CHAPTER 18

Lyme Neuroborreliosis

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Infectious causes of nervous system disease are surprisingly common. Worldwide, leprosy is one of the most frequent causes of peripheral neuropathy. Human immunodeficiency virus infection obviously is a widespread disorder with frequent and prominent nervous system involvement. In the past two decades, a relatively novel but far less common infection, Lyme disease, has gained tremendous notoriety as a potential cause of nervous system dysfunction. Although now the most common vectorborne disease in the United States, this tickborne spirochetosis only affects about 16,000 patients in the United States, the most recent year for which final data are available (1). The nervous system is thought to be involved in about 15% of untreated infected individuals (2), resulting in an annual incidence of nervous system Lyme disease, or neuroborreliosis, of about 0.6 per 100,000, slightly less than that of amyotrophic lateral sclerosis. In most patients, the involvement consists of a self-limited and readily treatable lymphocytic meningitis.

One might well ask then why this disease has been the subject of so much concern and debate. To some extent, these numbers are misleading in that this disease is very focally prevalent, that is, in regions of high prevalence, as many as 0.1% of the population may be infected annually. In these areas, this obviously is a legitimate source of concern. In other areas, however, the likelihood of acquiring the disease is extremely improbable, although it is always worth inquiring if affected patients have traveled to endemic areas.

EPIDEMIOLOGY

Because the epidemiology is such an important component of diagnosis, it is worthwhile to start by reviewing the unusual zoonosis that puts patients at risk for infection. The responsible spirochete, *Borrelia burgdorferi*, is transmitted essentially exclusively by the bite of infected hard-shelled *Ixodes* ticks. These ticks occur only in specific locales in which appropriate hosts are available. Larval ticks hatch uninfected, insomuch as transovarial transmission of *B. burgdorferi* rarely if ever occurs. The larva then typically feeds on a small mammal such as a field mouse and matures into a nymph. If this initial host is infected, the tick will generally become infected as well. When the nymphal tick partakes of its blood meal, it can transmit infection or it can become infected if it was not previously and its second host was. Infecting this second host requires a complex process and prolonged attachment. Ingestion of blood triggers spirochete proliferation in the tick gut and subsequent dissemination to its salivary glands. From there the tick can inject spirochetes into the new host, typically a deer or bear but sometimes inadvertently humans. Because this proliferation and dissemination of spirochetes within the tick takes some time, the tick must typically be attached for at least 48 to 72 hours before the host is at significant risk of becoming infected.

Endemic cycles have become established in discrete areas of North America, Europe, and Asia. Along the eastern coast of the United States, from Maryland to Massachusetts, infected *Ixodes scapularis* ticks, known colloquially as “deer ticks” for the preferred host of the adult forms, are widely prevalent. The same ticks are also found in Minnesota and Wisconsin, where they are known as “bear ticks.” Related ticks, *I. ricinus*, known as the “sheep tick,” are found in Europe, whereas *I. persulcatus* predominates in Asia. In general, the tick lives where its animal hosts are widespread, usually in relatively undeveloped areas. People are at greatest risk of infection when their habitat infringes on these regions, for example, in rural and exurban environments.

Although the spirochete and the specifics of its life cycle have only been characterized within the last two decades (3), many of the clinical disorders it causes have

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been well known for many years. After infection, most patients develop the characteristic erythema migrans or erythema chronica migrans rash (4). This slowly enlarging erythromed, which may reach many inches in diameter, is often asymptomatic. It typically develops over days to weeks at the site of the tick bite; in some patients the spirochetes disseminate early and cause multifocal erythema migrans. Either at this stage or subsequently, patients may develop fever, arthralgias, and malaise and a flulike syndrome, but not flulike in the sense of having upper respiratory or gastrointestinal symptoms. Because the tick bite and rash are often both asymptomatic and because both may occur on parts of the body that are not easily seen, many patients are unaware of either. However, prospective studies in children suggest that the rash occurs in as many as 90% of infected individuals (5).

The rash was first described early in this century (4). Shortly thereafter, the neurologic consequences were well described (6). The first clearly identifiable patient with neuroborreliosis in the literature developed a painful polyradiculopathy with prominent segmental weakness and a lymphocytic meningitis. The authors postulated that the illness was caused by a tickborne spirochete, treated the patient with arsenicals, and he recovered. By the 1950s, European physicians were quite familiar with this disorder and routinely treated it with penicillin. In the United States, the disease was first recognized as a form of childhood arthritis, occurring in near-epidemic proportions in the towns surrounding Lyme, Connecticut (7). Detailed epidemiologic studies demonstrated that this disorder occurred in children with histories of *Ixodes* tick bites and erythema migrans. Additional studies demonstrated that these same individuals frequently developed a constellation of neurologic disorders (8) quite similar to those described in Europe years before, that is, lymphocytic meningitis, painful radiculitis, and cranial neuritis. These studies ultimately led to the isolation and identification of a novel spirochete, named *B. burgdorferi*, as the causative organism (9,10). The following year, an apparently identical organism was isolated in Europe (11).

Clinical manifestations of this infection appear to differ in different parts of the world. In Europe, most studies have emphasized neurologic and cutaneous abnormalities, including several rather unusual dermatologic abnormalities, known as acrodermatitis chronica atrophicans and lymphocytoma cutis, which have rarely been recognized in the United States. Cardiac and rheumatologic abnormalities were not emphasized in early European patients, but a clue to this may be found in a sentinel paper describing the neurologic manifestations, which referred to rheumatism in the title (12). In fact, they appear to be far less prominent in European patients, in contrast to the United States where rheumatologic involvement has received a great deal of emphasis, whereas neurologic complications were, at least initially, believed to be less important (7).

Several factors have contributed to these apparent differences. In part, it undoubtedly represents a bias of ascertainment, because rheumatologists have been in the forefront of dealing with this disease in the United States, whereas in Europe this disease has historically been treated primarily by neurologists. At least equally important, though, it is now known that there are important differences in the prevalent strains of infecting organisms in different parts of the world; the broad group of organisms is now known as *B. burgdorferi sensu lato*. In Europe two strains are most prevalent; *B. garinii* is responsible for most neurologic disease and *B. afzelii* causes the unusual dermatologic manifestations. In North America one strain predominates, known as *B. burgdorferi sensu stricto*. Presumably different strains have tropisms for different organ systems, leading to the observed clinical differences.

**DIAGNOSIS**

The spectrum of neurologic and behavioral disorders ascribed to Lyme neuroborreliosis has been the subject of much debate. For some, clear epidemiologic associations have been established, whereas the causal nature in others has been the subject of anecdotal case reports or small series. Determining a true cause and effect relationship in a given disorder has been difficult because of the limitations of currently available diagnostic techniques. They have led to attribution of all manner of symptoms to this infection, often despite a lack of definitive data.

In general, the laboratory diagnosis of Lyme disease has relied on the demonstration of peripheral blood immunoreactivity against the causative organism. Microbiologic culture has not been useful for several reasons. The spirochete, *B. burgdorferi*, is fastidious, requiring specific media, known as BSK II, which is not commonly stocked by most microbiology laboratories. The bacterial load is probably rather small except in skin lesions, for which microbiologic diagnosis is usually superfluous, giving rise to problems of sampling and limiting sensitivity (13). The organism grows slowly in vitro, requiring that cultures be maintained for several weeks before being considered clearly positive or negative. This approach is impractical in all but research laboratories devoted to this effort.

Other organism-based techniques have similarly proven to be disappointing. Polymerase chain reaction, which detects genetic material from one or a small number of organisms, has typically been positive in 50 to 75% of patients (14-18), depending on the primer set chosen, the laboratory performing the assay, and the sample size. Antigen-based assays have been quite variable, and none to date has stood the test of time. As a result, most laboratory-based support for the diagnosis has been based on serologic testing, using primarily an enzyme-linked immunosorbent assay (ELISA) and Western blots.
Serologic testing has several inherent limitations. First, after the immune system is exposed to a new antigen, it takes time for a specific detectable immune response to develop—typically 3 to 6 weeks. During this time, even a very specific and sensitive antibody-based assay will generally be negative. Second, because antibody responses in general persist for an extended period of time, a single positive serologic test can at best be taken as evidence of prior exposure and not necessarily of active infection. Although in other infections it is commonplace to look at evolving titers, using an acute change in titer as evidence of active infection has not generally been done in Lyme disease. Perhaps this has been accepted by analogy to diagnosis in syphilis, the other well-known spirochetal infection, in which a single positive Venereal Disease Research Laboratory (VDRL) or fluorescent treponemal antibody test is taken as evidence of infection in need of treatment.

Although the combination of a positive reagin-based test such as a VDRL or rapid plasma reagin and a positive fluorescent treponemal antibody-absorbed is quite specific for syphilis, the same cannot be said for a positive Lyme ELISA. For example, there is cross-reactivity with other organisms. Some are due to antigenically similar organisms, such as other spirochetes including syphilis, relapsing fever, and periodontal disease from *Treponema denticola*. Other cross-reactions are due to nonspecific polyclonal B-cell activation, such as occurs in subacute bacterial endocarditis, parvovirus infection, or infectious mononucleosis. The laboratory can have great difficulty differentiating true positives from false positives due to related organisms. Nonspecific false positives can often be addressed by using Western blots, which examine the specific antigens with which the host's antibodies react.

Consensus criteria have been developed for Western blots (Table 1), which have very high specificity, that is, in patients with what appears to be acute Lyme disease, a positive IgM Western blot provides very compelling confirmation that the disorder is indeed due to *B. burgdorferi* infection (19,20). Similarly, a positive IgG blot provides strong evidence in support of a more long-standing infection. Notably, though, the sensitivity of neither is very high. In the original study giving rise to these criteria (19), only 32% of patients with acute disease met IgM criteria, whereas 83% of those with chronic disease met IgG criteria. It is important to emphasize that this technique should be used primarily to improve the specificity of serologic testing, not the sensitivity; for example, a positive Western blot in a patient with a negative ELISA is unlikely to be meaningful.

Other general limitations of serologic testing relate to the concept of positive and negative predictive values. In most assays, the normal range is defined by assuming that most values cluster within a range extending either 2 or 3 standard deviations from the mean. Approximately 95% of all values will fall within 2 standard deviations, 99% within 2.5 standard deviations, and 99.7% within 3 standard deviations. This becomes important if serologic testing is performed indiscriminately. Nationwide the incidence of Lyme disease is approximately 5 per 100,000 (1). Using a 3 standard deviation cutoff, 3 individuals per 1,000 will fall outside the normal range, purely due to statistical variation; half of these values will exceed the upper limit of normal. As a result, in 100,000 samples, 150 will be false positives, whereas 5 will be true positives, even with this very restrictive statistical definition. Even in an endemic area, where the annual incidence is typically about 1 per 1,000, 100 of every 100,000 samples will be true positives compared with 150 false positives. In such areas, interpretation is made more difficult by the fact that seroprevalence rates are about 10% (21,22). In other words, of the 100,000 samples, 10,000 will be true positives but 9,000 of these will presumably reflect past exposure and not necessarily active infection. All of this makes interpretation of a positive result difficult in an endemic area and virtually impossible in a nonendemic area.

Finally, there are limitations peculiar to serologic testing for Lyme disease. Different laboratories have used highly divergent technical approaches to this procedure, ranging from testing against a single highly purified antigen from the flagellae of the organism (23), to the use of whole spirochete sonicates, to other combinations in between. Most laboratories use conventional ELISA kits, and some use a capture ELISA. There is no agreement on how to define positive or negative results, and because each of these approaches has some validity, there is as yet limited agreement on how best to perform and interpret these assays, resulting in significant divergence of results among different labs (24,25).

Serologic diagnosis of central nervous system (CNS) infection is actually easier and potentially more informative because little or no antibody is normally produced and the local production of specific antibody within the CNS can be measured (26-28). Although cross-reactivity does occur with other infections, only syphilis causes

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From Refs. 19 and 20.
both prominent cross-reactivity and a CNS infection; hence, if the CSF VDRL is negative, a positive result can be assumed to be indicative of CNS Lyme disease. The major limitation of this technique from a diagnostic point of view is that it can remain positive for years after cure of the CNS infection (29), making it difficult to use to follow treatment response. However, because most individuals with active infection have other CSF evidence of active inflammation, such as an elevated CSF protein or a pleocytosis, these less specific markers can be used to assess response.

Different laboratories have used different approaches in assessing CSF Lyme serologies. The one important consideration is that the proportion of specific antibody in CSF must be compared with that in blood. Some laboratories do not do this but rather compare CSF results to serum normals. Such an approach is valid in all but two circumstances. Patients with positive peripheral blood serologies will typically have positive CSF results by this approach, because some antibody diffuses into the CSF. Only by comparing the two values, demonstrating proportionately more specific antibody in the CSF, can CNS infection be inferred. The other source of confusion is patients with blood-brain barrier breakdown or other causes of increased CSF immunoglobulin, as for example, multiple sclerosis (MS). In such patients the standard techniques underdilute CSF, so that the proportion of specific antibody appears to be much greater than it is. This allows small amounts of nonspecific cross-reacting antibody to appear to cause significant positives; however, these are obviously meaningless. Consequently, proper interpretation of the results of CSF Lyme testing requires appropriate comparison with serum antibody results.

CLINICAL MANIFESTATIONS

Among the large range of neurologic disorders that has been attributed to Lyme disease, some occur with such frequency that they can be considered firmly linked. Others are uncommon but have compelling laboratory support for a linkage and therefore can be considered as real. Others are plausible, based on what is known of the pathophysiology. Others must be considered highly speculative.

The syndrome first described by Garin and Bujadoux (6) 75 years ago and named in their honor consists of a lymphocytic meningitis and painful polyradiculitis clearly due to the Lyme spirochete (2,8). In about 10% of such patients, the organism can be cultured from CSF (13), and intrathecal antibody production is demonstrable in over 90% (27). The lymphocytic meningitis—which can occur in isolation or in combination with cranial or peripheral nerve involvement—is indistinguishable clinically from viral meningitis. Patients develop varying degrees of headache, neck stiffness, and photophobia. CSF demonstrates a lymphocytic pleocytosis, typically up to a few hundred cells, mild elevation of protein, and typically normal glucose. Symptoms can be self-limited but probably resolve more quickly with antibiotics. Radicular involvement is similarly common. This can precisely mimic a mechanical mononradiculopathy or may be more widespread, resembling either a plexopathy, a mononeuritis multiplex, or even a disseminated polyneuropathy clinically similar to the Guillain-Barré syndrome. However, neurophysiologic testing does not usually demonstrate typical demyelinating changes, and a CSF pleocytosis is usually present (30). Cranial nerve involvement also occurs frequently. The facial nerve is probably the most commonly involved and may be affected bilaterally. The nerves to the extraocular muscles also are affected with some frequency, as are the trigeminal and the VIIth. Lower cranial nerves seem to be the least likely to be involved. In most instances, cranial nerve involvement probably occurs as part of a basilar meningitis, with nerves affected as they pass through the inflamed subarachnoid space. However, Lyme disease also commonly causes a mononeuropathy multiplex; in many instances at least facial nerve involvement may occur as part of this peripheral nervous system (PNS) disorder, even in the absence of meningitis (30).

All these disorders tend to occur fairly early in disease. Common to all is a vigorous immune response, prominent symptoms of radicular-type pain, focal weakness, and acute to subacute onset, typically within a few months of the onset of the infection. Other patients may develop much more indolent syndromes. In contrast to the more acute syndromes, symptoms tend to be mild and develop slowly. Patients commonly describe mild positive and negative sensory symptoms with mild paresthesias, sensory loss, perhaps gait instability, and minimal weakness (31). This may occur in as many as a third of untreated patients with chronic infection. Why some patients develop acute dramatic syndromes whereas others develop a more protracted and subtle disorder is not clear. Presumably it reflects a combination of factors, including differences in host immunity, both in terms of human leukocyte antigen-dictated immune characteristics and prior immune experience, strain differences in spirochetes, and perhaps coinfection with other tickborne organisms such as ehrlichia, babesia, or tickborne encephalitis virus.

Interestingly, in patients with both acute and indolent PNS involvement, neurophysiologic studies are usually indicative of a mononeuropathy multiplex (30). Nerve biopsies in both populations typically show axon loss and perivascular inflammatory infiltrates (31,32). Patients generally do not develop frank necrotizing vasculitis with vessel wall necrosis. In the only good animal model of human neuroborreliosis, the tick-infected rhesus macaque monkey, all untreated monkeys studied to date developed mononeuropathy multiplex (33). As in humans, it has not been possible to demonstrate spirochetes, immune complexes, or other proof of a pathophysiologic mechanism.