CME

Psychiatric and Cognitive Features of Lyme Disease

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Lyme disease, the most common vector-borne disease in the United States, causes neurologic or psychiatric symptoms in up to 40% of symptomatic cases.[1] Because the most common neurologic presentation of late Lyme disease is an encephalopathy characterized by disturbances of memory, attention, mood, and sleep, psychiatrists who work in areas where Lyme disease is endemic will be referred such patients, often before the diagnosis of Lyme disease has been made. The more rapid the diagnosis and treatment, the less likely the patient is to have a chronic relapsing–remitting disorder. This article aims to help the clinician by describing the signs and symptoms that are typical of Lyme disease, reviewing the published literature on the cognitive and psychiatric aspects of Lyme disease, and describing the tests that are useful to either confirm or support the clinical diagnosis.

THE HISTORY OF LYME DISEASE

Erythema migrans, the early skin lesion now recognized as pathognomonic for Lyme disease, was first reported in the United States in 1970.[2] Lyme arthritis was first identified in 1977, stemming from a geographic clustering of children in Lyme, Connecticut.[3] However, Lyme disease had been documented in the late 19th century in Europe under a variety of different names, including Bannwarth's syndrome, acrodermatitis atrophicans, and Garin–Bujadoux syndrome. The manifold syndromes were brought together in 1981 when Burgdorfer identified a new bacterial organism, a *Borrelia* spirochete, in the midgut of a tick that had caused an erythema migrans rash. This spirochete, similar in several respects to the agent of syphilis, was named *Borrelia burgdorferi* in honor of its founder. The disorder is now referred to as either Lyme disease or Lyme borreliosis.[4]

EPIDEMIOLOGY

Lyme disease is endemic in several areas of the world, including the United States, Canada, Europe, and Asia. Areas in the Northeast, Midwest, and Pacific coastal states account for most of the reported cases in the United States. Between 1993 and 1997, more than 62,000 cases were reported to the Centers for Disease Control and Prevention (CDC), a figure widely regarded as an underestimation of the actual number of cases (CDC, unpublished data, 1998).

TRANSMISSION

Lyme borreliosis is transmitted by an *Ixodes* tick infected with *B. burgdorferi*. The nymphal stage of this tick is the size of a poppy seed and may easily be missed on a cursory examination of exposed skin. The most common carriers of the tick are deer and the white-footed mouse. However, these ticks have been found on at least 30 types of wild animals and 49 species of birds.[5] The avian transmission may account for its rapid spread throughout the United States.

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The bite is generally not felt by the individual and transmission of the spirochete itself generally takes between 12 and 24 hours.[6] For this reason, if a tick is found and removed in the correct manner before transmission of the disease is completed, Lyme disease can often (but not always) be averted. The same ticks may also transmit concurrent infections with *Babesia* and *Ehrlichia*.

PATHOGENESIS

B. burgdorferi rapidly disseminates through the bloodstream, appearing in the central nervous system within days of the initial skin infection.[7,8] Once it is sequestered in the central nervous system, a local inflammatory reaction may occur, resulting in meningitis or encephalitis, or *B. burgdorferi* may remain dormant, causing illness months to years later.[9] The spirochete is known to grow slowly, dividing every 8 to 12 hours. *B. burgdorferi* can attach to a number of mammalian cells (eg, neurons, glia, and Schwann cells), invade fibroblasts and lymphocytes, bind host proteins, and alter the secretion of host cytokines and antibodies.[10]

The primary assumptions regarding the cause of neurologic damage in neuroborreliosis are: (1) the direct action of spirochetes and spirochetal products on neural cells; (2) the induction of local, neurally produced cytotoxic or inflammatory mediators by small amounts of persistent organisms; or (3) the induction of an amplified inflammatory response, mediated by cross-reactive antibodies or cellular immune mediators.

CLINICAL MANIFESTATIONS

Lyme disease is often classified into three stages: early localized, early disseminated, and late. Initial symptoms of early localized infection may present days or even weeks after the tick bite. A typical presentation would include a localized skin reaction (an erythema migrans or bull's eye rash) followed by flu-like symptoms, characterized by fever, malaise, arthralgias, and myalgias. Approximately one-third of the patients do not recall any rash and the flu-like symptoms may be mild,[11] so they may not realize that they have been infected. Therefore, later neurologic or neuropsychiatric symptoms may be the presenting symptoms.

Early disseminated disease results from the early dissemination of the spirochete from the skin into the bloodstream to the various organs of the body. This may occur within days or weeks after the initial infection, resulting in musculoskeletal, cardiac, ophthalmologic, or nervous system involvement. Patients may experience headaches as an early symptom of neurologic Lyme disease without any sign of inflammation in the cerebrospinal fluid.[12] Subsequently, patients may have meningitis with symptoms such as severe headaches, a stiff neck, photophobia, and sometimes nausea and vomiting. A mild encephalitis characterized by recurring disturbances of mood, concentration, memory, and sleep develops in fewer than 50% of the patients with meningitis. Cranial neuritis, such as Bell's palsy, occurs in 5% to 10% of patients with neurologic Lyme disease.[13] Peripheral nerve involvement may include sensory or motor neuropathies.

Late-stage illness, which can present months or years after the initial infection, may affect the joints (beginning with migratory arthralgias and progressing to inflammatory arthritis in some cases), the eyes (including conjunctivitis and localized inflammation of the uvea or iris), and the central nervous system. Late neurologic involvement may present as an encephalomyelitis or, more commonly, encephalopathy.[12] Encephalopathy is signified by minor to severe cognitive changes, marked fatigue, sleep problems, and irritability or emotional lability. The cognitive changes may be manifest by problems with short-term memory or word finding, a slower speed of thinking, dyslexia, and spatial disorientation.[11]

In one early series of 18 patients with erythema migrans, Lyme arthritis, or both, neurologic involvement included aseptic meningitis, encephalitis, chorea, cerebellar ataxia, cranial neuropathy, motor and sensory peripheral neuropathy, mononeuritis multiplex, and myelopathy.[14]

Uncommon neurologic presentations of Lyme disease include mild to moderate dementia, Guillain–Barré syndrome, spastic paraparesis, hemiparesis, optic neuritis, transverse myelitis, seizures (grand mal and complex partial), and

cerebrovascular involvement (vasculitis, thrombosis, aneurysm, and infarction).[15-19] Neurologic Lyme disease may mimic and be misdiagnosed as multiple sclerosis, Alzheimer's disease, chronic fatigue syndrome, migraine, conversion disorder, somatization, or hypochondriasis.[9,20,21]

DIAGNOSIS

The diagnosis of Lyme disease is based on the clinical presentation, supported by results of serologic and cerebrospinal fluid tests.[22] For epidemiologic surveillance purposes, the CDC[23] defined Lyme disease as the presence of an erythema migrans rash 5 cm or larger in diameter or laboratory confirmation of infection with *B. burgdorferi* and at least one objective sign of musculoskeletal, neurologic, or cardiovascular disease. These symptoms must be present along with a history of exposure to an area where Lyme disease is endemic.

The CDC criteria are useful for epidemiologic studies, but were not meant to be used as the diagnostic standard for clinical Lyme disease. For clinical diagnostic purposes, these criteria are unduly restrictive. First, approximately one-third of patients will not recall a rash. Second, one of the most common manifestations of late neurologic Lyme disease (encephalopathy) is not included on the CDC's list of objective neurologic manifestations. Third, a sizable number of patients do not mount an adequate immune response to *B. burgdorferi* and thus have negative results on routine serologic antibody tests, possibly due to the dampening of the immune response by prior antibiotic therapy.

Given the limitations of laboratory diagnosis, clinicians must consider many factors in the diagnosis of Lyme disease. Questions should address exposure to an area where Lyme disease is endemic, history of an expanding erythematous rash (eg, erythema migrans), history of a tick bite with attachment longer than 12 hours, presence of arthralgias or arthritis, signs of a peripheral neuropathy (eg, numbness, tingling, or burning sensations) or radiculoneuropathy (eg, shooting pains), symptoms of a cognitive disturbance, marked fatigue, persistent marked headaches, and atypical neuropsychiatric symptoms.

The differential diagnosis for Lyme disease is broad. Other disorders need to be ruled out, such as viral infections, rheumatoid arthritis, primary psychiatric disorders, connective tissue disorders, thyroid disorders, sleep disorders, other central or peripheral neurologic disorders, fibromyalgia, and chronic fatigue syndrome.

DIAGNOSTIC TOOLS

Laboratory Tests

Direct culturing of *B. burgdorferi* from patient specimens is difficult. Therefore, serologic testing is currently the only pragmatic laboratory aid in diagnosis.[4] The detection of the *B. burgdorferi* antibodies typically is determined by the enzyme-linked immunosorbent assay (ELISA) and the Western blot test. The ELISA relies on the immune response following exposure to *B. burgdorferi* and the Western blot test is used to inspect the serum for antibodies against epitopes that are specific to *B. burgdorferi* (eg, 23-, 28-, or 39-kd bands).

Although most laboratories have adopted the criteria recommended by the CDC for interpretation of a Western blot test (ie, a minimum of 5 bands to be considered positive), the serum of some patients with Lyme disease may have fewer bands initially. Later, after antibiotic therapy, some of these patients have fully positive results on serologic tests. Serologic testing for Lyme disease is standardized, but not reliable, and for this reason the results obtained from different laboratories may vary. Serologic tests must then be interpreted with caution; the clinician must be cognizant of the possibility of both false-negative and false-positive results.

False-negative results may occur because the testing was done soon after initial infection or because the immune response had been abrogated or masked either by the effect of the organism or by early antibiotic therapy. False-positive results occur because several *B. burgdorferi* antigens are shared by other spirochetes. For example, a false-positive result on the ELISA may be seen for patients with syphilis, Rocky Mountain spotted fever, or autoimmune diseases.[24] Immunoblotting has been supported as a means of identifying false-positive results, because patients with Lyme disease who have positive results on ELISA may also have them on

immunoblotting, whereas control subjects usually will not.[24] The Western blot is also the preferred test for patients who have received the Lyme disease vaccine, because the vaccine will cause a false-positive result on the ELISA but will produce only one band of reactivity (31 kd) on the immunoblot.

The cerebrospinal fluid in early neurologic Lyme disease (eg, encephalitis or meningitis) may demonstrate a lymphocytic pleocytosis, whereas an elevated level of cerebrospinal fluid protein is more often seen in late neurologic Lyme disease. However, research studies indicate that 25% to 50% of patients with late neurologic Lyme disease may have no evidence of elevated protein levels, increased white blood cells, or Lyme antibodies on routine cerebrospinal fluid assays.[8,25] To be absolutely confident that a patient has Lyme disease of the central nervous system, production of intrathecal antibody needs to be demonstrated (ie, higher levels of Lyme antibody in the cerebrospinal fluid than in the serum). However, this is rarely seen among patients with later-stage Lyme encephalopathy.

Neuropsychological Assessment

Neuropsychological testing can be particularly helpful as a method of identifying and describing cognitive dysfunction among patients with Lyme disease.[26] Comprehensive cognitive assessments are better able to tease out subtle cognitive deficits not otherwise apparent from a routine neuropsychiatric assessment in the office and are also able to present a "neuropsychological profile" that may help in differentiating between organic or neurologic and psychiatric causes of cognitive problems.[27] Because subjective reports of cognitive difficulties, such as memory problems, do not always correlate with objective data,[28] it is crucial not to rely only on self-reported cognitive problems.

The sensitivity of neuropsychological tests in ascertaining brain dysfunction is high (80% to 90%), although specificity is lower.[25] For this reason, a comprehensive battery should include measures of general intellectual functioning, as well as specific areas of functioning such as verbal and visual memory and learning, attention or concentration, language, fine and gross motor functioning, executive functioning, and academic functioning. Measures of psychopathology, particularly depression and anxiety, are also recommended because affective states may affect cognitive performance due to problems with attention or motivation.

Cognitive dysfunction can be determined in two ways: through the use of a normative comparison standard or an individual comparison standard.[29] Comparison with a normative sample can report how an individual is performing in relation to others of the same age, sex, and educational level. Impairment is generally determined by a predetermined cutoff score, such as when an individual's scores fall approximately 1½ to 2 standard deviations below the mean. However, this method could be misleading if, for example, an individual was previously functioning in the superior range across functions and is currently scoring in the average range. Based on the normative comparison standard, this individual would be considered to be functioning within the normal range, with no cognitive impairments. To address this issue, an individual comparison standard is used.

The ideal for an individual comparison standard would be to compare an individual's premorbid and current scores on the same task. Often, this is not possible due to age or lack of premorbid scores. Estimates of premorbid ability are the other alternative. There have been a variety of techniques presented to measure premorbid ability, including reading test scores, the best performance method, or the Vocabulary, Information, and Picture Completion subtests of the Wechsler intelligence scales.[29] Once the premorbid ability has been established, an individual's scores on a variety of tests can be compared with his or her estimated level of functioning to determine whether there has been any change.

Neuropsychological assessments are best used to examine patterns of various test scores.[29] Pattern analysis can help determine an individual's areas of strength and weakness. In addition, certain patterns of deficits may be more reflective of particular diseases or conditions than others. For example, perseverative behavior, poor cognitive flexibility, and impaired verbal fluency tend to be associated with frontal lobe dysfunction.

Additionally, although poor memory performance can be seen in patients with depression or organic dementia, recognition memory tends to remain intact in patients with primary depression.

Brain Imaging

The typical clinical single-photon emission computed tomography (SPECT) report for a patient with Lyme disease might indicate "diffuse heterogenous hypoperfusion consistent with Lyme disease, vasculitis, chronic fatigue syndrome, or stimulant abuse." It is unclear whether this heterogeneity is due to an abnormality in vascular flow or neuronal metabolic dysfunction.

As noted in the report, the pattern of heterogeneity on SPECT scans is not specific to Lyme disease. However, based on reports from the literature[30] regarding functional brain imaging in primary psychiatric disorders, such a pattern would not be expected from patients with primary depression, anxiety, or other psychiatric disorders (other than chronic cocaine abuse), thus providing the clinician with a tool to help tease out primary psychiatric disorders from secondary ones triggered or perpetuated by a disease affecting the brain diffusely. If abnormalities are seen on magnetic resonance imaging (MRI), they tend to be white matter hyperintense areas, best visualized on T2-weighted images or FLAIR sequences. Both the SPECT abnormalities and the MRI hyperintensities may improve after antibiotic therapy.

Belman et al.[31] described MRI abnormalities in eight children with neurologic problems following Lyme infection. Abnormalities were located predominantly in the deep white matter, which is consistent with reports of MRI lesions seen in adults with neuroborreliosis.[32] These patchy white matter lesions appear similar to the MRI findings of children with parainfectious or postinfectious acute disseminated encephalomyelitis.

TREATMENT

Antibiotic therapy is the recommended mode of treatment for Lyme disease. Treatment tends to be most successful earlier in the course of the illness and less effective in the late stages. For early-stage illness, oral antibiotics such as amoxicillin and doxycycline are effective. Once involvement of the central nervous system has occurred, intravenous antibiotic treatment is suggested, usually with ceftriaxone or cefotaxime.

When patients experience a relapse, the question arises as to whether the symptoms represent current persistent infection or a past infection that either caused residual damage or triggered a self-perpetuating autoimmune response. The recent medical literature has considerable evidence to support the hypothesis of a low-grade, persistent infection among patients with persistent symptoms and less evidence to support an autoimmune reaction. Uncertainty now exists regarding whether patients with persistent cognitive deficits would do better if treated with repeated courses or longer courses of antibiotic therapy. A recently published open trial indicated that patients with persistent cognitive complaints may in fact benefit from repeated antibiotic treatment, even if serologic markers of current *B. burgdorferi* reactivity are absent.[33] Only controlled trials of short-term versus long-term antibiotic therapy will determine the optimal length of therapy.

PSYCHIATRIC MANIFESTATIONS IN ADULTS AND CHILDREN WITH LYME DISEASE

Reports from Europe and the United States suggest that psychiatric symptoms may be a prominent characteristic of Lyme disease. This is significant for clinicians who practice in areas where Lyme disease is endemic and may have to rule out Lyme disease when presented with patients complaining of marked fatigue, irritability, mood lability, sleep disturbances, diffuse arthralgias and myalgias, impaired cognition, or all of these. Clinical case reports have linked Lyme disease with depression.[34,35] Controlled studies[36] found significantly more depression among patients with late Lyme disease than among normal control subjects. A review of 9 studies[12] recounted psychiatric disorders in a series of patients with Lyme disease and found that the frequency of concomitant depression ranged from 23% to 70% depending on how the questions were phrased.

Case reports[35] have described patients with

Lyme disease who had psychiatric disorders for the first time after being infected with the spirochete. With the use of the Structured Clinical Interview for *DSM-III-R*, one patient was diagnosed with major depression and panic disorder, another had an organic mood syndrome with both depression and mania, and a third patient had panic disorder.[35]

Lyme disease has been associated with Lyme-induced hyperacusis accompanied by posttraumatic stress–like behaviors.[37] Pachner et al.[38] presented the case of a 21-year-old man who was seropositive for *B. burgdorferi* and had psychiatric symptoms, including confusion, agitation, disorientation, inappropriate laughter, and violent outbursts; many of these symptoms abated after treatment with antibiotics. Cases of new-onset psychosis,[39,40] schizophreniform disorders,[41-44] delirium, and dementia also have been linked to Lyme disease. Fallon et al.[21] emphasize that Lyme disease may go unrecognized in children and adults who present with atypical neuropsychiatric symptoms.

Although children and adults with Lyme disease have numerous overlapping symptoms, published reports suggest that memory problems are less frequent in children, whereas headache, behavioral problems, mood problems, or all three may be more frequent.[45] Reports from Europe indicate that children with Lyme disease are more likely than adults to present with neurologic symptoms such as facial nerve palsy and aseptic meningitis than with arthritis.[46] Children have the additional problem of school-related issues (eg, being too tired to wake up and get to school on time, or being unable to pay attention in class). However, research is sparse regarding the psychiatric and neuropsychiatric clinical spectrum of Lyme disease in children.

Children and adolescents treated in a timely manner for early Lyme disease have been reported to have no significant psychiatric problems based on interviews and self-report measures at initial evaluation and up to 4 years after treatment.[47,48] If not treated until well after the initial infection, children may be at risk for cognitive problems. Tager et al.[49] found increased mood, attention, and learning problems in a subgroup of children with Lyme disease who were referred because of persistent cognitive complaints that developed concurrently with Lyme disease. Case studies have linked Lyme disease in children and adolescents with anorexia nervosa,[38] obsessive–compulsive disorder and panic disorder,[50] psychotic features,[51] and Tourette's syndrome.[52]

COGNITIVE FUNCTIONING IN ADULTS AND CHILDREN WITH LYME DISEASE

Impairments in memory, attention and mental activation, language conceptual ability, and motor function have been documented in adults with Lyme disease.[10,14,53,54] In particular, deficits in verbal memory usually assessed by list learning have been found to be one of the most consistent problems for adults with Lyme disease.[14,27,36] Difficulties with list learning and retrieval of information is a pattern of memory dysfunction similar to that caused by multiple sclerosis.[55]

Kaplan et al.[26] studied memory impairment and depression in patients with Lyme encephalopathy. They found that patients with Lyme disease had statistically significant memory deficits compared with patients who had fibromyalgia and nonpsychotically depressed patients independent of physical complaints and depression, supporting the hypothesis that cognitive impairments are caused by dysfunction of the central nervous system and are not secondary to a psychological response to chronic illness. However, subjective memory impairments may be greater in patients with Lyme disease who have comorbid depression.[56]

Similarly, in a later study by Kaplan et al.,[57] patients with Lyme disease who had abnormal cerebrospinal fluid were found to have objective memory impairments, whereas perceived memory dysfunction in patients with Lyme disease without other evidence of pathology of the central nervous system was hypothesized to reflect affective symptoms prevalent in other chronic illnesses. In addition, they found a small group of patients with Lyme disease who had been previously treated and who continued to have neurologic deficits, including objective memory impairments, in the absence of evidence of current apparent infection.

Two published studies have examined the cognitive functioning of children with Lyme dis-

ease.[47,48,58] In one study[47] and follow-up study,[48] children appropriately treated for Lyme disease were found to have an excellent prognosis for short-term and long-term (4 years) unimpaired cognitive functioning. Adams et al. studied a clinic population of 41 children with Lyme disease, 14 control subjects who had subacute rheumatologic diseases, and 23 healthy control subjects. Neuropsychological measures were used to assess IQ, information processing speed, fine-motor dexterity, novel-problem solving and executive functioning, short-term and intermediate memory, and the ability to acquire new learning. Adams et al. found no differences between the Lyme disease group and the control group on any of the neuropsychologic measures. In addition, they found no difference in pre-disease versus post-disease academic performance.

In contrast, Bloom et al.[58] evaluated 86 children who had previously met the CDC criteria for Lyme disease for possible late manifestations of Lyme disease; 12 of these children had neurocognitive symptoms thought to be related to Lyme infection. They described 5 of those children with past or present *B. burgdorferi* infection in serum and cerebrospinal fluid who had neurocognitive symptoms either at the time of onset of Lyme infection or months after classic manifestations of the disease.

The most prevalent neurocognitive symptoms were behavioral changes, forgetfulness, declining school performance, headache, and fatigue. When assessed with a battery of neuropsychological tests, these children were found to have normal intellectual functioning, but particular deficits related to auditory or visual sequential processing. These deficits, as well as many other symptoms, gradually improved following treatment with ceftriaxone, although 2 of the children continued to have auditory sequential processing deficits.

In another controlled study of cognitive deficits in children treated for Lyme disease who had persistent cognitive complaints, objective cognitive deficits were found. These were related to attention and processing of auditory and visual information.[51]

PSYCHIATRIC TREATMENT

Lyme disease may induce a spectrum of neuropsychiatric disorders.[59-64] If the cause of a neuropsychiatric disorder is active infection, then antibiotic therapy is essential for augmenting pharmacologic therapy for symptoms.[60] If a patient is no longer responding to antibiotic therapy, then either the infection is no longer present, the spirochete has developed a resistance to that antibiotic, or the penetration of the antibiotic to the sequestered site of the organism is inadequate. Some physicians try different antibiotic courses for patients with residual symptoms. Others recommend that patients stop seeking antibiotics and instead work on palliative therapies. These therapies, such as a formal program of cognitive remediation, may be helpful and may be akin to what would be used in the rehabilitation of patients with brain injury.

Psychopharmacologic strategies for patients with Lyme disease tend to focus on medications that can help with irritability, insomnia, pain, fatigue, attention, and sensory hypersensitivity. Serotonin reuptake inhibitors are recommended for irritability.[59] Low-dose tricyclic antidepressants such as amitriptyline can be helpful in reducing pain and in promoting sleep for patients with sleep disorders.[59] Carbamazepine and gabapentin may be particularly helpful for neuropathic pain.[59] Methylphenidate, modafanil, and bupropion are often useful for fatigue and attentional problems.[59] Anticonvulsants such as carbamazepine and gabapentin can help to raise the threshold of sensory tolerance for sensory hypersensitivity such as hyperacusis.[37]

Because patients with Lyme disease may have neuropsychiatric symptoms that impair day-to-day functioning, ongoing psychological care can be beneficial as well. Patients with Lyme disease who experience moderate to severe fatigue may be unable to go to work or school, take care of a family, or both. Somewhat unique to Lyme disease is the waxing and waning of symptoms on a daily or weekly basis, a picture that can be confusing to both family members and physicians; this symptom fluctuation may appear psychologically motivated. Many of these patients have gone to multiple physicians who failed to diagnose Lyme disease and instead referred them for psychiatric care. They often feel disheartened and disbelieved.

Further confounding is the uncertainty among

physicians as to whether the organism that causes Lyme disease is still present and what the appropriate course of therapy should be. Equally reputable physicians in the same community may have completely opposite perspectives on both diagnosis and treatment. Patients often feel caught in the middle of a controversy. Because of these uncertainties, patients will need help from physicians in finding the best treatment plan. Education about neuropsychiatric Lyme disease, couples therapy, family therapy, and individual therapy can be essential tools to help patients cope with this challenging illness.

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