Neuroborreliosis

John H. J. Wokke* and Jan A. L. Vanneste†
*Department of Neurology, University Medical Centre, Utrecht, the Netherlands and †Department of Neurology, Sint Lucas Andreas Ziekenhuis, Amsterdam, the Netherlands;
E-mail: j.wokke@neuro.azu.nl
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THE DISCOVERY OF A ‘NEW’ DISEASE
Neuroborreliosis is part of the spectrum of Lyme disease which was first described about a quarter of a century ago, although it existed long before that. For example, in 1909 the Swedish dermatologist Afzelius incriminated ticks as the potential vectors of an agent causing erythema migrans (Burgdorfer 1986) and DNA of the causative agent Borrelia burgdorferi has been demonstrated in archival tick specimens collected in New England in the 1940s (Persing et al. 1990).

In 1922 Garin and Bujadoux described a French peasant with erythema migrans on the left buttock (Garin & Bujadoux 1922). He had shooting pains in his legs, trunk and one arm, and developed increasing weakness and atrophy of the right deltoid muscle. The cerebrospinal fluid (CSF) protein was raised, and there was a pleocytosis. The authors labelled the disease ‘tick paralysis’ and suggested an unknown infection transmitted by a sheep tick. As the patient had erythema migrans, which is pathognomonic for infection with B. burgdorferi (Berger 1984), this in retrospect must have been the first description of a patient with neuroborreliosis. Two decades later, the German physician Alfred Bannwarth described a series of similar patients with painful polyneuritis following tick bite (Bannwarth 1941). Many also had a facial palsy. Following similar reports in other European countries, the syndrome was called lymphocytic meningoradiculitis following tick bite (Garin-Bujadoux-Bannwarth, or Bannwarth’s syndrome). Because a tick-borne infection was suspected, some patients were empirically treated with penicillin and rapidly recovered.

Then, in the late 1970s, a tick-borne disease was diagnosed in children in Lyme, Connecticut. The first manifestation of what at first was thought to be a novel disease, named Lyme disease, was erythema around the tick bite. In some patients disseminated infection evolved within days or weeks, affecting the nervous system, heart or joints (Steere 2001). The neurological features were unilateral or bilateral facial palsy, sometimes accompanied by headache as a sign of mild meningitis, and features of a motor or sensory radiculoneuropathy. The CSF showed a mild lymphocytic pleocytosis. By elegant analyses of the intestines of ticks that were recovered from skin and arthritic lesions, and antibody testing, Dr Willy Burgdorfer and colleagues showed that a Borrelia species was responsible for the infection (Burgdorfer et al. 1982). Diagnostic tests were then developed and a few years later antibodies against B. burgdorferi were demonstrated in European patients with Bannwarth’s syndrome.

TICKS AND SPIROCHETES
The vectors of Lyme disease, ticks of the genus Ixodes, are ubiquitous in the Americas and Eurasia but there are local variations. In the eastern USA, the black leg tick I. scapularis (syn. I.
Dammini) and I. dentatus are abundant. In the pacific coastal regions from Canada to Mexico, I. pacificus is found. In Europe, central Asia and North Africa the sheep tick I. ricinus is present (Hengge et al. 2003). These ticks carry and may transfect many microorganisms, especially various strains of Borrelia and Rickettsia.

An adult tick develops over about two years in three stages - larval, nymphal and adult (Fig. 1). Larvae measure about 1 mm, and adults reach a length of 3–4 mm. Birds and small rodents are the hosts of larvae and nymphs, especially the white-footed mouse in North America and the dormouse in Europe, and these are the most important natural reservoirs for B burgdorferi (Hengge et al. 2003). Adult ticks feed mainly on larger mammals, deer in the USA and sheep in Europe. Dogs and cats can also get ticks and become infected (Barbour & Fish 1993).

Ticks acquire infection in a complex tick-vertebrate cycle (Nadelman et al. 1998). As the small nymphae are difficult to find and to remove, they are probably the most likely stage to infect the host. Various ticks can be infected by different strains of B. burgdorferi, and in various geographical areas the proportion of infected ticks differs, which may explain regional differences in both the incidence and features of Lyme disease.

Because ticks become inactive in colder temperatures, infections with B. burgdorferi occur especially during the warmer months from May to October. The risk of transmission to humans depends on several factors, mainly the prevalence of infected ticks in a particular region and how long the tick feeds for (Hengge et al. 2003). This time during which the tick remains attached to the skin is crucial for transmission of B. burgdorferi. If the tick is removed within 24 h, the risk of infection is negligible (Kahl et al. 1998). However, when infected ticks remain attached to the skin for more than 48 h, the risk substantially increases. If exposure to ticks is increased by professional or recreational activities, the risk of tick bite and infection also become higher.

Although Lyme disease is a three-stage disease, with potential involvement of skin, joints and nervous system, similar in Europe and North America, the type and frequency of the various clinical manifestations may differ. This might be because of infection with distinct subpecies of B. burgdorferi (Van Dam et al. 1993). For example, the chronic skin infection acrodermatitis chronica atrophicans is associated

![Figure 1](image_url)  
**Figure 1** Life cycle of the Ixodes ricinus tick. (a) Larvae grow from eggs and feed on mice (host 1). Next larvae moult and change into (b) nymphae that may feed on mice and birds, and also on humans (host 2). During the next step nymphae moult and change into (c) adult ticks that feed on larger mammals (host 3). Adult ticks can more easily be traced.
with B. afzelii, and meningoradiculitis with B. garinii, strongly suggesting that different Borrelia subspecies have different organotropic and pathogenic potentials. This notion may have implications for the interpretation of immunological tests (Van Dam et al. 1993; Nadelman & Wormser 1998). Another explanation for differences between countries may just be case selection (Garcia-Monco & Benach 1995).

Finally, it must be born in mind that not all the problems in a patient with Lyme disease are necessarily caused by infection with B. burgdorferi. Co-infection of ticks with other microorganisms such as anaplasma phagocytophilum, the agent of human granulocytiehrlichiosis, and Bartonella henselae, the agent of cat-scratch disease, may alter the clinical presentation (Nadelman et al. 1996; Nadelman & Wormser 1998; Eskow et al. 2001; Hengge et al. 2003).

In forest workers, the prevalence of IgG antibodies against B. burgdorferi increases with age without any relationship to the clinical manifestations of infection (Münchhof et al. 1986). Most of these seropositive individuals were asymptomatic and could not remember a tick bite. This suggests that after a tick bite not everyone develops overt Lyme disease – B. burgdorferi can clearly cause asymptomatic infection (Steere 2001).

THE CLINICAL MANIFESTATIONS OF LYME DISEASE

Erythema migrans
Ticks may be difficult to trace and hard to remove (Fig. 2). Erythema migrans is the first recognizable manifestation of infection with B burgdorferi (Fig. 3) (Berger 1984). After a tick bite, it usually appears within 7–10 days (Nadelman & Wormser 1998), but sometimes as early as after 2 days. A solitary lesion must reach a size of at least 5 cm for definitive diagnosis (Table 1). The erythema spreads outwards, presumably reflecting spread of spirochetes from the bite to the periphery. Over days or weeks it can reach a diameter of 20 cm. It may look like a target lesion with central clearing of the erythema. Secondary lesions occur from haematogenous spread (Berger 1984; Hengge et al. 2003). In the USA, influenza-like symptoms such as fatigue, malaise, headache, arthralgia, myalgia, mild fever and lymphadenopathy commonly accompany or precede the skin lesion (Nadelman et al. 1996; Steere 2001). If untreated, erythema migrans usually disappears gradually (Berger 1984; Wokke et al. 1984; Schmidt & Ackermann 1985).

In forest workers, the prevalence of IgG antibodies against B. burgdorferi increases with age without any relationship to the clinical manifestations of infection.
**Figure 2** Tick *in situ* on the human skin, sucking blood.

**Figure 3**
(a) Erythema migrans over the deltoid; note the tick is still present in the centre.
(b) Two days later.
anyone from endemic areas – or who has recently been in an endemic area – with severe headache or back pain, radicular pain and signs compatible with multiple peripheral nerve or nerve root dysfunction, should be investigated for early neuroborreliosis.

### Early neuroborreliosis

After 1–12 weeks, manifestations of infection and inflammation of the central nervous or peripheral nervous system occur in some patients. Early neuroborreliosis is an acute disease that may be dramatic and it includes severe neurogenic pain. It follows untreated erythema migrans, and also tick bite without erythema migrans (Wokke et al. 1984; Garcia-Monco & Benach 1995; Nadelman & Wormser 1998; Oschmann et al. 1998; Steere 2001). In about two-thirds of European patients with neuroborreliosis a tick bite is not spontaneously mentioned, or even recalled, or it may have escaped attention (Hansen & Lebech 1992). These patients are a problem for neurologists: anyone from endemic areas – or who has recently been in an endemic area – with severe headache or back pain, radicular pain and signs compatible with multiple peripheral nerve or nerve root dysfunction, should be investigated for early neuroborreliosis, especially if the MRI scan of the spine is normal. The next step should be CSF analysis.

Most of the literature details small series of selected patients, or just case reports. However, a pattern of the clinical syndromes emerges from the few large and relatively unbiased studies (Hansen & Lebech 1992; Oschmann et al. 1998).

### Lymphocytic meningitis and meningoradiculitis

In lymphocytic meningitis, inflammation of one or multiple nerve roots and or cranial or peripheral nerves occurs. This may cause pain, axonal degeneration of affected nerves and a residual neurological deficit. Meningitis is usually mild with headache and neck stiffness, and almost never any fever (Stanek & Strle 2003). Sometimes there is no meningitis at all, just radiculitis. Burning excruciating pain along the spine, the trunk or in a limb or limbs, or combinations, may be extreme, especially at night. Neurological signs consist of reduced sensation and dysesthesia in one or more dermatomes, weakness in one or several myotomes, and reduced or absent deep tendon reflexes reflecting dysfunction of affected nerve roots. These may correspond with the area of the erythema migrans (Hansen & Lebech 1992). The facial nerve is involved in about one-half of the patients, and in about one-third bilaterally (Hansen & Lebech 1992; Oschmann et al. 1998).

In a large German study of 330 adult patients with neuroborreliosis, 12 (4%) had only meningitis and 249 (75%) had meningitis and radiculitis of cranial and/or spinal nerves; in other words, Bannwarth’s syndrome (Oschmann et al. 1998). 31 (9%) had CN dysfunctions (myelitis or encephalitis). These groups were not very different in disease duration, frequency of erythema migrans, CSF abnormalities or serology.

Therefore, the hallmark of early neuroborreliosis is meningitis. What then determines which neural structures – cranial or spinal nerve, spinal cord or even brain – become af-
fected is unknown. It is unlikely that different B. burgdorferi subspecies are responsible.

In children, meningitis without spinal radiculitis occurs more frequently than in adults (Hansen & Lebech 1992; Bingham et al. 1995; Christen 1996). Clinical features are headache and also papilloedema in some. In a large prospective study of 169 patients, 55% had facial palsy and 29% lymphocytic meningitis (Christen 1996). In endemic regions, isolated unilateral or bilateral facial palsy in children must raise the suspicion of neuroborreliosis (Albisetti et al. 1997). In contrast, there is no evidence that facial palsy in adults, without previous erythema migrans or involvement of other cranial nerves or signs of meningoradiculitis, is caused by infection with B. burgdorferi (Kuiper et al. 1992).

Multiple mononeuropathy

Interestingly, 10 patients (3%) in the German study had acute mononeuritis or polyneuritis and a normal CSF (Oschmann et al. 1998). All had previous erythema migrans and positive serology. In these patients, the erythema migrans was the key to the diagnosis. Neuroborreliosis may therefore rarely present as dysfunction of peripheral and or cranial nerves only, without meningitis. Haematogenous spread of the spirochete is the most likely explanation. This concept is supported by the discovery of mononuclear cell infiltrates in sural nerves (Vallat et al. 1987).

Lyme myositis

The large European series did not describe any patients with myositis. Although one series reported eight patients, strict criteria for serological diagnosis were not met and the clinical and pathological diagnosis of myositis was doubtful (Reimers et al. 1993).

Late neuroborreliosis

From the first studies of neuroborreliosis it was clear that a few untreated patients with early neuroborreliosis developed chronic disease. But, sometimes, late neuroborreliosis may be the first manifestation of Lyme disease. Erythema migrans may not have been noticed or even have been absent at all. Late neuroborreliosis may present as:

- Persistent chronic meningitis, meningo-radiculitis and progressive radiculomyelitis or encephalomyelitis (Wokke et al. 1987; Logigian et al. 1990; Oschmann et al. 1998). In the latter group small cerebral infarcts leading to focal deficits, and sometimes epilepsy, may occur. Pain is not a prominent feature. CSF abnormalities are similar to those with early neuroborreliosis and the serology is diagnostic.
- Chronic mononeuropathy or asymmetrical polyneuropathy and acrodermatitis chronica atrophicans (ACA, Fig. 4) was found in 1.5% of the German series (Oschmann et al. 1998).

Figure 4 (a) Acrodermatitis chronica atrophicans of the right hand. (b) In another patient affecting the upper leg.
ACA mostly affects the leg and sometimes the arm. As a result of the accompanying neuropathy there may be mild weakness or sensory deficit (Oschmann et al. 1998). Up to as long as 10 years after the onset of ACA, B. afzelii may be cultured from the skin lesions (Nadelman & Wormser 1998). The CSF is normal. How peripheral nerves become infected has not been systematically analysed.

- Subacute encephalopathy (Logigian et al. 1990). Patients have memory loss, sleep disturbance and also mild impairment of word retrieval. There is seldom any CSF pleocytosis, but increased intrathecal synthesis of IgG against B. burgdorferi is diagnostic. Some respond to treatment with ceftriaxone. Further studies with adequate control groups and sound diagnostic criteria should confirm whether B. burgdorferi is indeed causal.

- Axonal peripheral neuropathy (Halperin et al. 1990; Logigian et al. 1990). Chronic peripheral nerve system involvement is claimed to occur in American patients, usually following arthritis (Halperin et al. 1990). However, patients in that early study were highly selected and there was no two-step serological diagnosis. The patients had intermittent limb paraesthesia and minimal distal sensory loss. Some had the carpal tunnel syndrome. What is needed is a prospective study of a well defined cohort using adequate control groups. However, this will probably never be done because most patients with Lyme disease are treated before any chronic stage develops.

**Post-Lyme syndrome**

Most patients with erythema migrans, and early or late neuroborreliosis, recover even if untreated (Kalish et al. 2001). Treatment with antibiotics leads to more rapid recovery and possibly fewer residual complaints, but no placebo-controlled trials have been or will be done for erythema migrans.

In spite of effective standard treatment of erythema migrans and neuroborreliosis with antibiotics, some patients have persistent non-specific symptoms such as chronic fatigue, myalgia, dysaesthesia, paraesthesia, memory disturbances and depression. This complex of symptoms is referred to as ‘chronic Lyme disease’, ‘post-Lyme disease syndrome’ or ‘post-treatment chronic Lyme disease’ (Klempner et al. 2001; Stanek & Strle 2003). The cause is unknown, and indeed the whole syndrome is still controversial (Klempner et al. 2001; Sigal 2002). In adequately treated patients, their symptoms are not different from control groups (Seltzer et al. 2000; Kalish et al. 2001). Double-blind randomised trials of prolonged treatment with antibiotics have also failed to show any benefit (Klempner et al. 2001; Kaplan et al. 2003; Krupp et al. 2003). Therefore, non-specific complaints after treated Lyme disease are unlikely to be due to persistent infection. It is possible that this obscure post-infectious syndrome can be explained by depression or somatization.

Recently misconceptions about Lyme disease have been elegantly reviewed, and after adequate treatment there is no evidence for a chronic active form (Sigal 2002). Confusion about the diagnosis and efficacy of treatment can be explained by the use of inaccurate diagnostic criteria, unsound methodology of clinical and experimental studies, and possibly also by social and medicolegal motives. It must be borne in mind that following treatment, serological tests usually remain positive. Finally, it is not surprising that the recognition and definition of a new disease takes some years.

**HOW TO DIAGNOSE LYME DISEASE**

**Case definition**

At present there is no gold standard for the diagnosis of neuroborreliosis but the case definition by the Center for Disease Control is helpful (Table 1). Even many erythema migrans has subsided before the neurological symptoms appear and many patients develop neuroborreliosis without the skin lesion being noticed or even present. When there is a skin lesion, the neurologist must feel secure about the diagnosis of erythema migrans, perhaps retrospectively, which is not easy (Fig. 3).

In early neuroborreliosis, the CSF of most patients shows a pleocytosis of lymphocytes and plasma cells. Undifferentiated and dividing white cells may even suggest a haematological malignancy (Fig. 5). The number of cells may be as high as 1000/mm$^3$ (Oschmann et al. 1998). The protein content may also be raised but the glucose level is normal. With progressive disease, oligoclonal bands may develop and the IgG index rises. There is widespread agreement that laboratory support for the secure diagnosis of extracutaneous Lyme borreliosis is mandatory (Nadelman & Wormser 1998; Steere 2001; Hengge et al. 2003; Sigal 2003).

**Testing for antibodies**

Serological tests were first developed as an adjunct to clinical diagnosis (Anon 1995; Sigal 2003). In the first decade after the recognition of Lyme disease, indirect immunofluorescence assay (IFA) was the main method to demonstrate IgG and IgM antibodies against B. burgdorferi in serum and CSF. IFA has now been largely replaced by the enzyme-linked immunosorbent assay (ELISA) (Garcia-Monco et al. 2003; Stanek & Strle 2003)
& Benach 1995). In the USA, a two-step serological approach has been proposed to increase specificity (Anonymous 1995). If ELISA or IFA are positive, or equivocal, Western blotting is performed on the same sample to detect IgG and IgM antibodies to individual B. burgdorferi antigens (Nadelman & Wormser 1998). In general, two independent bands are needed for a positive immunoblot test result. This two-step approach helps to increase the sensitivity and specificity of serodiagnosis, which at present has not been standardized (Hengge et al. 2003). If the immunoblot is negative, a positive ELISA or IFA is very probably a false-positive result (Hengge et al. 2003). Serology in Europe is complicated by the considerable variation of immunoblotting between reference laboratories (Robertson et al. 2000). Standardization of the diagnostic tests is urgently needed.

Antibodies appear and titres rise with ongoing disease in untreated patients. Initially IgM antibodies may be demonstrated, but after a month most patients have IgG antibodies (Dressler et al. 1993). Therefore, if a patient has been ill for more than a month, an IgM antibody response alone is probably a false positive (Steere 2001; Sigal 2003). Patients with untreated and even treated Lyme borreliosis may remain seropositive for years (Dressler et al. 1993). IgM antibodies may also persist. Therefore, serology has no role in monitoring treatment (Steere et al. 1993; Steere 2001).

With antibody-capture, ELISA specific IgG and IgM antibodies can be demonstrated in CSF from many but not all European and American patients with neuroborreliosis and meningitis, or meningoradiculitis (Steere et al. 1989; Hansen & Lebech 1992). Intrathecal antibodies without a CSF pleocytosis exclude active early or late neuroborreliosis involving the CNS. Their presence suggests previous infection, or blood–brain barrier disruption and leakage from serum, or a false positive test (Hengge et al. 2003).

**Other diagnostic tests have limited value**

These include culture of the spirochete and the polymerase chain reaction (PCR) to detect the DNA of B. burgdorferi. Spirochetes have been isolated from skin lesions of some patients with erythema migrans and acrodermatitis chronica atrophicans, and occasionally from plasma samples or CSF in early Lyme disease (Steere 2001). The reliability and value of other methods to detect material from spirochetes is under discussion (Nadelman & Wormser 1998; Steere 2001). PCR can sometimes detect B. burgdorferi DNA in CSF of patients with neuroborreliosis, but the sensitivity is less than 40% (Nocton et al. 1996). Finally, PCR cannot distinguish between the DNA from dead or live organisms. Therefore, neither culture nor PCR are useful in the diagnosis of neuroborreliosis.

**HOW TO BEAT THE SPIROCHETE**

Neurological manifestations of early neuroborreliosis usually respond well to antibiotics, but may resolve spontaneously although more slowly (Wokke et al. 1984; Kruger et al. 1990; Kalish et al. 2001; Steere 2001). Without antibiotic treatment, residual pain or signs may become chronic in a few patients (Kruger et al. 1989; Logigian et al. 1990). Treatment will result in a rapid decline of pain and any neurological abnormalities, and must be started as soon as possible. Also axonal degeneration and residual deficits are prevented by early treatment. However, peripheral paresis can develop after initiation of treatment (Hansen & Lebech 1992).

It may take some days before the results of serological testing are known. Therefore, in a patient with a history of erythema migrans and neurological manifestations compatible with neuroborreliosis, Lyme disease is the most likely explanation and immediate treatment is justified. This also holds true for patients from endemic regions with what looks like neuroborreliosis but who do not recall erythema migrans, or a recent tick bite. In both cases antibody testing must be done to confirm the diagnosis. If there are only the features of lymphocytic meningitis or meningoradiculitis, the results of antibody testing should be awaited before Lyme disease can be diagnosed and treatment started.

The various treatment options are summarized in Table 2. There is some evidence that oral doxycycline may be as effective as intravenous penicillin G in early neuroborreliosis (Karlsson et al. 1994), but intravenous ceftriaxone has become the standard treatment.

With adequate treatment acute neuroborreliosis will resolve within weeks (Steere 2001). Chronic neuroborreliosis improves more slowly over a period of months. Following treatment an immunological ‘scar’ may persist in serum and CSF – specific antibodies and oligoclonal bands (Kruger et al. 1989).
**CONCLUSIONS**

- Neuroborreliosis is rare. Even if the annual incidence is 6/100 000, most patients have only erythema migrans — less than one-fifth develop neuroborreliosis. Therefore most neurologists will only see a few patients every 2 or 3 years. In endemic regions and in countries with few neurologists the numbers are higher.
- Most patients with neuroborreliosis present with subacute lymphocytic meningoradiculitis and facial palsy, or meningitis.
- Antibiotic treatment leads to complete recovery unless axonal degeneration of cranial or spinal nerves has already occurred.
- Chronic neuroborreliosis is extremely rare and is usually diagnosed by the CSF abnormalities.
- Post-Lyme syndrome cannot be explained by chronic persistent infection with *B. burgdorferi*, or autoimmune inflammation of the central nervous system (Sigal 2002).
- Many healthy people have circulating antibodies against the spirochete. Haphazardly screening patients with a low clinical suspicion of neuroborreliosis, particularly in an endemic area, will result in a high number of false positives.
- As the commonly used ELISA test is very sensitive, the risk of a false negative test is extremely low. Immunoblotting, the second step of serology with high specificity, will avoid false positive results.
- Neurologists should reassure their patients who, in spite of negative test results, still believe in the mystique of a diagnosis of neuroborreliosis.
- Further useful information can be found at the CDC website: http://www.cdc.gov/ncidod/dvbid/lyme.
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