

CYSTINURIA:

The “3 Ts”: Testicles, Testosterone and Two genes

By Lori Hunt, DVM

Cystinuria is one of those “new” diseases that has everyone talking! Well, it’s not NEW really, just new to us as French bulldog breeders. Whenever anything new comes along, there is the usual fear, finger pointing, and denial – all three are detrimental to any breed. When a breed is in existence long enough, and people start discussing things, we start to hear of commonalities and issues that exist. Cystinuria is one of those... It starts something like this... Sally says, “My dog just had to have emergency surgery for bladder stones” and Suzie says, “Oh, he did? One of my friends’ dogs also had stones and had to have a Scrotal urethrostomy”... and then the conversation (hopefully) continues... And information is gained!!! I am hoping this article will dispel some myths and explain why so many of you have not seen it personally. Remember everyone, knowledge is power!

Let’s start with some basics of bladder stones. There are several kinds in dogs; the most common being Struvite, Oxalate, Urate and Cystine. Struvite stones are usually caused by pH variances and/or chronic, often low grade, urinary infections. Oxalates can be caused by pH imbalance. Urates are inherited in certain breeds, like Dalmatians. And then there is cystine, which is a bit more complicated. Cystine stones have been known about and managed in many breeds for a while now, including Newfoundlands, Mastiffs, and bulldogs. French Bulldogs are the newest breed discovered to be affected by them. Cystinuria is the name for the disease caused by cystine stones (cystin-) in the bladder and urine (-uria). In French bulldogs, the ability to develop Cystinuria is inherited by a simple autosomal recessive gene and current information is that neutering is curative.

As I type, I can hear many of you saying.... “But I have been in frenchies forever, and I have NEVER seen it!” Well I am writing this article to tell you THAT IT IS OUT THERE! And dogs have DIED from it, due to lack of knowledge... I have at least 40 cases that I have consulted on and discussed with the owners’ of said dogs, either on the phone, via email or through my survey on my website (<http://www.assisifrenchbulldogs.com/cystinuria>).

You see, Cystine stones are a bit tricky in Frenchies... In order for a dog to make cystine stones, three things MUST happen: 1) the dog is a male 2) the dog is NOT neutered, thus having testosterone in his system and 3) the dog has two copies of the gene. A quick way to remember it is the “3 Ts”: Testicles, Testosterone and Two Genes. In my humble opinion, one of the biggest reasons many people have not seen this disease is that MOST male puppies are neutered in pet homes. I will go one step further and say that I believe many male frenchies, even champion show dogs, are neutered by the age 3 – 4, and placed in a pet home. According to my survey results, the average age for Cystinuria to raise its ugly head is 3.58 years of age. Now hopefully you can see how many dogs may escape it by being neutered young. Also if you unknowingly breed a carrier to a carrier, your chances of getting an AFFECTED MALE puppy are only 12.5%. Even breeding a carrier to an affected, only gives you a 25% chance of producing an affected male. As you can see these are small percentages, which gets even smaller when you account for the small litter size we see in French bulldogs, and so we don’t always see statistics working out as perfectly as Mendel intended them....

In order to see these affected male dogs become clinical, they must grow up, not be neutered, be fertile (not sub fertile or infertile) and reach an age that allows significant cystine stone

formation. Once a large amount of cystine stones are present, they can obstruct the urethra. When the urethra is obstructed, a dog cannot urinate; they become toxic and at risk for bladder rupture. What an owner may see is a dog who is lethargic, painful, and inappetent (symptoms often seen with other frenchie issues, including backs, which begs the question how many have been misdiagnosed). If the stones are not found and treated, the dog can die ... and quickly!

At this point, I want to relate some information from my informal survey, so that you may be aware of what dogs suffering from this disease experience. My survey revealed an average diagnosis age of 3.6 years old, with a range of 1 – 7.5 years. The latest I've heard is stones forming and causing blockage was 11 years. There was one 6.5 year old dog who passed away from unrelated causes and was stone free, BUT sterile (Missing one of the 3 Ts = Testosterone). To my knowledge, there is only one dog who is over 8 and fertile, who is still stone free. The following symptoms prompted owners to seek their veterinarian: blood in the urine, straining to urinate, frequent urination, housebroken dogs urinating in the house, blocked and could not urinate at all, not eating, pain and lethargy/depression. Most of these stones were diagnosed on ultrasound, a few by radiograph (likely involving a special procedure to inject air in the bladder to highlight stones, as they are not generally radio opaque), and some were not diagnosed until they were able to “unblock” the dog and see the stones.

The most difficult part for me to read in these surveys was the procedures these dogs had performed on them, especially in light of the fact that we now know that Cystinuria can be CURED by removing stones and neutering the dog. But before I get into what these dogs endured, a few definitions are necessary. The urethra is the tube that carries urine from the bladder out of the body. In the male dog, it passes along the backside of the dog and between the rear legs. Within the penis, the urethra lies within a trough of bone, the os penis, and becomes narrower. Stones that develop within the urinary tract will often become stuck within the urethra behind this bone, blocking the urethra and thus rendering the dog unable to urinate. If stones are stuck in the urethra, hydropulsion can be attempted. This is done with the animal anesthetized. A catheter is then passed through the urethra if possible or until blockage is felt and an infusion - most times with great force - of sterile saline is used to try to push the stones back into the bladder so a cystotomy can be performed. To remove stones from the bladder, a cystotomy is required. In this procedure, the dog is under general anesthesia. The bladder is accessed through a small abdominal incision. Then the bladder is opened, stones are removed, and the urinary tract is flushed thoroughly to make sure no stones are left behind. If stones in the urethra cannot be flushed into the bladder for removal, a scrotal urethrostomy (see below) may be necessary. Stones removed at surgery are submitted for chemical analysis and in some cases, for culture as well. Biopsy of any abnormal bladder tissue may be collected as well. Dogs which have a urethral obstruction that cannot be unblocked or are recurrent stone formers may require surgery to form a new permanent opening to the urethra, called a scrotal urethrostomy. Scrotal urethrostomies may be required because stones in the urethra may become trapped and cannot be removed. An opening is created behind the os penis where the urethra is wider so that urine and small stones may pass through. For most dogs having a scrotal urethrostomy, the penis is left in place, so that a male dog will look the same when he is walking down the street. However, he will urinate from the new opening in the location where his scrotum used to be, similar to how a female dog urinates.

Many dogs in my survey had MULTIPLE cystotomies, hydropulsion and more than half of the dogs ended up with scrotal urethrostomies after undergoing multiple surgeries. If only those owners and/or their veterinarians had known that neutering was curative!!!! Many were not

neutered until after the urethrostomies were performed. If they had been, there would have been no need for further surgeries. If Cystinuria statuses of these dogs had been known, all but neutering could likely have been avoided, as careful monitoring of the urine could have been done with a nitroprusside test. We are lucky now... we can get our dogs' status with a simple cheek swab DNA test!

Due to research performed by Paula Henthorn, PhD at the University of Pennsylvania Veterinary School, we have learned a lot about Cystinuria in frenchies. Dr. Henthorn's official paper will be published sometime soon. But as a synopsis, French bulldogs are either CLEAR (1-1), CARRIER (1-2) or AFFECTED (2-2) (a female would be considered a double carrier). Cystine stones can often be difficult to diagnose on radiograph and/or ultrasound. Sometimes cystine crystals can be found in a urine sample. There is now a urine nitroprusside test available for those who want to monitor urine status and their dog's risk for stone formation. This can be especially helpful for people with 2-2 males. In Dr. Henthorn's original study, there were close to 215 french bulldogs involved, approximately half male and half female. She had 10 stone formers (5%) who were ALL 2-2 intact males. Approximately 37% of the dogs in the study were Clear, approximately 41% carriers and approximately 22% affected. There were two 2-2 males who did not form stones, but one was later determined to be sterile, thus missing one of the 3 Ts – Testosterone!

How do I get my dog tested for the Cystinuria gene?

You will have to send a blood sample or cheek brushes. Cheek brushes can be obtained from: www.ezswabs.com

A. Login the PennGen's home page (<http://research.vet.upenn.edu/>)

1. As a new user, "Create an Account"

2. Animal Owner/Agent

3. Create a New Account

4. Request a New Test

5. Complete animal information

6. Test Type: Type3 Cystinuria-Associated Marker – DNA

B. Follow the "Sample Collection & Shipping Instructions"

C. Print off "Submission Form", complete and sign.

D. Mail Sample Collection & Submission Form to: Dr. Paula Henthorn per instructions

E. You will be notified by email when the test is completed.

F. Login to your PennGen account, pay for test via credit card, and receive the results.

G. Turn around time is a few weeks

As a side note, there are multiple companies offering "Cystinuria" testing for frenchies. They have offered it in the past for some of the other affected breeds, mentioned earlier in this article, but it is NOT the same as for French Bulldogs, who have Type 3 cystinuria. To paraphrase Dr. Henthorn, a woman I consider as our breed's Cystinuria authority, "These (other companies) may be using one marker that has been published with others as a part of polymorphism (multiple genes seen in animals with disease).... It has been known about for years but is not believed to alone cause cystinuria. PennGen uses multiple markers, ... Including the 8 additional markers that we've identified in the research to actually cause disease"

In summary, Cystinuria is definitely affecting our French bulldog males. I think we are seeing an increase in cases for a few reasons. One being the more natural approach the dog community

is taking to neutering, as we now see benefits to delaying neutering. However with 2-2 males, this can be detrimental. I think we are also hearing about it more due to the internet and our shrinking world... more communication and knowledge. Cystinuria is a simple autosomal recessive and we can breed away from it with the help of a simple cheek swab DNA test. As of the writing of this article, there is only ONE proven place to do this test and it is at PennGen, aka the University of Pennsylvania's School of Veterinary Medicine (<http://research.vet.upenn.edu/>). You can still confidentially submit surveys on my website <http://www.assisifrenchbulldogs.com/cystinuria>

Let's not bury our heads in the sand... test and be aware. We can confidently breed carriers, and even affected dogs, so long as we know what we are matching up, and what may need to be neutered as a result of the cross. You can even breed two carriers or two affected and easily keep a bitch with no worry, as 2-2 bitches will never get disease and should just be treated as a double carrier. It's imperative to know the status of males in particular from a health stand point for the dog, in order to lessen his chances of making stones.

Be open and honest and share information... Test, share, don't judge, and for goodness sake, don't throw the baby out with the bath water. Use it as a piece of the puzzle that is breeding! It's the least we can do for the breed we all love and who gives us so much in return!

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www.freewebs.com/assisifrenchies