

BORDER TERRIER BREED HEALTH GROUP

Fact Sheet on Shaking Puppy Syndrome (SPS) in Border Terriers

What is SPS?

Shaking Puppy Syndrome (SPS) is the common descriptive terminology of the clinical signs described in a case study published in 2012 (J. Vet. Intern Med 2012;26:402–406 P. Martin-Vaquero, R.C. da Costa et al). Pathologically it is described as a degenerative spongiform change of myelin in the white matter of the brain, principally in the cerebellum, brainstem and spinal cord and to a lesser extent in the thalamus and cerebral hemispheres. In plain English, this translates as a breakdown of the insulation (myelin) surrounding the nerve fibres in nerve bundles (white matter) principally in the rear most parts of the brain but with signs of some involvement of other areas too.

This description provides the scientific terminology Spongiform Leuco-Encephalo-Myelopathy (now being shortened to the acronym SLEM) which is the technical descriptive terminology. SPS and SLEM are therefore the same condition.

What are the symptoms of SPS

In the original case study from 2012, the affected puppies started to 'shake' at the time they commenced early attempts to walk (around two weeks of age). Most of the tremors (shaking) were seen in the hindquarters of the affected puppies.

The same symptoms have been seen in other cases anecdotally reported in the UK and from world-wide reports. However, more recently some puppies in the UK are reported to commence tremors at 8-12 weeks of age. It is not yet clear if this signals a significant variation in the presentation of clinical signs of SLEM.

Across the spectrum of affected litters the onset of symptoms seems to be consistent in timing between affected puppies in a single litter. Thus puppies in the same litter do not appear to start shaking at significantly different time points.

An associated symptom is poor weight gain and it is suggested that this is because of the extra energy expended by the tremors as these pups try to move about, although it is also possible these pups do not feed as well as they should due to their general decreased ability to co-ordinate their movements. As the affected puppies are reported to be smaller and weigh less even from birth (before they start shaking) this tends to challenge the more simplistic theories on poor weight gain.

Most owners elect to have their affected puppies put to sleep although there are reports of pups surviving and improving with care and nursing, however a full recovery is not to be expected given the damage to the myelin in the brain.

Historical reports of SPS

The first report of SPS in the UK was probably in an article written in the Scottish Border Terrier Club newsletter in 2008. A breeder reported tremors in a litter and, at that time, veterinary advice was to wait and see if this was a one off event. As further cases have arisen, examination of the pedigrees of affected pups have led to the conclusion that the Sire called Scots Guardsman (registered in 1985 as Scots Gaurdsman - an assumed misspelling) is a potential origin of a genetic mutation. However, the case report published in

2012 offered an earlier sire as a common ancestor (born in 1975) of affected pups from three separate litters. The identity of this Sire remains unconfirmed.

In the USA the Border Terrier Club of America has identified a number of affected puppies since 2012 and has initiated research at the [University of Missouri](#) with the aim of identifying the potential genetic mutation(s). This research is ongoing.

Why does this happen in Border Terriers

There are a number of breeds (Springer Spaniel, Australian Silky Terrier, Weimaraner, Golden Retriever, Dalmatian, Chow Chow, Welsh Springer Spaniel, Vizsla, Samoyed and Bernese Mountain Dog) which have been reported around the world where a form of shaking (tremor) is seen in some litters of young puppies. All are assumed to be inherited and in some of them a genetic mutation has been identified (i.e. Springer Spaniel and Weimaraner).

Myelin provides insulation around nerve fibres and aids the conduction of nerve impulses in individual nerve fibres. A serious defect in either the formation of the myelin sheath (most common defect), or alternatively a degeneration of normally formed myelin (as seen in Border Terriers), is likely to lead to poor transmission of nerve impulses and, as a result, neurological symptoms of incoordination, tremors or seizures are most likely.

The underlying cause in both forms of defective myelin is assumed to be related to gene mutation and a single recessive gene (or a number of genes) is the working assumption. If the base assumption on inheritance is correct, 'carriers' of a recessive mutation are generally free of symptoms. However, where two carriers of a recessive mutation are bred together, clinically affected puppies are likely to be seen in the litter (see section below on inheriting the mutation).

How is the mutation inherited (working assumption)?

Recessive genes require two copies of the mutated gene to be present to produce an affected puppy. A single mutation will produce a carrier state. **Carriers are free of symptoms** but capable of passing on the mutation to their offspring. Where no mutation is present the dog is termed 'clear'.

If both parents are carriers some of the puppies in litter could be affected by SLEM. Those that are either 'clear' or 'carriers' will not be clinically affected. It is important to note that a mating of two carriers may produce all three types of puppy (i.e. clear, carrier or affected).

Across several litters bred from two carrier parents it is predicted that 25% will be affected pups, 50% will be carriers and 25% will be clear. However, in the absence of a genetic test capable of identifying the mutation, it is not possible to readily predict which dogs are carriers and which are clear. Affected dogs are identifiable given the associated tremors evident at an early stage of their lives.

Thus, it is quite possible for a litter to be born from two carrier parents completely without any symptoms (i.e. the pups are either clear or carrier) thus an unaffected litter does not prove that either parent is not a carrier.

Research may reveal either the mutation or marker genes associated with SLEM that may aid breeders in their selection of a sire and dam so that affected puppies are not produced (see below - Current research)

Can it be treated

The working assumption is that SPS is an inherited condition however the faulty metabolic process leading to spongiform degeneration of myelin is unknown and, therefore, at this time there is no known effective therapy for puppies suffering from SLEM. Any apparent partial recovery is possibly a reflection of the lack of severity of the degenerative change rather than improvement in the quality of the myelin in the brain unless there is some regeneration of myelin as the puppy matures. This is possibly an area for further study as new cases emerge.

Current Research

Research funded by the Border Terrier Club of America on the genetics of SLEM is being conducted at University of Missouri. So far, no candidate mutations have been reported. In the UK genetic research is centred around the The Kennel Club Genetic Centre at the Animal Health Trust, Newmarket, Suffolk.

Several clinical centres have an interest in cases of SLEM. They are currently neurologists with an interest in SLEM at Liverpool Veterinary School, Glasgow Veterinary School and the AHT. Mark Lowrie, the specialist leading on the study on CECS, also is able to aid in the diagnosis of cases. However further veterinary neurologists are likely to be recruited in due course.

The current centres are working together to gather clinical and pathological information to aid an understanding of the disease process. Each clinician is also supplying suitable samples from diagnosed cases to the AHT for genetic research to find candidate mutations in the genome of affected pups.

How can you help?

People interested in the breed can help in a number of ways. If you are aware of a possible new case of shaking puppy syndrome (SLEM) please direct those involved to contact the Breed Health Coordinator (Prof Steve Dean email stevedean@tyrianborder.com tel no. 01628 782787).

We will ask the owner of any affected pups to arrange to take them to one of the preferred clinical facilities for confirmation of the diagnosis and recommendations for the future management of the pups. As this may require the use of expensive veterinary diagnostic techniques there is a significant cost involved. The possibility of help with funding might be available from the Breed Health Group through generous funding from the Breed Clubs but this must be agreed before clinical cases are investigated.

It is a good idea to record a short video of the behaviour of the pups to aid the veterinary neurologist with the diagnosis. It is likely that a blood sample will be required for clinical evaluation and a sample of this will be provided to the AHT for further genetic research. A copy of the pedigree for affected pups or their individual parents or alternatively the

registered Kennel Club names of the sire and the dam should be provided to the Breed Health Coordinator to aid ongoing pedigree analysis. All of this can be done entirely confidentially.

The breed clubs have established a health fund to aid the commissioning of research and collection of information from new cases in the UK and donations to this fund are welcome from those who wish to assist the breed in looking for a solution for SLEM. Any of the Breed Clubs will accept donations to this fund.

Why has this condition only recently arisen in the breed?

It is believed this is a relatively new gene mutation occurring possibly around 1975 or earlier. The pattern of affected puppies and litters would suggest this is a recessive inheritance and therefore two copies of the gene are necessary to produce clinically affected puppies. Thus dogs with a single copy of the mutation are genetically termed carriers and will be clinically unaffected.

From the original emergence of the mutation subsequent matings of some of the progeny of carrier dogs and bitches will have produced further carriers. The owners' account of an early affected litter is the first known report and since then litters have been reported around the world with around 65 affected litters reported at this time. Anecdotal evidence may not always be accurate, however the typical signs of this condition and its similarities with other myelin defects in other breeds give reasonable assurance that diagnosis is generally accurate.

If our working assumptions on inheritance are correct, then it is not surprising to see that more than forty years have elapsed before clinical cases started to emerge in a significant number of litters. This is likely to have been promoted by a significant degree of inbreeding during the period which has brought carrier dogs and bitches together in mating pairs.

Pedigree analysis of known cases continues but provides reasonable support for identifying some breed lines which contain dogs and bitches considered to be carriers. However this does not mean we have the full spectrum of carrier lines identified.

Popular sires/ inbreeding/ genetic diversity

There has been much concern expressed about the potential damage SLEM may yet yield for the breed. Cases have appeared in a relatively small proportion of the litters bred in the UK over the past decade. Although the impact of SLEM on the small population of dogs that are regularly shown is likely to be greater, we should keep in mind that the gene pool of the breed is considerably greater than those lines used to produce 'show dogs'. This point deserves further analysis.

However, it would appear the use of popular sires alongside inbreeding of certain lines has promoted the problem in the core of the show community. However the relatively low breed inbreeding co-efficient should ensure there are unaffected lines available across the breeding population of Border Terriers. In summary it is suggested that the genetic diversity of the breed can withstand this challenge if suitable breeding strategies are used.

Further points to consider

Although we can be reasonably optimistic that the breed can survive this threat, this view should be tempered by some unanswered questions which may lead to a change of approach. We must accept that this view is based on the overall working assumption that this is a single gene, recessive mutation - it may not prove to be that simple however and this may add complexity to the challenge we face and the solutions we may or may not recommend.

At the outset the condition seems to affect puppies at the two week stage, a time when they are beginning to attempt to walk and when co-ordination of movement starts to develop. This was logical given the pathology identified at that time. However cases since have revealed some pups do not suffer incoordination (i.e. shaking) until 10-12 weeks of age. This could indicate a delay in the onset of the spongiform degeneration of the myelin in the brain.

Another emerging feature of SLEM appears to be a variation in the severity of the clinical symptoms associated with the spongiform degeneration of myelin. The severity of the shaking and the wider impact of the lack of co-ordination affecting the fore-limbs and possibly the head and neck may all have an impact on an affected pup's ability to survive.

Affected pups may have a number of significant challenges. a) their lack of coordination uses more energy and thus these pups appear under-nourished and grow poorly b) incoordination affects their ability to feed and compete for milk with other members of the litter c) Myelin defects in higher brain areas may affect the mental development of the pups.

The majority of affected pups either die or, more likely, are euthanased as their condition becomes increasingly untenable and their breeder/owner finds the stress of attempting to hand rear the pups too great. In addition, an abnormal puppy in a litter can disrupt the maternal behaviour of the bitch putting other pups in the litter at risk.

MRI scans of affected pups have shown signs of myelin changes in areas of the brain that are not normally engaged functionally in coordination of movement, The effect of this defective myelin in higher regions of the brain is not yet understood. Furthermore, we do not yet know if the regional distribution of the myelin defect correlates with the severity of the symptoms or the effects on coordination. Variation of the regional areas of the brain affected also raises questions about what directs the regional distribution of the myelin defect.

A couple of reported cases appear in lines unrelated to Scots Guardsman. It is not known yet whether this signals the presence of the mutation from a much earlier genetic source; the effect of an unrecorded misalliance or error in pedigree accuracy; or the presence of an alternative cause for the clinical signs which is unrelated to SLEM.

Discussion

Although at first examination the available data appears to support the inheritance from a single gene, recessive mutation as the source of SLEM in Border Terriers, it is important to realise how more critical assessment of clinical cases is beginning to reveal variation in the severity of this assumed genetic mutation.

This may be the result of a number of confounding factors. Firstly, much of the evidence is anecdotal and is therefore without clinical confirmation of the diagnosis. Thus important features of individual cases may not be available or verifiable. None of this is a criticism of the collection of the bulk of the current data. Anecdotal information is often the starting point for many studies of diseases both acquired and inherited. However, anecdotal data has limitations and as more critical data emerges it is likely to change the level of understanding and as a consequence the information and advice given to breeders and other interested parties.

The variation of clinical symptoms may indicate there are other gene mutations or environmental factors that might influence the progression of the myelin defect and its effect on the neurological function of an affected puppy. This is a very good reason for all new cases to be reported and followed through with supporting accurate diagnostic and pathology reports.

Early onset of the symptoms is helpful in the control of the condition. It alerts breeders to the likelihood of the carrier status of the parents of an affected puppy at an early stage and as the symptoms frequently occur before the puppy is sold to a new owner the emotional damage is often limited to the breeder.

A significant challenge to this investigation is the cost of professional intervention. Each case deserves a primary clinical investigation (possibly including an MRI scan) and a subsequent pathological examination of a euthanased puppy. Typically costs might be between £2K and £5k depending upon what procedures are carried out. Thus the Breed Clubs have started a health fund to try and assist with these costs where it is agreed they would provide good information for our research.

It is very important that either a blood sample (EDTA) or a cheek swab is submitted to the Animal Health Trust for use in the genetic research being conducted. Samples should be accurately labeled and accompanied by a suitable veterinary and pathological report wherever possible.

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