Craniomandibular Osteopathy

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A brief history and overview:

Cradiomandibular osteopathy, known simply as CMO or "lion's jaw," is the bane of a trio of Scottish Highland terriers: the Cairn, the West Highland, and Scottish terrier. Their common ancestry, and the commonness of this disorder in them and mixed breeds thereof, suggests the genetic mutation responsible for the disorder was present prior to the separation of the breeds in the early 20th century. CMO is characterized by pain, swelling and thickening of the skull bones, especially the ramus of the mandible (the vertical portion of the jaw), the bone near the jaw joint, and the tympanic bulla (the inner ear case). This pain and inflammation can result in fever, weight loss, decreased appetite, drooling, unwillingness to open the mouth, and changes in behavior. Clinical signs typically first appear between 4 and 8 months of age. Bony spurs can proliferate, and may or may not disappear with resolution of clinical signs once growth is finished. It can also affect the long bones, especially in the area of the growth plates, where rapid growth occurs, and reoccurrence can be seen in adults. CMO has been reported in other breeds, such as the Bullmastiff, English Bulldog, Boxer dog, Doberman Pinscher, Great Dane, and Great Pyrenees, but experts believe it is unlikely these cases were caused by the same genetic mutation as that found in the Scottish Highland terriers.[i] [ii]

In 1986 researchers Padgett and Mostosky suggested CMO was an autosomal recessive genetic disorder in the West Highland White terrier (WHWT).[iii] Autosomal recessive disorders are those that occur in the paired non-sex chromosomes, and two mutated copies of the same gene must be inherited, i.e. from both the sire and dam. However, it was many more years until the causative mutation was found, by researchers at the University of Bern in 2012, and a genetic test was first offered, but no publication was made. The disorder was again thought to be an autosomal recessive disorder.

Fast forward to three years ago, in 2016, when researchers at the University of Helsinki tied CMO, along with two other canine genetic disorders, to human ones. CMO was found to be clinically equivalent to the human disorder called Caffey disease, or infantile cortical hyperostosis. In humans, first clinical signs of Caffey disease are seen between birth and 5 months of age, with spontaneous resolution by 2 years, but with recurrence into adulthood sometimes seen. The disease is associated with joint laxity, stretchy skin, hernias, decreased height and increased risk of bone fractures and deformities in adulthood.[iv] Using genome wide association studies and next generation sequencing, the mutation at fault in the Scottish Highland terriers was found to occur in the *SLC37A2* gene. Studies are still ongoing to determine its full function.[v] The gene is known to be expressed in many tissues, including bone cells, and the mutation disrupts glucose transport, thus interfering with normal bone growth, leading to hyperostosis, or proliferative bone. Of greatest note, however, is that the study showed that the mutation caused the production of both the normal, expected protein, as well as an abnormally short one, even in dogs with two copies of the mutation, and the abnormally short protein was found to be produced in dogs that were carriers of the mutation (heterozygous), in smaller amounts. Dogs without the mutation were only found to produce the normal, or "wild type" protein. Because even dogs with two copies of the mutation (homozygous) expressed some normal protein, the mutation is termed "leaky" and likely accounts for some of the variability in degree or presence of clinical signs seen, called incomplete penetrance.

However, because dogs with only one copy of the mutation also expressed some abnormal protein, we now know that the disorder is autosomal dominant, with incomplete penetrance, just like Caffey disease.

This study therefore changed our understanding of the disease's mode of inheritance. We now believe that inheriting only a single copy of the mutated gene is required for a dog to develop clinical signs of CMO. Because more normal protein is produced in heterozygous dogs (those with one copy of the mutation), and clinical signs were found to be correlated with amount of normal protein produced, it can be anticipated that although heterozygous dogs can manifest CMO, their clinical signs, and the pain associated with this condition, can be expected to be less than that compared to homozygous dogs in most cases.

How big is the problem?

Because the Scottish Highland terriers, as with most terriers in general, are tough dogs that may be quite stoic in the face of serious pain, it's extremely important that owners and breeders are especially vigilant in monitoring their dogs for subtle signs of pain associated with this disorder, so these dogs receive the best care possible. Just because the dogs may hide the pain, does not mean they should not be treated! In humans, this disorder is known to be quite painful, and pain control is a mainstay of therapy. Preparedness is best achieved by knowing *each puppy's* genotype in advance, and even better, the genotypes of the parents to plan breedings accordingly. If even one of the parents is a heterozygous at risk dog (1 copy at risk), each puppy can have a different genotype. Based on data published by Wisdom Health™, we know that CMO is extremely common in the Cairn, WHWT and Scottish terrier. In contrast, the reported rate of Caffey disease in infants younger than 6 months in the US is 3 per 1000 (<0.01%), but genetic testing is discussed as part of genetic counseling if either parent has displayed clinical signs of the familial form as an infant. The below figures represent more than 100 dogs tested of each breed by Wisdom Health™, from several countries, and as data are anonymized for all tested dogs, there is no reporting bias, so these figures may differ from those found elsewhere:[vi]

Breed	Genetically at risk (heterozygotes/1 copy)	Genetically at risk (homozygotes/2 copies)
Cairn terrier	14.57%	1.51%
Scottish terrier	10.19%	<1%
West Highland White terrier	35.34%	7.52%

Because of the extremely high rate of CMO in the WHWT, it is of utmost importance to realize that carriers must not be suddenly eliminated from the population. Doing so could result in a loss of over 1/3 of breeding dogs which would likely have a negative, bottleneck-type impact on the breed's diversity. Diversity lost by excluding this mass from the breeding population may never be recovered, and loss of genetic diversity is associated with increased risk for genetic disease in humans and in dogs. Avoidance of all carriers in the instance of the WHWT would be trading CMO for potentially worse, yet unknown, genetic disease. Though neither the Cairn or Scottish terriers have quite the mutation burden within the population as the WHWT, similar recommendations would be appropriate to ensure that genetic diversity is not unnecessarily lost.

In such cases, a gradual program focusing first on avoidance of genetically homozygous (2 copy at risk) dogs, which are at greatest risk for severe disease, followed by a slow elimination of carriers, to preserve the diversity and other good features of the lines, along with other standard holistic considerations in breeding and common sense, should be the goal.

Where to get testing in the US?

Testing is available through a number of laboratories in the United States, but as mentioned previously, there are other considerations in breeding beyond simply the CMO mutation. The test with the most comprehensive offerings in disorders, traits, and diversity, along with a comparative global population database, is Optimal Selection™, in the US and Canada (excluding Quebec) and made available in Europe, Asia, and Australia as MyDogDNA®. For members of the Cairn Terrier Club of America, a discount code will be available soon for online purchase of Optimal Selection™ around the time of the National, in partnership with the Foundation of the Cairn Terrier Club. See the CTCA website for details.

About the Author:

Casey Knox, DVM, HonBS, has been an associate with Wisdom Health since 2013, and works with breeders, breed clubs, and veterinarians. She received her DVM degree from Oregon State University in 2007 and practiced in both small animal and mixed animal hospitals. She has special interests in educating dog owners about their role in preventative medicine and the human-animal bond, immune and endocrine disease, and dermatology. In her spare time she enjoys organic gardening, crafting, and hiking with her family and their Border terrier.

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