LYME DISEASE IN DOGS: DIAGNOSIS, DRUG TREATMENT AND PREVENTION

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Simon Tappin considers the aetiology of a disease that was first documented in the UK 20 years ago and is passed between vertebrate hosts by ticks

Summary

Lyme disease is a relatively new clinical entity caused by the spirochaete *Borrelia burgdorferi*. It is transmitted by a variety of tick vectors, depending on the geographical location, with *Ixodes ricinus* being the most common vector in the UK. Only five to 10 per cent of dogs exposed to *Borrelia* develop clinical signs, which classically present as fever – with associated lethargy – followed by shifting limb lameness. These signs are not pathognomonic, and PCR-based tests to document the presence of the *Borrelia* spirochaetes are needed to confirm borreliosis. Serology documents exposure to *Borrelia* and a high or rising antibody level can support the diagnosis. Treatment with doxycycline leads to resolution of clinical signs in most cases. However, chronic non-erosive polyarthritis and glomerular nephritis are seen in chronic infections. The aetiology of these signs is not fully understood, but are most likely due to the ability of *Borrelia* to evade the immune system and the chronic inflammatory response this evokes. Prevention is based on preventive acaricide treatments and prompt tick removal.

Key words

Lyme disease, Borrelia, ticks, polyarthritis, glomerular nephritis

LYME disease takes its name from the town in Connecticut, United States, where the symptoms of infectious polyarthritis were first described in humans in the mid-1970s.

Since then, the spirochaete *Borrelia burgdorferi sensu lato* has been found to be the causal agent of Lyme disease, and has been documented to cause disease in veterinary species.

Most published research relates to *B burgdorferi sensu stricto,* which is the primary isolate that causes disease in the United States. However, considerable genetic heterogeneity in *B burgdorferi* species exists between North America and the UK.

In northern Europe, isolates of *B afzelii* and *B garinii* have also been found to cause borreliosis in humans.

Classic signs of canine Lyme disease follow a history of a tick bite and, initially, signs of fever and lethargy, followed by a shifting limb lameness.

Unfortunately, these classic signs are not always seen and are also found in a wide range of other diseases, which can make diagnosing Lyme disease difficult. *B burgdorferi* is also associated with glomerulonephritis and a chronic non-erosive arthritis, which are generally seen later in the course of the disease.

Signs are usually seen within a month of the tick bite. However, in experimental studies, disease has taken up to six months to develop.

B burgdorferi cannot survive free in the environment and is passed between vertebrate hosts by tick vectors. In the UK, the most common vector is *Ixodes ricinus*, but *B burgdorferi* has also been isolated from other *Ixodes* species – *Dermacentor reticulatus* and *Rhipicephalus sanguineus* in the UK.

I ricinus has a two to threeyear life cycle and can harbour *Borrelia* for most of that period. As adults, *B burgdorferi* are transmitted to the host as the tick feeds. Spirochaetes multiply within the tick, crossing into the saliva and passing into the host – the process requires the tick to be attached for at least 50 hours for transmission to occur. Most ticks are removed before spirochaete transmission takes place, but when spirochaetes do move in the host, they divide locally within the skin at the site of infection.

The immune system clears most *Borrelia* infections before systemic signs are seen, but in approximately five to 10 per cent of cases, active migration then occurs through tissue to cause systemic clinical signs.

Once present, *Borrelia* is a persistent pathogen and evades the immune system by undergoing changes in surface proteins. It can remain undetected in skin, connective tissue and the nervous

system for long periods.

Clinical signs are caused by the host's immunological response, which is often in response to a small number of spirochaetes.

In humans, certain major histocompatibility complex (MHC) haplotypes are more prone to severe treatmentresistant disease, which is probably also the case in dogs.

The UK's first documented case of canine Lyme disease was reported in 1990 (May et al, 1990). However, PCR studies of ticks held at the Natural History Museum document the presence of *B burgdorferi* in UK ticks back to the late 1800s, suggesting the disease has been present longer than it has been recognised (Hubbard et al, 1998).

The exact incidence of canine Lyme disease in the UK is largely unknown, but studies have documented seropositivity to *B burgdorferi* in dogs across the country.

Seropositivity is higher in dogs living in rural areas compared to those living in urban areas, and in animals with a history of tick bites (May et al, 1991).

Despite high seropositivity, relatively few dogs develop clinical signs. The exact proportion of seropositive animals that develop disease is unknown, but is believed to be around five to 10 per cent (Greene and Straubinger, 2006).

A higher proportion is seen in humans, with around 90 per cent of people developing clinical signs (Littman et al, 2006).

The overall incidence of Lyme disease in humans is estimated at 0.3 cases per 100,000 of the UK population.

Clinical signs

Initial signs of borreliosis are of acute fever (more than 40°C), shifting limb lameness and associated lethargy. There may also be joint swelling and enlargement of the local lymph nodes. These signs appear to be most severe in younger dogs and immunocompromised animals.

Lameness is usually first seen in the limb closest to the site of tick attachment, and is thought to be caused by the spread of spirochaetes through the skin, muscle and joint. Classically, the lameness improves over two to three days, at which point the lameness may resolve completely or appear in a different limb. In a proportion of dogs, a chronic non-erosive polyarthritis may develop – is most likely in patients with chronic infection that has been incompletely cleared by the immune system (Figure 1), representing an immune-mediated polyarthritis.

Diagnosing *Borrelia* as the trigger can be difficult, but prolonged treatment with antibiotics and, in some cases, descending immunosuppressive steroids, will lead to improvement in most cases.

Protein-losing nephropathy (PLN) has been documented in dogs with spontaneous *Borrelia* infection. This so-called “Lyme nephropathy” has not been documented in experimental models, and the underlying pathophysiology is unclear. It has most commonly been reported in north America, but has also been seen in the UK.

Dogs develop glomerular nephritis, lymphocytic plasmacytic interstitial nephritis and tubular necrosis. This leads to weight loss, lethargy and anorexia as a result of the PLN, leading to renal failure.

About half of dogs developing Lyme nephritis have a history of lameness, with the PLN signs being the first indication of *Borrelia* in many cases.

In humans, a dramatic bull’s eye-like skin lesion called erythema chronica migrans (ECM) develops in around 80 to 90 per cent of people with Lyme disease. This classic bull’s eye lesion is not seen in dogs, but a red-ish rash can be seen for the first week or so after tick attachment.

Neurological signs due to meningitis, encephalitis and perineuritis are occasionally seen in the latter stages of human infection. Although focal meningitis and encephalitis lesions have been documented in experimental models, neurological signs secondary to *Borrelia* in dogs are extremely rare.

Arrhythmia secondary to *Borrelia*-induced myocarditis has been occasionally reported in dogs, which is similar to Lyme carditis seen in humans.

Diagnosis

As described, diagnosis of Lyme disease by clinical signs alone is challenging – therefore, supportive laboratory testing is essential (Figure 2).

Haematological and biochemical changes are not pathognomonic of borreliosis, although it may support the presence of an inflammatory response. Signs of leukopaenia or thrombocytopaenia may suggest concurrent infection with a rickettsial pathogen, such as *Anaplasma phagocytophilum*, as co-infection is relatively common.

Regular urinalysis to monitor for protein-losing nephropathy is suggested, with a urine protein:creatinine (UPC) ratio being the best marker of proteinuria. Joint taps will have a high number of non-degenerate neutrophils, with increased protein content. Joint fluid will have a reduced viscosity and should be negative on bacterial culture.

Serological testing proves exposure to *B burgdorferi,* but, given the high seropositivity in asymptomatic animals, it does not prove that the organism is the cause of the clinical disease. Therefore, although positive serology is supportive, only tests looking to the organism itself allow definitive diagnosis.

Occasionally, *B burgdorferi* can be visualised in body fluids (such as synovial fluid) using dark-field microscopy or in tissue after silver or immunological stains. However, the spirochaete density is usually very low, making diagnosis difficult by this method. Culture of *Borrelia* organisms is similarly difficult and not applicable to clinical application.

Quantitative PCR tests, such as real-time PCR, have revolutionised diagnostic protocols in many areas of veterinary medicine, and the same is true of canine Lyme disease. A variety of PCR tests exist, but those with primers to plasmid DNA are thought to be more sensitive due to the multiple copies present within each bacterium.

Although blood and joint fluid can be used for PCR, spirochaetes tend to invade through tissue rather than passive dissemination through the bloodstream – therefore, tissue PCR is much more sensitive. In particular, PCR of synovial membrane and skin has been shown to be much more sensitive, especially in the latter disease stages.

Treatment

Earlier antibiotic therapy has been shown to be very effective in reducing spirochaete numbers, leading to rapid improvement in arthritis signs over a 24 to 48-hour period.

Doxycycline is the drug of choice for treating *B burgdorferi,* although a number of other antimicrobials also have efficacy (Table 1).

Doxycycline is lipid-soluble, and thus has good tissue and cellular penetration and is generally used for four weeks.

Doxycycline should not be used in growing animals due its deleterious, but mainly cosmetic, effects on skin, nails and tooth enamel. Although doxycycline is less likely to cause these effects compared to other tetracyclines, alternatives – such as amoxicillin – are suggested. Doxycycline also has immunomodulatory and chondroprotective effects, which are helpful in treating polyarthritis (Yu et al, 1992).

If proteinuria is documented (and other causes of PLN excluded), early treatment for glomerular nephritis should be instigated alongside antibiotic therapy. Angiotensin-converting enzyme (ACE) inhibitors will reduce renal protein loss through altered glomerular filtration pressure. Ultra-low aspirin therapy (0.5mg/kg/bid) is suggested to prevent thromboembolism as a result of antithrombin loss and platelet dysfunction.

Prevention

Preventing ticks from attaching provides the best method of reducing the risk of Lyme disease. A number of products have been shown to have good activity in preventing tick attachment and in killing ticks once they are in place. Regular use of a selamectin, fipronil or permethrin-containing product should be suggested to all owners of dogs walked regularly in areas with high tick numbers, especially at high-risk times of the year in autumn and spring.

As spirochaete transmission does not occur until at least 24 hours after tick attachment, prompt removal of the ticks during this period will stop transmission of *Borrelia*. As any acaricide will not be 100 per cent effective in preventing tick attachment, owner vigilance and prompt tick removal using a tick hook will reduce risks further (Figure 3).

In the US, a vaccine has been marketed for preventing canine borreliosis. Although this appears to be a very effective vaccine, it is generally only used in dogs in geographically at-risk areas and with a high degree of possible exposure (such as outdoor or hunting dogs). Due to the lower prevalence and marked genetic heterogeneity between the north American and European *B burgdorferi* species, the vaccine is not used in the UK.

Cats

In the UK, 4.2 per cent of cats are seropositive to *B burgdorferi* (May et al, 1994). However, none of the cats tested as part of that study had signs associated with lameness or recent disease. Therefore, despite their seroconversion, Lyme disease has not been described as a distinct entity in feline medicine.

In experimental studies, cats do develop lameness, but at much higher doses than dogs, suggesting cats are more resistant to the infection.

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