# A case of Bannwarth syndrome

*Maria E Farrugia*

## INTRODUCTION

A patient presented with a subacute radiculopathy and motor neuropathy. Her clinical presentation was thought to represent Guillain–Barré syndrome but CSF examination showed a marked lymphocyte pleocytosis. An enzyme linked immunosorbent assay (ELISA) test was strongly positive for *Borrelia burgdorferi*. The clinical presentation fitted with that of Bannwarth syndrome, especially with her previous exposure to tick bites. The chronic manifestations of Borrelia infection can be disabling if untreated. The laboratory tests available are not fully specific or sensitive and research is looking into modalities to improve these assays.

## DISCUSSION

### The clinical stages of Lyme disease

The infectious agent for Lyme disease is *B. burgdorferi*, a fastidious microaerophilic spirochaete transmitted by the ixodid tick, which varies according to the geographical region. In 60–80% of cases, the illness initiates as an expanding skin lesion called erythema migrans. It is often seen on the legs, at the site of the tick bite, initially as an erythematous papule. This enlarges over several days, with partial healing in the centre giving it its characteristic 'bull's eye' appearance (*Figure 1*). It may become red, angry and indurated (*Figure 2*) as in a hypersensitivity reaction and rarely may become necrotic. This is stage I or localized disease and is followed by haematogenous spread (stage II) during which there is dissemination of infection. This may be associated with annular skin lesions, cranial neuritis, radiculopathy, peripheral neuritis, meningitis, carditis and musculoskeletal pain. Stage III or persistent infection will follow if treatment is not instituted and there may be chronic skin or neurological manifestations.

Neuroborreliosis occurs in about 20% of cases, arthritis in 10% and carditis is

### CASE REPORT

A 72-year-old woman presented with a short history of radicular pain down her left leg. She was admitted to a cottage hospital where she developed progressive weakness in both legs. She was noted to develop a rash with target-like lesions, thought to be erythema multiforme. She was otherwise well and apyrexial.

A few days later, she developed bilateral facial weakness and complained of diplopia. The rash had subsequently resolved. It was felt that expert opinion should be sought in view of the deterioration of her mobility and she was transferred to a neurology ward.

On examination, she had bilateral facial weakness (lower motor neuron pattern) with positive Bell's phenomenon and a left abducent nerve palsy. The tone was flaccid in all four limbs with some weakness in the upper limbs limited to the distal muscle groups and more pronounced and generalized weakness in the lower limbs, worse in the left leg with weaker flexor muscle groups. She was areflexic except for a preserved left triceps jerk, plantar responses were flexor and she had a sensory deficit limited to left L5 dermatomal distribution.

Her nerve conduction studies showed no features of demyelination but revealed an axonal motor neuropathy in the lower limbs with asymmetry. Cerebrospinal fluid (CSF) analysis showed a raised protein level of 2.4 g/litre with a lymphocyte pleocytosis of 185 cells/$10^6$/litre, suggesting an underlying meningitic process. The CSF immunoglobulin G was 553 mg/litre and there was no hypoglycorrachia. Oligoclonal bands were present in the CSF but not in the serum. Her blood results were unremarkable but serology for *Borrelia burgdorferi* was strongly positive.

She was, therefore, commenced on a 5-day course of intravenous immunoglobulin treatment in view of the possible inflammatory component to her neuropathy and subsequently also commenced on intravenous ceftriaxone, which she received for a total period of 6 weeks. It was felt that full treatment for Borrelia infection would be appropriate despite the fact that subsequent Western blot analysis and polymerase chain reaction on CSF for Borrelia proved to be negative.

It was learnt retrospectively that she had been badly bitten by a tick a year earlier and had sought medical advice. At the time, she was treated with tetanus anti-toxin only. It was therefore felt appropriate to treat this woman for *B. burgdorferi* infection in view of her history of previous exposure and her clinical presentation. She made a gradual but significant recovery.

***Figure 1. Erythema migrans: bull's eye appearance. This is often seen on the legs but it can develop anywhere at the site of a tick bite.***

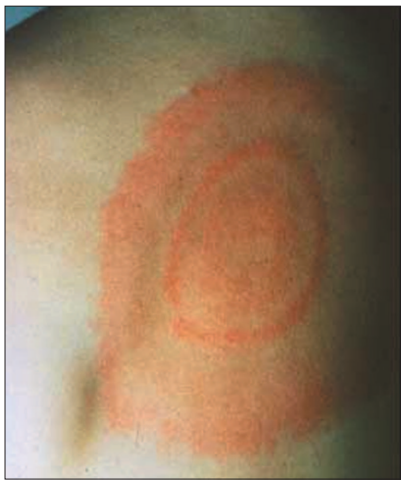
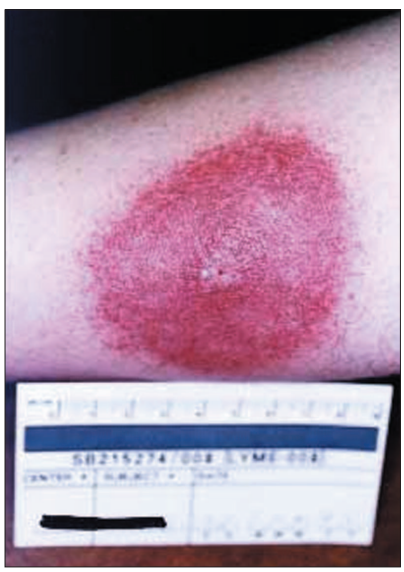


***Figure 2. Erythema migrans: the rash has lost the bull's eye appearance and has become inflamed and indurated.***



**Dr Maria E Farrugia** is Neuromuscular Research Fellow, The Weatherall Institute of Molecular Medicine, Neurosciences Group, John Radcliffe Hospital, Oxford OX3 9DS

extremely rare. Chronic neuroborreliosis is extremely rare in Europe and there have been very few deaths from Lyme borreliosis reported in the medical literature. The neurological manifestations include meningitis, cranial neuritis such as facial palsies, motor or sensory radiculoneuropathy, mononeuritis multiplex, chorea and myelitis, and some of these features will be dealt with later in the discussion.

**Epidemiology of Lyme borreliosis**

There is an uneven distribution of the different species of *B. burgdorferi*. Moreover, the different manifestations do not follow an even geographical pattern. A particular genospecies of *B. burgdorferi* (sensu stricto) predominates in North America much more than in mainland Europe, causing mainly musculoskeletal symptoms.

In Europe, three genospecies, *B. afzelii*, *B. garinii* and *B. burgdorferi* sensu stricto, are pathogenic while other species have been identified, for example *B. valaisiana* and *B. lusitaniae*, although their pathogenicity is not entirely clear. *B. afzelii* appears to be more associated with acrodermatitis chronica atrophicans while *B. garinii* is more associated with neurological manifestations (European Union Concerted Action on Lyme Borreliosis, 2000).

Notifications of Lyme borreliosis are often performed via the laboratory after acquisition of a positive result. Therefore, the incidence figures for Europe may not be entirely accurate. The report of the World Health Organisation workshop on Lyme Borreliosis Diagnosis and Surveillance, Warsaw, Poland in June 1995 showed an increasing incidence from west to east so that in the UK there are around 200 new cases annually with higher incidences in Eastern Europe ranging around 2000 cases annually in Slovenia and 3500 new cases per year in the Czech Republic. In the Scandinavian countries there is a gradient of decreasing incidence from south to north while in Italy, Spain and Greece the gradient exists in the opposite direction.

The seroprevalence varies with occupational and recreational groups. Forestry workers, veterinary surgeons, deer hunters and tourists traveling in endemic regions are at risk. There appears to be a higher incidence among males and this probably reflects a higher tendency for men to partake in the above mentioned activities. Some symptoms are more prevalent in specific age groups. For example, children commonly suffer from facial palsies while elderly women are more commonly affected by the chronic skin condition acrodermatitis chronica atrophicans (European Union Concerted Action on Lyme Borreliosis, 2000).

Surveillance for Lyme borreliosis in England and Wales was carried out between 1986 and 1998. This was based primarily on voluntary reporting of serologically confirmed cases by laboratories to the Public Health Laboratory Service Communicable Disease Surveillance Centre. This showed an increase in the incidence from 0.06/100 000 population between 1986 and 1992 to 0.32/100 000 in the period 1996–1998 (Smith et al, 2000). The case reports appear to peak between the months of July and September, reflecting the increase in outdoor activity in the summer season.

The increase in the figures quoted, however, may be purely related to improved laboratory techniques in serological testing, including immunoglobulin (Ig) M testing, Borrelia cultures, the use of polymerase chain reaction (PCR) and genotyping. Some kits detect IgM in the early stages of infection in an improved fashion and also earlier.

**Laboratory diagnosis**

The diagnosis of Lyme borreliosis is often based on the clinical findings supported by a previous history of a tick bite. It is difficult to isolate and culture the spirochaete but indirect tests with Western blot analysis and ELISA detect the presence of serum antibodies specific for antigens against *B. burgdorferi*.

It is recommended that one proves active disease or previous infection using a sensitive ELISA or an indirect immunofluorescent antibody test followed by more specific Western immunoblotting for equivocal or positive results acquired by the initial tests. The initiation of antimicrobial treatment may mask the antibody response in early localized disease but patients with early disseminated or late stage disease will have strong serological reactivity and expanded Western blot IgG banding patterns. The antibodies will persist for months even years following effectively treated or untreated infection.

Both the Western blots and ELISA tests are difficult to reproduce and are associated with false positive and false negative results depending on the specific patient population under study. They are not quantitative techniques and therefore cannot be used to monitor efficacy of treatment. The recommendation issued by the Centers for Disease Control and Prevention (1995) specify that a history of a previous tick bite followed by the development of a rash and flu-like symptoms justifies the initiation of treatment even if Western blot and/or ELISA are negative. It is therefore important to have a test available that demonstrates active infection as well as allows effective monitoring of therapy.

*B. burgdorferi* can be cultured from about 80% of biopsy specimens taken from an early erythema migrans lesion, as Berger et al (1992) have shown, but this technique is limited because it requires special bacteriological medium (modified Barbour–Stoenner–Kelly medium) and protracted observation of cultures. The genome of *B. burgdorferi* has been sequenced. PCR allows amplification of genomic DNA in skin, blood and CSF (Brettschneider et al, 1998) or synovial fluid (Nocton et al, 1994), although this is not used for routine diagnostic methods. Research is looking into novel approaches such as new PCR assays, new culture media, the use of specific recombinant protein antigens in Western blot and ELISA analysis, testing for specific immune complexes, microarray technology and proteomics and all these appear promising techniques for the future.

**Neuroborreliosis and Bannwarth syndrome**

A mild chronic axonal sensorimotor polyradiculoneuropathy or polyradiculopathy is a common manifestation in stage II Lyme disease and may be of

varying severity. Patients may have symmetric non-painful paraesthesia, an asymptomatic neuropathy or asymmetric radicular pain. The patients with sensory symptoms or who present with radicular pain may have evidence of denervation on electromyography testing of the limb muscles (Logigian and Steere, 1992). Clinical improvement is the norm after treatment with intravenous antibiotics.

The most frequent manifestation of the second stage is Bannwarth syndrome, which is caused by a meningoradiculitis and associated with a CSF lymphocytic pleocytosis. If untreated, patients will go on to develop persistent infection (stage III) with chronic arthritis, often involving the large joints such as the knee but the small joints may also be involved. Chronic CNS involvement with subtle encephalopathy, axonal polyneuropathy or skin manifestations such as acrodermatitis chronica atrophicans may occur months to years later.

There is an association between neuroborreliosis and Guillain–Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy, and previous Borrelia infection may be an important trigger. When CSF and serum are analysed for IgM and IgG antibodies to gangliosides, there is a lack of specificity for the ganglioside antibody patterns in these patients, suggesting that the ganglioside antibodies are not the link between Borrelia infection and the demyelination of peripheral nerves in Guillain–Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy. This has been shown by Weller et al (1992).

The pathogenesis of neuroborreliosis may have a vasculitic component. Nerve biopsies performed on patients with a meningoradiculoneuritis revealed perivasculitis with thrombosis of the epineural vasa nervorum while some biopsies showed evidence of angiopathic ischaemia. Meier and Grehl (1988) described evidence of a local immune reaction with the presence of pericapillary infiltrates with many plasma cells within the endoneurium.

### Treatment

Parenteral antibiotics are necessary to treat neurological complications, usually ceftriaxone 2 g daily for 4–6 weeks but sometimes penicillin G is also effective. In patients with heart block, intravenous treatment is important for at least 10 days with cardiac monitoring. Glucocorticoids may be beneficial for those patients who fail to respond within 24 hours. Other manifestations may be adequately treated with oral antibiotics such as doxycycline usually for a period of 4 weeks.

The vaccine LYMErix is a genetically engineered vaccine pioneered by Yale university researchers. It contains the lipoprotein OspA, an outer surface protein of *B. burgdorferi*. The hypothesis underlying the vaccine was that the vaccine-induced antibodies would be taken up by the tick and interact with the *B. burgdorferi* in the midgut of the tick thus preventing transmission of the organism to the host. The vaccine, however, was withdrawn from the market in February 2002 when there was some controversy as to whether some people receiving the vaccine had been made ill.

## CONCLUSION

Lyme disease must be recognized, correctly diagnosed and treated because its associated morbidity can be severe, chronic and disabling. It is important to be aware of the diverse neurological presentations associated with Borrelia infection. Its laboratory diagnosis is less than straightforward. Newer techniques are being developed, some of which will hopefully be sensitive enough to detect active disease particularly in those situations where the results may be difficult to interpret, for example in patients who live in endemic areas and are therefore chronically exposed to Borrelia. If the laboratory studies are not entirely supportive but the clinical presentation fits that of Lyme disease, then it is advisable to pursue one's clinical judgment and treat accordingly. HM

Figures 1 *and* 2 *are reproduced courtesy of the Lyme Disease Foundation (www.lyme.org)*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