). An important step in obtaining an appropriate diagnosis is to have a dog with clinical signs be evaluated by a board-certified veterinary neurologist (www.acvim.org; then go to *find a specialist*). Signs of orthopedic disease can be confused with neurologic diseases. A proprioceptive placement test, where the foot is placed such that the paw is positioned knuckled over, is an important diagnostic tool. If the dog can quickly recognize that its foot has been mispositioned, then the signs of limb dysfunction may be orthopedic. DM can only be definitively diagnosed by histopathology of the spinal cord, which is performed by autopsy examination (Coates and Wininger 2010). DM is characterized by degeneration of the axons (processes carrying electrical transmission) and secondary loss of the myelin sheaths (insulation) that wrap around the axons. Another key feature is astroglial proliferation, which is most severe in the lateral and dorsal columns (Averill 1973, March et al. 2009). Neuron loss occurs in terminal disease (Ogawa et al. 2014). A veterinary pathologist is

able to discern these characteristics on a post mortem examination to establish a diagnosis of DM (Coates and Wininger 2010).

Physical rehabilitation may improve the dog's quality of life as the disease progresses. Dogs who received physiotherapy survived longer on average than those who did not, an average of 255 days and 55 days respectively, and these passive and active exercises were tailored to the dog's disease progression (Kathmann et al. 2006). Studies surrounding the impact of diet have been performed, but it was concluded that there is no definitive evidence of improvement over the treatment of physical therapy alone. Caution must be taken when facilitating any sort of exercise therapy as the already weakened muscles can be easily damaged and fatigued, which may increase the rate of disease progression (Polizopoulou et al. 2008).

In connection to research surrounding the human disease ALS, therapeutic models are being investigated in dogs. Since the *SOD1* mutation is important in both ALS and DM, canine DM serves as a model for disease translation (Awano et al. 2009, Fiszdon et al. 2020). As a result, studies are being conducted surrounding silencing the SOD1 gene and observing its effect on the mobility of dogs affected with DM (Story et al. 2020). While these studies are in their early stages, there is a possibility of successfully applying a canine disease model to ALS, with benefits for both humans suffering from ALS and dogs suffering from DM (Coates and Wininger 2010).

Since there are currently no effective treatments for DM, breeders perform genetic testing to mitigate transmission of the risk mutation to offspring. If a risk factor for DM is discovered early, it allows the owner to be more responsible in the management of their breeding program. Since the mutant allele is known to be present in over 180 purebred and mixed breeds, it is important to be aware of its wide presence in the canine population. Research to find treatments

and study DM is being led by Dr. Joan R. Coates at the University of Missouri Veterinary Health

Center and other researchers worldwide. Laboratories are studying ways to diagnose and

measure disease progression with similar diagnostic modalities used in ALS patients. The

diseased tissues also are studied at all stages of progression. The nervous system tissue may be

harvested after the dog's death by a necropsy (Coates and Wininger 2010). Spinal cord tissue

will also be retained for research purposes for other DM and ALS researchers in hopes of

understanding the molecular and genetic spectrum of this disease. The first step is to

characterize and document canine DM in the Mastiff.

Key References:

Averill DJ. (1973) Degenerative myelopathy in the aging German Shepherd dog: clinical and

   pathologic findings. *J Am Vet Med Assoc* 162:1045-1051.

Awano T, Johnson GS, Wade C, Katz ML, et al. (2009) Genome-wide association analysis

   reveals a SOD1 mutation in canine degenerative myelopathy that resembles amyotrophic

   lateral sclerosis. *Proc Natl Acad Sci U S A* 106:2794-2799.

Coates JR, March PA, Ogelsbee M, et al. (2007) Clinical characterization of a familial

   degenerative myelopathy in Pembroke Welsh Corgi dogs. *J Vet Intern Med*

   21(6):1323-1331.

Coates JR, Wininger FA. (2010) Canine degenerative myelopathy. *Vet Clin North Am Small*

Anim

   Pract 40:929-950.

Fiszdon K, Gruszcynska J, Siewruk K. (2020) Canine Degenerative Myelopathy – pathogenesis,

   current diagnostics possibilities and breeding implications regarding genetic testing. *Acta*

   Sci. Pol. Zootechnica 19(1): 3-10.

Kathmann I, Cizinauskas S, Doherr MG, et al. (2006) Daily controlled physiotherapy increases

   survival time in dogs with suspected degenerative myelopathy. *J Vet Intern Med*

   20:927-932.

March PA, Coates JR, Abyad R, et al. (2009) Degenerative myelopathy in 18 Pembroke Welsh

   corgi dogs. *Vet Pathol* 49:241-250.

Morgan BR, Coates JR, Johnson GC, Bujnak AC, Katz ML. (2013) Characterization of

   Intercostal Muscle Pathology in Canine Degenerative Myelopathy: A Disease Model for

Amyotrophic Lateral Sclerosis. *J Neurosci Res* 91:1639–1650.

Morgan BR, Coates JR, Johnson GC, Shelton GD, Katz ML. (2014) Characterization of Thoracic Motor and Sensory Neurons and Spinal Nerve Roots in Canine Degenerative Myelopathy, a Potential Disease Model of Amyotrophic Lateral Sclerosis. *J Neurosci Res*. 92: 531–541.

Polizopoulou ZS, Koutinas AF, Patsikas MN, et al. (2008) Evaluation of a proposed therapeutic protocol in 12 dogs with tentative degenerative myelopathy. *Acta Vet Hung.* 56(3): 293-301.

Ogawa M, Uchida K, Yamato O, et al. (2013) Neuronal Loss and Decreased GLT-1 Expression Observed in the Spinal Cord of Pembroke Welsh Corgi Dogs With Canine Degenerative Myelopathy. *Vet Path* 51(3):591-602.

Story BD, Miller ME, Bradbury AM, et al. (2020) Canine Models of Inherited Musculoskeletal and Neurodegenerative Diseases. *Front. Vet. Sci.* 7: 80.

Wininger FA, Zeng R, Johnson GS, et al. Degenerative myelopathy in a Bernese mountain dog with a novel SOD1 missense mutation. *J Vet Intern Med* 2011;25:1166-1170.

Zeng R, Coates JR, Johnson GC, Hansen L, Awano T, Kolicheski A, et al. (2014) Breed Distribution of SOD1 Alleles Previously Associated with Canine Degenerative Myelopathy *J Vet Intern Med* 28:515.