

Neurologic Manifestations of Lyme Disease, the New “Great Imitator”

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The causative agent of Lyme disease, *Borrelia burgdorferi*, is a highly neurotropic organism that not only can produce symptomatic neurologic disease but also can exist dormant within the central nervous system (CNS) for long periods. Two distinct types of neuroborreliosis occur at different stages of Lyme disease. Second-stage Lyme meningitis resembles aseptic meningitis and is often associated with facial palsies, peripheral nerve involvement, and/or radiculopathies. Lyme meningitis may be the first evidence of Lyme disease, occurring without a history of erythema chronicum migrans or flu-like illness. Third-stage parenchymal involvement causes a multitude of nonspecific CNS manifestations that can be confused with conditions such as multiple sclerosis, brain tumor, and psychiatric derangements. Manifestations of CNS parenchymal involvement in Lyme disease are generally associated, however, with a history of erythema chronicum migrans, meningitis, or carditis. Both second- and third-stage Lyme neuroborrelioses are commonly misdiagnosed because they are relatively uncommon and because they mimic many better-known disorders.

Syphilis has long been known as the “great imitator” because of its protean clinical manifestations. Today, there is another illness deserving of this description, an infection not even recognized until 1977: Lyme disease. While a thorough review of all the neurologic manifestations of Lyme disease is beyond the scope of this paper, the major neurologic presentations will be discussed, as well as some syndromes that mimic other neurologic diseases.

While we have centuries of experience telling us what to expect of the first “great imitator,” we have but a decade of experience with Lyme disease—less if we consider only the time since the causative organism, *Borrelia burgdorferi*, was identified. Furthermore, because antibiotic treatment for Lyme disease became available shortly after the condition was recognized [1, 2], we have little information on the natural course of the disease; in contrast, for most of the time syphilis was being studied, no effective treatment was available. Information about the natural course of Lyme disease would be of considerable value to the practitioner, since the first stage of Lyme infection is often mild and patients may not present until months or even years after the initial infection.

Lyme disease has many features in common with syphilis in addition to its multiple-organ presentation. Both diseases, for example, are caused by

spirochetes—syphilis by *Treponema pallidum* and Lyme disease by *B. burgdorferi*. Both conditions occur in stages characterized by symptoms that, although overlapping, are relatively distinct. The initial manifestation of both diseases is usually a characteristic skin lesion, which is followed by a systemic flu-like illness of varying severity. In both diseases, latent periods between symptomatic stages can be part of the clinical course. Later stages involve the skin, cardiovascular structures, and central nervous system.

The syphilis spirochete can live in the CNS for long periods, as evidenced by the fact that patients with general paresis usually do not manifest neurologic symptoms until 15 years after infection. A lengthy latency within the CNS also appears to exist in Lyme disease, with neurologic symptoms not becoming manifest for months or even years [3]. If, as it now seems, the Lyme spirochete is indeed highly neurotropic and able to remain dormant in the CNS for long periods, we may well see a sizable number of individuals who currently have latent neuroborreliosis presenting in the future with symptomatic infection.

The extent of CNS involvement in Lyme disease is only now beginning to be understood. Although second-stage neurologic involvement, with its subacute to chronic meningitis, radiculoneuritis, and cranial neuritis, seems to be by far the most common presentation, parenchymal brain or spinal cord involvement does occur. This parenchymal CNS disease generally appears in late Lyme disease, which

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we are only now starting to see in patients infected when the entity was first described. This circumstance results in the documentation of parenchymal CNS Lyme disease in case reports [4–9] rather than large series, and the information we have on this aspect of neurologic Lyme disease is far from quantitative. In fact, the spectrum of neurologic manifestations associated with Lyme disease is constantly expanding, a fact that exacerbates an already-difficult diagnostic situation. The degree of difficulty can be readily appreciated when it is recognized that the diagnosis is currently made largely on the basis of a nonspecific clinical presentation, serologic testing (the significance of which may not be clear), and relatively indirect methods of documenting infection.

Staging of Lyme Neuroborreliosis

Staging of Lyme disease is helpful in understanding its pathophysiology and clinical manifestations and in diagnosis. The first stage consists of a characteristic skin lesion, erythema chronicum migrans (ECM), and a viral-like systemic illness [10]. While overt signs of neurologic involvement are not present at this time, there is a good possibility (in light of the similarities of the disease to syphilis) that the organism does disseminate to the CNS at this stage. Some evidence for this possibility comes from animal models of Lyme disease. Brain cultures are positive 5 days after intraperitoneal inoculation of *B. burgdorferi* into rats [11, 12] and 2 weeks after its inoculation into hamsters [13].

The second stage of Lyme neuroborreliosis is manifested by the appearance of Lyme meningitis, often associated with cranial neuropathy and/or polyneuritis. In general, this stage occurs a few weeks to a few months after the initial infection.

The third stage is associated with parenchymal involvement. It is not known how often the organism actually invades brain tissue as compared with the CSF or the leptomeninges, but it has been established that it does so. Presently, however, it is believed that parenchymal involvement is less frequent.

Problems in Diagnosis

A multiplicity of neurologic manifestations may be associated with both second- and third-stage Lyme neuroborreliosis. Because these signs and symptoms are also associated with other better-known diseases,

this infection is often misdiagnosed, at least initially. A discussion of the diagnosis and misdiagnosis of Lyme disease follows.

Lyme meningitis. The second-stage neurologic involvement of Lyme disease usually manifests itself as aseptic meningitis. There is a lymphocytic pleocytosis in the CSF, but no microorganisms are detectable. Patients, often afebrile, present with signs and symptoms of meningeal irritation, but usually appear relatively nontoxic. Bannwarth's syndrome (i.e., chronic, aching, radicular pain) is a common manifestation of Lyme meningitis in Europe, although it is seen less frequently in the United States. Seventh cranial nerve involvement (Bell's palsy) is often present. Symptoms of peripheral neuropathy can be confirmed by neurophysiologic testing [14].

In some patients, these neurologic complaints appear to be the first evidence of Lyme disease. However, because Lyme disease was first described as ECM, many physicians still do not entertain a diagnosis of Lyme meningitis unless a history of the skin lesion is elicited. This should not be the case. Neurologic Lyme disease frequently presents without a history of a previous skin rash [15]. In fact, the combination of meningitis with facial palsies, peripheral neuropathies, and/or radicular pain is so highly suggestive of second-stage neuroborreliosis that Lyme disease must be considered a likely possibility regardless of medical history, particularly in those parts of the United States where the disease is endemic. Even in nonendemic regions, the diagnosis should be considered for any individual who has traveled to or through an endemic area.

Nonetheless, it is my experience that Lyme neuroborreliosis continues to be misdiagnosed and that, as a consequence, appropriate therapy is not administered. Patients are diagnosed as having aseptic meningitis when, in fact, a bacterial meningitis is present. Patients may be told that they have Bell's palsy, which will simply resolve with time. Because a variety of systemic symptoms are associated with the neurologic manifestations of second-stage Lyme disease, the condition may be misdiagnosed as hysteria. In addition, because headache is a prominent part of the symptom complex, patients are often told that they suffer from migraines.

Even when all of the classic manifestations of Lyme meningitis are present, the diagnosis is often missed. While growing experience with this infection is facilitating its recognition in endemic areas such as Connecticut, diagnostic problems continue un-

abated in other parts of the United States. This situation is typified by a patient I recently saw in consultation. A Washington, D.C., business executive had developed pain in both shoulders and arms. The pain, described as aching or gnawing and sometimes electrical, was worse on the left side. A diagnosis of cervical disk disease was made, and a number of remedies appropriate for such a diagnosis were attempted. None was successful.

Subsequent computed tomography and magnetic resonance imaging of the cervical spine revealed a small right C5 disk. The patient's discomfort was attributed to this disk despite the fact that he had bilateral symptoms that were more severe on the contralateral side.

Because symptoms continued, the patient was referred to a rheumatologist. On routine blood studies, an erythrocyte sedimentation rate of 72 mm/h was observed. When serologic studies revealed a positive fluorescent treponemal antibody absorption test, the patient was told he had syphilis. After his wife tested negative for syphilis and the patient continued to deny any exposure to a sexually transmitted disease, serologic studies for Lyme disease were performed. The result was positive, with a titer of 1:1,200. The fluorescent treponemal antibody absorption test at this time was negative.

At this point, the patient was referred to me. His history was significant for a prolonged flu-like illness the preceding summer, shortly after a visit to an area of New Jersey highly endemic for Lyme disease. There was no history of skin rash or arthritis. Neurologic examination gave negative results except for decreased neck movement and a borderline decrease in left biceps reflex. A positive Lyme serology was confirmed in my laboratory (titer, 1:51,200), and therapy with intravenous penicillin (20 million units per day for 2 weeks) was begun. The patient has done well, with resolution of his pain and no progression of his disease.

Parenchymal involvement. Third-stage involvement of the brain tissue itself is even more difficult to identify than second-stage neuroborreliosis. Because invasion of the brain parenchyma by the Lyme spirochete can produce such a multitude of symptoms, because these symptoms are also associated with other CNS-related disorders, and because third-stage parenchymal involvement is even less well known than Lyme meningitis, misdiagnosis is even more common than in second-stage disease. I have

seen patients whose conditions were confused with multiple sclerosis, brain tumor, dementia, encephalitis, and psychiatric illness before Lyme disease was finally diagnosed.

As more experience is garnered with CNS Lyme disease, certain characteristics are emerging that can facilitate more prompt and accurate diagnosis. While exceptions do occur, parenchymal involvement (although developing many months to years after the initial infection) is usually associated with a history of rash, meningitis, or arthritis. The patient almost always lives in or can remember visiting an endemic area. In general, borrelial infections in the brain, like neurosyphilis, are inflammatory; thus these patients generally have CSF pleocytosis. Finally, patients with CNS Lyme disease have IgG antibodies to *B. burgdorferi* in serum. Many patients also have these antibodies in the CSF, although this finding is not requisite for the diagnosis.

Because third-stage parenchymal CNS involvement in Lyme disease is so difficult to identify with certainty, I have established a set of diagnostic criteria, all of which must be met before a definitive diagnosis is made: (1) objective CNS involvement without any other possible cause, "objective" being defined as some clear finding on physical examination or on radiologic testing (usually magnetic resonance imaging) and/or some clear psychiatric involvement; (2) reproducible, high-titer Lyme serology (even though by the elimination of low-titer tests some true cases are undoubtedly excluded); (3) other organ system involvement, i.e., ECM, arthritis (pain, inflammation, and swelling—not just arthralgia alone), or meningitis; (4) lymphocytic pleocytosis in CSF; and (5) a positive response to intravenous antibiotics.

Because each patient had to meet this strict diagnostic definition before parenchymal involvement could be diagnosed, many patients referred to us could not be said with certainty to have CNS Lyme disease. Many, however, who met most but not all criteria were put into a "possible" group.

Among a group of 58 patients I evaluated at Yale-New Haven Hospital, 26 had symptoms that were suggestive of parenchymal invasion of the Lyme spirochete and that were attributed to definite or possible CNS Lyme disease and 10 were diagnosed as having Lyme meningitis. Thirteen patients clearly did not have Lyme disease but had a variety of other problems, including tension headaches and psy-

chiatric problems. One patient had systemic lupus erythematosus. Nine patients did not have a complete evaluation before being lost to follow-up.

Unresolved Issues

Despite the growing body of knowledge regarding the neurologic involvement of Lyme disease, many issues remain unresolved and many questions are yet unanswered. Much is unknown, for example, about the latency of *B. burgdorferi* within the CNS. What keeps the Lyme spirochete quiescent for long periods? What causes its reactivation? As in syphilis, there are currently no answers.

The actual effect of oral antibiotics on the course and presentation of CNS Lyme disease is not clearly understood. For instance, does resolution of ECM following antibiotic therapy mean that the organism has also been eliminated from the CNS?

Another unanswered question is whether the results of treatment can be used as a diagnostic criterion. In other words, if patients fail to respond to appropriate treatment, does that mean that they do not have Lyme disease? This question leads to yet another: What exactly is the pathogenesis of CNS involvement in Lyme disease? Is it in some instances not infectious but parainfectious? If so, should immunosuppressive medication be used for Lyme disease not responsive to antibiotics?

Questions still arise concerning the value of the anti-*B. burgdorferi* serologic assay in identifying Lyme disease as the cause of a neurologic syndrome. In other words, if individuals living in an endemic area present with neurologic symptoms and a positive antibody titer, does that mean that they have Lyme neuroborreliosis?

Summary

While much remains to be learned about Lyme neuroborreliosis, the experience of the last decade has taught us a great deal about the causative agent. *B. burgdorferi* is now known to be a highly neurotropic organism that can exist in dormant fashion for long periods within the CNS and elsewhere in the body. It can cause Lyme meningitis, a condition resembling aseptic meningitis, with CSF pleocytosis and typical manifestations of meningeal irritation. This syndrome is often associated with facial

palsies, peripheral nerve involvement, and/or radiculopathies.

Despite the relatively characteristic picture of second-stage neurologic involvement, the condition is still sufficiently uncommon that it is often misdiagnosed, especially in the absence of a history suggestive of Lyme disease (i.e., the occurrence of ECM or a flu-like illness). Third-stage parenchymal invasion by *B. burgdorferi* is even more often misdiagnosed, since its occurrence is even less well known and its myriad nonspecific CNS effects may easily be attributed to better-recognized conditions, such as multiple sclerosis, brain tumors, and psychiatric disturbances. It is hoped that ongoing experience with Lyme neuroborreliosis will continue to refine diagnostic criteria so that appropriate treatment can be more promptly and properly instituted in patients with this infection.

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