Boxer Hypothyroidism

I am enclosing a copy of a manuscript that my colleagues and I have written regarding the prevalence of autoimmune thyroid disease in Boxers. Our work at the Animal Health Diagnostic Laboratory at Michigan State University indicates that there is a lot of interest in hypothyroidism in dogs. We get many calls from practitioners about problems breeders face and would like to share our experiences with members of the Boxer breed club. Please feel free to include this manuscript in your breed publication and let members make as many copies of it as they like. We hope you find this information useful and will periodically update you as new information about thyroid disease in the Boxer becomes available. If you have questions regarding this manuscript please don't hesitate to contact me. Ray Nachreiner, DVM, PhD

CANINE HYPOTHYROIDISM: PREVALENCE OF POSITIVE TgAA IN 871 LABORATORY SAMPLES FROM BOXERS

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Hypothyroidism is the most common endocrine disease in dogs. The thyroid gland controls the speed of metabolism of almost all body cells. When thyroid hormones are subnormal, many different body systems can be affected; so the clinical appearance of the disease can vary. The most common clinical signs include: weight gain, sluggishness, skin and hair coat problems (including hair loss), weakness, cold intolerance, and infertility. Although hypothyroidism is not life threatening, the quality of life is subnormal. Veterinary testing procedures have improved over the past 25 years, and hypothyroidism and its therapy are well understood by most practitioners.

Breeders, however, are faced with a dilemma. The disease seldom demonstrates clinical signs before 3 to 5 years of age, well into the showing and breeding years for many dogs. An economical and early detection procedure is needed. Progress is being made toward this objective.

The 1997 AKC Parent Club Survey' found that breeders are quite concerned about this disease. In fact, it was ranked first, with hip dysplasia and epilepsy close behind.

Boxer breeders were among the breeders identifying thyroid disease as a major problem. As a result of breeder and veterinary interest, a number of progressive changes have occurred in the past few years. AKC and other groups sponsored an International Symposium on Canine Hypothyroidism2. Participants agreed that breeders should test their dogs for thyroid disease and this test profile should include Total Thyroxine (T4), Thyroid Stimulating Hormone (TSH), Free T4 by Dialysis, and Thyroglobulin Autoantibody (TgAA). The Orthopedic Foundation for Animals (OFA)3 started a Canine Thyroid Registry and has certified a number of regional veterinary laboratories in the US and Canada qualified to perform the thyroid profile for registry purposes. Oxford Laboratories4 began producing a commercially available assay for TgAA so all reagents for the OFA profile are standard among certified laboratories.

About half of canine hypothyroidism has been reported to be associated with autoimmune thyroiditis (positive TgAA).5 The majority of the remaining hypothyroidism is idiopathic (without apparent cause and TgAA negative), while a small fraction is from a pituitary disorder. Recent data from Michigan State University have shown that idiopathic hypothyroidism can be the end stage of autoimmune thyroid diseases. Hence, the majority of canine hypothyroidism is the result of autoimmune thyroiditis. This makes testing for the disease marker in breeding dogs important for reducing its incidence. The best current marker for this disease is a positive TgAA test result. This is present when there is active thyroid disease (inflammation). Assuming a single gene disorder and recessive trait, TgAA will be positive only in dogs having both genes for thyroiditis. TgAA will not be positive in the carriers (having only one gene for the trait) and may not be positive early in the life of some dogs which become affected later.

A number of scientific publications have presented data to support the genetic transmission of autoimmune thyroid itis'~8. Others have reported the familial (occurring among relatives) incidence of the disease','" "'2. In addition to screening breeding animals, the TgAA assay has been useful for disease diagnosis. In June 1998, the Michigan State University Animal Health Diagnostic Laboratory began running the TgAA assay as part of routine thyroid function testing, making it possible to detect autoimmune thyroid disease long before complete thyroid atrophy and clinical hypothyroidism (when clinical signs are present) occurred. Of course, most of the samples were from dogs with at least one clinical sign suggestive of hypothyroidism.

A study done on the first 51,201 laboratory samples that were tested for thyroid disease using the new TgAA test indicated that 7.9% of samples were positive and 4.0% were inconclusive. There were 4045 dogs positive for TgAA and 2809 classified as having idiopathic hypothyroidism. Dogs less than 2 years of age had few (less than 5%) TgAA positive samples (Figure 1); samples from dogs 2 to 6 years of age were positive 9 to 11.5% of the time, while samples from dogs older than 6 were positive less often. It appears that autoimmune thyroid disease occurs earlier in life than idiopathic hypothyroidism, supporting the concept that the idiopathic form may result from the autoimmune disease. Semi-annual thyroid biopsy results from a small group of affected dogs at MSU also support the conclusion that idiopathic hypothyroidism is the end stage of autoimmune thyroid disease.

Table 1 -- Percentage of TgAA positive samples within breeds with statistically over-represented and under-represented for prevalence

HIGHEST PREVALENCE		LOWEST PREVALENCE	
English Setter	26.0%	German Shepherd	5.4%
Dalmatian	16.8%	Labrador Retriever	5.1%
Basenji	16.3%	Collie	5.1%
Rhodesian Ridgeback	16.1%	Poodle	4.4%
Old English Sheepdog	15.0%	English Bulldog	3.9%
Boxer	13.8%	Dachshund	3.7%
Maltese	13.5%	English Springer Spaniel	3.7%
Chesapeake Bay Retriever	13.5%	Shih Tzu	3.6%
Beagle	13.4%	West Highland White Terrier	3.5%
Cocker Spaniel	12.6%	Chihuahua	2.9%
Shetland Sheepdog	12.5%	Lhasa Apso	2.8%

Siberian Husky	12.3%
Border Collie	11.9%
Husky	11.5%
Akita	10.8%
Golden Retriever	9.1%
Pomeranian	2.7%
Miniature Pinscher	2.5%
Cairn Terrier	2.5%
Basset Hound	2.5%
Schnauzer	2.3%
Yorkshire Terrier	2.3%
Boston Terrier	2.1%
Norwegian Elkhound	2.1%
Greyhound	2.0%
Portguese Water Dog	2.0%
Newfoundland	1.9%
Bichon Frise	1.4%
Welsh Corgi	1.3%
Minature Schnauzer	1.2%
Cavalier King Charles Spaniel	1.1%
Flat-Coated Retriever	0%

Another way of looking at these data is that over 50% of TgAA positive samples were from dogs less than or equal to 5 years of age, while it took 8 years to obtain more than 50% of the samples from dogs with idiopathic hypothyroidism (Figure 2). Since idiopathic hypothyroidism appears to be the end stage of autoimmune thyroiditis, the majority of primary hypothyroidism in dogs is most likely a result of the autoimmune disease. An important fact for breeders is that the TgAA test can detect this disease rears before clinical signs of hypothyroidism occur.

Table 2: Prevalence of positive and inconclusive TgAA in breeds of the Working Group

BREED	PERCENT POSITIVE	INCONCLUSIVE	TOTAL
Akita	10.8	4.4	453
Alaskan Malamute	11.3	6.7	239
Anatolian Shepherd	14.3	0	14
Bernese Mountain Dog	8.1	4.1	172
Boxer#	13.8	3.4	871
Bullmastiff	4.5	4.5	156
Doberman Pinscher	8.2	4.4	1630
Giant Schnauzer	12.4	2.9	105
Great Dane	7.9	2.1	290
Great Pyrenees	7.3	4.8	124
Mastiff	8.8	4.4	249
Newfoundland*	1.9	2.6	310
Portuguese Water Dog*	2.0	5.0	101
Rottweiler	7.2	5.0	913
Saint Bernard	8.3	4.2	96
Samoyed	7.4	3.3	299
Siberian Husky#	11.1	5.7	424
Schnauzer-Unspecified*	2.3	1.9	474
All Working Dogs	8.4	4.1	6920
All Breeds	7.9	4.0	51201

= OVER-REPRESENTED * = UNDER-REPRESENTED FOR THYROIDITIS

After 6 years, the TgAA test becomes less relevant, as dogs that were positive can become negative when the thyroid is destroyed, and there is no longer a stimulus for TgAA production. After that time, T4 and TSH become more important indicators of thyroid disease.

As one would expect from a genetically transmitted disease, 16 breeds had significantly higher laboratory prevalence of TgAA compared to the total number of dogs (overrepresented) and 27 breeds had a significantly lower prevalence (underrepresented) (Table 1).

Table 1--Percentage of TgAA positive samples within breeds which were statistically over-represented and under-represented for prevalence.

HIGHEST PREVALENCE	**LOWEST PREVALENCE**
English Setter 26.0%	German Shepherd Dog 5.4%
Dalmatian 16.8%	Labrador Retriever 5.1
Basenji 16.3%	Collie 5.1
Rhodesian Ridgeback 16.1 %	Poodle 4.4%
Old English Sheepdog 15.0%	English Bulldog 3.9%
Boxer 13.8%	Dachshund 3.7%
Maltese Dog 13.5%	English Springer Sp. 3.7%
Chesapeake Bay Ret 13.5%	Shih Tzu 3.6%
Beagle 13.4%	West Highland White T. 3.5%
Cocker Spaniel 12.6%	Chihuahua 2.9%
Shetland Sheepdog 12.5%	Lhasa Apso 2.8%
Siberian Husky 12.3%	Pomeranian 2.7%
Border Collie 11.9%	Miniature Pinscher 2.5%
Husky 11.5%	Cairn Terrier 2.5%
Akita 10.8%	Basset Hound 2.5%
Golden Retriever 9.1 %	Schnauzer 2.3%
Yorkshire Terrier 2.3%	
Boston Terrier 2.1	
Norwegian Elkhound 2.1	
Greyhound 2.0%	
Portuguese Water Dog 2.0%	
Newfoundland 1.9%	
Bichon Frise 1.4%	
Welsh Corgi 1.3%	
Miniature Schnauzer 1.2%	
Cavalier King Charles Sp. 1.1	
Flat-Coated Retriever 0%	

Some additional breeds also had high or low percent positive, but the number of samples from those breeds may have been too small to achieve statistical significance. As additional samples are analyzed, presumably these additional breeds will become statistically significant as well.

As groups, Herding and Sporting dogs were significantly over-represented for TgAA positive samples while Hounds, Non-Sporting dogs, Terriers, and Toy

breeds were under-represented (Figure 3). Within those groups, some breeds were significantly over-represented while others may be under-represented.

Table 2: Prevalence of positive and inconclusive TgAA tests in breeds of the Working Group.

PERCENT	POSITIVE	INCONCLUSIVE	TOTAL
AKITA#	10.8	4.4	453
ALASKAN MALAMUTE	11.3	6.7	239
ANATOLIAN SHEPHERD	14.3	0.0	14
BERNESE MOUNTAIN	8.1	4.1	172
DOG	13.8	3.4	871
BOXER#	4.5	4.5	156
BULLMASTIFF	8.2	4.4	1630
DOBERMAN PINSCHER	12.4	2.9	105
GIANT SCHNAUZER	7.9	2.1	290
GREAT DANE	7.3	4.8	124
GREAT PYRENEES	8.8	4.4	249
MASTIFF	1.9	2.6	310
NEWFOUNDLAND	2.0	5.0	101
PORTUGUESE WATER	7.2	5.0	913
DOG*	8.3	4.2	96
ROTTWEILER	7.4	3.3	299
SAINT BERNARD	11.1	5.7	424
SAMOYED	2.3	1.9	474
SIBERIAN HUSKY#	8.4	4.1	6920
SCHNAUZER-UNSPECIFIED*	7.9	4.0	51201
All Working Dogs			
All Breeds			

= OVER-REPRESENTED * = UNDER-REPRESENTED FOR THYROIDITIS

The Working Group (Table 2) has 3 breeds with over 500 samples, 2 were similar to the average for the Working Group (Doberman Pinscher and Rottweiler) and 1 is over-represented (Boxer). Though Boxers, along with Huskies, and Akitas were over-represented, others were significantly underrepresented (Newfoundland Portuguese Water Dog and Schnauzer). Hence, the Working Group as a whole had an average prevalence that was similar to the all breed average. This is not to say that since the group is average, one should not be concerned about autoimmune thyroid disease.

Since there is a genetic component to the disease, some breeds have a higher prevalence while others have less. One should strive to reduce the disease in the higher prevalence breeds and keep it low in the lower prevalence breeds. The Boxer had 13.8% of the samples positive for autoimmune thyroid disease. This is higher than the all breed average, and was statistically significant.

Breeders should strive to reduce the prevalence of autoimmune thyroiditis within the breed. Testing breeding animals for TgAA during their early reproductive years and breeding appropriately will help accomplish that objective. The assay can be performed on serum samples at most of the larger veterinary laboratories or on blood spots at Oxford Laboratories.

In conclusion, while there is no DNA based testing procedure at this time, testing with the best available marker, TgAA, can be beneficial. Selective breeding should reduce the prevalence in high incidence breeds and prevent an increasing prevalence in low incidence breeds. Although males were similar to females in prevalence, you can imagine the impact one important but affected male could have on the breed, especially a breed with small numbers. The TgAA portion of the thyroid profile is most important during the first 5 years of life as few dogs are found to have idiopathic hypothyroidism before this age.

Since idiopathic hypothyroidism appears to be the end stage of autoimmune thyroiditis, the majority of hypothyroidism in dogs is a result of this inherited autoimmune disease. An increased focus on testing for autoimmune thyroiditis and selective breeding should help decrease the prevalence of canine hypothyroidism. In addition, knowing which are affected dogs within a pedigree will help to identify which dogs have a high probability of being carriers (ie. one affected gene if a single gene trait).

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