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CENTRAL NERVOUS SYSTEM INFECTIONS (J LYONS, SECTION EDITOR)

Nervous System Lyme Disease

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Abstract Lyme disease, a multisystem spirochetal infection, continues to be the subject of considerable debate, but not controversy. Recent years have seen improvements in diagnostic tools, better understanding of pathophysiology, and increasing evidence of efficacy of standard treatment regimens. Nervous system involvement is particularly confusing to patients and many physicians. A rational approach based on objective findings can clarify the cause and dictate the best treatment of patients' difficulties. Diagnosis for all but the earliest cases rests on the combination of likely contact with infected *Ixodes* ticks and laboratory confirmation of exposure to the causative organism, *Borrelia burgdorferi* (two-tier serology, combining ELISA with a confirmatory Western blot). Treatment is generally with oral antimicrobials such as doxycycline. Parenteral regimens are usually necessary only for the most severe cases.

Keywords Lyme disease · *Borrelia burgdorferi* · Neuroborreliosis · Nervous system · Bannwarth syndrome · Treatment · Diagnosis

Introduction

How is it that Lyme disease, infection with the tick-borne spirochete *Borrelia burgdorferi*, can be described both as an easily treated bacterial infection and as causing symptoms "defying any answers that science has so far provided" [1]? Annually 30,000 patients in the USA meet the CDC Lyme disease case definition [2], but medical insurance claims and other data suggest 10 times that number are treated for this diagnosis [3]. Searching Amazon.com® for books about Lyme disease (August 2, 2014) yields 10,181 results, comparable to the total of 10,589 scholarly articles identified by PubMed! The contrast between the well-established medical facts about this illness and the public misconceptions, fears, and anger concerning the diagnosis is truly remarkable.

History

The term "Lyme arthritis" was coined in the 1970s to describe a disorder resembling juvenile rheumatoid arthritis, affecting a cluster of children living in the vicinity of Lyme and Old Lyme, CT [4]. A series of epidemiologic and microbiologic studies led to the conclusion that the illness was caused by a spirochete, subsequently named *B. burgdorferi sensu stricto*, transmitted exclusively by bites of hard-shelled *Ixodes* ticks [5, 6]—in this case *I. scapularis*, commonly referred to as the deer tick. Infected patients frequently had experienced an unusual rash, termed erythema migrans (EM; originally erythema chronica migrans (ECM)). It rapidly became apparent that the illness also frequently affected the nervous system [7] and occasionally the cardiac conduction system. The recognition of this expanded spectrum of disease led both to a name change—to Lyme disease—and to the recognition that a closely related group of disorders had been recognized in Europe since early in the twentieth century [8, 9]. Identification of the causative microorganism rapidly led to the development of diagnostic tests and the introduction of effective antimicrobial treatment [10].

In Europe, the initial focus had been on the rash, first described in 1910 [8], then on nervous system manifestations. Although the responsible organism was not identified until

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1984 [11], the 1922 description of nervous system manifestations [9] actually hypothesized that this was a spirochetal infection; European physicians began treating the illness successfully with antibiotics in the 1950s [12].

Several aspects of this history shed some light on the current debate and atmosphere. The original recognition of the outbreak in Lyme, CT, was triggered by concerned parents who, overriding their own physicians' advice, reached out to the CDC and Yale, urging more detailed study to explain what was happening to their children. The causative organism was identified, and diagnostic tests developed, almost a decade after the disease was first characterized; until serologic testing became available, diagnosis was based on clinical phenomenology. This, coupled with some inherent limitations of serologic diagnosis, fostered the notion that the diagnosis of Lyme disease is "a clinical diagnosis," based solely on clinical observations, with laboratory support being ancillary at best. This in turn was taken as "carte blanche" by some clinicians to define the spectrum of the disease to include whatever they wished. Finally, the fact that the emphasis in the USA was initially on rheumatologic manifestations, while in Europe this was largely seen as a nervous system infection, led to the assumption that the European and US disorders were quite different, limiting the transfer of insights gained in one group of patients to the other. Early efforts to broaden the understanding of the impact of this illness on the nervous system in US patients were broadly misunderstood, probably reflecting a more widespread misunderstanding of what is, and is not, nervous system disease generally. All of these areas of misunderstanding collectively conspired to create the current debate.

Microbiology

Lyme disease in the USA, and the related disorders in Europe and elsewhere, is caused by a group of closely related *Borrelia*, known collectively as *B. burgdorferi sensu lato*. *B. burgdorferi sensu stricto* is responsible for essentially all Lyme disease in the USA, but a small minority of European cases. *B. garinii* and *B. afzelii* are responsible for most European borreliosis, with the former causing the majority of cases of nervous system involvement [13]. Additional strains (*B. spielmanii* and others [14]) have been reported in smaller numbers of European cases. All strains are highly sensitive to penicillins and tetracyclines in vitro and in vivo.

Infection is transmitted exclusively by bites of *Ixodes* (hard-shelled) ticks. In temperate climates, these ticks have a 2-year, three-meal life cycle. Eggs hatch as uninfected larvae that then seek their first blood meal. If they feed on an infected host (typically a field mouse or other small animal), they may become infected. After feeding, the tick matures into a nymph; spirochetes remain in its gut until its next meal. Ingested host blood can then trigger spirochete proliferation in the tick; these spirochetes then migrate to the tick's salivary glands, from which they can be injected into this second host. Since nymphs are very small (about the size of a period on a printed page and therefore difficult to see) and quite numerous (all adults were nymphs but only a fraction of nymphs survive to become adults), they are the most common cause of human infection. This process—spirochete proliferation, migration, and injection into the new host—typically requires 24–48 h, so less prolonged tick attachment carries minimal risk of infecting the second host. Finally, the adult tick will have a final meal, again potentially infecting its host. This again requires at least a day of attachment. Since adults are both larger and less numerous than nymphs, they are less frequently responsible for human infection.

Diagnostic Testing

Because it is difficult to culture (or even detect with polymerase chain reaction-based approaches) *B. burgdorferi* from clinical material (except erythema migrans, where the appearance is so characteristic that laboratory testing is unneeded), laboratory confirmation of the diagnosis has relied on demonstration of the antibody response to the causative organism. Serologic testing in general has three inherent limitations. First, it takes time for antibodies to reach measurable concentrations in peripheral blood—in the case of Lyme disease, this may require 3 to 6 weeks after initial infection. Because of this, serologic testing is unhelpful—and unnecessary—in EM, where fewer than 50 % of patients may be seropositive [15]. Patients with the characteristic rash should simply be treated; there is no reason to wait for—or even request—laboratory confirmation. However, the delay in seropositivity can be problematic in less black and white circumstances, such as an at-risk patient with acute facial nerve paralysis, where occasional individuals only become seropositive after their initial neurological presentation [13, 16]. Here, the more traditional serologic approach comparing acute and convalescent serologies may be necessary.

Second, once a patient starts producing specific antibodies, seropositivity will typically persist, often long after the infection has resolved [17]. Because of this, serologies cannot be used as a marker of treatment efficacy. Treating until a patient becomes seronegative is unnecessary, illogical, and potentially harmful.

Finally, serologic testing is of varying specificity. Current Lyme ELISAs are optimized as screening tests—they have high sensitivity but somewhat limited specificity. For that reason, they should be performed as the first part of two-tier testing. If the ELISA is positive or borderline, a Western blot should then be performed. Based on statistical studies of large numbers of patients with and without Lyme disease, 10 IgG

bands (immunoreactivities to antigens of specific molecular weights) have been identified such that if a patient has measurable reactivity to any 5, there is a very high probability that they have—or have previously had—*B. burgdorferi* infection. Importantly, in the absence of a positive or borderline ELISA, a Western blot is usually uninformative—and should not be performed. Also importantly, although IgM criteria have also been defined (2 of 3 identified bands), this should only be used in patients with very early disease. Given the high degree of cross reactivity of IgM antibodies in general, and the lower inherent specificity of using only 2 instead of 5 bands, outside the acute setting, positive IgM blots are almost always false positives. In interpreting Western blots, it is important to understand that no bands individually have high predictive value for infection. The choice of bands was based on statistical analysis and not the uniqueness of the selected epitopes.

Recent efforts have focused on simplifying and enhancing serodiagnosis, particularly in European patients where the presence of multiple *B. burgdorferi* strains has made the development of broadly applicable Western blot criteria challenging. Detection of antibody to C6, the sixth invariable sequence within VlsE (Vmp-like sequence, expressed) protein, has proven useful, as this antigen appears to be common to multiple strains. Accuracy of C6-based assays appears to be comparable to that of two-tier testing for European patients [18]. Studies in US patients [19•] have shown that the C6 ELISA has substantially higher sensitivity than two-tier testing in patients with EM (66.5 vs. 35.2 %) and comparable sensitivity in early neurologic disease (88.6 vs. 77.3 %) with only a minimal loss of specificity (98.9 vs. 99.5 %). Studies are in progress to determine if the C6 assay could be used in US patients either to replace two-tier testing with a single test or to replace the confirmatory Western blot with a confirmatory C6 assay, eliminating issues due to misconceptions surrounding Western blot interpretation [20].

Improved test sensitivity and specificity do not resolve the important issue of the relevance of a positive result. The presence of antibodies to *B. burgdorferi* indicates exposure, past or present. An individual with an illness such as multiple sclerosis or amyotrophic lateral sclerosis may have been exposed to this infection prior to their neurologic illness. The positive serology does not establish a causal relationship, any more than it would in a victim of a car crash. How to interpret the result, and whether or not to treat, requires a careful weighing of all the risks and benefits. There may well be circumstances where alternative treatments are limited and a therapeutic trial of conventional anti-*B. burgdorferi* therapy may be indicated. However, since it is clear that standard courses of antimicrobial therapy will cure even severe central nervous system (CNS) infections with this organism, failure of this trial should be interpreted as evidence that this infection is not relevant, not as a rationale for indefinite antimicrobial therapy.

An additional tool is available in patients with suspected CNS infection. The CNS, separated from the circulation by the blood–brain barrier, behaves as a separate immunologic compartment. CNS infection leads to in-migration followed by local proliferation of B cells targeting the causative organisms; the resulting local production of specific antibodies can be quantitated to provide evidence of specific CNS infections. Several different methodologies are available to determine the presence of intrathecal production of specific antibody; all are conceptually similar. All require simultaneous measurement of both specific and total immunoglobulins in cerebrospinal fluid (CSF) and serum, measuring the amount of specific antibody in each, corrected for the overall immunoglobulin concentrations [21–23]. Just as with peripheral blood serologic testing, different antigens have been tried in assays in an effort to improve accuracy [24]. It appears that using purified native flagellum protein, vs. a combination of recombinant VlsE, outer surface protein C (OspC), and decorin-binding protein A, vs. a combination of multiple specific recombinant antigens all have comparable accuracy, although the third may have the greatest sensitivity, at least in European patients where strain variability makes serodiagnosis particularly challenging.

One of the major challenges with laboratory approaches in CNS infection is that apparent intrathecal antibody production has been shown to persist for up to a decade after presumed microbiologic cure [17]. Although the presence of active infection can usually be inferred by the degree of CSF pleocytosis and elevation of CSF protein, neither normalizes immediately after treatment. Since there is a prominent B cell response to this infection, there has been particular interest in measuring CXCL13, a B cell-attracting chemokine, which has been shown to be elevated in CSF in virtually all patients with neuroborreliosis [25, 26]. The hope is that this will provide a sensitive marker of active infection; however, its specificity remains to be determined [27].

Clinical Manifestations

Erythema migrans, the slowly expanding erythroderm that can reach many inches in diameter, occurs as spirochetes migrate centrifugally from the central site of the tick bite. This rash is reported to occur in as many as 90 % of infected children [28]. In adults, who may be less observant, particularly of areas of the body that are less readily visible, this is reported to occur in about 50 %. In patients infected with *B. burgdorferi sensu stricto*, as many as a quarter may develop multifocal EM, as spirochetes disseminate hematogenously, with secondary EMs occurring at the sites of remote spirochete deposition. Spirochete dissemination is typically associated with the usual symptoms of a bacteremia—fever aches, pains, headaches, malaise, and fatigue, often referred to as "flu-like" symptoms. Importantly, it is distinctly uncommon for patients with Lyme

disease to develop respiratory or GI symptoms as part of this flu-like disorder, the latter being more suggestive of a summer enteroviral infection.

Joint symptoms are common, particularly in US patients. In early disease, arthralgias are more common; in later disease, frank arthritis, as described in the original group of children, occurs relatively frequently. This typically affects large joints, usually one at a time, and tends to wax and wane over time, beginning several months after infection and continuing to cause symptoms for years. Arthritis usually resolves with appropriate treatment, but even without it, the frequency of attacks decreases over time [29].

It is important to be somewhat circumspect in considering nervous system disease in general and nervous system infections in particular. There are few disorders more terrifying to patients than neurodegenerative disease, and both patients and many nonneurologist physicians are very uncomfortable differentiating neurologic disease from other, more benign problems affecting cognitive function. As soon as the specter of brain disease is raised, patients' anxiety climbs substantially, creating a level of concern that can be extremely difficult to assuage or reverse [30•].

Nervous system involvement occurs in 10 to 15 % of patients, both in Europe and in the USA. The classic triad (syndrome of Garin-Bujadoux-Bannwarth [7, 9, 31, 32]) of lymphocytic meningitis, cranial neuritis, and radiculoneuritis remains the hallmark of this infection. Meningitis is variably symptomatic. Some patients with severe headaches have normal CSF; others with cranial neuropathy may have >50 white cells/mm^3 but no headache, photosensitivity, or meningismus. A pseudotumor-like picture can occur in children [33, 34]. Most affected children have had a CSF pleocytosis, indicating that this is actually intracranial hypertension due to an infection, an entity pathophysiologically distinct from pseudotumor. That notwithstanding, the clinical presentation is similar with headaches, visual obscuration, and papilledema. Patients are at risk of vision loss, and rapid treatment of both the infection and the raised intracranial pressure is paramount.

In a recent European study [13], patients presenting with EM and one or more of headache, vertigo, disturbances of sleep, memory or concentration disorders, radicular pain, paresthesias, neck stiffness, and peripheral facial palsy underwent lumbar puncture. Only 19 % had a CSF pleocytosis. Two thirds of patients with a CSF pleocytosis had either intrathecal antibody production or positive CSF borrelia cultures. Of those without a pleocytosis, <10 % had any findings to suggest CNS neuroborreliosis. Those patients who had a pleocytosis generally had clinical evidence of radiculitis, cranial neuritis, or meningitis. Patients with only nonspecific symptoms such as headaches, memory or concentration difficulty, or sleep disturbances did not have CSF findings indicative of CNS infection.

When considering nervous system Lyme disease, or neuroborreliosis, it is helpful to separate peripheral from central nervous system involvement. CNS Lyme disease primarily consists of meningitis. Very rare patients may have inflammation of the CNS parenchyma—most commonly in European patients with radiculitis who may have segmental spinal cord involvement at the same level. Very rarely, there may be parenchymal involvement of the brain itself [35, 36]. Patients with neuroborreliosis involving the meninges, brain, or spinal cord would be expected to have abnormal CSF. If duration is more than a few weeks, most would be expected to have evidence of intrathecal antibody (ITAb) production, as well. In fact, European consensus criteria require evidence of ITAb for the diagnosis of definite neuroborreliosis [37••].

Peripheral nervous system (PNS) involvement may co-occur with meningitis but often does not. There is good evidence that both cranial neuritis and radiculoneuritis actually represent more peripheral involvement of cranial or peripheral nerves [38], so CSF may well be normal. Cranial neuritis most commonly involves the seventh (facial) cranial nerve, presenting with acute facial paralysis. In about 25 % of these cases, this may be bilateral, Lyme disease being one of the few disorders (along with sarcoidosis, HIV, and Guillain–Barré syndrome) that causes a facial diplegia. The cranial nerves to the extraocular muscles are occasionally involved (causing diplopia), as are cranial nerves V and VIII, causing facial pain and numbness or hearing and balance difficulty. The optic nerve is very rarely involved [39]; there have only been scattered case reports of involvement of cranial nerves IX to XII.

Classically, radiculoneuritis involves acute, severe neuropathic pain, involving one or several dermatomes. There can be accompanying muscle weakness; physical findings correspond to the nerves involved. Until the diagnosis of Lyme neuroborreliosis is considered, symptoms are often assumed to be on the basis of a mechanical radiculopathy, as this is far more common. This entity can be particularly confusing when truncal dermatomes are involved, in which case patients are often extensively evaluated for visceral disease.

In these patients, both radiculoneuritis and cranial neuritis appear to be specific examples of a mononeuropathy multiplex—a disorder usually occurring in patients with vasculitic (e.g., polyarteritis) or vasculopathic (e.g., diabetes mellitus) disorders in which focal damage to nerves causes focal deficits. Other forms of mononeuropathy multiplex also occur in patients with PNS neuroborreliosis, including plexopathies, mononeuropathies, and confluent mononeuropathy multiplex, the last resembling a more disseminated polyneuropathy.

One area that has been a source of ongoing confusion—among both physicians and patients—is the disorder termed "Lyme encephalopathy" [30•]. As is well known in all of clinical medicine, patients who are ill often suffer from headaches, malaise, and cognitive, memory, and concentration

difficulties. As well shown by Ogrinc [13], these patients have neither abnormal CSF nor clinical evidence of CNS disease. Early efforts to understand the pathophysiology of this symptomatology in patients with Lyme disease [23, 40–42] led to the misperception that this was specific to Lyme disease and was evidence of CNS infection. The overwhelming evidence at this point is that both assertions are incorrect. This symptomatology occurs in myriad circumstances and in fact at any given time probably affects 2 % of the population [43] to a sufficient degree to impair daily activities. The mechanism is not clear, but it is clear that, in and of itself, this should not be construed to be diagnostic of Lyme disease or neurologic disease, nor should antibiotics be prescribed for it unless there is evidence of a specific infection.

The same misunderstanding has led to the concept of "chronic Lyme disease" or "post treatment Lyme disease syndrome." True chronic Lyme disease, long-standing infection with *B. burgdorferi*, occurs in the setting of prolonged untreated infection, something seen infrequently nowadays. The original cases of Lyme arthritis, the rare cases of Lyme encephalomyelitis described years ago, and acrodermatitis atrophicans, an unusual dermatologic manifestation seen only in Europe, are all examples of the results of long-standing untreated *Borrelia* infection. In contrast, there is no reason to conclude that patients with long-standing nonspecific symptoms, such as those experienced by 80 % of Ogrinc's patients, have chronic *B. burgdorferi* infection. This is not to say that these symptoms are not real or that they are not terribly disruptive to the patients' functioning, but rather that they cannot be attributed to ongoing *B. burgdorferi* infection.

The observation that this same nonspecific symptom complex occurs in some patients who have been treated appropriately for Lyme disease has led to the concept of post treatment Lyme disease syndrome. These symptoms are very common after many illnesses, infectious and noninfectious, and are of unclear etiology. The evidence is clear they do not respond to additional antibiotics [44•], and the few available studies indicate that this state is no more common in individuals with neuroborreliosis than in those with Lyme borreliosis not involving the nervous system [45], again reinforcing the notion that this is not due to nervous system damage or infection.

Treatment

Lyme disease remains highly responsive to antimicrobial therapy. Clinical guidelines now generally recommend oral treatment with amoxicillin, doxycycline or cefuroxime axetil, or related drugs, with the possible exception of patients with nervous system involvement [46, 47] (Table 1). Although it is clear that parenteral ceftriaxone, cefotaxime, and penicillin are all highly effective in all forms of this infection, it is becoming increasingly clear that these are unnecessary, at least as first-line therapy, for arthritis and many other extracutaneous manifestations. There is abundant evidence from European studies that oral doxycycline is effective in Lyme meningitis, cranial neuritis, and radiculoneuritis [47]. It is reasonable to assume—though unproven—that this is equally true in North American Lyme disease, as well as in patients with other forms of PNS Lyme disease. There has been considerable reluctance to use oral antibiotics in patients with parenchymal

Table 1 Nervous system Lyme disease: treatment recommendations [50]. Reproduced by permission of the JRCPE. Pediatric weight-based doses should never exceed the recommended adult dose

Disorder	Adults	Children
Acute neuroborreliosis (meningitis, radiculitis, cranial neuritis)	Ceftriaxone[a] 2 g/day IV, 2–4 weeks,	50–75 mg/kg/day
	or	
	cefotaxime 2 g q8 IV, 2–4 weeks,	150–200 mg/kg/day in 3–4 divided doses
	or	
	penicillin, 20–24 million units IV/day, 2–4 weeks,	300,000 units/kg/day
	or	
	Probably doxycycline[b] 100 mg PO b.i.d. to q.i.d. for 3–4 weeks	1–2 mg/kg b.i.d.
	Possible alternatives	
	Amoxicillin 500 mg PO t.i.d., 21 days,	50 mg/kg/day in 3 divided doses
	or	
	cefuroxime axetil 500 mg PO b.i.d., 21 days	30 mg/kg/day in 3–4 divided doses
Encephalomyelitis	Ceftriaxone[a] or cefotaxime or penicillin IV—as above	
Chronic or recurrent neuroborreliosis (e.g., treatment failure after 2 weeks of treatment)	Ceftriaxone[a] or cefotaxime IV as above	

[a] Ceftriaxone should not be used late in pregnancy

[b] Doxycycline should not be used in pregnant women or children under the age of 8 years

CNS neuroborreliosis. However, a recent European study suggests this may be effective in many instances [48•] and provides enough evidence of equipoise to warrant more detailed study [49].

Conclusion

Lyme disease remains a readily treatable spirochetal infection. Diagnosis requires a combination of plausible exposure to the only vector, clinical manifestations within the spectrum of disorders known to be attributable to this infection, and, in all but the earliest cases, serologic confirmation. Nervous system involvement is the source of great consternation among patients and physicians but is readily diagnosed, generally evident by virtue of objectively demonstrable neurologic abnormalities on examination or tests, and is generally treatable. CSF examination can provide helpful information in the small subset of patients thought to have central nervous system involvement. Treatment for most manifestations can be oral; a treatment course of no more than 4 weeks suffices in virtually all patients. Parenchymal brain or spinal cord involvement may require parenteral antibiotics, but even for these patients, there is some evidence that oral doxycycline may be sufficient.

Compliance with Ethics Guidelines

Conflict of Interest John Halperin has no conflicts of interest relevant to this work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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