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*Beloved Keeshond Rescue Dog & PHPT Survivor
Participant in the Study that Identified the PHPT Gene*

THE KEESHOND AND PRIMARY HYPERPARATHYROIDISM

by Debbie Eldredge, RVT

Primary hyperparathyroidism (PHPT) is a relatively rare disease in dogs. Many veterinarians may never see a case in their entire careers. However, the Keeshond is 50 times more likely to be diagnosed with PHPT than other breeds, so Keeshond owners must be familiar with this disease!

PHPT is a curable disease! If treated early, dogs can enjoy a normal life. It's up to Keeshond owners to inform our veterinarians that this unusual disease runs in the breed. We must make certain our dogs are screened for it!

WHAT IS PRIMARY HYPERPARATHYROIDISM?

The dog has four parathyroid glands. "Para" means "beside" -- the parathyroid glands are located in the neck, beside the thyroid gland. (People are often confused by the words thyroid and parathyroid. The parathyroid glands are located *beside the thyroid*, but they are separate glands. PHPT is not a thyroid problem!)

The tiny parathyroid glands, normally less than 2 mm in diameter, produce parathyroid hormone (PTH.) PTH controls the calcium level in the dog's blood. When the calcium level is low, the parathyroid glands secrete PTH, which causes the calcium level to rise. When the calcium level is normal, the parathyroid glands turn off -- they stop secreting PTH, so the calcium level doesn't rise too high.

In PHPT, one or more of the parathyroid glands fail to turn off. They continue to secrete PTH, causing the blood calcium to continue rising to dangerous levels. In 80-85% of cases, this is caused by a benign tumor (called an adenoma) on one parathyroid gland. Occasionally, two or more parathyroid glands are involved, which is called hyperplasia. PHPT can also be caused by a malignant carcinoma, but in dogs, this is very rare. The disease typically strikes middle-aged and older dogs.

If PHPT is treated in the early stages, it can be cured with few or no permanent effects on the dog. As the disease progresses and calcium levels continue to rise, painful calcium deposits form in the soft tissues of the body, the dog's kidneys are damaged, and bone disease can occur. If untreated, the dog eventually dies from severe kidney failure.

In the Keeshond, PHPT is a genetic disease transmitted by a dominant gene. To get PHPT, a dog only needs to inherit the defective gene from one parent. (So Keeshond mixes are at risk, too.) If a dog with the abnormal gene is bred, half of his or her puppies will get the defective gene. If they live long enough, nearly all dogs with the defective gene will develop PHPT.

WHAT ARE THE SYMPTOMS OF PHPT?

The signs of PHPT are subtle and insidious. In the early stages, the dog may have no symptoms. As the disease progresses, you may notice the dog is drinking more water and urinating more than usual. Gradually, the signs may include weakness, lethargy, shaking, decreased activity, loss of appetite and possibly weight loss. Many dogs develop calcium-containing bladder or kidney stones.

By monitoring the dog's blood calcium levels on a regular basis, PHPT can be caught and treated early, before the dog shows signs and kidney damage occurs.

SHOULD MY DOG BE SCREENED FOR PHPT?

Keeshonden and Keeshond mixes **MUST** be screened for PHPT! The average age of Keeshonden when diagnosed with PHPT is 7-9 years. Since some dogs get PHPT at younger ages, screening should begin before age 7.

Option 1: Monitoring blood calcium levels: Until recently, this was the only way to screen for PHPT. It is still an excellent option. It is essential for dogs who have the PHPT gene.

Starting at age 5 years, a comprehensive blood panel should be done annually, including complete blood count (CBC) and blood chemistries. Beginning at age 7, we recommend a blood panel every 6 months. High blood calcium indicates possible PHPT. If the calcium is above normal, more diagnostic work must be done to determine whether the dog has PHPT or another illness.

Option 2: Genetic Testing for the PHPT Gene: In November, 2004, Dr. Richard Goldstein at Cornell University College of Veterinary Medicine began a successful study to identify the defective gene responsible for PHPT in Keeshonden. Thanks to Dr. Goldstein and the Keeshond owners and breeders who contributed samples for the study, we now have a test available to determine whether a dog has the PHPT gene.

Dogs who test positive for the defective gene will almost certainly develop PHPT during their lifetimes. These dogs must have their calcium monitored closely (see option 1 above), to detect and treat PHPT in its early stages, before they suffer permanent kidney damage.

Dogs who test negative do not have the PHPT gene and are not likely to develop PHPT. (Middle aged and older dogs should still have blood panels done at least annually, to detect other problems.)

Reputable Keeshond breeders are now testing their dogs prior to breeding them. If the dam and sire are both PHPT negative, the puppies will be free of the PHPT gene. Before purchasing a Keeshond puppy, ask to see proof that both parents are PHPT negative!

You will find more information on the genetic test for PHPT, including instructions for submitting samples, at <http://www.vet.cornell.edu/labs/goldstein/>.

HOW IS PHPT DIAGNOSED?





The first step in diagnosing PHPT is a blood panel that shows high blood calcium, or hypercalcemia. Before proceeding with other testing, it's a good idea to recheck the calcium level to confirm that it is elevated.

Hypercalcemia has many possible causes. Some of them include: PHPT, kidney disease, various types of cancer, Addison's disease, Vitamin D overdose (from rat poison, excessive supplementation or eating certain plants), and fungal infections. So the second step in diagnosing PHPT is a thorough physical exam to look for causes of hypercalcemia, such as tumors.

If no cause for hypercalcemia is found, a blood sample should be submitted to Michigan State University (MSU) for a hypercalcemia of malignancy profile.

Some reference labs are now offering these panels, so veterinarians may be tempted to submit the samples to their usual lab instead of to MSU. We recommend submitting the samples directly to MSU! The reference labs do part of the panel themselves and forward the samples to MSU for completion of the tests, causing a delay in the results. For accurate results, samples MUST be kept very cold and shipped by overnight express; additional shipping and handling may affect the accuracy of the tests. You'll find submission forms and instructions for sample collection and shipping at <http://www.animalhealth.msu.edu>.

The profile includes the following tests:

-  **Ionized calcium:** "Ionized calcium" is the active form of calcium. It travels in the blood, ready for use in important body functions, such as muscle contraction, nerve function and blood clotting. "Bound calcium" also travels in the blood, but it's carried by protein molecules or connected to other ions. The calcium test on a routine blood panel measures the total of both forms of calcium. Measuring the ionized calcium helps to differentiate between the possible causes of hypercalcemia. Ionized calcium is typically high if the cause is PHPT or cancer, but not if the dog has kidney disease or Addison's disease.
-  **Intact parathyroid hormone (iPTH):** If the blood calcium is high, the parathyroid glands are supposed to shut down and stop secreting PTH! If they are still producing PTH, the parathyroid glands are not working properly!
-  **Parathyroid-related protein (PTHrP):** This protein is similar to PTH and also causes the blood calcium to rise. Some tumors produce it in very high amounts, so high PTHrP is a sign of cancer.
-  **High ionized calcium, normal to high PTH, and low PTHrP are diagnostic for PHPT.**

If the tests from MSU and other tests indicate PHPT, the next step is an ultrasound exam to confirm the diagnosis and locate and measure the affected gland(s). The appropriate treatment options depend on the number, size and location of the affected gland(s).

Parathyroid glands can be very difficult to find on ultrasound because they're so tiny (only a few mm in diameter.) It's important to have the ultrasound done by a board-certified radiologist who has experience with PHPT!

WHAT ARE THE TREATMENT OPTIONS FOR PHPT?

To treat PHPT, the affected parathyroid gland(s) are removed surgically or destroyed. There are 3 methods available. Which of the methods may be appropriate depends on how many parathyroid glands are affected and their size and location.

PHPT is an uncommon disease. Treating it requires special training and expertise. No matter which treatment option you choose, be sure to have it done by an experienced veterinary specialist!

- 🐾 **Surgery:** Surgery to remove the affected gland(s) is available throughout the country. When done by an experienced, board-certified surgeon, the success rate is nearly 100%. Up to 3 affected glands can be removed during one surgical procedure.
- 🐾 **Percutaneous ethanol injection (PEI):** Ultrasound is used to guide a very small needle into the affected gland. The gland is then destroyed by injecting it with ethanol. The procedure usually takes about 10-20 minutes. In experienced hands, the success rate is about 90%. **Advantages:** It is less invasive than surgery and the dog recovers more quickly. It may be slightly less expensive. **Limitations:** The glands must be at least 3-4 mm in diameter. It can cause the tissues to swell temporarily, so if glands are affected on both sides of the neck, they should not be injected at the same time. PEI requires special ultrasound equipment. It takes skill and practice to insert the needle accurately – for the best results, it must be done by an experienced veterinarian. Here in Northern California, we are fortunate to have one of the veterinarians who developed this procedure.
- 🐾 **Heat ablation:** As in PEI, ultrasound is used to guide a special probe into the affected gland. High frequency radio waves are then used to heat the gland and destroy it. The success rate is about 90%. **Advantages:** It is less invasive than surgery and the dog's recovery time is shorter. There is less tissue swelling than with PEI. **Limitations:** This procedure is done only at UC Davis, using a very expensive machine that was a special donation. Like PEI, placement of the probe requires skill and practice, so it is done by experienced specialists.

The most important part of treatment is caring for the dog after the procedure!

The affected gland (which was producing PTH) has been removed surgically or destroyed. Because the dog's blood calcium level was high, the remaining normal parathyroid glands have turned off -- they are dormant, not producing PTH. It takes time for the dormant glands to turn back on. Until they do, the dog is in danger of his calcium dropping to life-threatening levels! Proper care after treatment is critical -- dogs have died from low blood calcium during this time.

The calcium must be allowed to drop low enough to wake up the dormant parathyroid glands and cause them to begin secreting PTH again. But it must not be allowed to drop dangerously low. If the calcium level drops too low, the dog may need calcium and vitamin D supplementation. If the supplementation is started too soon, the dormant parathyroid glands won't turn back on. It's a difficult balancing act, and should be managed by a veterinarian who is board-certified in internal medicine.

The calcium can drop very suddenly. Typically, this happens 3-7 days after treatment, and it can be life threatening. For safety's sake, the dog should be in the hospital for 7-10 days, with calcium tested twice a day, so treatment for low blood calcium can be started immediately if needed.

When the calcium level has stabilized, the dog can go home. The blood calcium level will still need monitoring, and supplemental calcium and vitamin D may still be necessary.

WHERE CAN I GET MORE INFORMATION?

An excellent series of articles appeared in Keeshonden magazine in 2005. These articles, written by Cathy Bosnic, were published during the study that identified the PHPT gene. You will find them here: <http://www.vet.cornell.edu/labs/goldstein/PHPTArticles.pdf>

Dr. Richard Goldstein conducted the study that identified the gene responsible for PHPT in Keeshonden and developed the genetic test for the gene. He has offered to help any Keeshond owner with questions about PHPT. He can be reached at rq225@cornell.edu

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About the author: Debbie Eldredge, RVT, has been rescuing Keeshond dogs since 1993. Her beloved Keeshond rescue dog, Toby, was diagnosed with PHPT after a routine blood panel revealed hypercalcemia. Toby was treated successfully and was one of the dogs in Dr. Goldstein's study. Thanks to Toby and other Keeshonden who contributed to the study, we now have a genetic test that enables us to identify dogs who are at risk of developing PHPT and avoid passing the disease on to future generations. It's a fitting legacy for a very special dog.