What's the Risk?
HYPOTHYROIDISM IN BEAGLES

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Both statistics and personal experience leave little doubt that beagles are a higher risk breed for autoimmune thyroiditis (AT) and hence, hypothyroidism. The Michigan State University diagnostic laboratory database contains the results from 329,477 samples submitted by veterinarians from dogs with clinical signs of thyroid disease and for breeding assessment. There were 6,435 samples from beagles with roughly 18% that were affected with autoimmune thryroiditis.

To test or not to test:

I would recommend testing all breeding stock due to this increased risk demonstrated by statistics alone, and because there have been other studies to show that autoimmune thyroiditis is a genetic disorder.

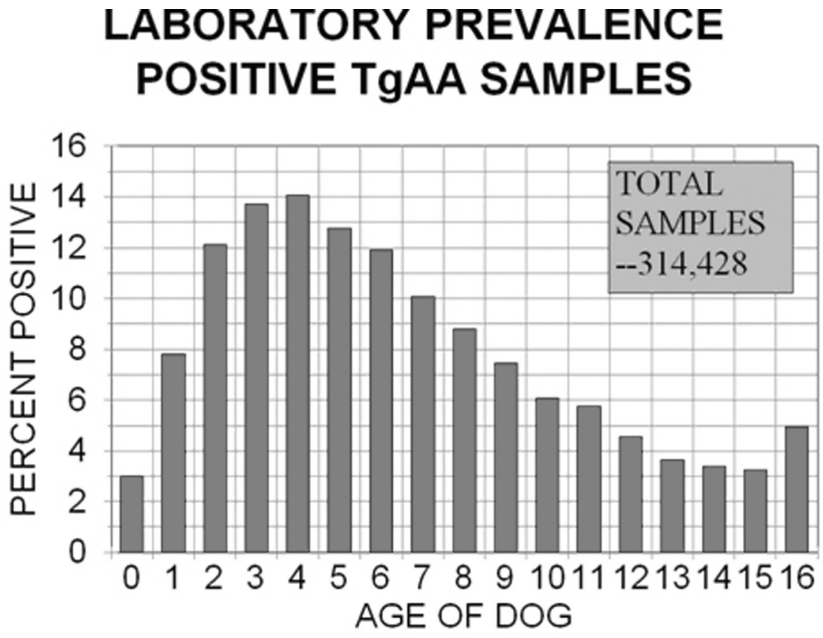
One of the best studies was done in beagles and published by Benjamin et.al. in 1997. It was a huge study and 276 normal beagles lived a normal lifespan under colony conditions. They found that autoimmune thyroiditis was highly heritable. Thyroiditis was present in 26.3% of the beagles and 25% of the sires produced 68.2% of the affected pups.

At present there is not a gene based test for autoimmune thyroiditis so we must count on a phenotypic test to determine which dogs are affected. The best test for that is the thyroglobulin autoantibody assay (TgAA). This assay has been available for quite some time and in recent years has been improved to reduce the number of false positive and inconclusive tests by adding an assessment of non-specific binding (NSB).

One of the times when NSB can occur is after vaccination. The immune globulins increase because of the vaccine and NSB increases as well. Other factors, such as any wound or disease process which increases IgG probably increases NSB as well. The modified test with the correction for NSB avoids errors from these problems. The NSB modified test procedure gives us confidence that dogs that are positive have autoimmune thyroiditis and that they have affected genes which will be passed on to their offspring. I would recommend testing all breeding stock to reduce the amount of thyroid disease in beagles.

When and how to test:

Very few dogs are affected with this autoimmune disease prior to one year of age. At the start of the disease there is a small focal infiltration of lymphocytes beneath the capsule of the thyroid. At this point the dog will have an increase in the amount of TgAA in its serum. We do not understand the inducers of the disease and it appears that there are some factors which induce the onset of lymphocytic infiltration. One animal model (the obese chicken) in studies by Dr. Brown (Wayne State University) has shown that excess iodine in the diet would induce an earlier onset of thyroiditis than the chickens fed normal iodine. Whether iodine is also an inducer in the dog is not known, but the obese chicken model has shown that inducers can be an important factor in the onset of the disease. Perhaps that is why we see such a varied age prevalence for the diagnosis of thyroiditis and hypothyroidism. Even though a dog may have the genes for thyroiditis, without the inducer the genes may remain dormant.



The above graph shows the prevalence of positive TgAA based on age. Note that the peak prevalence is in the 3, 4, and 5 year range, but that there are positive dogs at any age. The fact that the prevalence is lower during the early years indicates that dogs may be negative on one test only to become positive later in life, which is an unfortunate fact for breeders since a considerable amount of money and effort may be put into a dog because it is negative when first tested and then it turns out to be positive at a later age. We have shown that when positive dogs are known and identified within a pedigree, one can see the "genes" trickling down through the pedigree and causing thyroiditis and hypothyroidism. (A study done in Welsh Springer Spaniels gives a strong indication of a simple autosomal recessive trait.)

Unfortunately, there have been no clinical changes observed which would give the owner or the veterinarian a clue that autoimmune thyroiditis is present, which is why it is important, when screening breeding stock. to have a full thyroid panel done, versus the in-house T4 panel that most veterinarians provide.

Especially note that there are two stages in the disease process (positive TgAA and eleveated TSH) which can be detected with a full thyroid panel prior to the stage when T4 finally drops. Dogs with thyroiditis may be detected a year or more before this with the full profile, but would have been classified as normal with a T4 assay alone.

In addition, any T4 assay can give you a false indication of thyroid disease. There are many conditions that are not related to thyroid disease which can cause T4 to drop, such as using Cortisone like drugs which will suppress T4 in any dog. Yet, this is not hypothyroidism. Use of sulfa drugs can cause a transient hypothyroidism which will recover after the drug is stopped. If a dog is off food for a few days, its thyroid hormone production will be lowered. This is a normal physiological process and will reverse

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when the dog starts eating again. Finally, any chronic debilitation condition (chronic kidney disease, liver disease, infectious processes causing fevers, diabetes, etc.) will result in a normal process which lowers thyroid hormone production. T4 is low in these dogs, but this is not hypothyroidism and has no bearing on the assessment of the genetics of the dog regarding its thyroid.

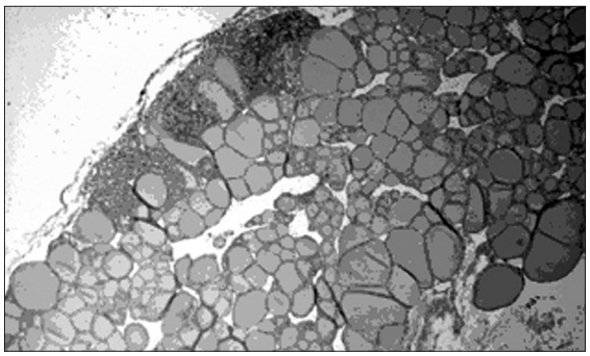
So forget about looking at T4 alone. Some vets will look at T4 alone if they suspect thyroid disease, but it is important that they follow up that analysis with a broader profile which will help them clarify the actual thyroid function.

It is best to start testing at one year of age, keeping in mind that the dog should be rechecked periodically to see if the disease develops at an older age.

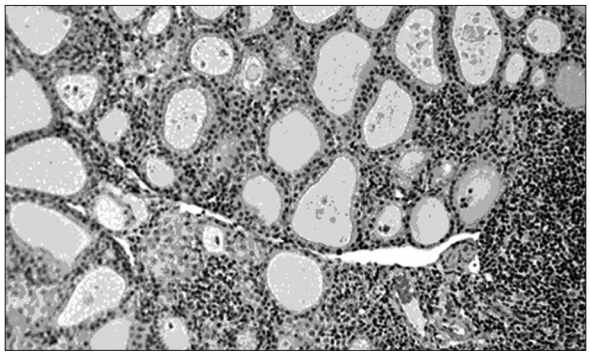
By the same token, the odds of a dog becoming positive after 6 years of age are slim. But, if the dog was showing clinical signs of thyroid disease at any age, I would test them just the same.

A number of studies have shown that young dogs have higher T4 and T3 than old dogs. Though older dogs, over the age of 8-9, normally do have lower thyroid levels, even old dogs should have concentrations within the reference range, just on the lower end of the range.

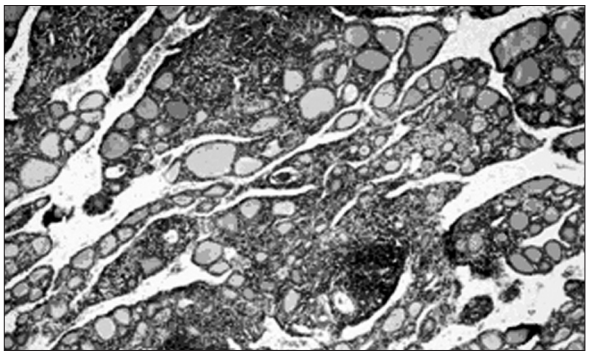
THE PROGRESSION OF THE DISEASE:



A - The first lesion to appear in the thyroid that can be identified is microscopic. A focal infiltration of the thyroid by lymphocytes occurs. Note the dark blue cells on the upper left of the thyroid biopsy. At this stage only the TgAA will be positive. There will be no changes in the TSH, T4, or T3. A thyroid with focal thyroiditis would be expected to be classified by the Orthopedic Foundation for Animals (OFA) Thyroid Database as Positive Compensative Autoimmune Thyroiditis though a few may have antibody titers in the equivocal range and be classified as Equivocal.



B - Then the lymphocytic infiltrate becomes more diffuse and starts to interfere with thyroid hormone production. The pituitary compensates with an increase in TSH to stimulate more T4 and T3 production from the remaining normal tissue. At this stage, TgAA will be positive and TSH will be elevated, but T4 and T3 will still be normal. This is also classified as Positive Compensative Autoimmune Thyroiditis by OFA.



C - Finally, considerable lymphocytic infiltrate occurs and the normal thyroid cells are so few that they cannot compensate. At this stage, TgAA is positive, TSH is elevated and T4 and T3 are low. This would be classified as Positive Autoimmune Thyroiditis by OFA. Note that it is not until this stage that T4 and T3 are low. There are two stages prior to this which have significant changes that the breeder can use to identify the presence of autoimmune thyroid disease. That is why OFA requires TgAA, TSH and Free T4 in its thyroid database for thyroid registry.

The genetics of it all:

It is not known whether AT is strictly genetic or can develop from other factors. In humans some viral diseases have been shown to cause thyroiditis. However, these are usually transient and the thyroid returns to normal after a period of time. Similar studies have not been done in dogs.

Breeding stock diagnosed as follows are more or less predisposed to passing on thyroid disease:

a. Positive autoimmune thyroiditis

These dogs have a strong indication of having the genes that cause thyroid disease and many are already showing clinical signs of hypothyroidism.

b. Positive compensative autoimmune thyroiditis

These dogs have a strong indication of having the genes for thyroid disease.

c. Idiopathically reduced thyroid function

These dogs should be rechecked as some of these dogs may have a transient problem which will improve over time. For others, it may be the end stage of autoimmune thyroiditis and they would be expected to have the genes for thyroid disease.

d. Equivocal

Many of these dogs can be shown to be normal if retested. I'd wait at least 3 or 4 months for things to return to normal before retesting.

Though the addition of the Non-Specific Binding correction of the TgAA assay has corrected for the potential of false positive results because of vaccinations, stress or estrus, I would avoid testing during estrus and after stress (heavy exercise has been shown to cause decreases in T4 and T3) as you may get equivocal results because of the low T4. Remember, an equivocal result does not imply anything about the genetic status of the dog.

Seeing physical symptoms:

Chronic ear infections, skin infections, dry eye, allergies, early sterility, abnormal reproductive seasons, epilepsy have all been suggested to be possibly linked to hypothyroidism, and some of these commonly

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perceived symptoms of hypothyroidism are noted with submission of lab samples from the general population of affected beagles.

I'm not sure that epilepsy is more commonly seen in dogs with thyroid disease. However, dogs on Phenobarbital therapy often have lowered T4 and T3 which may result in some clinical signs of hypothyroidism. Perhaps that is why an association has been made between thyroid disease and epilepsy.

Reproductive problems are not as commonly seen in hypothyroid dogs as they are in hypothyroid humans. But, we certainly do see instances when a dog of low fertility that is also hypothyroid will have normal fertility after thyroid therapy.

We have not seen eye problems other than some increase in cholesterol clefts in the lens with untreated hypothyroidism.

Finally, the thyroid hormones control the metabolism of almost all cells in the body. As a result, there are many varied clinical signs that have been associated with hypothyroidism. When a cell's function becomes slower than normal, problems can occur. With the slow metabolism, obesity can occur. Skin problems, loss of hair, ear problems, and chronic infections are often seen. The dogs become sluggish and no longer want to exercise or hunt. Not all of these signs are seen in every hypothyroid dog. There really isn't anything "classic" about hypothyroidism and that is why a good laboratory test is required to determine whether the thyroid is involved with the signs observed.

When and how to medicate:

Unless the dog is not dosed correctly, there are no long term side effects of L-thyroxine therapy. Excessive medication can cause hyperactivity, panting, heart problems, excessive weight loss, and diarrhea. Dogs on therapy should be monitored periodically - about once a year unless the clinical condition indicates a need for earlier testing.

If a beagle is diagnosed as compensated AT, some literature suggests that supplementation should be started before the beagle actually tests as hypothyroid. My own bias is to wait until there is some clinical sign of thyroid disease. That way, the owner can see an improvement in the dog and realize that therapy is important.

In addition, some dogs with autoimmune thyroiditis will never become hypothyroid. They either don't get exposure to the inducers that are necessary to move the disease along to the point of hypothyroidism or die from something else before the disease progresses. Once the dog has a high enough titer for autoimmune thyroiditis to put it into the Positive Compensative Autoimmune Thyroiditis category it is most likely going to progress. However, some do not progress to hypothyroidism and others progress slowly. So, I'd wait rather than begin thyroid replacement therapy.

To breed or not to breed:

Although hypothyroidism is easily treated with daily oral medication, with a high incidence breed like beagles, it remains important that the disease be controlled through selective breeding.

I have estimated that the cost of hypothyroidism in a dog is about $1500. over the life of the dog. That includes the initial diagnosis, therapy, monitoring, etc. Certainly, hypothyroidism isn't something like blindness or hip dysplasia or elbow dysplasia. Those diseases are irreversible. Hypothyroidism is easily treatable with a simple pill once or twice a day. So, it is a philosophical discussion whether to breed or not to breed.

(This article was compiled from a question-and-answer session conducted by the NBC Health and Genetics Committee.)

BEFORE THERAPY

TWO MONTHS OF THERAPY

FOUR MONTHS OF THERAPY

SIX MONTHS OF THERAPY

THERAPY AND THE RATE OF IMPROVEMENT

Prior to therapy, this dog was depressed and very sluggish. Note the calluses on the hock. A patch of hair had been shaved one year earlier and had not grown back. After two months of therapy, the dog was already quite bright and responding well. The calllus was improving and the patch of lost hair was slowly improving. At four months the dog continued to improve and by six months a total transformation of the dog was apparent. Though this seems like a miracle, it is just good diagnostics and medicine.