Nervous system Lyme disease

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This review is based on a presentation given by Professor Halperin at the RCPE Infectious Diseases Symposium on 11 June 2010.

ABSTRACT Lyme disease, the multi-system infection caused by the tick-borne spirochaete Borrelia burgdorferi, can involve the nervous system, most commonly causing, alone or in combination, lymphocytic meningitis or abnormalities of cranial or peripheral nerves, the latter most typically presenting as a painful radicular syndrome. Diagnosis is based on appropriately used, standard serological tests; in instances where the central nervous system is involved, cerebrospinal fluid assessment for organism-specific antibodies can be useful. Treatment with any of several standard regimens of oral or parenteral antimicrobials is highly effective. Prolonged treatment beyond four weeks is rarely if ever warranted, and carries significant risk.

KEYWORDS Borrelia burgdorferi, diagnosis, Garin-Bujadoux-Bannwarth syndrome, Lyme disease, neuroborreliosis, treatment

DECLARATION OF INTERESTS No conflict of interests declared.

BACKGROUND

Although much has been learned about Lyme disease in the century since its typical cutaneous manifestation, erythema migrans, was first described,1 this multisystem infection by the tick-borne spirochaete Borrelia burgdorferi continues to be the source of spirited debate. The classic neurological picture has been recognised for almost 90 years.2 The responsible organism was identified three decades ago.3,4 Reliable diagnostic testing is available, and straightforward treatment regimens have been shown to be effective.4,5 Despite this, some continue to portray this infection as a great unknown, suggesting a role for it in a broad range of disorders – a role often neither supported by compelling evidence nor even biologically plausible. Many factors contribute to this paradox; most important is probably a fundamental misunderstanding of the nature of neurological disease in general and the neurological manifestations of this infection in particular.

To understand both the debate and the reality, it is helpful to appreciate the two key elements of this ‘controversy’ – first, the pathophysiology, diagnosis and treatment of Lyme disease and, second, what actually constitutes neurological disease. Sadly, neurological disease is simultaneously terrifying to patients and discomfiting if not intimidating to many practitioners. When clinicians mistakenly attribute non-specific symptoms to a brain infection, which in turn is believed by many to be difficult to treat, the stage is set for desperate patients to seek inappropriate treatment – the essence of the current unfortunate ‘debate’.

AETIOLOGY

The term ‘Lyme disease’ was coined in the 1970s when two mothers in Lyme, Connecticut, recognised that an inordinate number of children in their rural area were being diagnosed with juvenile rheumatoid arthritis.7 The resulting investigation by Steere and his colleagues led to the conclusion that this was a tick-borne infection, initially named Lyme arthritis, then, as its more disseminated elements were recognised, Lyme disease. This work ultimately led to the identification of the causative spirochaete, B. burgdorferi, first in ticks, then in humans.8,9

The characteristic rash, erythema migrans, was actually first reported in Scandinavia in 1910; the typical neurological triad was described in 1922 at which time the authors even conjectured it was due to a spirochaetal infection. By the 1940s it was recognised that patients could have rheumatological symptoms,10 and by the 1950s penicillin was known to provide effective treatment.11 European work in the 1970s and 1980s ultimately led to the characterisation of the causative spirochaetes.4

Subsequent extensive microbiological work led to the identification of four strains of what has come to be known as B. burgdorferi sensu lato: B. burgdorferi sensu stricto, B. afzelii, B. garinii and, most recently, B. spielmanii. Sensu stricto is the only strain identified in North America; all four occur in Europe, although B. garinii and B. afzelii predominate. Many argue that clinical phenomenology varies substantially between Europe and the US, attributing this to strain differences. Neglected in this discussion is the fact that, as a systemic
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disease, this infection was initially treated for years primarily by neurologists in Europe and rheumatologists in the US – leading to substantial potential for ascertainment bias in the clinical disorders identified with this infection.

Infection is transmitted virtually exclusively by the bites of hard-shelled Ixodes ticks – Ixodes scapularis and I. pacificus in the US, I. ricinus in Europe, I. persulcatus elsewhere. Although Borrelia have been identified in other blood-feeding arthropods, transmission of this zoonosis requires the specific feeding cycle of these ticks. Ixodes larvae hatch uninfected and feed once. If there is an available reservoir of infected hosts – most often field mice – and the tick feeds on one, the tick can become infected. Following this blood meal, the larva matures into a nymph. An infected nymph, the size of a full stop on a printed page, can then feed on a second host, potentially transmitting infection.

Transmission is not instantaneous. Both initially during attachment and subsequently during its several days of feeding, the tick injects local anaesthetics, anticoagulants and other compounds to allow it to feed undisturbed. Arrival of the host’s blood in the tick gut triggers spirochaete proliferation, then migration throughout the tick, including to its salivary glands, from which spirochaetes can be injected into this second host. This process requires 24–48 hours or more; hence only bites of more than a day or two’s duration pose a significant risk of infection.

During feeding, ticks become visibly larger and engorged with blood. This provides a useful measure of risk of infection – if a removed tick is tiny and contains minimal blood, the risk of infection is virtually non-existent. If it is engorged from prolonged feeding, risk is increased – though still relatively small. A recent meta-analysis suggests that treating tick bites – in high-risk areas – with a single dose of doxycycline may be beneficial, although individual studies have indicated that the risk of infection is quite low, that when infection occurs treatment response is essentially 100% and that the risk of antibiotic side effects approximates the risk of treatment response is essentially 100% and that the risk of antibiotic side effects approximates the risk of becoming infected and requiring treatment.

After its second meal, the tick matures into the larger adult. These too can transmit infection. However, their larger size makes them more noticeable and less of a risk since they can be noticed earlier in their feeding and removed. The adults tend to overwinter on large furry animals such as sheep (Europe), deer or bears (US), leading to the ticks’ popular names.

Transmission to humans occurs when people enter endemic areas where Ixodes ticks, reservoir hosts and B. borrelia all co-localise – a co-occurrence found only in specific environments, strongly influenced by local soil type, vegetation and climate. Even when ecological conditions permit the coexistence of ticks, Borrelia and reservoir hosts, an endemic focus can only exist when all three have been successfully introduced. Because ticks travel only short distances by themselves and field mice travel only slightly more, there is substantial variability in the proportion of ticks carrying B. burgdorferi, even in geographically adjacent areas. Expansion of endemic areas, such as has been noted in recent years, probably occurs primarily when larger hosts – birds, dogs, cats, raccoons, etc. – carry infected ticks to new areas. If the new areas are capable of supporting all elements of this zoonosis, a new endemic focus can be established. Some of the recent expansion of Lyme-endemic areas may have been facilitated by climate change, transforming areas previously too cold for the interacting life cycles into more hospitable environments.

If a sufficient number of spirochaetes is injected they will multiply at the site of the bite, then gradually migrate centripetally. This leads to an enlarging erythromel – erythema migrans (EM). Typically round to oval, often with concentric rings as the inflammatory response to the spirochaetes subsides more centrally just as it is flaring up more peripherally, the defining characteristics of this rash are its large size (typically >5 cm in diameter) and the fact that it enlarges day by day and persists for many days or weeks. The rash is often remarkably asymptomatic (reminiscent of the painless chancre of its cousin spirochaete, syphilis). Patients often have systemic symptoms reflecting the presence of a systemic bacterial infection. In the US, up to 15% or more of patients develop multifocal EM. Each secondary focus represents a nidus of spirochaetes that has metastasised from the primary site, lodged in the skin, and then gradually recapitulated the initial outward migration. This is one manifestation that appears to be less common in European patients.

The reported proportion of infected patients who develop EM varies widely. In children, whose parents are presumably more likely to observe the rash than patients themselves (particularly if in a difficult-to-see location), EM is thought to occur in about 90% of infected individuals.

In theory the systemic dissemination of spirochaetes could involve any part of the body. However, in humans infection primarily involves three extra-cutaneous organ systems – the heart, most commonly causing otherwise unexplained conduction block; the joints, causing arthralgias or, typically much later in infection, frank arthritis; and the nervous system.

Studies using polymerase chain reaction (PCR) suggest the central nervous system can be seeded quite early and often; however, only 10–15% of patients ever develop symptomatic nervous system involvement. As will be detailed below, nervous system infection most
commonly consists of cranial neuropathy, painful radiculopathy or lymphocytic meningitis.

DIAGNOSIS

*Borrelia burgdorferi* is difficult – but not impossible – to grow in culture. Since the required medium, BSK II, is not routinely available in most laboratories, and since cultures must be incubated at lower than usual temperatures and must be monitored for several weeks because of the organism’s slow doubling time, microbiological-based diagnosis has been challenging at best. Even PCR-based detection has proven disappointing, probably because very few organisms are present in readily sampled fluids. As a result, much as in syphilis, diagnosis typically rests largely on demonstration of a targeted antibody response.

Just as in syphilis, at the onset, inspection of the cutaneous lesion provides definitive diagnosis. Like the chancre, EM contains innumerable spirochaetes; however, the rash is usually so characteristic that microbiological examination is generally unnecessary. Not surprisingly, since the rash occurs within days (typically <30 days) of initial inoculation of organisms, many patients with EM do not yet have a measurable antibody response. This is not due to any particular flaw in the immune system or the available test methodology but rather is the natural consequence of the time-consuming processes by which B cells are selected, multiply and mature into antibody-producing cells, ultimately producing appropriately targeted immunoglobulin G (IgG) antibodies.

Some early studies suggested that partially treated patients might not develop measurable peripheral blood antibody responses. This observation has been difficult to reproduce with more modern techniques and is now widely thought to have been an artefact of the then-available technology.

Laboratory testing begins with a screening test – most commonly an enzyme-linked immunosorbent assay (ELISA), a measure of the total amount of antibody present in the patient’s blood that binds to *B. burgdorferi*. If this is positive (three standard deviations above the mean of a control population) or borderline (between two and three standard deviations), a more specific test, the Western blot, is performed to identify the specific antigens (represented by bands on the blots) to which these antibodies bind. Importantly, since the criteria for interpreting Western blots were defined in individuals with positive or borderline ELISAs, blots are not informative – and should not be performed – in patients with negative ELISAs.

Western blot criteria differ in Europe and the US, largely because of the greater strain variability in Europe. In the US, statistical studies of large populations led to identification of three IgM bands (Table 1) present in many infected patients. Presence of two of the three in a patient with symptoms of early disease and a positive or borderline ELISA has near 100% specificity, but somewhat lower sensitivity. The IgM reactivity becomes irrelevant in individuals with symptoms of more than one to two months’ duration, as by then the IgG response should be measurable. Again, a statistical analysis led to the identification of ten bands; the presence of five of the ten in a patient with symptoms of early disease and a positive or borderline ELISA indicates the presence of Lyme disease with near 100% specificity and very high sensitivity.

In Europe, the approach has been to look for a smaller number of bands, each of which is thought to be quite specific to *B. burgdorferi sensu lato*. The presence of several of these in a seropositive patient provides compelling diagnostic confirmation (Table 1). In both the US and Europe, a newer assay for the C6 peptide (VlsE) has drawn increasing attention. Although not perfect, the results of this single-peptide ELISA appear to compare favourably in sensitivity and specificity to the two-tier approach.

There are several key limitations to serological diagnosis. Not only does it take time for a directed immune response to become measurable, but, once developed, it persists long after successful eradication of the inciting cause – hence the ELISA does not provide a meaningful measure of disease activity or of treatment response.

One of the biggest challenges concerns the concept of any test’s positive predictive value. In any test a value will differ from the mean by three standard deviations approximately 0.1% of the time. In the US, with approximately 30,000 confirmed cases per year, sampling the entire population would produce 30,000 true positives.

### Table 1 Western blot criteria for confirmation of positive or borderline ELISA in Lyme disease

<table>
<thead>
<tr>
<th>Region</th>
<th>IgM</th>
<th>IgG</th>
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<tbody>
<tr>
<td>US</td>
<td>At least two of (41, 39, 23)</td>
<td>At least five of (93, 66, 58, 45, 41, 39, 30, 28, 23, 18)</td>
</tr>
<tr>
<td>Germany</td>
<td>B. afzelii at least one of (39, OspC, &amp; 17), or strong 41 B. garinii at least one of (39, OspC) or strong 41</td>
<td>B. afzelii at least two of (83/100, 58, 43, 39, 30, OspC, 21, 17, 14) B. garinii at least one of (83/100, 39, 30, OspC, 21, 17)</td>
</tr>
<tr>
<td>Most other European countries</td>
<td>At least two of (11, 22 [OspC], 39, 41, B. garinii OspC)</td>
<td>At least three of (14, 17, 22 [OspC], 39, 43, 58, 100, B. garinii OspC, BbVlsE)</td>
</tr>
</tbody>
</table>

Bands bolded felt to be particularly important in Germany.

*These patterns are specific for Trinity Biotech MarDx blot kits, widely used in Europe. Criteria differ with different kits in different countries; sensitivity and specificity vary among kits and depend on the specific criteria selected (personal communication, S O’Connell).*
but approximately 300,000 false positives! Without a reasonable a priori likelihood of the disease, the ELISA is ten times as likely to be misleading as helpful. For this reason, testing should only be performed in a clinically appropriate setting. Specifically, there should be a reasonable likelihood of exposure to infected *Ixodes* ticks, and symptoms should be within the realm of disorders reasonably attributed to this infection.

**WHAT IS NERVOUS SYSTEM DISEASE?**

Virtually all the controversy surrounding the diagnosis of Lyme disease stems from one fundamental misconception: that a broad range of symptoms that, in fact, reflect either behavioural phenomena or physiological (i.e. non-structural) changes in brain function are indicative of nervous system infection. Many patients with chronic illnesses develop depression – this does not mean that depression is caused by brain damage from that chronic illness. Epidemiologic studies have not shown depression to be more common in patients with Lyme disease than in any other chronic illness.27,28 Conversely, Lyme disease does not occur more frequently than expected by chance in any specific psychiatric disorder.29,30

Individuals with many inflammatory states – pneumonia, urinary tract infections, inflammatory bowel disease, lupus – describe fatigue, memory difficulty and difficulty concentrating – yet nobody would suggest these disorders are causing brain damage. This notwithstanding, some have suggested that symptoms of fatigue, difficulty concentrating, depression and so on, are themselves sufficient to make the diagnosis of Lyme disease. When such patients fail to respond to standard courses of antimicrobial therapy – regimens that are almost invariably curative in patients with even severe nervous system infections – the possibility of an incorrect diagnosis is discarded in favour of postulating ever more non-evidence-based hypotheses for persistent, resistant infection.

Changes in behaviour and function arise for one of three reasons – neurological disease, psychiatric disease and physiological changes impacting brain function but due to systemic disease. Neurological disease reflects alteration in the structure of the nervous system – be it focal, such as in stroke, trauma or Parkinson’s disease, or more diffuse, such as in meningitis, neuropathies or Alzheimer’s. No such structural abnormalities have yet been identified in psychiatric disease, disorders that likely reflect biochemical and physiological changes in brain function but are not caused by loss of specific neuronal populations. In contrast, in many systemic disorders – hepatic or renal insufficiency, systemic infections as common as the flu, other inflammatory disorders – patients often experience impaired concentration and cognitive function, yet have no demonstrable damage to the nervous system.

<table>
<thead>
<tr>
<th>TABLE 2 Neurological disorders in Lyme disease</th>
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</thead>
<tbody>
<tr>
<td><strong>Presumed process</strong></td>
</tr>
<tr>
<td><strong>Peripheral nervous system</strong></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
</tr>
<tr>
<td><strong>Diffuse neuro-inflammatory</strong></td>
</tr>
<tr>
<td>Lymphocytic meningitis</td>
</tr>
<tr>
<td><strong>Multifocal neuro-inflammatory</strong></td>
</tr>
<tr>
<td>Mononeuropathy multiplex</td>
</tr>
<tr>
<td>Myelitis (with radiculopathy)</td>
</tr>
<tr>
<td>Cranial neuropathy (5–10%)</td>
</tr>
<tr>
<td>Encephalitis (very rare)</td>
</tr>
<tr>
<td>Radiculopathy (3–5%)</td>
</tr>
<tr>
<td>Plexopathy (lumbo-sacral, brachial)</td>
</tr>
<tr>
<td>Confluent mononeuropathy multiplex</td>
</tr>
<tr>
<td><strong>Non-neurological inflammatory</strong></td>
</tr>
<tr>
<td>Encephalopathy (common)</td>
</tr>
</tbody>
</table>

This framework provides an appropriate context for a consideration of what constitutes nervous system Lyme disease (Table 2). The best-described disorders constitute the triad described initially in Europe by Garin and Bujadoux2 and then in the US by Reik21 and Pachner.22 Early in infection, patients develop lymphocytic meningitis, cranial neuritis and/or radiculonueitis. The lymphocytic meningitis is, by itself, largely indistinguishable from viral meningitis. Algorithms33,34 that have been proposed to differentiate the two are largely dependent on co-occurring phenomena, such as cranial nerve palsies.

Since Lyme disease results from the bites of ticks that are inactive in cold weather, the seasonal incidence of Lyme and of enteroviral meningitis are similar. Onset of headache and other systemic symptoms may be somewhat less acute in Lyme disease than in viral meningitis, with onset bringing patients to medical attention after several days, rather than hours. Severity of headache and other symptoms in Lyme neuroborreliosis is highly variable, with only a weak correlation with the degree of cerebrospinal fluid (CSF) pleocytosis. An examination of CSF shows a lymphocytic pleocytosis, with counts typically of no more than 100 or 200 cells/mm³. Protein is only modestly increased – typically no more than two to four times the upper limit of normal. Glucose is normal to minimally decreased. Somewhat unusual is a rather striking B cell predominance in the CSF. In both Lyme disease and syphilis there is an unusually prominent and early increase in CSF concentration of CXCL1335 – a chemokine that is a very strong B cell attractant; the concentration of CSF B cells in these two spirochaetal infections is higher than in just about any other disorder. Presumably reflective of the disproportionate elevation in B cells, many patients – particularly those symptomatic more than a few weeks – will have evident excess total IgG synthesis in the CSF.
and even oligoclonal bands. (This is reported more frequently in patients in Europe than in the US.)

The most common manifestation of nervous system infection in both Europe and the US is cranial nerve involvement – most often facial nerve palsy, which is reported in 5–8% of early, untreated patients. The disorder itself is indistinguishable from Bell’s palsy in other circumstances except that in Lyme disease it can be bilateral in up to 20–25% of affected individuals. Bilateral involvement occurs infrequently otherwise (occurring in sarcoidosis, Guillain-Barré syndrome and human immunodeficiency virus infection). Similarly, idiopathic Bell’s palsy is otherwise quite uncommon in young children. It is important to consider this treatable cause of facial nerve palsy in appropriate contexts, but it is also important to realise that neuroborreliosis accounts for only about 25% of summertime facial nerve palsies in hyperendemic areas.34

Although many patients with Lyme-associated facial nerve palsies have co-occurring meningitis, others do not. Clinical and neurophysiologic evidence suggests that nerve involvement occurs in the peripheral portion of the nerve, not as a result of the meningitis, but rather due to a mononeuropathy multiplex.17,18

Although 80% of Lyme-associated cranial nerve palsies affect the facial nerve, others can be involved. Involvement of nerves to the extra-ocular muscles (III, IV, VI) can cause diplopia. Involvement of the Vth nerve can cause hypeaesthesia or pain; VIIIth nerve involvement can result in hearing changes or vertigo. Optic nerve involvement (II; actually part of the central nervous system) occurs rarely if ever.37 Individual case reports describe lower cranial nerve deficits (IX to XII).38

The most commonly misdiagnosed disorder is what has been termed ‘radiculoneuropathy’, which probably occurs in up to 4–5% of untreated infected individuals. Patients typically have symptoms indistinguishable from a mechanical radiculopathy, such as that caused by an acute disc herniation. Pain is dermatomal in distribution, severe, and neuropathic in character – described as burning, stabbing, shock-like, debilitating and persistent. Pain can involve a limb or the trunk – the latter can be confused with a visceral process and patients are often extensively evaluated for intra-thoracic or intra-abdominal processes. In Europe, involvement is thought to occur most often in the limb that was the site of the tick bite, an association not described in the US. Although thought to be more common in European patients than in the US, the disorder is so under-recognised that it is very difficult to know its true incidence in either region.

As in Lyme-associated cranial neuropathies, patients with radiculopathy usually have an accompanying CSF pleocytosis. That notwithstanding, neurophysiological observations suggest that this radiculopathy, similarly, is actually part of a mononeuropathy multiplex.39 This pathophysiological construct is further reinforced by the observations that more typical mononeuropathies occur as well, as do brachial and lumbosacral plexopathies, suggesting a common mechanism for all forms of peripheral nerve involvement. Interestingly, all of these acute, localised forms of peripheral nerve involvement occur fairly early in infection (within months of initial infection). In patients who have had more longstanding infection (something seen only rarely in recent years) a more diffuse polyneuropathy can occur – with more typical signs and symptoms of distal sensorimotor loss.36,40 Neuro-physiological testing in these individuals again suggests that this represents a confluent mononeuropathy multiplex – the same underlying process but in more indolent form. Finally, the only good animal model of nervous system Lyme disease – the rhesus macaque monkey – is remarkable in that virtually all infected animals develop a mononeuropathy multiplex.41

In contrast to the peripheral nervous system, the central nervous system is involved – other than by meningitis – only rarely. A pseudotumour cerebri-like picture has been described in children. These children typically have had a CSF pleocytosis, an atypical finding in pseudotumour. However, the intracranial hypertension can lead to visual loss and must be managed, both with antimicrobials and with the same modalities used in idiopathic pseudotumour.

Particularly in Europe, patients with radicular symptoms not infrequently have spinal cord involvement at the affected level, with long track signs on examination and changes demonstrable on magnetic resonance imaging (MRI). Parenchymal brain involvement is extremely rare – estimated years ago to occur in about one patient per million population at risk per year.42 Now that patients are treated more aggressively early on, the incidence is undoubtedly even lower. These rare individuals develop focal neurological abnormalities, focal changes on brain MRI and inflammatory CSF. The process reflects a bacterial encephalitis and as such an inflammatory response in the CSF is virtually universal.

A useful technique in individuals with inflammatory CSF is measurement of local production of specific anti-B. burgdorferi antibodies in the CSF – referred to as intrathecal antibody production (ITAb).43–46 This approach is used in numerous other infections and can be performed by a number of different techniques. In all, the underlying principle is the determination of the proportion of immunoglobulin that is specific to the causative organism, comparing this proportion in CSF and serum. Since some IgG antibody crosses the blood–brain barrier, but infection leads to clonal proliferation of specific B cells in the CSF, patients with infection will have proportionally more specific immunoglobulin in the CSF. This determination requires measuring antibody in both CSF and blood and determining CSF positivity by showing proportionately more specific antibody in the CSF, not by comparing to normal values.
The technique is highly specific, with cross-reactions occurring only in other spirochaetal infections, specifically neurospirophils. However, since patients with neurospirophils almost always have anti-reaginic antibodies (VDRL, RPR) these two infections are usually readily differentiated. The greater challenge is that apparent ITAb synthesis has been demonstrated to persist as long as 10 years after curative therapy. The other issue is that, although this approach is highly specific, sensitivity is difficult to ascertain in the absence of a gold standard diagnostic test. Estimates range from 50–95%. The one setting in which sensitivity should approach 100% is patients with otherwise demonstrable intrathecal excess immunoglobulin production – patients with focal abnormalities on MRIs and increased IgG synthesis overall or oligoclonal bands. In such individuals, if the immune stimulation is due to a specific infection, the excess antibody that is present should be largely specific to the inciting organism.

The final entity to consider is ‘Lyme encephalopathy’. Originally described in patients with longstanding active Lyme arthritis,47 this consisted of perceived cognitive slowing, memory difficulty and difficulty concentrating in the context of chronic inflammatory symptoms. Most of these patients had nothing to suggest central nervous system (CNS) inflammation – with normal CSF; MRI scans and non-focal neurological examinations. In many, formal neuropsychological examinations confirmed the patients’ difficulties. Importantly, the concept was never that this disorder was unique to Lyme disease but rather that it was a particular example of the commonly observed ‘toxic metabolic’ encephalopathy seen in many inflammatory states – a model that might prove useful in learning about the pathophysiology of this very frequent phenomenon. Interpretation of this observation is further confounded by the fact that at any given time, a sizeable proportion of the general population experiences similar symptoms in the absence of any medical diagnosis – and these symptoms are significantly disabling in as many as 2% of the population.48

Unfortunately, some have concluded that the presence of this type of encephalopathy can lead to the ‘clinical diagnosis’ of Lyme disease – even in the absence of likely exposure to ticks, more typical signs or symptoms or positive laboratory tests. In fact, these symptoms warrant neither a diagnosis of Lyme disease nor a diagnosis of any neurological disorder.

Despite normal brain MRI scans in most of these patients, some have used single photon emission computed tomography (SPECT) scanning in an effort to demonstrate abnormalities, and in turn have used SPECT evidence of regional brain hypometabolism as confirmatory evidence of Lyme disease.49 Unfortunately, SPECT scanning is not particularly reliable or specific, making such an approach highly questionable. In fact, studies using positron emission tomography (PET) scans, a more reliable measure of brain metabolism, show that areas of Lyme encephalitis are actually hyper-metabolic, a more plausible observation given the hypercellular inflammatory infiltrates in involved areas.50 Although the mechanism of this encephalopathy – in Lyme or in other disorders – remains to be determined, several interesting observations may be relevant. A reasonable supposition would be that one or more soluble factors exist peripherally as part of the inflammatory response, are able to cross the blood–brain barrier, and then affect nervous system function. One such candidate molecule has been identified – quinolinic acid – which has been shown to be present in the serum and CSF of patients with a number of infectious disorders,51,52 including Lyme disease. What makes this molecule of particular interest is that it is known to activate the N-methyl-D-aspartic acid (NMDA) receptor in the brain. The activation of this receptor can not only affect behaviour but, if excessive, can lead to neuronal death.

**TABLE 3 Nervous system Lyme disease: treatment recommendations**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute neuroborreliosis (meningitis, radiculitis, cranial neuritis)</td>
<td>Ceftriaxone= 2 g/day IV; 2–4 wk or</td>
<td>75–100 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Cefotaxime 2 g 8-hourly IV; 2–4 wk or</td>
<td>150–200 mg/ kg/day in 3–4 divided doses</td>
</tr>
<tr>
<td></td>
<td>Penicillin, 20–24 million units IV/day; 2–4 wk or</td>
<td>300,000 units/ kg/day</td>
</tr>
<tr>
<td></td>
<td>Probably doxycycline= 100 mg PO b.i.d. to q.i.d. for 3–4 wk</td>
<td>≥8 yr 1–2 mg/kg b.i.d.</td>
</tr>
<tr>
<td></td>
<td>Possible alternatives: Amoxicillin 500 mg PO t.i.d.: 21 days or</td>
<td>50 mg/kg/day in 3 divided doses</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime axetil 500 mg PO b.i.d.: 21 days or</td>
<td>150–200 mg/ kg/day in 3–4 divided doses</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>Ceftriaxone= or cefotaxime or penicillin IV as above</td>
<td></td>
</tr>
<tr>
<td>Chronic or recurrent neuroborreliosis (e.g. treatment failure after 2 wk of treatment)</td>
<td>Ceftriaxone= or cefotaxime IV as above</td>
<td></td>
</tr>
</tbody>
</table>

* Ceftriaxone should not be used late in pregnancy.
† Doxycycline should not be used in pregnant women or children under the age of eight years.

**TREATMENT**

Although some have focused on groups of patients who do not respond to standard treatment regimens, in the vast majority of cases this is likely due to inaccurate diagnosis. *Borrelia burgdorferi* is quite sensitive to beta-lactams and tetracyclines; no meaningful antimicrobial
resistance has been observed.\textsuperscript{1} Treatment of early disease with simple oral regimens is highly effective.\textsuperscript{2,3} There is excellent evidence that, at least with European strains of \textit{Borrelia}, oral doxycycline is as effective as high-dose intravenous beta-lactams for Lyme meningitis, cranial neuritis and radiculoneuropathy.\textsuperscript{4,5} This is untested in the US, so parenteral treatment of such patients is commonplace but probably unnecessary. In those rare patients with demonstrable parenchymal involvement of the brain or spinal cord, intravenous regimens are appropriate, as they are in those uncommon patients who do not respond to oral regimens.

Currently recommended regimens are summarised in Table 3; although these were questioned by some, a recent review by an independent panel established by the Infectious Diseases Society of America confirmed that the evidence supporting these regimens is excellent and compelling.\textsuperscript{5} Similarly, the review committee reaffirmed the evidence-based consensus that prolonged antibiotic treatment beyond four weeks was generally of no benefit and potentially harmful.

\textbf{PATHOPHYSIOLOGY}

Although a great deal is known about this infection and the host response to it, the fundamental processes underlying nervous system involvement remain unclear.\textsuperscript{6} Plausible mechanisms include active infiltration with spirochaetes, deposition of spirochaetal antigens with an inflammatory response, ‘molecular mimicry’ with a molecular similarity between spirochaete and host antigens resulting in a misdirected host immune response, and an exaggerated host response to the spirochaete.

At the most basic level, ongoing infection appears essential, as all peripheral and central nervous system manifestations respond – although not instantaneously – to antimicrobial therapy. This same observation would seem to argue against molecular mimicry, since such a persistent immune response would presumably continue even after removal of the precipitating micro-organism. Several observations provide additional useful insights. Polymerase chain reaction studies indicate that spirochaetes enter the CNS early and frequently, although this may only lead to ongoing nervous system infection in a subset of patients. The CSF concentration of CXCL13 climbs rapidly\textsuperscript{7} – before the serum concentration – indicating early immune activation resulting in a rapid and persisting proliferation of a B cell response in the nervous system. The frequent presence of CSF oligoclonal bands and persisting intrathecal antibody production speak to prominent and persisting stimulation of the humoral immune response within the CNS. Peripheral nerve from both infected patients and experimentally infected rhesus macaque monkeys\textsuperscript{8} demonstrates prominent perivascular inflammation without evidence of vasculitis (no vessel wall necrosis), spirochaetes, spirochaetal antigens or DNA, or immune complexes. \textit{Borrelia burgdorferi} bind to gangliosides and to glia, and can induce glial proliferation.\textsuperscript{9,10} The best synthesis suggests that a small number of spirochaetes lodge in the nervous system and elicit a vigorous inflammatory response that produces most of the end-organ effects but subsides after eradication of the infection.

\textbf{SUMMARY/FUTURE DIRECTIONS}

Although Lyme disease has taken on almost mythological proportions, it is clear that this is a largely straightforward bacterial infection. Readily available diagnostic tools are as accurate as those used in most other illnesses, and straightforward therapeutic regimens are highly effective, even in most cases in which the nervous system is involved. Future research will need to focus on a better understanding of the pathophysiological mechanisms responsible for nervous system involvement – both to inform new therapeutic strategies in this infection and hopefully to provide insights into mechanisms underlying neurological abnormalities in other inflammatory and infectious diseases.

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