

# Lyme neuroborreliosis: infection, immunity, and inflammation

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Lyme neuroborreliosis (LNB), the neurological manifestation of systemic infection with the complex spirochaete *Borrelia burgdorferi*, can pose a challenge for practising neurologists. This Review is a summary of clinical presentation, diagnosis, and therapy, as well as of recent advances in our understanding of LNB. Many new insights have been gained through work in experimental models of the disease. An appreciation of the genetic heterogeneity of the causative pathogen has helped clinicians in their understanding of the diverse presentations of LNB.

## Neuroborreliosis and Lyme disease

Lyme neuroborreliosis (LNB) designates neurological involvement during systemic infection with the spirochaete *Borrelia burgdorferi*.<sup>1–4</sup> This spirochaete, with characteristic genetic features such as a linear chromosome<sup>5</sup> and multiple plasmids containing genes important for host infection,<sup>6</sup> resembles that causing neurosyphilis, *Treponema pallidum*, under dark-field microscopy (figure 1). The two spirochaetes can, however, be distinguished morphologically by experienced microbiologists. Both spirochaetes share genetic and antigenic features<sup>7</sup> and are capable of evading the host immune defences to persist in infected vertebrate hosts.

Human beings become infected with *B burgdorferi* by the bite of infected ticks,<sup>8,9</sup> and most patients with LNB present to a neurologist within a few weeks to a few months of the initial bite.<sup>10,11</sup> Neurologists must be aware of several factors that determine the risk of LNB diagnosis in individual patients. The likelihood of having LNB is

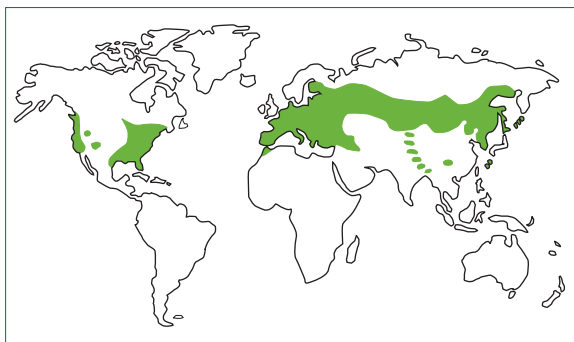
dependent on geography, recreational habits of the patient, and season. The importance of geography cannot be underestimated. Because the spirochaetes can be transmitted to human beings only by the bite of infected ticks, patients who have never been in a situation where they could have been bitten by an infected tick cannot have LNB. The infection is a zoonosis, in which the spirochaete is maintained at high levels in populations of field mice or birds and spread by the bite of ixodid ticks.<sup>8,12</sup> Some areas of the world have no ticks, no vertebrate hosts, or no *B burgdorferi* and are called non-endemic areas (figure 2), whereas others have particularly high concentrations of these ticks and vertebrate hosts infected with the spirochaete and are considered hyperendemic areas.<sup>9</sup> Nymphal ticks, which primarily transmit *B burgdorferi* to human beings, are active only in warm weather. A businessman in Montreal who does not leave the city but who develops neurological illness in March is highly unlikely to have LNB, but a forest ranger in Munich with an identical condition that appears in September is much more likely to have LNB.

Most evidence points to the pathogenesis of LNB being invasion of the CNS and peripheral nervous system by *B burgdorferi*, although a toxic-metabolic source (eg, from infection outside the nervous system) cannot be ruled out. Symptoms of LNB are consistent with a mild to moderate inflammatory involvement, predominantly in the subarachnoid space and perineural tissue. Common features of LNB are a subacute course over weeks to months after infection, cerebrospinal fluid (CSF) pleocytosis that is primarily lymphomonocytic, and cranial neuropathy usually involving the seventh nerve.<sup>10,11</sup> Some clinicians find a distinction between early and late LNB useful.<sup>13</sup> The former is more inflammatory with meningitis, cranial neuritis, and radiculitis, whereas the latter, which may follow Lyme arthritis, can present as a subtle encephalopathy or mild peripheral neuropathy.<sup>14,15</sup>

A great deal of knowledge has been gained from animal models of Lyme borreliosis, particularly those in mice and rhesus macaques. Mice do not develop neurological infection, even in immunocompromised conditions, unless the spirochaete is injected directly into the brain,<sup>16</sup> but mice do acquire persistent infection of heart, bladder, skin, and other tissues.<sup>17–21</sup> The mice do not seem to be significantly affected in their behaviour, despite high levels of spirochaetes in tissues and significant inflammation. Mice also mount a strong



**Figure 1:** Dark-field microscopy of *B burgdorferi*  
Live borrelia are highly motile under dark-field microscopy. The average length of *B burgdorferi* is 15–20 µm.

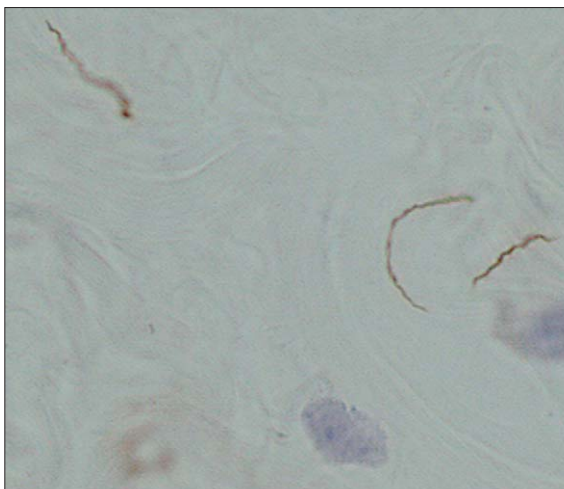


**Figure 2: World-wide distribution of ixodid ticks capable of carrying and transmitting *B burgdorferi* to humans**  
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humoral and cellular immune response, which is ineffective in clearing the spirochaete. The human and non-human primate immune response is much more effective against the spirochaete. However, when mild immunosuppression is induced in rhesus macaques, the spirochaete establishes infection<sup>22,23</sup> with nests of spirochaetes surrounded by inflammatory cells in many organs, including the CNS and peripheral nervous system.<sup>24–28</sup> Inflammation in the nervous system in rhesus macaques is primarily localised to nerve roots, dorsal root ganglia, and leptomeninges. T cells and plasma cells are the predominant inflammatory cells. Significantly increased amounts of IgG, IgM, and C1q are found in inflamed spinal cords. Spirochaetes can be visualised by immunohistochemistry<sup>24</sup> in the leptomeninges, nerve roots, and dorsal root ganglia, but not in the CNS parenchyma (figure 3). These data are consistent with the pattern of clinical involvement in infected human beings, with meningitis and radiculitis predominating, and parenchymal involvement occurring only rarely.

### Epidemiology

There are substantial clinical differences in LNB depending on whether infection occurred in the USA or Europe (table), because of genetic differences between the strain that causes all cases of US LNB, *B burgdorferi* sensu stricto, and the European strains *B garinii* and *B afzelii*;<sup>29,30</sup> *B burgdorferi* sensu stricto has been isolated from a small percentage of European patients but almost never causes LNB in Europe. Different disease manifestations were induced when *B burgdorferi* sensu stricto spirochaetes isolated from the CSF of American patients and *B garinii* or *B afzelii* from European patients were injected into mice.<sup>31</sup> There are also differences in the life cycle of *B burgdorferi* in the various continents. The tick *Ixodes scapularis*, which primarily feeds on field mice but may also be maintained in other rodents, is the main host for the spirochaete in the USA, whereas in Europe *I ricinus* feeds on several animals, but may become infected with *B garinii*, mostly from birds;<sup>32</sup> in



**Figure 3: *B burgdorferi* in the dorsal root ganglia of Rhesus macaques during chronic experimental infection**  
Spirochaetes have been labelled by immunohistochemistry with a high-titre rabbit polyclonal antiserum. The average length of *B burgdorferi* is 15–20  $\mu$ m.

addition, these bird tick *Iurria* may be important for *B garinii* infection in Europe, especially in the North Atlantic.<sup>33</sup> LNB probably also occurs in Asia, and is under active investigation in China, Japan, and Korea. Russian LNB has been well documented.<sup>34</sup> Lyme disease may not exist in South America<sup>35</sup> or Africa,<sup>36</sup> and there are many areas of Asia and even Europe and North America that have no Lyme disease because of the absence of the spirochaetes in ticks or of the vertebrate hosts. Consistent with the complex epidemiology is the great degree of genetic heterogeneity among the three main species. Further complicating the picture is the fact that ticks may also carry other infectious organisms such as *Babesia* and *Ehrlichia*, and coinfections, although uncommon, are possible.

### Diagnosis

Diagnosis of LNB would ideally be made by demonstration of the causative pathogen in the CSF. Culture<sup>37</sup> or PCR<sup>38</sup> of CSF samples have been used for this purpose, and spirochaetes can readily be detected by PCR<sup>39–41</sup> or histology<sup>19,24</sup> in tissues of experimentally infected animals. The yield of CSF culture in patients with LNB is less than 5%; CSF PCR has a higher sensitivity. While it can be positive in up to 40% of patients with LNB, especially in patients with meningitis,<sup>38</sup> this is usually early in the course of infection. Unfortunately, the spirochaete is primarily a tissue-based organism, and does not appear for extended durations in blood or CSF. Consequently, direct demonstration of the spirochaete in blood or CSF is impractical in routine clinical settings because of its low yield. Thus, the diagnosis must rely on a combination of history, examination, routine analyses of CSF, and antibody studies of serum and CSF.<sup>42,43</sup>

Clinical feature	American LNB	European LNB
Causative <i>Borrelia</i> subspecies	<i>B burgdorferi</i> sensu stricto	Mostly <i>B garinii</i> , occasionally <i>B afzelii</i>
LNB as a percentage of all Lyme cases	<10%	>35%
Multiple erythema migrans lesions	Common	Uncommon
Painful radiculitis	Rare (<10%)	Common (>50%)
"Aseptic" meningitis presentation	Majority	Minority
Cranial nerve involvement	VII, very rarely others	Usually VII, but can include others
Associated chronic skin manifestation (lymphocytoma or ACA)	Never	Not rare
Associated with Lyme arthritis	Common	Almost never
Chronic encephalomyelorradiculitis	Very rare (<0.1% of LNB)	More frequent, but unusual (<3% of LNB)
Intrathecal antibody production	Minority of cases	Common (>50%)

ACA=acrodermatitis chronica atrophicans.

**Table: Differences between European and American LNB**

## History

### Exposure

As mentioned, geography and outdoor exposure are critical factors. Neurologists in non-endemic areas should obtain a travel history from patients who might have travelled to an endemic area and been infected there. Infected ticks are usually present in suburbs or countryside, especially where there are many deer, although it is theoretically possible to be infected in city parks.<sup>44</sup> However, an individual who stays in the city and does not venture out is very unlikely to develop LNB. Because the ixodid ticks are small and inconspicuous, most patients do not recall the tick bite that resulted in LNB. Thus, asking the patient about tick bites is not necessarily a helpful addition to the history.

### Erythema migrans

Erythema migrans, which is a diagnostic hallmark of the disease, is a chronic area of expanding erythema greater than 5 cm in diameter, commonly raised and sometimes itchy. This circular or elliptical red area that spreads centrifugally daily (figure 4) is caused by movement of spirochaetes through the skin. A history of erythema migrans is very common in LNB, and should be actively explored. Because LNB typically occurs within the first few months of infection and erythema migrans is an early manifestation, usually in the first few weeks, the rash is commonly recalled by patients.

LNB in the USA usually occurs after the erythema migrans rash. In the placebo group of a large vaccine study involving more than 5000 patients in each arm<sup>45</sup> in areas of northeast USA that are endemic in Lyme disease, there were only two patients who developed LNB de novo without an earlier manifestation of the systemic disease including erythema migrans. In this study, neurological involvement occurred in only 3% of the 86 patients with Lyme borreliosis. By contrast, 81 of the 86 patients (94%) who developed Lyme borreliosis had erythema migrans as their manifestation.

The situation is very different with the European forms of LNB. In Bannwarth's syndrome in Europe, erythema migrans can occur, but is a preceding event in only a few cases. In a study of 404 patients of Bannwarth's syndrome in Germany,<sup>46</sup> most cases of LNB (58%) occurred without a preceding erythema migrans. In this study, LNB was the presentation of Lyme disease in 49% of cases and was the most common manifestation, and erythema migrans, arthritis, carditis, and acrodermatitis were less common. Thus, many patients infected in Europe will not have erythema migrans before their LNB, which makes it important to obtain a history of foreign travel. Nevertheless, now that erythema migrans is generally recognised and treated aggressively in the USA, the incidence of LNB without this preceding symptom will probably be higher, although no studies have addressed this issue.

Erythema migrans also affects children with Lyme disease. In a large study of pediatric Lyme disease in the USA,<sup>47</sup> the spectrum of the disease was similar to that of adult LNB, with 90% of children presenting with erythema migrans, and only 5% had either facial palsy or meningitis; smaller studies have noted a higher incidence of LNB in children than in adults.<sup>48</sup> As with European adults, the incidence of neurological involvement relative to other disease manifestations is high in children in Europe.

### Symptoms of LNB

American LNB almost always presents as a subacute meningitis without or with associated facial palsy within a few weeks to a few months of infection or the erythema migrans rash.<sup>11,42</sup> Headache, meningismus, numbness and tingling that is not attributable to a definite anatomical localisation, myalgia, fatigue, and malaise are all common. Patients may have mild cognitive symptoms but do not have severe organic brain syndromes. Although radicular symptoms may be present, painful radiculitis is uncommon.

European LNB usually presents as Bannwarth's syndrome<sup>10,49</sup> (also called Garin-Bujadoux syndrome).<sup>50</sup> Bannwarth's syndrome is more easily identified because of its presentation as painful radiculitis.<sup>51</sup> 86% of LNB cases in Europe present with painful radiculitis with or without associated paresis. This is of course not pathognomonic and European neurologists have been warned that not all painful radiculitides are caused by spirochaetes.<sup>52</sup> The pain of Bannwarth's syndrome is frequently chronic, lasting for weeks to months after initial infection; it may be severe, commonly worsening at night, and is often described as lancinating. Bannwarth's syndrome is also sometimes called "lymphocytic meningoradiculitis",<sup>53</sup> because of accompanying meningitis and the lymphocytosis in the spinal fluid. Some clinicians feel that Bannwarth's syndrome may be a unique clinical hallmark of LNB caused by *B garinii*,<sup>54</sup> but Bannwarth's syndrome can occasionally be seen in American LNB, caused by *B burgdorferi* sensu stricto.<sup>55</sup>



**Figure 4: Erythema migrans in an infant during the summer in a highly endemic area (New Jersey, USA)**

Day 1: the rash was first identified on this day; note the "bull's-eye" appearance, which is commonly, but not universally present (A). Day 5: the rash has spread centrifugally, and there is relative central clearing (B). Day 6: more spread (C). Day 9: 3 days after antibiotic therapy, the rash has almost completely cleared (D).

In both forms of LNB, peripheral neuropathy, as distinct from facial neuropathy, can occur with symptoms of numbness and tingling. The neuropathy is generally not severe, and disabling weakness is unusual. Differentiation between the radiculitis of Bannwarth's syndrome and neuritis is clinically impossible in some cases. Most neuropathies from Lyme disease are axonal,<sup>56</sup> especially those associated with acrodermatitis chronicum atrophicum, a chronic skin lesion primarily caused by north European strains of *B burgdorferi*.

### Signs

There are no findings on neurological examination that are absolutely specific for LNB. Some patients have bilateral facial palsy in the summer or autumn, a finding that, in endemic areas, is highly predictive of LNB. Examination should also include the dermatological search for erythema migrans. The combination of headache, facial palsy, and a characteristic erythema migrans in areas endemic for Lyme disease in the summer or autumn is sufficient for a diagnosis. A search of the skin for coexisting erythema migrans in patients with chronic headache in an area endemic for Lyme disease may be rewarding. Unfortunately, erythema migrans is usually not present when patients

with LNB present to physicians,<sup>58</sup> and suspicion of LNB needs to be confirmed by looking for antibodies for spirochaetes in serum<sup>59</sup> and CSF.<sup>60</sup>

### Laboratory studies

#### CSF or serum antibody index

The gold standard for the laboratory diagnosis of bacterial infections is identification of the pathogen. Unfortunately, in LNB, as in neurosyphilis, the yield of PCR or culture is too low. However, LNB usually presents at a time when a strong immune response to the spirochaetes is mounted, resulting in high titres of specific antibodies for *B burgdorferi* in serum and CSF. In European LNB, the antibody index is typically used to aid the diagnosis of LNB:<sup>61</sup> specific antibody titres are measured in the CSF and in the serum and are calculated to measure intrathecal synthesis of antibodies for spirochaetes. An antibody index above 1 means that the antibody is at a higher relative level in the CSF than in the serum.<sup>62</sup> Lumbar puncture in patients with LNB will also generally support the diagnosis by showing a monocytic or lymphocytic pleocytosis, commonly with a mild to moderately high protein concentration, consistent with an inflammatory process.<sup>63</sup> Imaging studies are generally not helpful,<sup>64</sup>

except to rule out other neurological processes, although occasionally the subarachnoid inflammation will be profound enough for gadolinium enhancement of the meninges. SPECT scanning has been used by some clinicians, but its reliability in LNB is unproven.

In American LNB, the CSF antibody index is not commonly used, possibly because there has not been an extensive study to assess its usefulness in the American LNB setting relative to the usefulness of serum antibodies in patients with possible LNB. Using an antibody capture technique, Steere and colleagues<sup>65</sup> showed significant differences between American and European patients with LNB, indicating that the sensitivity of the CSF antibody-index assay for American LNB may not be high relative to European LNB. Thus, at this time, there are no well-accepted criteria for the diagnosis of American LNB, and it is reasonable to look for antibodies for *B burgdorferi* in serum for diagnosis with the approach outlined below.

#### Two-step approach for serum antibody assays

Patients with American LNB are infected with strains of *B burgdorferi* sensu stricto that are relatively homogeneous compared to the situation in Europe, where there is great genetic heterogeneity among the strains that infect human beings. Thus, immune responses in American patients are directed to a predictable medley of antigens, and antibody testing is reasonably straightforward. In 1994, the American Centers for Disease Control in association with the Association of State and Territorial Public Health Laboratory Directors recommended a two-step approach to testing in which the first step was an ELISA. If the ELISA—which is fast, inexpensive, and highly sensitive—is positive, the serum sample is further tested in an immunoblot assay (a western blot).<sup>66</sup> The western blot, using the so-called Dressler criteria,<sup>67</sup> adds the specificity missing in the ELISA assay. The ELISA–western blot combination has been validated both in formal studies<sup>68</sup> and in clinical experience. Although in extensive use, this technique suffers from the same problems as any serological assay: it is not highly sensitive for very early Lyme borreliosis, and it cannot readily distinguish between active infection and previous exposure. Nevertheless, the assay is very useful for LNB, because neurological involvement presents weeks to months after initial infection.<sup>11,58</sup> Thus, a negative serum assay for antibodies for *B burgdorferi* in the USA will generally rule out LNB. Because the strains of *B burgdorferi* causing LNB in Europe are much more heterogeneous, the ELISA–western blotting of serum becomes more complicated and less reliable,<sup>69</sup> and the antibody index remains the mainstay of laboratory diagnosis in Europe. The development of recombinant *Borrelia* proteins for immunodiagnosis in European Lyme disease research centres<sup>70,71</sup> may help address this problem because in animal models, *Borrelia* recombinant proteins have proven very helpful in defining the humoral response.<sup>23</sup> The recent development of an assay for serum antibodies to the peptide from the sixth invariant region of the VlsE

lipoprotein of *B burgdorferi* (see below) may pave the way for the development of a more useful assay in serum for LNB in Europe.<sup>72</sup>

#### Overlap with other neurological diseases

Despite the combination of clinical setting and serological confirmation, the diagnosis of LNB can sometimes be less than straightforward. The diagnosis is sometimes considered in patients with multiple sclerosis,<sup>73,74</sup> although Lyme disease rarely presents with evidence of focal CNS damage, or a clearly abnormal MRI;<sup>75</sup> non-specific small white-matter abnormalities on brain MRI can be seen in a few patients<sup>76</sup> and there is a report of gadolinium-enhanced cranial nerves in a patient with European LNB.<sup>77</sup> Sometimes, an MRI brain scan in a patient with seropositivity can be abnormal because patients with multiple sclerosis can be seropositive from previous exposure to the spirochaete.<sup>78</sup> Fatigue, myalgia, and arthralgia can be major symptoms of any chronic infection, and occasionally LNB may be considered in patients with chronic fatigue syndrome<sup>79</sup> or fibromyalgia.<sup>80,81</sup> Fatigue, malaise, and headache were common symptoms of LNB in chronic LNB caused by *B afzelii* in a series reported by Strle and co-workers.<sup>54</sup> These patients had milder CSF abnormalities than those with LNB caused by *B garinii*.

Active encephalitis in LNB is highly unusual, but encephalopathy has been reported.<sup>82–85</sup> This encephalopathy, which is an uncommon manifestation of LNB, generally consists of symptoms of malaise and difficulties with concentration, sometimes with deficits of verbal memory, mental agility, and verbal functions; problem solving skills, mental speed, and visuospatial functions are commonly unimpaired.<sup>85</sup> Associated fatigue and arthralgias are common with the encephalopathy. This encephalopathy can also be seen in children.<sup>86</sup> The overlap with fibromyalgia is evident, although fibromyalgia with its disabling pain and trigger points can usually be differentiated from LNB. The encephalopathy has generally been seen in patients in whom the infection has proceeded for months to years without previous treatment. The pathogenesis is unclear, although the fact that about two-thirds of patients with it respond to 2 weeks of intravenous antibiotics indicates that it may be secondary to persistent infection.

#### Therapy

The natural history and ultimate prognosis of untreated LNB is unknown, but in many patients the infection can probably resolve without antibiotics. However, antibiotics are given to hasten clearance of the infection, speed resolution of symptoms, and prevent the development of late manifestations of the disease such as arthritis and acrodermatitis chronica atrophicans. The antibiotic treatment of choice for LNB in the USA at this time is an intravenous cephalosporin,<sup>87</sup> such as ceftriaxone, or penicillin for 2–4 weeks. In the first study of antibiotic therapy for Lyme neuroborreliosis, it was found that penicillin G, 20 million units/day in divided doses for

10 days was successful.<sup>88</sup> Others have used ceftriaxone, which is thought to be better in view of its long half-life, resulting in maintenance of high concentrations in serum for a longer period of time, and its ability to penetrate the blood–brain barrier readily and maintain high CSF concentrations.<sup>89</sup> The dose of ceftriaxone is generally intravenous or intramuscular 1–2 g twice a day for 14–28 days.<sup>13,90,91</sup> In a large European study, oral doxycycline was as effective as intravenous antibiotics in treating LNB. The dose of doxycycline used was 200 mg orally daily for 14 days.<sup>92,93</sup> Thus, oral therapy is a reasonable alternative to intravenous agents in neurological involvement in this infection.<sup>91</sup> Therapy is highly successful, and residual symptoms after therapy have been found predominantly in patients who had irreversible damage to the facial nerve or nerve roots before therapy.<sup>94</sup> However, treatment failures have been seen in response to both doxycycline and ceftriaxone therapy and it is reasonable to try additional therapy with an alternative antibiotic under those circumstances.

Lyme disease is a highly inflammatory disease in many cases. In fact one of the mysteries of the infection is how a few spirochaetes are able to provoke such intense inflammation. Some of the symptoms are secondary to the inflammation induced by the spirochaete, not by the spirochaete load. Thus, effective therapy includes minimisation of inflammation as well as eradication of infection. In our experience, non-steroidal anti-inflammatory drugs can be effective in improving symptoms of arthralgias, myalgias, and headache in selected patients with active symptoms of LNB. Because LNB responds relatively quickly to antibiotics, the need, if there is one, for non-steroidal anti-inflammatory drugs is usually for short periods.

Corticosteroids have been used by some clinicians to treat inflammatory syndromes in Lyme disease.<sup>15</sup> Corticosteroids may interfere with immune-mediated killing of spirochaetes, and thus should not be given unless a patient has undergone an adequate period of antibiotics to control the infection. Corticosteroids may be indicated in a small subset of patients who have inflammatory syndromes that persist after antibiotics and do not respond to non-steroidal anti-inflammatory drugs,<sup>95</sup> but they are not considered standard therapy in patients with Lyme borreliosis.

Neurologists might occasionally be faced with idiopathic facial palsies for which they are considering corticosteroid therapy, but there is a possibility that the facial palsy may be due to infection with *B burgdorferi*. For such patients, a positive Lyme serology or history of erythema migrans will tip the scales towards LNB. Alternatively, absence of exposure in an endemic area, or presentation after months of winter weather will suggest Bell's palsy, because *B burgdorferi* infection is rare in the winter months. In those situations in which differentiation is difficult, neurologists have many options for both diagnosis and therapy. Obtaining a Lyme antibody assay is definitely indicated,

because if Lyme disease is present, it should be treated. If the results of the Lyme antibody assay are negative, it should be repeated after 2–4 weeks, because facial palsy can be an early manifestation of infection before seroconversion; neurologists should also be aware that if steroid treatment for Lyme disease is chosen, it can delay seroconversion during infection. The therapeutic decisions are even further complicated by the facts that antibiotics do not affect the natural history of the facial palsy in LNB but do prevent late manifestations such as arthritis,<sup>96</sup> that corticosteroids are not universally accepted as being effective therapy in Bell's palsy, and that steroids increase spirochaetal load in the rhesus macaque model of LNB.<sup>22</sup> These considerations dictate that therapeutic decisions on patients with facial palsy need to be made on a case-by-case basis.

### Post-Lyme disease syndrome

Most patients with LNB who received adequate antibiotic therapy will have a prompt recovery, with complete resolution of symptoms within a few weeks to months. However, some patients continue to have prolonged symptoms such as fatigue, myalgias, arthralgias, low-grade cognitive difficulties, and sleep problems despite therapy,<sup>97</sup> and these patients are sometimes diagnosed as having post-Lyme disease<sup>98</sup> and may come to the attention of neurologists. The pathogenesis of post-Lyme disease is unknown, but could be due to persistence of the spirochaete after antibiotics, a situation that has been documented, using PCR but not culture, in some animal models.<sup>99,100</sup> However, the results of two careful clinical trials have provided strong evidence against this possibility in human beings.<sup>101</sup> Alternatively, symptoms may be due to the lack of complete clearance of *Borrelia* glycolipids that are highly inflammatory.<sup>102–104</sup> The optimum pathogenesis and management of post-Lyme syndrome remain controversial, although most clinicians treat it symptomatically; fortunately, it is uncommon.

### CXCL13—a new biomarker for LNB

Given the absence of direct diagnosis of pathogen in the CSF either by PCR or culture, and the vagaries of serological measures, it would be ideal to have a biomarker for the disease. In 2002, we reported that the chemokine CXCL13 was highly expressed in the tissue of infected rhesus macaques and that CXCL13 correlated well with the presence of spirochaetes.<sup>28,105</sup> We subsequently showed that this was probably related to direct spirochaete stimulation of dendritic cells.<sup>106</sup> Rupprecht and co-workers<sup>107,108</sup> then described the presence of CXCL13 in the CSF of all patients with Bannwarth's syndrome and its absence in all patients with other diagnoses. Chemokines are signalling molecules for leucocyte migration, and CXCL13 is primarily a B-cell-tropic molecule.<sup>109</sup> The findings are consistent with the fact that the humoral component of the immune response is primarily involved in spirochaete killing.<sup>110</sup>

### Host evasion and complement inhibition

The inability of murine antibodies to clear the spirochaete is probably due to active mechanisms of immune evasion by the spirochaete, particularly the production of proteins that bind to and inactivate mouse complement, markedly decreasing the destructive capacity of antibodies against the spirochaete.<sup>111,112</sup> Molecules produced by pathogens that specifically target the immune system of the host to allow persistent infection are known as immunoevasins; complement inactivators are likely to be only one of several immunoevasins produced by *B burgdorferi*. Mice serve as a reservoir for the infection in the wild, so it is not surprising that such mechanisms exist to allow persistence at high levels. However, primates, such as human beings and rhesus macaques, are dead-end hosts for *B burgdorferi* (ie, they do not transmit the infection to ticks). Hence, most *Borrelia* strains generally do not have mechanisms to evade primate complement, and infection results in rapid rises in antibodies for the spirochaetes, with unimpeded complement activity and clearance of the spirochaete in most animals without the necessity for antibiotics.<sup>27,113,114</sup> Some *B garinii* strains may represent exceptions to this rule; a recent study<sup>115</sup> documented that neuroinvasive *B garinii* strains express complement factor H-binding proteins.

### Improvement in diagnosis using serology—the C6 assay

Although the two-step technique of ELISA followed by western blot has been very successful in assisting neurologists in the diagnosis of LNB, a one-step, less expensive technique, would be preferred. Recent studies<sup>116,117</sup> have confirmed that a new technique, called the C6 ELISA, is a promising candidate to replace the two-step testing. This ELISA takes advantage of the conserved sequence of this protein and its nearly universal expression. C6 is a portion of the vls (variable major protein-like sequence) E locus of *B burgdorferi*,<sup>118</sup> which encodes an antigenic variation system that is related to the VMP system of relapsing fever borreliae,<sup>119,120</sup> and uses a combinatorial strategy of gene cassettes. The assay remains experimental and should not be used as a replacement for the two-step technique; studies are ongoing.

### Conclusion

Great strides have been made over the past two decades in understanding LNB since its first description almost

30 years ago as a manifestation of disseminated Lyme disease<sup>3</sup> and since its first description as a clinical entity 85 years ago.<sup>50</sup> The pathogenesis is to a great degree understood, the diagnosis has become straightforward with potentially improved diagnostic assays on the horizon, biomarkers with great promise are being developed, therapy has been defined, and the prognosis of the treated infection well-characterised. Given its lack of a distinctive and unique clinical presentation, neurologists can occasionally find recognition of this infection difficult, but should be confident in the currently available diagnostic assays and antibiotics.

#### Contributions

ARP was responsible for the literature search and for writing most sections of the Review. IS was responsible for writing some sections and editing the Review.

#### Conflicts of interest

We have no conflicts of interest.

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#### Search strategy and selection criteria

References were identified through searches of PubMed from January 1975 to March 2007 with the terms “Lyme”, “neuroborreliosis”, “brain”, “spinal cord”, “nerve”, “radiculopathy”, “encephalopathy”, “Borrelia”, “CSF”, “therapy”, and “facial” and through searches of the authors’ own files. Only papers written in English were reviewed.

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