Research in Degenerative Myelopathy with Special Emphasis on Corgis

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There is so much confusion about what is known in Degenerative Myelopathy (DM) and what is known is also changing fast, so I wanted to write this article to summarize current (2014) research on the disease in corgis specifically.

Background

DM has been known as a disease for over fifty years, and was first officially characterized in German Shepherds, so many think of it as a disease of German Shepherds. However, it is actually more prevalent in other breeds, including corgis. It may be most prevalent in Pembroke Welsh Corgis, though some vets will not even know it is a possible diagnosis. It is also called chronic degenerative radiculomyelopathy, or CDRM.

In the nineties, Dr. Joan Coates at the University of Missouri, along with numerous colleagues, began a project to study DM in corgis and boxers. The research was sponsored by the AKC Canine Health Foundation and the Pembroke Welsh Corgi Club of America. Corgi and Boxer owners were asked to send in blood samples from dogs with DM and from dogs without DM, and eventually also to donate tissue samples, including spinal cords, from dogs that had died.

Breakthrough- the gene is found

In 2008 the researchers had a breakthrough- they found a gene associated with DM! Because DM is similar to Amyotrophic Lateral Sclerosis, or ALS (Lou Gehrig's disease), which affects humans, they had looked for a gene in the same region that one gene causing ALS had been found.

They found that both Boxers and Pembroke welsh corgis with DM had two copies (AA) of a mutated gene for SOD1, the superoxide dismutase enzyme, which is responsible for destroying free radicals. Normal dogs (no DM) had either two non-mutated copies (GG) or one of each (AG), but also could have two copies (AA) and no DM.[1] (Note: OFA labels the genes NN instead of GG and AN instead of AG.)

Although many dogs testing AA did not have DM, as the age of the dogs increased the likelihood that an AA dog would have DM also increased.

The researchers developed a DNA test, which was initially available only from OFA, to test for the mutated genes. The test, which is now also available from other unlicensed labs, is a simple cheek swab, though a blood test can also be done.

What do the results of genetic testing mean?

When you send in a sample to be tested, you receive one of three possible results.

Clear- GG
Carrier- AG
At Risk or Affected – AA

Clear means that that corgi does not carry the gene for DM and can be bred to any other dog and the offspring will not be able to get DM.

Carrier means that the corgi can produce offspring with DM if mated to another carrier or an At Risk corgi, but will not itself get DM. (Although a very minute number of carriers with DM have been found in other breeds, none have been found in corgis, so the odds that a carrier could get DM are very, very low if not zero.) Initially there was some speculation that if a carrier lived long enough it might get DM, but at this writing, no carrier corgis with DM have been identified.

At Risk (Affected) means that the corgi has the potential to develop DM. We'll discuss later how many At Risk corgis are likely to develop DM.

Further Research

The initial research publication left many questions unanswered.

- What percent of At Risk corgis get DM?
- What triggers the onset of DM?
- How can we breed to reduce DM without overly narrowing the gene pool?
- How can we prevent DM?
- How can we treat DM?

Some of these questions are on the way to being answered.

Characterizing the disease process

In 2010, Dr. Coates' group published a paper which further characterized the disease. [2] They established that the average age of onset in Pems is 10.9 years, and they reported that the median disease time (onset to euthanasia) in smaller dogs, such as corgis, who could be more easily cared for after becoming unable to walk, was 19 months. This does not mean that the corgi died of DM after 19 months, though, it means that was the average age at which, for whatever reason, euthanasia was elected. (A later report from Japan, where DM corgis are maintained even further through the disease, included corgis that survived as long as 48 months with DM.)[3]

As corgi owners who have had dogs with DM already knew, after the back legs were affected by DM eventually the trunk and front legs would also become involved, advancing eventually to quadriplegia and respiratory failure. Some of the Japanese corgis that were maintained late into the disease did have respiratory distress.

In this paper, written for veterinarians, they also noted that other possible diseases that can mimic DM include *cauda equine* (lumbosacral disease), intervertebral disk disease (type II, non-acute), cancer of the spinal cord, and degenerative joint diseases. A diagnosis of DM cannot be confirmed without ruling out these other possible causes (ideally by MRI and not just X-rays.) This is an important point because when someone believes their corgi has DM, or even has a veterinarian's diagnosis, but the dog is under eight years old or has Clear or Carrier status, it is most likely the dog has one of these other diseases, most of which are treatable.

Several other published works describe the disease process at a cellular level and are beyond the scope of this discussion.

What percent get DM?

This question remains unanswered, but some information is available.

Some At Risk corgis have lived into advanced years (14 and older) and their spinal cords donated for research, and no signs of DM have been found. For example, one corgi breeder had At Risk littermates, one of whom developed DM at age 13, the other was euthanized past 14 with no signs of DM.[4] Other breeders have noted the same thing, that is, that being related and At Risk is not a predictor of developing DM or not.

However, in 2014 the researchers published a paper in which they reported the results of an owner-survey.[5] They had sent questionnaires to owners who had At Risk corgis tested by DNA before age 8, but whose corgis were now past age 10. This gave us the first rough measurement of what percent of at risk Pems would develop DM.

Survey results were received from 17 Pembroke Welsh corgi owners. One GG (Clear) had, as expected, no clinical signs of DM. Six AG (Carrier) also had no clinical signs of DM. Of ten AA (At Risk) Pems, 7 had no clinical signs of DM and 3 had clinical signs of DM.

This information suggests a rough 30% get DM, but that number should be used with caution for several reasons. It could be higher as more of the 7 now without DM could develop it as they age, or it could be lower, if owners with DM in their line were more likely to have tested or responded to the survey. Also, because the survey size is quite small, the room for error is large. However, it IS clear that it is not a small percent, but neither is it 100%.

Cardigan Welsh Corgis were also included in the survey but only 1 Clear and 4 Carriers were included in the response, all of which were without any sign of DM (as expected.)

Thanks to owners who have continued to donate blood and tissue samples from corgis, the researchers may be able to find a difference that will predict whether or not an At Risk corgi can develop DM.[6]

Breeding

How to breed away from DM remains a controversial issue. Statistics published by OFA are that 52% of tested Pembroke Welsh Corgis are At Risk (AA), 37% are Carrier (AG) and 11% are Clear (GG). These statistics have not improved much since the test was first available nearly five years ago and now represent the results from over 2000 Pems (mainly in the United States.) The extremely high incidence of the gene mutation means it is nowhere near as simple as eliminating all dogs with the mutation from a breeding program. Even in the US that would devastate the breed and likely create other problems.

If all European test results were made public, we would have a better idea of the scope of the DM problem here in the USA.

Ideally, all At Risk and Carrier Pems should be bred to Clear Pems. But with only 11% Clear, this, too, presents problems. A breeder with an At Risk or Carrier bitch may have a very hard time finding an appropriate Clear dog, and vice versa.

Here are the possible breedings and their statistical results:

At Risk to At Risk - all pups will be At Risk
At Risk to Carrier - 50% At Risk, 50% Carrier
At Risk to Clear - all pups will be Carrier

Carrier to Carrier- 25% At Risk, 50% Carrier, 25% Clear
Carrier to Clear- 50% Carrier, 50% Clear
Clear to Clear- 100% Clear

Currently, any breeding producing less than 50% At Risk is probably an acceptable one, including Carrier to Carrier. Carrier to Carrier can produce At Risk, but overall only at 25%, and can produce Clear at a higher percent (25%) than they are currently in the population.

So for a breeder trying to improve the breed, but willing to take a chance of getting At Risk, Carrier to Carrier is an acceptable breeding. However, unless one parent is Clear, a breeding can produce At Risk pups.

What would help with this problem would be for all breeders to test their breeding stock, and make any clear males publically known and available for breeding to acceptable quality Carrier and At Risk females. Finding those Clear males to sire litters is critical to being able to breed away from DM.

In addition, if owners of Clear females would breed them to the best At Risk males, this would be a way to preserve great lines without producing At Risk puppies.

It is also very important to make puppy buyers aware that a Carrier pup is a fine pet and will not get DM, and reserve any Clears that are breeding quality as breeding stock. If you, as a breeder, do not choose to breed a particular Clear who otherwise is perfectly decent, make it available to someone who needs it.

What triggers the onset of DM and how can we prevent it?

Nobody knows - yet. It may be genetic, and a test may be developed for the factor that makes the difference. It may be environmental, or it may be a combination of reasons. Right now, we don't know how to prevent it or how to predict which At Risk dogs will get it.

Some things have been suggested as triggering signs of DM. One is anesthesia, another is neutering. However, it is extremely unlikely that these have anything to do with DM beyond coincidence.

Humans - like all organisms- are genetically programmed to look for cause and effect in things. Our survival depends on it. Saber-toothed tiger bites someone, he dies. We conclude that we should avoid saber-toothed tigers. Wooly mammoth tramples someone, and we concluded that we should stay out of the way of stampeding mammoths.

But although we are programmed to believe that if A precedes B, A caused B, it is not always - or even usually - true. There are many reasons it may not be true. A and B can be caused by the same thing, for example, or it can simply be coincidence. In the case of anesthesia and DM, I think coincidence explains the cases where anesthesia seemed to hasten DM.

In fact, DM starts before you see any visible signs of a problem. A breeder who is still showing- and gaiting- a corgi in competition may notice a subtle change in gait. An owner

who is running a corgi in agility may notice slower times or ticking jumps. These signs can appear up to a year before the classic foot drag that usually signals the onset of DM. Only when enough nerve cells are affected will the obvious signs of DM appear. So a neuter or teeth cleaning done a few weeks before a foot drag is observed is, in fact, occurring long after DM has actually started its disease process.

Some people have speculated that it is an environmental factor that "turns on" DM. Nobody knows. (Although a small percentage of ALS is known to be familial, 90% occurs without a known genetic predisposition, so is presumably environmental.)

I do know of at least one case where littermates, both at risk, raised and living together for a lifetime, had different outcomes (one developed DM and one did not). In another case, the littermate that remained with the breeder and had good nutrition and was kept at a healthy weight with good vet care got DM, the overweight and less-well-cared-for sibling did not.

Preventing DM

At this point the only known way to prevent DM is by not producing At Risk puppies.

Treating DM

There are only two proposed treatments for DM that have been published.

The diet and supplements suggested by Dr. Clemmons has been widely publicized.[7] Unfortunately, he never published any data that showed that it worked or had any effect on DM. He made the claim multiple times, but did not back it up with science. One set of researchers did attempt to find out if it worked, and found no effect, but the study had flaws.[8] Only a few dogs were studied, and the only criterion was "time to euthanasia", which is a decision of the owner and not objective. Some individuals claim the diet works, others have seen no effect, and likely this is based on individual differences in the rate at which dogs progress with DM and not on the diet itself.

The other proposed treatment is canine rehabilitation therapy (physical therapy or physiotherapy.) Published work showed that the time to euthanasia was longer for dogs undergoing controlled therapy.[9] Again, however, the study is flawed, as time to euthanasia is not a useful measurement. However, many owners have reported that keeping their dogs exercising and doing therapy helped them remain mobile (in or out of a cart) longer. It is almost certain to keep the dog healthier as the disease progresses.

In the relatively near future tests may begin on possible pharmaceutical treatments for DM. While this is promising, it should be noted that no particularly useful drugs have been found for ALS.

Further information and useful links:

Progression of DM in video: http://scoutshouse.com/videos/video_progressionDM.html
The dog in the video was a US Champion and an OTCH (obedience trial champion).

Corgis on Wheels book:
http://www.corgiaid.org/cart/corgisonwheels

Information on DM and on the DNA test:
http://www.caninegeneticdiseases.net/DM/mainDM.htm

OFA link to buy the DNA test:
http://www.offa.org/dnatesting/dm.html

For DNA tests in Europe:
http://laboklin.de/

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[1] Awano, Tomoyuki, et al. "Genome-wide association analysis reveals a SOD1 mutation in canine degenerative myelopathy that resembles amyotrophic lateral sclerosis." *Proceedings of the National Academy of Sciences* 106.8 (2009): 2794-2799.

[2] Coates JR, Wininger FA. Canine degenerative myelopathy. Vet Clin North Am Small Anim Pract. 2010 Sep; 40(5):929-50

[3] Katz, et. Al, J. Neuroscience Research, 92:531-541 (2014); Ogawa, et. al., J. Vet. Med. Sci (0916-7250), 2011 73:10 1275-1279.

[4] Personal communication.

[5] Zeng, R., et al. "Breed Distribution of SOD1 Alleles Previously Associated with Canine Degenerative Myelopathy." *Journal of Veterinary Internal Medicine* 28.2 (2014): 515-521.

[6] Personal communication.

[7] Clemmons, R. M. "Degenerative myelopathy." *The Veterinary clinics of North America. Small animal practice* 22.4 (1992): 965-971.

[8] Polizopoulou, Zoe S., et al. "Evaluation of a proposed therapeutic protocol in 12 dogs with tentative degenerative myelopathy." *Acta Veterinaria Hungarica* 56.3 (2008): 293-301.

[9] Kathmann, I., et al. "Daily controlled physiotherapy increases survival time in dogs with suspected degenerative myelopathy." *Journal of veterinary internal medicine* 20.4 (2006): 927-932.