NERVOUS SYSTEM LYME DISEASE

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Background

Lyme disease is a multisystem infectious disease[1] caused by the tick-borne spirochete, *Borrelia burgdorferi*, a family that includes 3 major subspecies[2]. *B. burgdorferi sensu stricto* is the strain responsible for virtually all Lyme disease in North America, but is also present in Europe; *B. afzelii* and *B. garinii* are responsible for many European cases of neuroborreliosis. *B. burgdorferi* has a predilection for certain organ systems – skin, heart, joints and nervous system. Over a century ago European dermatologists identified 2 unusual cutaneous manifestations – acrodermatitis atrophicans, caused by a strain found only in Europe, *B. afzelii*, and erythema migrans (previously known as erythema chronicum migrans[3]). The latter remains the most pathognomonic manifestation of the illness. Typically occurring in the first month of infection, this is most often an enlarging single erythroderm, expanding over days to weeks, to become many (usually >5) centimeters in diameter. It is typically painless, though often associated with systemic symptoms suggestive of a bacterial infection – fever, aches, etc. Biopsies of the rash demonstrate innumerable spirochetes. In a significant number of patients the rash is multifocal – each focus represents a nidus of hematogenously disseminated infection.

The nervous system is frequently seeded[4-6] often with clinically apparent involvement. Europeans have long recognized the triad of meningitis, painful radiculitis and cranial neuritis – associating it with erythema migrans (EM), and treating it with penicillin since the 1950's[7]. In the US, the disease was first recognized as a form of large joint oligoarthritis, subseqeuently[8] identified as a tick-bite associated infectious disease. The causative organism, *Borrelia burgdorferi,* was identified in1983[9, 10]; the closely related organisms responsible for European borreliosis were identified the following year[11].

Lyme disease is a zoonosis, requiring a temperate, somewhat damp environment, with an appropriate complement of hosts and vectors. The white-footed field mouse is the most common reservoir for the spirochetes; they appear to remain spirochetemic for an extended period of time, with minimal symptomatology. Competent vectors appear to consist exclusively of hard-shelled *Ixodes* ticks, which similarly can harbor spirochetes for an extended period of time. These ticks generally require a large mammalian host to complete their life cycle – typically deer, bears, or sheep; hence these also must be present in the environment. Humans become involved inadvertently, when they happen to stray into an area supportive of this cycle. Such environments are widespread but not ubiquitous –this illness occurs in North America, Europe and Asia, but only in highly localized areas on each continent. The requisite hosts are not available in urban areas, nor can the cycle persist in climates that are too hot, cold or arid for ticks to survive. In North America, 95% of all human cases occur in suburban and rural areas along the east coast, stretching from Maine to Virginia, with a second focus in Minnesota and Wisconsin[12]. These endemic areas have gradually enlarged as ticks have been carried to contiguous areas.

In temperate climates, the tick has a 2-year life cycle. Tick eggs are not infected. Once the egg hatches, the larva will seek its first blood meal. If this is obtained from a spirochetemic host, the tick can become infected. Following this meal, the larva transforms into a nymph, and will subsequently have its second meal, this time potentially transmitting infection. Nymphs are tiny; their bites are typically asymptomatic, as they inject local anesthetics, anti-inflammatories and anticoagulants to permit prolonged (days) attachment and feeding. The arrival of host blood in the tick gut triggers multiplication of spirochetes, which then migrate through the tick, including to its salivary glands, from which they are injected into the host. This cycle typically requires at least 24 and more often 48 hours of continued attachment and feeding. Removal of the tick in the first 24 hours generally prevents infection. In endemic areas about 2% of confirmed *Ixodes* tick bites lead to infection[13]. Following its second meal, the tick becomes an adult, which will also have a single meal, potentially infecting a second host. Finally, ticks over-winter on a large host, then ultimately lay their eggs and die.

Diagnostic testing

Diagnosis of Lyme disease requires possible exposure, appropriate clinical symptoms and laboratory confirmation[14]. Diagnostic culture of *B. burgdorferi* is technically impractical. Other than in EM the bacterial load in obtainable samples is so low that even PCR is of limited diagnostic sensitivity[6, 15] – under optimal conditions no better than 10-15% for either culture or PCR. Consequently, laboratory confirmation rests primarily on serologic testing – demonstration, primarily in serum, and in selected circumstances in CSF, of antibodies to *B. burgdorferi*.

As with any serologic test it takes time for the immune system to produce measurable antibody. Serologies are negative in 50% of patients with EM[16], perhaps 10% with Lyme associated facial nerve palsy[17]. In EM, treatment should be instituted immediately, based on the rash, regardless of serologic results. In some studies, 50% of patients seroconverting are asymptomatic. Since antibody production persists for years after resolution of an infection, seropositivity only implies exposure past or present, not necessarily active symptomatic infection. There is no expectation that successful treatment would immediately lower antibody concentration, so treating until the serology becomes negative is illogical. Early notions that partial treatment might abrogate the antibody response, or that concurrent antibiotic use might interfere with serologic testing performed at that time, have not been substantiated.

IgM (2 required)	**IgG (5 required)**
24 (OspC)	18
39	21
41 (Fla)	28
	30
	39
	41
	45
	58
	66
	93
For use in acute disease only:	For patients with established disease:
Sensitivity: 32%	Sensitivity: 83%

Table 1: Western Blot criteria for confirmation of positive serology[18, 19]

ELISAs, which measure total immunoreactivity against *B. burgdorferi* antigens, are more sensitive than specific, making them useful screening tests. Specificity is addressed using 2 tier testing, in which positive or borderline ELISA results are confirmed by Western blot, a test that should be interpreted with great caution in ELISA-negative individuals. Criteria for interpretation of Western blots were determined based on statistical analyses of large numbers of patients with and without Lyme disease (Table 1). Various combinations of bands were identified based on their positive and negative predictive values – not because any of the epitopes were unique to *borrelia.* IgM blots can only be used in early disease (1st month or so). After that, patients should have developed IgG positivity; in patients with symptoms of a month or more duration with only IgM immunoreactivity, the positive result is almost always spurious.

Interpretation of all serologic tests requires consideration of their positive and negative predictive values. A common criterion for test positivity is a value exceeding the mean of a control population by 3 standard deviations. With this approach, approximately 1 sample/1,000 will be positive by chance (false positive). In many endemic areas, as much as 5% of the population has been exposed and therefore is seropositive, so the 50/1,000 true positives vs. 1/1,000 false will be informative. In non-endemic areas, only 1 sample in 10,000 might be a true positive, vs. 1/1,000 false positives so 90% of positive results will be false. Interpreting a positive serologic test – and for that matter even ordering it – is highly dependent on the *a priori* likelihood that the patient has the disease in question (Bayes theorem). C6 testing is a modification of traditional ELISAs that uses a highly conserved region of the VlsE peptide[20]. This approach appears to add specificity to conventional ELISA testing[21] and may eventually supplant it.

Testing in CNS disease: CNS infections generally elicit a local inflammatory response. In neuroborreliosis there is evidence spirochetes invade the CNS quite early[5]. This seems to trigger local production of the B cell attracting chemokine CXCL13, CXCL13 has been suggested as a marker of CNS *B burgdorferi* infection[22] but appears to lack specificity. Production of this chemokine in turn results in substantial in-migration of B cells, followed by the

local production of immunoglobulins. This may be more prominent in European neuroborreliosis where CSF oligoclonal bands and increased total IgG synthesis are seen frequently. The most important consequence of this sequence is the proliferation of B cells targeting *B burgdorferi*, with the intra-CNS (intrathecal) production of specific anti-*B. burgdorferi* antibody. Since some peripheral blood IgG does filter into the CSF, intrathecal antibody (ITAb) production is best determined by measuring total specific anti-*B. burgdorferi* antibody in serum and CSF, normalizing for total IgG in the 2 samples, then determining whether there is proportionally more specific antibody than could be explained by passive diffusion. This measure seems both sensitive and specific; however, an elevated antibody index may persist for more than a decade after successful treatment. As in neurosyphilis, useful markers of disease activity include the CSF cell count and protein, both of which remain elevated in active infection but decline following successful treatment.

Clinical:

General manifestations: Acute localized Lyme disease consists of EM. Like a syphilitic chancre this rash looks inflamed but is usually asymptomatic. It can be homogeneously red or target-like with central clearing as the leading red edge advances; it may be round or elliptical, depending on local anatomy. Spirochetemic patients often experience 'flu-like' fever, aches and pains, headaches and malaise – but typically not GI or upper respiratory symptoms. Fewer than 5% develop cardiac conduction abnormalities, including heart block. Joint involvement can occur early or late, typically[1] involves large joints (knee, elbow, hip, shoulder), usually one at a time, and is subject to spontaneous remissions and relapses. Although generally responsive to antimicrobial therapy, there appears to be a subset of patients who develop persistent, immune mediated non-infectious arthritis, even after successful eradication of all organisms[23].

Neurologic manifestations/Neuroborreliosis: The central and peripheral nervous systems are frequently involved[24-27] (Table 2). Classically, patients may develop any combination of lymphocytic meningitis, cranial neuritis, and painful radiculitis[28, 29].

Peripheral Nervous System	Central Nervous System
Mononeuropathy multiplex	Meningitis (common)
Radiculitis (Bannwarth Syndrome)	Myelitis (partic. with Bannwarth's)
Cranial neuropathy (VII in most)	Encephalitis (rare)
Plexopathy	Encephalopathy
Acute disseminated polyneuropathy	
Chronic indolent polyneuropathy	
Entrapment neuropathies	

Table 2: Nervous system Lyme Disease: predominant clinical presentations. Note that all syndromes listed under "Mononeuropathy multiplex" are merely different clinical presentations of this single pathophysiologic entity.

Meningitis: Lymphocytic meningitis is probably the single most common form of neuroborreliosis, occurring in about 10% of untreated affected individuals. Symptoms are highly variable; they resolve with appropriate antimicrobials but also will resolve spontaneously. CSF findings resemble those in viral meningitis – modest lymphocyte-predominant pleocytosis (usually <100 wbc's/mm^3), mild protein elevation (on the order of 100 mg/dl) and essentially normal CSF glucose. Occasionally large atypical lymphocytes are seen on cytology[30, 31]. In patients in whom CNS infection has been relatively chronic, oligoclonal bands may be present and IgG index elevated (both reported more frequently in European than US patients). Particularly in patients with the latter CSF findings, intrathecal production of anti-*B. burgdorferi* antibody (ITAb) is usually demonstrable. In one study sensitivity of ITAb measurement was approximately 90% in patients with Lyme-associated meningitis[32]. Studies of more heterogeneous groups of patients suggest sensitivity of approximately 75%, and specificity of 97%[33].

Peripheral nervous system: Peripheral and cranial nerve involvement are quite common. Although initially described as co-occurring with meningitis, these are probably independent phenomena that may simply coexist in some individuals. Involvement of the cranial nerves, particularly the facial nerve, is usually emphasized; multiple cranial neuropathies occur in about 15% of patients with cranial neuropathies[34]. The olfactory and optic nerves are involved rarely if ever[35]. Cranial nerves 9-12 are similarly described only in case reports.

Peripheral nerve involvement is probably at least as common as cranial neuropathies. Early, acute disease may involve single nerves, a plexus or multiple nerves. Pathophysiologically all represent forms of mononeuropathy multiplex. Often pain and other radicular symptoms are prominent. Radiculitis is probably the most under-recognized PNS manifestation. Patients present with otherwise typical acute radicular pain in a dermatomal distribution, often with corresponding associated sensory, motor or reflex changes. In endemic areas, this should be suspected in individuals with otherwise typical radiculopathies but without a precipitating injury or relevant findings on imaging studies. Some may develop segmental spinal cord involvement at the involved nerve root level. As with cranial neuropathies, many but by no means all will have CSF abnormalities. Because of this some suggest CSF be examined in these patients. However, increasing evidence, all from European studies, suggests that Lyme meningitis and radiculoneuritis may be adequately treated with oral doxycycline[36, 37] making CSF findings irrelevant.

Patients with more indolent and protracted disease may develop a confluent mononeuropathy multiplex, clinically resembling a 'stocking glove' neuropathy, often with sensory more than motor symptoms[25]. Neurophysiologic and neuropathologic studies in experimentally infected rhesus macaque monkeys, the only animal model with nervous system involvement resembling the human illness, demonstrate a mononeuropathy multiplex in virtually all infected animals[38, 39].

Central nervous system: Parenchymal brain involvement is extremely rare. In experimentally infected monkeys, the contrast between PNS and CNS involvement is quite striking – virtually all animals develop a multifocal inflammatory mononeuropathy multiplex, but not one has been observed to develop parenchymal brain disease. CNS involvement, like that in the PNS, appears to consist of a multifocal inflammatory process. Appropriate antimicrobial therapy results in improvement, although deficits due to established parenchymal damage may remain.

Lyme encephalopathy remains a highly misunderstood construct[40, 41]. Originally described in individuals with active Lyme arthritis or other active inflammatory processes, patients develop mild memory and cognitive deficits, which reverse following appropriate antimicrobial therapy. These changes are indistinguishable from the encephalopathies commonly seen in patients with pneumonia, sepsis or other active inflammatory states. In the vast majority brain imaging (MRI, PET, SPECT) is normal, as is CSF. Some evidence suggests that peripherally generated cytokines and other neuroimmunolomodulators cross the blood brain barrier and affect behavior[42]. In virtually none of these patients is there evidence of CNS infection.

Treatment

Treatment of Lyme disease has been studied extensively; recommendations are well summarized in clinical guidelines[36, 43-45](Table 3). Studies of prolonged treatment indicate this offers no advantage but carries higher risk and cost[46-51]. Multiple well performed European studies indicate excellent therapeutic responses to oral doxycycline in patients with Lyme meningitis, cranial neuritis and radiculitis[37, 52-55]. Although no systematic studies have been performed in the US given the virtually identical antimicrobial sensitivities of European and US *borrelia*, as well as a growing body of anecdotal evidence, oral doxycycline seems a perfectly reasonable option in US neuroborreliosis. This notwithstanding it is probably prudent to use parenteral regimes in those rare patients with parenchymal CNS involvement.

Disorder	**Regimen**
Acute neuroborreliosis (meningitis, radiculitis, cranial neuritis)	Ceftriaxone 2 gms/d IV for 14-21 days *or* cefotaxime 2 gms tid IV for 14 -21 days, *or* penicillin 24 MU/d IV x 14-21 days *or* doxycycline 200-400 mg/d po for 21-30 days
Encephalomyelitis	Ceftriaxone 2 gms/d IV for 28 days *or* cefotaxime 2 gms tid IV for 28 days, *or* penicillin 24 MU/d IV x 28 days
Chronic or recurrent neuroborreliosis (e.g. treatment failure after 2 weeks treatment)	Ceftriaxone 2 gms/day IV for 28 days *or* cefotaxime 2 gms tid IV for 28 days
Non-neurologic disease	Amoxicillin 500 mg po tid *or* doxycycline 100 mg po bid *or* cefuroxime axetil 500 mg po bid a*ll for 14-28 days*
Disease resistant to oral treatment	Ceftriaxone 2 gms/d IV for 28 days *or* cefotaxime 2 gms tid IV for 28 days, *or* penicillin 24 MU/d IV x 28 days

Table 3: Treatment recommendations
Note: Tetracyclines such as doxycycline should not currently recommended in pregnant women or in children age 8 or under, although the recommendation regarding doxycycline may change in the next year.

Diagnostic Controversies

Lyme disease has been purported to cause ALS, MS, dementia, Parkinson's disease and virtually every other known neurologic illness, based largely on anecdotal reports. Causal relations are inherently improbable. The most important one to consider, because of the presence of multiple effective therapeutic options, is multiple sclerosis.

This issue arises because of early emphasis on white matter abnormalities on MRI scans of patients with CNS neuroborreliosis. Since this entity seems to be occurring less and less frequently, this may well be moot. That said, in cases where the question arises serologic testing – of CSF and serum – is quite helpful. Since these patients generally present with disease of more than a month or 2 duration, patients all should be seropositive. Among individuals with heightened B cell activity in the CNS (oligoclonal bands, elevated IgG synthesis rate) if this B cell stimulation is due to Lyme disease, there should invariably be evidence of intrathecal production of specific anti-*B. burgdorferi* antibody. If CSF is consistent with MS, and there is no evidence of intra-CNS production of specific antibody, Lyme disease can be excluded. However, it is essential to recognize that obtaining a CSF Lyme serology in such patients *without appropriate comparison to serum* will almost always result in a false positive result because of the elevated total IgG in these patients' CSF. Only by comparing specific to non-specific IgG concentrations in CSF and serum can the 2 disorders be reliably differentiated.

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