Shar-Pei Fever

MEGAN WORK
Megan graduated from the University of Glasgow in 2017, and is currently undertaking a rotating internship at Willows Veterinary Centre and Referral Service. She has a particular interest in small animal internal medicine and emergency and critical care.

FERGUS ALLERTON
Fergus is a European Veterinary Specialist in Small Animal Internal Medicine also working at Willows Veterinary Centre and Referral Service. His main clinical interests are in gastroenterology/hepatology, immune-mediated disease and antibacterial stewardship and he is currently Chairman of the Small Animal Medicine Society (SAMSoc).

Year	Shar-Pei registered with the Kennel Club
2009	2,174
2010	2,304
2011	2,067
2012	1,706
2013	1,808
2014	1,682
2015	1,339
2016	1,504
2017	1,395
2018	1,160

TABLE 1: Annual number of Shar Pei registered in the UK with the Kennel Club in the past 10 years.

Megan Work and *Fergus Allerton* from the Willows Veterinary Centre and Referral Service in Solihull focus on Shar-Pei Fever and explain how fellow vets can get involved with ongoing research.

Shar-Pei Fever (SPF) is an inherited autoinflammatory disorder of Shar-Pei dogs. It is also known as Familial Shar-Pei Fever, Swollen Hock Syndrome, Shar-Pei Hock, and Shar-Pei Autoinflammatory Disease (SPAID). Over 17,000 Shar-Pei dogs have been registered with the Kennel Club in the past decade (Table 1);[1] however, little is known about the incidence of SPF in the United Kingdom and how best it should be managed. To date, there are relatively few published guidelines and articles about this condition in the veterinary literature, and many of the recommendations for the diagnosis and management of Shar-Pei Fever come from non-peer reviewed sources. Affected animals suffer from recurrent bouts of fever, typically lasting between 24 and 36 hours, and occurring without a known trigger. Severe pyrexia (>41.0°C) requires urgent and aggressive management as such cases may be life-threatening. Episodes of fever may be accompanied by swelling of the tibiotarsal joints and occasionally the muzzle. Animals may exhibit signs of pain or discomfort as well as inappetance, lethargy, polyuria, polydipsia, and vomiting. Fever events often resolve spontaneously; however, in some cases reactive systemic amyloidosis may develop consequent to one or more acute inflammatory events. In dogs, the kidneys are the organs most frequently affected by amyloidosis; death due to renal failure is not uncommon in affected Shar-Pei. Amyloid deposits in the liver, spleen, stomach, pancreas, small intestine, prostate, lymph node, and adrenal glands have also been reported.[2] Besides the eponymous SPF, the breed is predisposed to a range of other conditions including entropion, skin disease (particularly allergic and bacterial), otitis externa, and dietary sensitivities/chronic enteropathy.

Pathophysiology: the role of hyaluronic acid

Shar-Pei have been strongly selected to exhibit a thickened, wrinkled skin and a 'meatmouth' padded muzzle appearance (Figure 1), although some Shar-Pei have mildly wrinkled skin and a narrower 'bonemouth'

FIGURE 1: 'Meatmouth' Shar-Pei with characteristic wrinkled skin and padded muzzle. (Image courtesy of Sarah Banbury)

Available in the BSAVA Library: DOI: 10.22233/20412495.0220.18

appearance. The more wrinkled skin phenotype is a result of excessive deposition of hyaluronic acid (HA) in the dermis. Hyaluronic acid production is regulated by three HA synthase enzymes, of which HAS2 acts as the rate-limiting enzyme. It has been demonstrated that Shar-Pei dogs exhibit a higher rate of HAS2 transcription in comparison with other breeds and have increased production of HA.[3] Furthermore, Shar-Pei have higher serum HA concentrations compared to other breeds.[4] Hyaluronic acid plays a complex role in the body and when fragmented can act as a danger-associated molecular pattern (DAMP), or warning signal, inappropriately activating the release of pro-inflammatory interleukins. Genetic tests have shown that a breed-specific mutation on the chromosome close to HAS2 positively correlates with both hyaluronosis and susceptibility to SPF. It has been hypothesized that an increased concentration of HA predisposes Shar-Pei to periodic sterile fever and inflammation.[5]

As a result of the HAS2 gene mutation and thus increased HA concentrations in both the skin and serum, Shar-Pei dogs are predisposed to sterile autoinflammation. Reactive systemic amyloidosis may occur in SPF as a result of chronically increased acute phase protein concentrations, following the inappropriate release of pro-inflammatory interleukins from HA (Figure 2). Current hypotheses suggest that acute phase proteins may persist even between fever episodes, resulting in a subclinical autoinflammatory state which precipitates and encourages amyloid deposition.[6] Given the renal predilection for amyloid, diagnosis of amyloidosis is often associated with clinical and laboratory evidence of progressive chronic kidney disease. Dogs diagnosed with renal amyloidosis (RA) predominantly exhibit glomerular disease; however, in the Shar-Pei, amyloid deposits are found primarily in the renal medulla.[7] Concurrent hepatic amyloidosis at the time of diagnosis has been previously reported in the breed.[2]

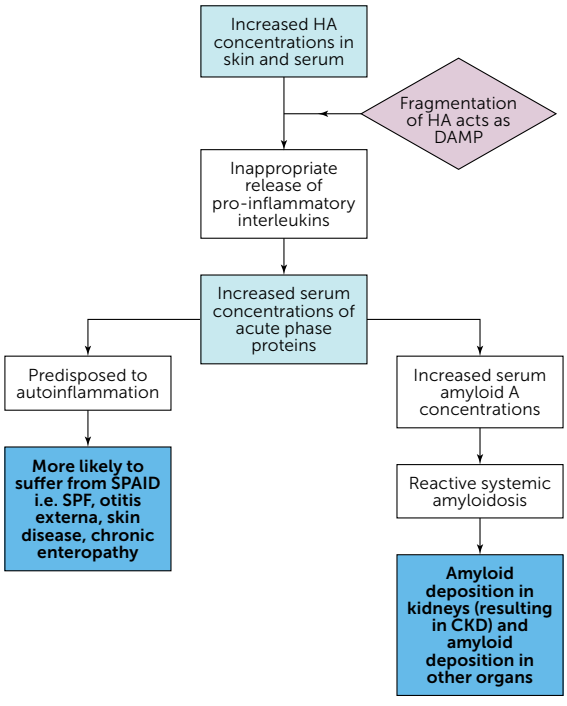

FIGURE 2: The role of hyaluronic acid (HA) in Shar-Pei Fever and amyloidosis.

Diagnosis

Accurate recognition of SPF presents a problem for clinical studies due to the short duration of pyrexic episodes and the high likelihood of spontaneous resolution. Not all episodes will be detected by owners (subclinical SPF), and there may also be significant under-reporting to their veterinary surgeons. Diagnosis of SPF is typically based on the presence of compatible clinical signs: lethargy, acute onset high fever, inappetance, and sometimes joint swelling and pain. When performed, arthrocentesis of swollen joints reveals acute sterile neutrophilic inflammation with negative synovial culture (Figures 3 and 4). If systemic amyloidosis is present, renal and hepatic biochemical parameters may be increased, and urinalysis may demonstrate persistent hyposthenuria and proteinuria, often with urine protein-creatinine ratio (UPC) >2. However, as renal amyloid deposits in Shar-Pei are more likely to be found in the medulla rather than the glomerulus, it is possible for a Shar-Pei with RA to have a UPC <0.5.[7] Other causes of pyrexia of unknown origin should be excluded, and tick-borne disease in particular should not be overlooked in these presentations – history of foreign travel should be discussed with the owner as endemic rickettsial disease is very rare in the UK.

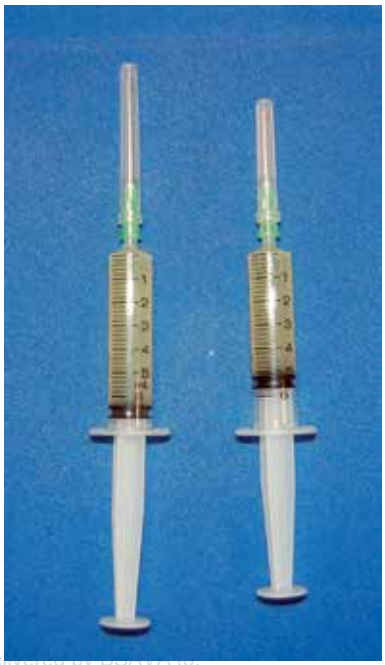

FIGURE 3: Gross appearance of inflammatory joint fluid.
Image courtesy of Toby Gemmill.

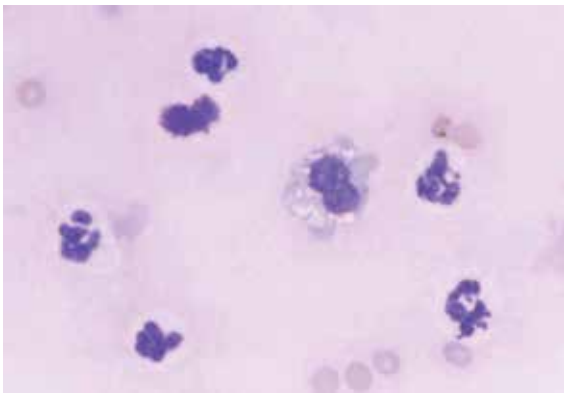

FIGURE 4: Microscopic image showing cytology of joint fluid demonstrating mild neutrophilic inflammation.
Image courtesy of Toby Gemmill.

More recently, genetic tests have become available to identify dogs at the highest risk of developing Shar-Pei Fever in their lifetime. Using a blood sample or buccal swab, polymerase chain reaction (PCR) testing detects the number of copies of the variant associated with SPF – a high copy number of this variant correlates with increased risk of developing the disease via increased expression of HAS2.[5] This test therefore identifies non-carriers, single carriers, and double carriers of the putative allele (Table 2); double carriers are eight times more likely to suffer from SPF compared with non-carriers.[8,9] This information can be used by breeders to estimate the likelihood of an individual developing signs of SPF and thus strategize breeding to minimize the risk of producing litters affected by the disease. The diagnostic blood test was developed by Cornell University College of Veterinary Medicine while the buccal swab test was developed by the University of Veterinary Medicine, Hannover. In the UK, both blood and buccal swab samples can be sent to Laboklin UK for processing, with results expected within 1–2 weeks.

Treatment

Treatment during short pyrexic episodes of SPF is conventionally conservative; non-steroidal anti-inflammatory drugs (NSAIDs) are most frequently used to control the fever and pain from any joint swelling; however, due to the spontaneously resolving nature it is difficult to prove that such therapy affects the time course or the severity of the episode. Furthermore, there are no published studies evaluating the role of NSAIDs in the treatment of acute fever episodes in Shar-Pei.

Life-threatening hyperthermia (>41.0°C) should be considered an emergency, and aggressive supportive care including intravenous fluid therapy, antipyretic medications, and further treatment may be required in these more severely affected dogs. In the USA, anecdotal reports of using the antipyretic dipyrone (metamizole) state that this drug rapidly reduces body temperature in severe hyperthermia in Shar-Pei, with minimal side effects noted at a low dose of 25–100 mg/kg i.v. or s.c. injection.[5,6] Importantly, clinicians in the USA use compounded formulations of dipyrone not available in the UK, although it is a component of Buscopan compositum® with hyoscine (butylscopolamine).

Colchicine is an anti-fibrotic drug which has been proposed for use in SPF as a preventative and for treatment of renal amyloidosis, due to its role in blocking the synthesis of serum amyloid A and amyloid deposition. Anecdotally, doses of 0.025–0.03 mg/kg given orally twice daily are advocated, or lower doses where GI intolerance is an issue.[6]

In human medicine, colchicine is used in the treatment of a variety of inflammatory conditions, including gout and Familial Mediterranean Fever (FMF). This disorder has been likened to SPF for decades due to the similar clinical signs of recurrent self-limiting fever events with associated pain. Colchicine treatment for FMF must be continued for life. A Cochrane review found that colchicine use reduced the frequency of

SPF test result	Group	Outcome	Explanation
CNV = 2 (alleles 1 and 1)	Non-carrier	Not expected to suffer from Shar-Pei Fever	This dog does not carry the variant associated with SPF (i.e. allele 5)
CNV = 6 (alleles 1 and 5)	Single carrier	Potential to suffer from Shar-Pei Fever	This dog carries one copy of the variant associated with SPF (i.e. allele 5) **This dog is four times more likely to suffer from SPF than a non-carrier** If bred with another single carrier, there is a 25% chance that a double carrier will be produced
CNV = 10 (alleles 5 and 5)	Double carrier	Most likely to suffer from Shar-Pei Fever	This dog carriers two copies of the allele associated with SPF (i.e. allele 5) **This dog is eight times more likely to suffer from SPF than a non-carrier** If bred with a single carrier, there is a 50% chance that a double carrier will be produced

TABLE 2: Results, outcomes, and explanations of the Shar-Pei Fever genetic test.

fever events.[10] A significant majority (87%) of people with FMF on long-term colchicine experience a reduction in severity, duration, and frequency of fever episodes.[11] It can also slow the progression of amyloidosis. A study into the drug's prophylactic efficacy in FMF demonstrated that 0 of 350 children treated with colchicine developed amyloidosis.[12] Reported adverse effects were minimal, and the children's development and subsequent fertility were not affected by continuous use. This concurred with previous research, where colchicine prevented the development of amyloidosis in an at-risk population and appeared to slow progression of amyloidosis in patients who had not developed nephrotic syndrome.[13]

However, colchicine has a narrow therapeutic index. While most common adverse reactions reported in humans are mild, reversible, and transient such as GI upset and pharyngolaryngeal pain, more severe adverse effects have been reported. These can include myelosuppression, neuromuscular toxicity, and rhabdomyolysis even at therapeutic doses.[11,14] This is often as a consequence of altered metabolic clearance in patients with hepatic or renal dysfunction, or in patients receiving other medications (including heart medications, immunosuppressives, and antifungals). Furthermore, the development of a marked bradyarrhythmia with first- and second-degree AV block has been described in a child following accidental ingestion of colchicine.[15] Although much of the literature regarding colchicine use and its associated side effects is from human medicine, the conclusions may be relevant to veterinary medicine – current guidelines in humans advise to consider the use of colchicine carefully, especially in patients with reduced renal or hepatic function.

In dogs, the therapeutic use of colchicine is less well-documented; much of the information regarding the role of the drug in RA has been extrapolated from other fields. One case review of a dog with hepatoportal fibrosis implies that the long-term daily use of colchicine stopped the progression of fibrosis with no side effects reported.[16]

However, similar to reports in the human literature, there is evidence of adverse reactions when used concurrently with antifungal medications in dogs. One study discusses a case in which a Shar-Pei dog with presumed SPF treated with both ketoconazole and colchicine in quick succession developed gastrointestinal signs, skeletal muscle myopathy and a biochemical hepatopathy.[17] Although the muscle myopathy and GI signs resolved shortly after withdrawal of colchicine, liver enzyme activities remained persistently increased for a further 3 months – other causes of a hepatopathy were not detected by hepatic biopsy. However, the dog was not re-challenged with either ketoconazole or colchicine so an alternate cause of the clinical presentation cannot be definitively excluded. Drug interactions of colchicine may be particularly relevant when considering its use for prevention or treatment of SPF as this breed is predisposed to skin disease of fungal, bacterial, and allergic aetiologies.

Acute colchicine toxicity in a dog following accidental ingestion caused vomiting, haemorrhagic diarrhoea, dehydration, bradycardia, and hypothermia.[18] The dog was subsequently euthanased after developing seizures and suspected disseminated intravascular coagulation; the clinical signs of this case mirrored those described in people with severe colchicine toxicity.[18]

Summary and future perspectives

In conclusion, Shar-Pei Fever is an inherited condition, which is likely under-recognized due to its self-limiting nature and tendency to spontaneously resolve. It is a result of excessive hyaluronic acid in the skin and serum, which predisposes to a pro-inflammatory state in this breed. Short fever episodes apparently respond well to systemic NSAIDs; however, the true efficacy of this treatment is difficult to assess. As a result of the pro-inflammatory state in Shar-Pei, affected dogs are at risk of developing renal amyloidosis. Interestingly, the renal distribution of amyloidosis in Shar-Pei is different to non-Shar-Pei dogs.

In people, colchicine has been shown to prevent the development of RA when used prophylactically in patients with Familial Mediterranean Fever. The medication is considered safe to use in children, although certain adverse effects are well known and must be taken into consideration. As colchicine has a narrow therapeutic margin, one must carefully consider the benefits of using the drug *versus* the risks, especially given the current sparse supportive evidence for using colchicine in SPF. Recommendations are largely extrapolated from the use in FMF. Furthermore, colchicine toxicity has been documented in dogs as well as clinically significant adverse drug interactions. C

Get involved with ongoing research

There are many potential areas of study when considering SPF. The Small Animal Medicine Society (SAMSoc) has recently launched a retrospective study into the disease and how it is approached in the UK. The study aims to collect first-hand information from Shar-Pei owners and members of the veterinary profession relating to all Shar-Pei dogs in the country, whether they have experienced SPF or not. It is hoped that this research will further our understanding of the criteria commonly used to diagnose SPF, a picture of the typical clinical signs, and approaches to management of these cases. Furthermore, it may be possible to determine how many Shar-Pei have been treated with colchicine either pre-emptively or as a treatment and if so, whether the treatment is well-tolerated or its adverse effect profile limits the use of colchicine. A greater knowledge of colchicine use in Shar-Pei dogs in the UK would be very valuable and may prompt further research into the use of this medication in veterinary medicine.

We are asking members of the veterinary profession to be aware of this research, and would welcome your participation in the study. With informed consent from the owner, we hope that clinical data may be entered into a simple online electronic data platform. For further information about the research, please get in touch at **SharPeiProject@willows.uk.net**. Copies of the consent form for owner completion are also available at **www.bsavalibrary.com**.

References and further reading are available at www.bsavalibrary.com and in *e-Companion*.