DEGENERATIVE MYELOPATHY IN THE NOVA SCOTIA DUCK TOLLING RETRIEVER

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WHAT IS IT?

Canine degenerative myelopathy (DM), previously known as chronic degenerative radiculomyelopathy (CDRM), is a spinal cord disease where there is death of nerve cells carrying messages to and from the limbs. DM is characterised by a non-painful progressive hind limb paralysis in older dogs. It is a fatal disease and many owners euthanatize affected dogs when they no longer able to use their hindquarters to walk and stand. If kept "going", for example in a canine cart, then eventually the forelimbs are affected although this can take many years.

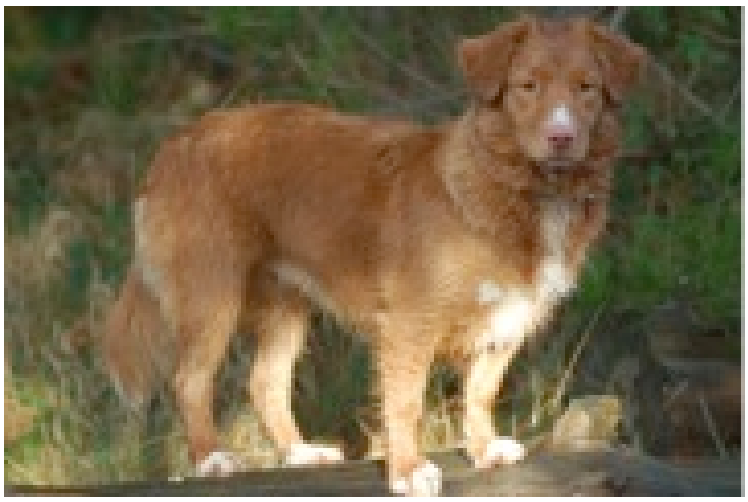
WHAT BREEDS ARE AFFECTED?

The disease affects older dogs over 5 years old [1] and typically over 8 years [2]. It used to be regarded as a "German Shepherd dog disease" however in recent years the disease has been identified in many breeds (Table 1). Anecdotally the disease has been recognised in Tollers since 2009. There is no sex predilection.

Table 1

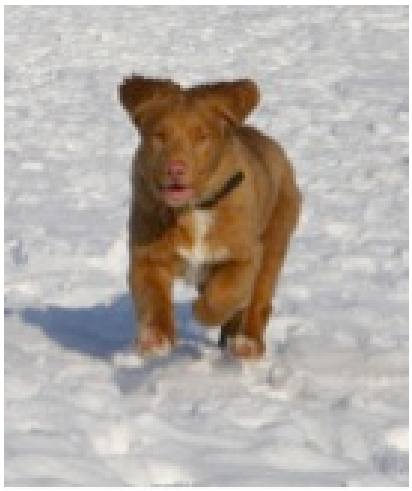
Purebred dogs at risk of degenerative myelopathy (SOD1 gene mutation)	
American Eskimo Dog	Kerry Blue Terriers
Bernese Mountain Dog	Pembroke Welsh Corgi
Borzoi	Poodle
Boxer Dog	Pug
Cardigan Welsh Corgi	Rhodesian Ridgeback
Cavalier King Charles spaniel	Shetland Sheepdog
Chesapeake Bay Retrievers	Soft Coated Wheaten Terriers
German Shepherd Dog	Wire Fox Terrier
Golden Retriever	…and many others!*
Great Pyreneen Mountain Dog	

Purebred dogs at risk of degenerative myelopathy. Source Orthopaedic Foundantion for Animals [3] fund http://www.offa.org/dnatesting/dm.html)
*SOD 1 mutation identified has been in over 115 breeds.



WHAT IS THE CAUSE?

Recent research studies at the University of Missouri (http://www.caninegeneticdiseases.net/DM/resrchDM.htm) has found that a mutation of the superoxide dismutase-1 (SOD 1) is strongly associated with this disorder [4, 5]. SOD 1 is a gene that encodes an enzyme (superoxide dismutase) responsible for destroying free radicals in the body. Free radicals are reactive elements that are part of the natural defence mechanism; however they become harmful when they are produced in excessive quantities, causing cell death and a variety of degenerative diseases. The same gene mutation also can cause a form of human motor neuron disease called amyotrophic lateral sclerosis (ALS) [6]. DM is an incompletely penetrant[A] autosomal recessive[A] disease; and two copies of the abnormal gene have to be present for the disease to develop. However the story of degenerative myelopathy is not that simple and the disease has been confirmed in some dogs with only one copy of the disease suggesting that there are other genetic or environment influences that determine whether a dog will development the disease. It should also be remembered that other degenerative spinal cord diseases exist for example the Kooikerhondje (another "duck tolling" breed with possible links to Tollers) is predisposed to Hereditary Necrotizing Myelopathy [7]. Importantly this affects much younger dogs (12-18 months) and has a different genetic cause.



The actual mechanism of disease is unknown. Studies looking at the spinal cord of Pembroke Welsh Corgi Dogs [8] with DM found a marked reduction of glutamate transporter 1 (GLT-1)[A] resulting in glutamate excitotoxicity[A] and nerve cell death.

The link to SOD 1 suggests oxidative (free radical) damage is pivotal however supplementation with antioxidants[A] (free radical scavengers) does not reverse the disease. Low blood levels of vitamins such as vitamin E (alpha-tocopherol), and vitamin B12 (cobalamin) have been demonstrated in DM, however supplementation did not cure the dogs or delay the time to paralysis. The mutation of SOD 1 is a "gain of function"[A] and it has been suggested that it is "toxic" to nerve cells. Inflammatory or immune-mediated processes have also been suggested and anecdotally many dogs will respond to low doses of glucocorticoids such as prednisolone. However this effect is not sustained and immunosuppressive treatments such as azathioprine or cyclophosphamide do not show any benefits.

Glossary

[A] **Penetrance** in genetics is the number of individuals that have a copy of a gene that also express trait or disease (phenotype). Therefore if a disease has complete penetrance then having the disease gene will guarantee development of disease. With incomplete penetrance having the disease gene does not guarantee development of disease and other genetic or environmental influences are important for expression. For example one can be genetically predisposed to diabetes mellitus but that tendency may never be expressed in an individual with normal body weight on a diet low in simple carbohydrates and sugars.

[A] **Autosomal recessive** means that two copies of the gene (one from the dam and one from the sire) are required for disease. **Autosomal dominant** means that only one copy is required

[A] **Glutamate transporter 1**. Glutamate is the main excitatory (i.e. stimulatory) neurotransmitter. Excessive glutamate damages nerve cells and the glutamate transporters serve to "mop up" excess glutamate and keep it from damaging cells.
[A] **Excitotoxicity** is the pathological process by which nerve cells are damaged and killed by excessive stimulation by neurotransmitters such as glutamate.
[A] **Antioxidants** such as vitamin C, vitamin A, vitamin E and superoxide dismutase protect against oxidative or free radical injury.

[A] In genetics a **mutation** is a change in building blocks of the DNA. A gene is a region of DNA that codes for a product such as an enzyme or a protein. **A gain of function mutation** means that the gene product has a **new and abnormal function**

A **Carrier** - animal with one copy of a recessive gene

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GENETIC TESTS and BREEDING GUIDELINES

A DNA test for the SOD-1 mutation is offered by many laboratories (Table 2).

Table 2. Laboratories offering DM genetic testing.

Laboklin	www.laboklin.co.uk/laboklin/showGeneticTest.jsp?testID=8158D
Orthopaedic Foundation For Animals (OFFA)	www.offa.org/dnatesting/dm.html
Small Animal Molecular Genetics Lab (University of Missouri)	www.caninegeneticdiseases.net/DM/DMsample.pdf
VetNostic Lab	www.vetnostic.com/degenerative-myelopathy
DNA Diagnostic Centre (DDC)	www.vetdnacenter.com/canine-disease-degenerative-myelopathy.html

The results identifies dogs that are '*clear*' or N/N i.e. the dog who have two normal copies of the gene and for whom is extremely unlikely to develop DM; those who are '*carriers*' or A/N i.e. dogs who have one normal copy of the gene and one mutated copy of the gene and should not develop the disease; those who are '*at risk*' or A/A i.e. dogs who have two mutated copies of the gene and are at risk of developing DM.

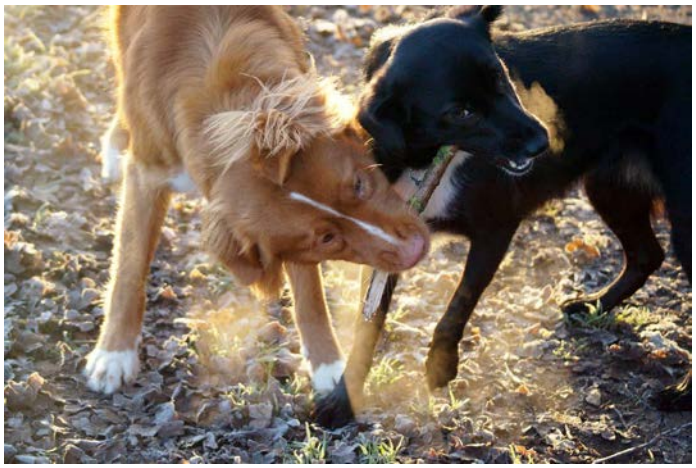
This genetic test does NOT identify dogs that are affected by this disorder, but only identifies dogs that are at risk of developing clinical signs but will not necessarily do so. There appear to be other risk factors (genetic or environmental) that influence disease development and these have still to be identified. In addition some dogs that might be destined to develop the disease do not do so in their lifespan for example the average age of death of Tollers has been reported to be 6.4 years (http://www.toller.ca/tollerhealth/SurveySummary.html). In other words the dog could die of something else before getting degenerative myelopathy. As the disease develops after for the recommended breeding age, dogs must be tested prior to mating.

Breeding risks can be calculated as following (Table 3):

Table 3–Breeding to reduce risk of Degenerative myelopathy

Parent A	Parent B	Statistical chance of puppies being at risk of DM
N/N	**N/N**	**100% 'clear'**
A/**N**	**N/N**	**50% 'clear'** & 50% 'carriers DM'
A/**N**	A/**N**	**25% 'clear'**, 50% 'carriers DM', 25% 'at risk DM'
N/N	A/A	100% 'carriers DM '
A/**N**	A/A	50% 'carriers DM' & 50% 'at risk DM'
A/A	A/A	100% 'at risk'

*N= normal; A= abnormal (SOD-1 mutation for DM)



Breed-wide genetic testing is advised in DM predisposed breeds. Although not yet a Kennel Club Assured Breeder scheme requirement, (http://www.thekennelclub.org.uk/services/public/breed/restrictions.aspx?id=2141), many Toller breeders now screen prospective breeding stock for DM and advertise the puppies as DM clear. However

Toller breeders need to take account of risk of other inherited diseases when making breeding decisions. Carriers[A] have low risk of developing DM. Although they have potential to pass on the disease gene, their offspring are at low risk of developing the disease **as long as a carrier is mated to a normal animal**. **The offspring of such a mating should also be tested**. Toller's have a small gene pool; in fact so small that breeding from the carrier state is recommended to maintain genetic diversity. The breed cannot afford to exclude individuals and their genetic material as this would increase the risk of other inherited disease and in particular susceptibility to immune mediated disorders [9, 10]. A worldwide study of the Tollers registration history in 17 countries shows that about 90% of the genetic diversity present in the founding population has been lost [11]. Tollers born between1999–2008 have an effective founder[A] size of 9.8, a realized effective population size[A] of 18 and an average inbreeding coefficient of 0.26 [A] [11]

As the effective gene pool for Tollers is so small and because they are predisposed to other inherited diseases there is a strong but controversial argument for breeding from dogs with two copies of the disease gene (A/A) especially if cross is desirable for reasons of genetic diversity for example if the mating has a low inbreeding coefficient [J]. A genetically affected dog does not necessarily get DM. Although breeding such dogs may be an unpalatable concept, there is no evidence (yet) that breeding is deleterious to that individual dog's welfare. However this dog can only be mated to a normal (N/N) dog and it should be realised that all the puppies will be carriers for DM (N/A) and therefore they too should only be mated to normal (N/N) dogs. It is essential that all dogs are tested and it is recommended that the decision to permit breeding of an A/A dog should be a made by a breed health committee (or similar) with the aim of maintaining breed-wide health.

Glossary

[A] **Founder population** is the number of animals, which have contributed genetic material to subsequent populations. Due to the historical popularity of some lines, genetic material from some member of the original foundation stock is often lost. For example the Icelandic Sheepdog has a population of ~ 2500 supposedly founded from 36 dogs. However over the years much genetic material has been lost and the actual diversity is equivalent to only 2.2 equally contributing founders [12].

[A] **Effective population size** is the population expressed in terms of the number of individuals that can contribute genes equally to the next generation. Most breeds are between 30-40 [13]

[A] The **coefficient of inbreeding** (COI) measures the common ancestors of dam and sire, and indicates the probability of how genetically similar they are. A COI of 0.25 is equivalent to a mother to son mating. For more information see http://www.dogbreedhealth.com/a-beginners-guide-to-coi/.

If the proposed program illustrated in Table 4 is followed then the incidence of DM and the prevalence of the SOD-1 gene in Tollers should gradually decrease generation by generation.

Table 4 Proposed breeding program to reduce incidence of DM in Tollers or other breeds with a small genetic pool and high risk of other inherited disease.

Dog	Mated to	Statistical chance DM status in puppies
A/A	**N/N**	100% A/N (Carrier DM)
A/N	**N/N**	50% N/N (normal) 50% A/N (Carrier DM)
N/N	**N/N**	100% N/N (normal)
	A/N	50% N/N (normal) 50% A/N (Carrier DM)
	A/A	100% A/N (Carrier DM)

All dogs in breeding program must be tested. *N= normal; A= abnormal (SOD-1 mutation for DM)

CLINICAL SIGNS

DM usually affects dogs older than 5 years old and typically older than 8 years. The first clinical sign is a non-painful and subtle weakness of one hind limb (i.e. often signs are asymmetric). This may be misinterpreted by the owner as a chronic orthopaedic disease, such as hip dysplasia [14]. The onset is insidious, and generally progressive over months leading to an ataxia i.e. “drunken sailor” hind limb gait with hindquarter weakness. This is accompanied by dragging paws (loss of proprioception[i]), crossing the hind limbs when walking and falling over when cornering. Neurological examination may reveal increased hind-limb tone and brisk spinal reflexes[ii] (figure 2). Eventually the disease progresses to hindquarter paralysis (i.e. inability to walk and support their own weight) and may ascend the spinal cord to affect the forelimbs or spread to involve the spinal nerves resulting in further weakness, muscle atrophy and faecal and urinary incontinence.

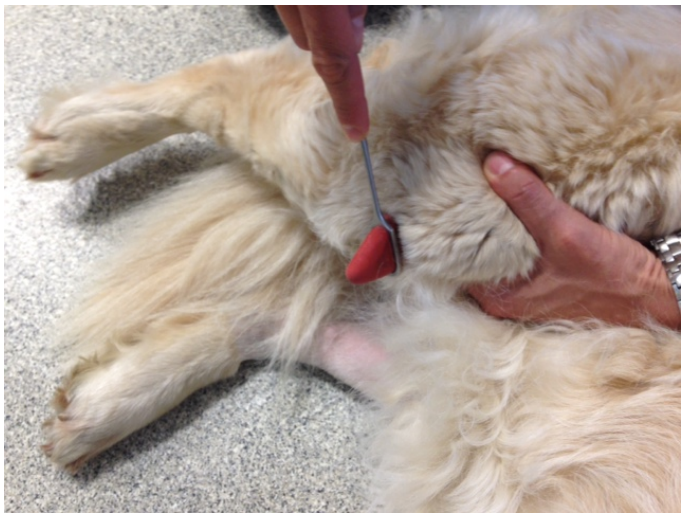


Figure 2. Assessing the patella spinal reflex in a dog

[A] **Proprioception** or joint position sense is the ability to sense stimuli arising within the body regarding position, motion, and equilibrium.

[A] **Increased spinal reflexes** indicate upper motor neuron or spinal cord white matter disease (i.e. ascending and descending tracts) mainly affecting the thoracic spinal cord (T3-L3 spinal segments). However some dog breeds, e.g. Rhodesian Ridgeback may be first presented with weakness, hypotonia, and hyporeflexia (i.e. loss of patellar reflex), which are lower motor neuron (LMN) signs similar to the human condition

DIAGNOSIS

A blood test for the SOD-1 mutation is useful to suggest risk of DM but it should be remembered that 1) having 2 copies of the gene does not confirm disease or rule out other contributory spinal cord diseases 2) not all degenerative spinal cord diseases are SOD 1 positive. 3) a definitive diagnosis of DM can be only obtained by post-mortem examination of the spinal cord performed by a pathologist. The suspected diagnosis of DM is based on clinical signs, breed, and age and supported by absence of other abnormal diagnostic tests and a positive SOD-1 mutation test. DM is a diagnosis of exclusion, which means that other diseases with similar clinical signs have to be excluded first. It must be differentiated from intervertebral disk protrusion and spinal neoplasia, so ideally spinal radiography (x-rays) and/or MRI scan should be performed. Older dogs may be affected by more than one disease process, so the presence of an intervertebral disk disease does not exclude the presence of DM and vice versa. Cerebrospinal fluid (CSF) analysis may show a mildly elevated protein concentration. Hypothyroidism should also be ruled out especially in susceptible breeds such as the Toller, Boxer dog and Rhodesian ridgeback.

TREATMENTS AVAILABLE AND PROGNOSIS

DM is an irreversible and progressive disease. The prognosis is poor, as no specific treatments are available although many dogs can be supported and maintain an acceptable quality of life for months to years [15]. Some anecdotal reports suggest that supplementation with combinations of antioxidants may help slow progression of the disease (Table 4).

It has been showed that daily controlled exercise and physiotherapy increases average survival time in dogs with suspected DM [16]. (see ACPAT, www.acpat.org, acpat@calra.net). **Hydrotherapy has been also recommended** (www.k9hydrotherapy.co.uk). Dogs affected by concurrent joint disease should commence pain management before undergoing a physiotherapy program. A “toe up sciatic sling” (http://www.orthopets.co.uk/products/assistive-items/sciatic-sling) may assist dogs preventing paw knuckling; and “toe grips” can help limit toenail wear (http://www.orthopets.co.uk/products/assistive-items/ToeGrips). Harnesses can be helpful to support a weak but ambulatory dog. Dogs that are unable to stand and walk on their hindquarters may benefit from using a cart.

Table 4

PROPOSED TREATMENT	DOSES	ANECDOTAL Notes	PEER REVIEWED SCIENTIFIC PUBLICATION
Anti-oxidant and other supplementations	**Docosahexaenoic Acid (DHA):** 40 mg/Kg a day **Eicosahexaenoic acid (EPA):** 25 mg/Kg a day **L-Carnitine:** 100mg/kg daily	It may help during the early stages of the disease (Rusbridge unpublished)	They do not harm, but unsure if beneficial
Corticosteroids at inflammatory doses.	**Prednisolone** 0.5mg/kg for 5-7days then taper to 0.1-0.25mg/kg every 24-48hours	Dogs that acutely deteriorate may benefit from short courses	Unsure if beneficial.
Epsilon-aminocaproic acid (EACA)	500mg twice a day	An antifibrolytic agent hypothesied to reduce the endothelial inflammation in the	Anecdotal beneficial reports

Available at WestLab Pharmacy, http://www.westlabpharmacy.com/		spinal cord associated to the disorder and due to immune-complexes and fibrin deposition.	
Other supplementations	**Vitamin E:** 2000 I.U. a day **Vitamin C:** 1000 mg twice a day **Vitamin B complex:** 100 mg a day **CoEnzyme Q10:** 100 mg a day **N-Acetylcysteine (NAC)** 75mg/Kg divided in 3 doses a day for 2 weeks, then 3 doses every other day	Nutraceuticals hypothesised to prevent tissue-damage due to free radicals that are formed secondary to inflammation.	Anecdotal beneficial reports
Riluzole [17]		Has shown to have neuroprotective properties, and has been used in ALS cases (the equivalent disease in human), showing delaying of the disease' progression and increasing survival time. This medication has not been used in DM cases, as its cost is a serious limitation.	Nothing reported

SUMMARY

DM is a non-painful, irreversible, progressive degenerative spinal cord disease that affects older dogs and causes hind limb paralysis and ultimately progresses to affect forelimbs and urinary and faecal continence. The prognosis is poor because no specific treatments are available. Physiotherapy, hydrotherapy, and various types of antioxidant nutritional supplementation are commonly used to slow disease progression. Dogs are commonly euthanatized when they are no longer able to walk and stand. Mutation of superoxide dismutase-1 (SOD 1) is associated with this disease. This mutation causes oxidative damage of the spinal cord; however the exact mechanism of disease is unknown. A genetic test is available which identifies dogs at risk of developing disease. DM is an incompletely penetrant autosomal recessive disease, which means that other as yet unknown factors (genetic or environmental) influence whether a genetically predisposed dog will develop disease.

Dogs should be tested before breeding. In ideal circumstances and in breeds with a large gene pool only normal (N/N) dogs would be bred from. However the Nova Scotia Duck Tolling breed has a very small gene pool and exclusive use of normal (N/N) dogs in a breeding program would 1) reduce the gene pool further 2) predispose for other inherited disease especially susceptibility to immune mediated disease. Therefore in the Toller breed it is recommended that carrier (N/A) and even affected dogs (A/A) be bred from. However these dogs can only be mated to tested normal (N/N) dogs and the offspring should also be tested with the aim of gradually reducing the prevalence of the disease gene generation by generation.

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USEFUL LINKS

http://www.acpat.org/ (Association of Physiotherapists in Animal Therapy)

http://neurovet.co.uk/spinal_disorders/ Clare Rusbridge's website)

http://vetmed.missouri.edu/news/DM2013.html (University of Missouri website)

www.finding-the-cure-for-dm-foundation.org (DM foundation)

http://www.handicappedpets.com/ (resources for handicapped dogs)

http://www.orthopets.co.uk (products for handicapped dogs)

http://www.freewebs.com/dmroster/eddies/eddiescarts.htm (dog-carts)

http://www.mzjf.info/links.htm (for useful links)

http://www.westlabpharmacy.com/ (supplier of EACA)

http://www.ufaw.org.uk/degenerativemyelopathygsd.php (UFAW)

http://www.offa.org/dnatesting/dmbreederguide.html (Guidelines for breeding)

http://www.toller.ca/tollerhealth/SurveySummary.html

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