Shar-Pei Autoinflammatory Disease & Hyaluronan

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Familial Shar-Pei Fever (FSF)[1] was introduced in the early 1990's as a term to identify a condition observed in some Shar-Pei that included renal amyloidosis and recurrent fever of unknown origin[2], similar to some humans affected with the inherited condition *Familial Mediterranean Fever*. Later research into the causes of FSF revealed that FSF was but one manifestation of a recently identified inherited overarching disease state in Shar-Pei called *Shar-Pei Autoinflammatory Disease* (SPAID)[3]. FSF is only one of several possible phenotypic[4] signs of SPAID, as is renal (or systemic) amyloidosis which can occur independently from FSF.

Shar-Pei produce excessive amounts of a substance called hyaluronan (HA). This causes their breed-specific wrinkled, thickened skin and has also been linked to SPAID. A mutation and copy number variation of a regulatory element upstream to the gene for hyaluronan synthase 2[5] leads to the overexpression of HA in Shar-Pei.[6][7] Anytime there is a need for HA within the body, they may make as much as 10 times more than dogs of other breeds. This may lead to problems because HA is a dynamic molecule with important roles in the maintenance of health.

We all have HA but some Shar-Pei have too much of a good thing.

An intricate network of HA cables, along with other molecules, form a mesh on the surfaces of cells and fills the spaces between cells comprising the extracellular matrix (ECM). Networks of HA also cover the intestinal tract microvilli and line blood vessels (endothelial glycocalyx). HA can also be a viscous gel that is an important component of joint fluid and the vitreous that fills the eyeball. It also plays critical roles in the kidney and the control of hydration, taking advantage of the molecule's sponge-like ability to hold up to 1000 times its molecular weight in water.

When it is first formed, HA is usually a very large molecule, one of the largest in the body. Frequently resynthesized, it is turned over rapidly and degraded into smaller fragments that are

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[1] **A canine febrile disorder associated with elevated interleukin-6.** Rivas AL, Tintle L, Kimball ES, et al. *Clin Immunol Immunopathol* 64:36-45, 1992.

[2] **Familial renal amyloidosis in Chinese Shar-Pei dogs.** Di Bartola S, Tarr MJ, Webb DM, et al. *JAVMA* 197(4): 483-487, 1990.

[3] **Thorough investigation of a canine autoinflammatory disease (AID) confirms one main risk locus and suggests a modifier locus for amyloidosis.** Olsson M, Tintle L, Kierczak M, et al. *PLOS ONE* 8:e75242, 2013.

[4] Phenotype = the appearance of an organism resulting from the interaction of the genotype and the environment.

[5] a control switch for the enzyme that makes hyaluronan

[6] **Novel unstable duplication upstream of HAS2 predisposes to a breed-defining skin phenotype and a periodic fever syndrome in Chinese Shar-Pei dogs.** Olsson M, Meadows JRS, Truve K, et al. *PLOS Genetics* 7: e1001332, 2011.

[7] **Absolute quantification reveals the stable transmission of a high copy number variant linked to autoinflammatory disease.** Olsson M, Kierczak M, Kaarlson Å, et al. *BMC Genomics* (2016) 17:299.

continuously recycled. The breakdown of a Shar-Pei's excessive HA into fragments for routine metabolism may also contribute to autoinflammation and randomly triggered fever events.

The long molecule of HA functions as one of the most primitive sentinels of innate immunity. If it is damaged and broken into small fragments, the body senses these small pieces as "wrong" and sounds the alarm. It is a fundamental barrier molecule of the innate immune system. Small fragments of HA can trigger the release of powerful messengers of fever and inflammation.[8] HA is necessary for and promotes wound healing. But in Shar-Pei, the screeching alarm signal may be out of proportion to the seriousness of the injury. They may then over-react to relatively minor insults. This can lead to episodic fever and chronic inflammation.

Familial Shar-Pei Fever is an episodic fever syndrome (39.4-41.7 degrees C) that may or may not be accompanied by joint (usually the tibiotarsal or hock joint/s) or muzzle swelling. Fevers typically last from just a few to 36 hours and if they last longer than 48 hours, a veterinarian should rule out underlying persistent triggers of fever including infection. A veterinarian should be consulted at the time of the first episode, if the fever approaches or exceeds 41 degrees C, or if the episode is unusual for that individual. In very rare cases, the fever events can be life-threatening but most are self-limiting. Prompt treatment with aspirin or nonsteroidal antinflammatory drugs will usually reduce fever and alleviate pain.

Some bacteria, yeast, insects and snakes secrete hyaluronidases. Hyaluronidases are enzymes that break down HA. These types of attacks can cause serious, dramatic and sometimes life-threatening problems for Shar-Pei.

Damage to HA that is lining blood vessels may contribute to the edema of chronic swollen hock syndrome as well as an acute necrotizing neutrophilic vasculitis syndrome (very similar to Streptococcal Toxic Shock Syndrome or STSS in humans) that may occur after an FSF event. The latter may cause extensive skin sloughing with high mortality in some dogs and requires prompt, aggressive veterinary treatment.

Hyaluronosis is the presence of excessive deposition of HA, often described by the more general term *mucinosis* in Shar-Pei. Shar-Pei have excessive production of HA from skin fibroblasts resulting in *hereditary cutaneous hyaluronosis*[9]. This can result in lakes or vesicles of HA in the skin. Fragile bubbles of mucin may disrupt the normal skin architecture causing vesicular cutaneous hereditary hyaluronosis (vHCH) in some individuals.

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[8] **NLRP3/cryopyrin is necessary for interleukin-1beta (IL-1beta) release in response to hyaluronan, an endogenous trigger of inflammation in response to injury.** Yamasaki K, Muto J, Taylor KR, et al. *J Biol Chem* 284(19):12762-71, 2009.

[9] **Hereditary cutaneous mucinosis in shar pei dogs is associated with increased hyaluronan synthase-2 mRNA transcription by cultured dermal fibroblasts.** Zanna G, Docampo MJ, Fondevila D, et al. *Vet Dermatol* 20(5-6):377-82, 2009.

Unfortunately, the selection for excess wrinkling and the heavy, padded muzzle (meatmouth) that persist into adulthood led to the selection of dogs for breeding that carried a high number of the mutations that cause excess production of HA. This inadvertently predisposed these dogs and their offspring to problems from autoinflammatory disorders, some of which can cause death at relatively young ages from complications of high fever, kidney or liver failure, and infections. The vast majority of dogs have no ill effects but they remain at risk.

What can a Shar-Pei owner do with this knowledge? The answer lies in HA's ability to promote health and healing when it remains in its native, high molecular weight state: Work to keep their HA healthy and undamaged and support their ability to respond appropriately to insults that may result in damage. Know what signs to look for that indicate serious problems and seek veterinary help swiftly when needed.

Feeding a high quality diet rich in the building blocks of HA and supplying the necessary vitamins and minerals for building HA is important. N-acetyl-glucosamine is the backbone of the large HA molecule and if inadequately supplied, less healthful smaller molecules may form. Glucosamine is abundant in the connective and joint tissue found in cheaper cuts of meat and fish as well as in home-made chicken soup stock. Magnesium is a requirement for HA synthesis and body stores may be depleted if it is inadequately supplied in the diet. HA is degraded by reactive oxidative species so antioxidants may be helpful to prevent oxidative damage. HA is up-regulated by hyperglycemia (high blood sugar) so feeding a relatively low carbohydrate diet with restricted snacking and avoiding over-feeding is suggested.

Keep their skin and ears clean and healthy. This is where regular, fanatical cleansing and grooming routines pay off handsomely. Very gently remove the opportunistic bacteria and yeast before they jump in and wreak havoc. Many Shar-Pei do not enjoy the bathtub and for these dogs, gently washing with a warm wash cloth or microfiber cleaning cloth may be more successful.

Many Shar-Pei have very narrow (stenotic) ear canals. It is particularly important that these dogs get preventive measures to keep the canals free of debris, infection and inflammation that may cause obstruction and pain.

Work closely with your veterinarian to manage the signs of autoinflammation including Shar-Pei Fever. It may be necessary to have aspirin or prescription non-steroidal antinflammatory medication available to you to administer for episodes of fever and inflammation like swollen hocks and/or muzzle. Prescription colchicine therapy may be needed to control the silent background inflammation that can lead to kidney or liver failure from reactive amyloidosis and to reduce the severity and frequency of fever events.

Some Shar-Pei develop gastrointestinal inflammation with chronic or intermittent diarrhea that requires veterinary assessment and treatment. Food intolerances in dogs that have intestinal inflammation is not uncommon and dietary adjustments, medication and probiotics may help.

Severe skin and ear infections may need microscopic examination, cytology, culture and sensitivity testing to identify appropriate therapy.

Abnormal lumps or thickening of the skin of Shar-Pei should be examined by fine needle aspirate and cytology and/or biopsy with histopathology. Mast cell cancer is unfortunately common in the breed, is the great pretender and sometimes mistaken for chronic infection or less serious conditions. Mast cells are frequently found in areas of mucinosis and it can take expert opinion to differentiate this from mast cell cancer.

A strong partnership with your veterinarian will help identify problems early. At least annual first morning sample urinalysis, complete blood count (CBC), blood chemistry profile, and total T4 thyroid testing are recommended for most Shar-Pei and may be needed more frequently if there is evidence of chronic inflammation. Advanced testing may be needed to eliminate other causes of their symptoms.

A test quantifying the number of inherited genetic mutations in the regulation of HA production present in an individual Shar-Pei has been developed. Increased number of mutated copies (higher copy number variation or CNV) has been shown to be associated with increased risk for SPAID (including FSF and amyloidosis). Because all Shar-Pei carry at least two mutations that can predispose to autoinflammation, this test will be an additional aid in diagnosis that may shed light on their relative risk and that will also help breeders avoid breeding high risk carriers to one another. The mutation can appear as a single copy or with five copies. This results in dogs with a possible 2, 6 or 10 copies of the mutation that causes up-regulation of hyaluronan. The 5 copy gene has been associated with increased risk for Shar-Pei Autoinflammatory Disease. We expect this test to be offered at designated university laboratories in the United States and Sweden later in 2016.

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