DISCUSSING INHERITED MEDICAL CONDITIONS IN BORDER COLLIES

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Roger Wilkinson explains the prognosis for genetic problems in this breed, and outlines treatment options, research findings and investigative suggestions

GENETIC problems are a justifiably hot topic at the moment in companion animal practice.

Although one might think of border collies as a practical working breed and not prone to the same inherited problems as more highly bred show dogs, an analysis of individual animals registered with the International Sheep Dog Society (ISDS) in the latter half of the 20th century shows a marked increase in the inbreeding coefficient – from a base of around two per cent in the 1940s, rising to almost eight per cent by the end of the century. Compare this to the published figure of four per cent for the dogue de Bordeaux (in France) – an example of a breed that one would perhaps more readily associate with heritable defects.

ISDS-registered border collies do not necessarily represent the whole story, and the data presented in Figure 1 demonstrates how the picture for border collies is more complex than the bare figures suggest.

If only the past six generations are taken into account, the degree of inbreeding has declined. The data is distorted by some extreme examples of inbreeding, and the ISDS database (www.bocd.info) is revealing on this point.

Several individuals in the British records have inbreeding coefficients of more than 40 per cent,
where extreme attempts have been made to “breed back” to outstanding individual champions. Indeed, there was a point in the early 1990s when there were almost no ISDS-registered border collies that did not have a talented individual known as Wiston Cap (Figure 2), an international champion, as an ancestor.

Overall, it is clear that at least some lines appear to have considerable potential for problems (Table 1). Understandably, many breeders are concerned and keen to rectify the situation.

The field of specific genetic tests for inherited diseases is rapidly developing. Sensitive and specific PCR tests for all of the following conditions, apart from cobalamin malabsorption and epilepsy, now exist. Not only does this allow for a rapid diagnosis in cases that might have previously required a lot of complex diagnostics, but it also greatly facilitates the elimination of inherited problems, through breeding stock testing.

**Trapped neutrophil syndrome (TNS)**

TNS is probably under-diagnosed in the UK. It appears to be an autosomal recessive trait specific to border collies, which in homozygotes causes a fatal immunodeficiency syndrome characterised by a release failure of neutrophils from the bone marrow into circulation.

The condition was first described in 1996 in New Zealand¹ and, subsequently, Australia. Anecdotally, likely UK cases are reported at least as far back as 1990². Work at the University of New South Wales by Alan Wilton and Jeremy Shearman identified the gene responsible and this resulted in the availability of a test that can identify both homozygous-affected individuals and heterozygous carriers.

Carriers of this gene and affected animals have subsequently been identified in the USA, the UK, Japan, Scandinavia, the Netherlands and Hungary. The incidence appears to be broadly similar in all populations studied thus far, with about 10 to 15 per cent of border collies being carriers. In the UK, of 714 dogs tested, three were found to be affected and another 163 to be carriers.

The presence of the same mutation in distantly related breeding lines around the world suggests that the mutation has been present and unrecognised in the breed for a long time.

There is no evidence as yet that carrier (heterozygous) individuals have subnormal immune function. Most (homozygous) affected collies become poorly within a few months of birth and die. However, some may survive to two or three years old. Presenting signs are variable, depending on the nature of secondary infections.

Some TNS-affected pups are born small, and may have narrow heads, giving a ferretlike appearance (Figure 3) and fine bones with thin cortices on radiographs.
TNS is probably the major cause of fading puppies in this breed. A fever that responds poorly to antibiotics is a frequent observation, and another common scenario is for pyrexic illness to develop after vaccination.

Osteomyelitis, particularly of the distal femur, proximal tibia and distal humerus, may result in pathological fractures, lameness and joint swelling. Radiographically, these areas may demonstrate a line of lucency similar to that seen in metaphyseal osteopathy. Diarrhoea has also been a feature in affected pups.

Neutropaenia in most samples is usually, but not invariably, a feature. Non-regenerative anaemia, hypoalbuminaemia, hypercholesterolaemia and elevated serum alkaline phosphatase levels are common.

In some animals, bone marrow biopsy is necessary to demonstrate abnormalities of neutrophil maturation and release – the marrow being hypercellular and packed with band and segmented neutrophils. However, the PCR test (on EDTA blood or cheek swabs) for the defective gene has largely superseded invasive procedures. For further details on submitting samples, visit www.bordercolliehealth.com

Breeding stock testing for the TNS gene is now advisable. Since the defect is common, to avoid loss of genetic diversity, it may still be justifiable to breed from carriers. However, two carriers should not be mated with each other.

**Cyclic neutropaenia (CN)**

CN (or cyclic haematopoiesis of grey collies – grey collie syndrome) is a rare problem of haematopoiesis affecting border collies with pale coat colours (grey, pinkish-grey or beige – not merle) in many parts of the world.

Characteristically, neutropaenia is present only periodically, usually on a 10 to 14-day (up to three-week) cycle. A phase of illness usually follows the neutropaenia after a delay of four or five days. As with TNS, pyrexic illness may follow routine vaccination. Many pups become ill and die within a few months of age, although others have survived to young adulthood with the help of antibiotics, antifungals and supportive care. Multi-limb lameness, painful joints, vomiting and diarrhoea are common features. Respiratory signs seem to be more of a feature with CN than with TNS, and fever is variably responsive to antibiotics.

Dogs that survive into young adulthood eventually succumb to anaemia, glomerulonephritis and/or amyloidosis. Affected dogs also demonstrate cyclic abnormalities of platelet function and may experience bleeding episodes. Again, CN is an autosomal recessive trait and the pale coat colour gene appears to be closely linked. A PCR test for this condition is available.
The story of one CN-affected collie treated with lentivirus-vectored gene therapy can be read on the website of the Border Collie Club of Great Britain (www.bordercollieclub.com). This treatment was originally developed for the treatment of CN-affected children in Seattle, but adapted for grey collies in the USA. At least partial success has been reported, although normal life expectancy was not achieved.

In humans, CN has also been treated with repeated injections of recombinant granulocyte colony stimulating factor.

**Selective cobalamin malabsorption**

Inherited selective malabsorption of cobalamin was first reported in 1991 in a family of giant schnauzers and, subsequently, in a handful of breeds – including border collies. It is believed to be an autosomal recessive trait.

The first recognised British border collie case was published in 2005, although others are anecdotally reported and the condition has probably occurred sporadically in the past.

Affected dogs present as pups or young adults – some as young as six weeks, but invariably less than two years old. Anaemia, inappetence, failure to thrive, cachexia and stupor due to hyperammonaemic hepatic encephalopathy have been reported. Neutropaenia may be a feature and bone marrow may show megaloblastic changes. Erythroblasts may be present on blood smears.

Ammonia tolerance test results are abnormal, although serum bile acids are within normal limits. Low serum cobalamin with a positive urine test for methylmalonic acid is more or less pathognomonic in a dog eating a balanced diet.

This can be a very satisfying disorder to treat, as vitamin B12 injections result in rapid improvement, and the prognosis is good, as long as these continue to be administered at regular intervals.

**Neuronal ceroid lipofuscinosis (NCL)**

NCL is a lysosomal storage disease manifesting in animals homozygous for the affected gene. This autosomal recessive trait has been studied predominantly in Australasian border collies. However, in addition to cases in Japan and the USA, at least one description of an affected British dog has been published, and it must be assumed that the gene responsible remains in the UK border collie population. At least one UK carrier has been identified by Dr Wilton’s team at the University of New South Wales using its PCR test. The condition also occurs in a number of other breeds, including English setters, American bulldogs and miniature schnauzers.
In humans, NCL is known as Batten’s disease, and is characterised primarily by neurological signs. Affected collies remain normal until around 18 months of age, after which they deteriorate rapidly and have not been known to survive beyond 2.5 years old.

Initial signs are often irrational fear or apprehension of previously tolerated phenomena, followed by abnormal gait and incoordination, and, ultimately, dementia and manic activity.

A genetic test, again developed at the University of New South Wales, is available. If breeding stock is tested, only homozygous normal individuals should be used for breeding.

**MDR1 defect conferring ivermectin sensitivity**

The gene MDR1 (multi drug resistance one) codes for a transmembrane protein (P-glycoprotein) in the blood-brain barrier that extracts drugs of various classes (avermectins, digoxin, vincristine, ciclosporine and dexamethasone, among others) from the central nervous system. An abnormality of the gene coding for MDR1 is yet another autosomal recessive trait affecting border collies and other breeds. Heterozygotes, again, are unaffected carriers. Homozygotes are susceptible to toxicity if treated with ivermectin and some related compounds (Figure 5). A specific test for the MDR1 gene is available.

The mutant MDR1 gene is common in collies, Shetland sheepdogs and old English sheepdogs. In other breeds, less severe sensitivity to ivermectin may be seen, which is not coded by MDR1 mutation.

**Collie eye anomaly (CEA)/choroidal hypoplasia**

CEA is another autosomal recessive disorder of border collies that is also common in rough collies and Shetland sheepdogs.

Homozygotes suffer variable and unpredictable degrees of choroidal hypoplasia. In mildly affected individuals, although the abnormality can readily be detected on ophthalmoscopy, vision remains unaffected.

In approximately 10 per cent of homozygotes, however, the structural defects have functional implications. Dogs with colobomas (out-pouching of the back of the eye) presented at birth are susceptible to later retinal detachment or haemorrhage from abnormal vasculature. Generally, this happens in young dogs. Total blindness is rare.

Research at Cornell University has shown that the same gene mutation is responsible in all affected breeds, and a test for this gene is available.

In the USA, about two per cent of border collies have been shown to be homozygous affected.
About one-quarter of these have colobomata, and about three per cent of affected individuals (in effect, 0.06 per cent of the population) have some degree of retinal detachment. Incidence of the mutant gene is actually much higher in other collie breeds.

In border collies, it should be possible to avoid breeding from homozygous-affected or heterozygous carriers of the gene, although especially valuable genetic material can be salvaged in an affected line by breeding with homozygous normal animals, and then testing the offspring before choosing the next generation of breeders. However, this would not generally be condoned by most breed organisations.

The availability of a genetic test has not replaced the BVA eye testing scheme, which can also pick up other abnormalities and allows for advising owners on managing affected dogs.

**Epilepsy**

The Animal Health Trust in Newmarket is working on a project to elucidate the genetic basis of epilepsy in the border collie, and is seeking blood samples from affected animals, close relatives of affected animals and unaffected individuals aged more than seven years.

Further details are available on the Border Collie Club of Great Britain’s website ([www.bordercollieclub.com](http://www.bordercollieclub.com)).

**Practical implications for breeders**

In principle, it would be nice to breed from animals completely clear of all of the genes responsible for the conditions described. The guidance of the breed societies and authorities in the various specialities involved should be sought.

Certainly, it seems sensible to test the genetic status of breeding stock for TNS and CEA, since these are relatively common genetic variants and routine testing, once in a lifetime, should not be too financially onerous. CN and NCL are relatively uncommon, and will probably remain less of a high priority. Ivermectin sensitivity has limited consequences – even for homozygotes – unless ivermectin therapy is specifically envisaged.

**Acknowledgements**

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- For more *Veterinary Times* articles, visit [www.vetsonline.com](http://www.vetsonline.com) to download them directly.
References

Figure 1. Changes in inbreeding coefficient for ISDS-registered border collies over the past century.

Diagram: TEUN VAN DEN DOOL.
Figure 2. Wiston Cap (1963-1972), was an international champion. The last litter of border collies registered with the International Sheep Dog Society without Wiston Cap as an ancestor was born in 1995. He appears in the pedigree of almost every border collie walking into a surgery today.
Figure 3. A 12-week-old pup with trapped neutrophil syndrome. Although appearing normal at birth, she was slightly small by six weeks old and succumbed to sepsis by 12 weeks of age. Her face was subtly thin – a characteristic of this condition.

Photo: WESSEX BORDER COLLIE CLUB/RACHEL BIRT.
Figure 4. A stunted 14-month-old border collie. Selective cobalamin deficiency can be successfully treated with repeated vitamin B12 injections.
Figure 5. Ivermectin intoxication in a border collie. Individuals homozygous for the MDR1 gene mutation are susceptible. A specific test for this gene now exists.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Mode of inheritance</th>
<th>Age at onset of signs or diagnosis</th>
<th>Clinical signs in homozygotes</th>
<th>Treatment</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trapped neutrophil</td>
<td>Autosomal recessive</td>
<td>Usually two to three months, up</td>
<td>Feeding pups, pyrexia, osteomyelitis and lameness</td>
<td>Antibiotics and supportive care, but fatal</td>
<td>Haematology, bone marrow biopsy and a genetic test</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td>to one or two years in rare cases</td>
<td></td>
<td>despite treatment</td>
<td></td>
</tr>
<tr>
<td>Cyclic haematopoiesis</td>
<td>Autosomal recessive</td>
<td>Usually two to three months, but</td>
<td>Cyclic pyrexia, diarrhoea, respiratory infections and, later, renal amyloidosis</td>
<td>Antibiotics and supportive care, but fatal</td>
<td>Haematology and a genetic test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sometimes up to one or two years</td>
<td></td>
<td>despite treatment</td>
<td></td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>Autosomal recessive</td>
<td>18 months</td>
<td>Incoordination, morbid fear and dementia</td>
<td>Fatal, with no treatment</td>
<td>Histopathology and a genetic test</td>
</tr>
<tr>
<td>Ivermectin sensitivity</td>
<td>Autosomal recessive</td>
<td>N/A</td>
<td>Only if exposed to ivermectins</td>
<td>Supportive care in event of intoxication</td>
<td>Genetic test</td>
</tr>
<tr>
<td>Cobalamin malabsorption</td>
<td>Autosomal recessive</td>
<td>Two to three months to two years</td>
<td>Ill-thrift, cachexia and anaemia</td>
<td>Repeated parenteral vitamin B12</td>
<td>Serum B12 and urine MMA</td>
</tr>
<tr>
<td>Collie eye anomaly</td>
<td>Autosomal recessive</td>
<td>Defect apparent from birth, with</td>
<td>Characteristic fundus changes and coloboma in some, with retinal detachment or haemorrhage in</td>
<td>None, as the afflicted rarely go blind</td>
<td>A genetic test, fundoscopy and the BVA eye</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vision problems shown in young</td>
<td>few</td>
<td></td>
<td>testing scheme</td>
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<td></td>
<td></td>
<td>adults</td>
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**TABLE 1.** Inherited medical conditions of border collies