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NEUROLOGIC COMPLICATIONS OF LYME DISEASE: DILEMMAS IN DIAGNOSIS AND TREATMENT

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There is not much doubt about the neurological manifestations of acute Lyme disease - headache, neck rigidity, facial nerve palsy, peripheral pain, numbness, and weakness.

But more than 20 years after Lyme disease was first linked to the tick-borne spirochete *Borrelia burgdorferi*, there is considerable doubt about chronic syndromes attributed to borreliosis. Ambiguities in testing and overlaps in symptoms and in timing complicate diagnosis.

As the AAN practice parameters for diagnosing patients with nervous system Lyme disease state: Highly rigorous and restrictive criteria should be required to establish a general cause-and-effect linkage between a given neurologic syndrome and *B. burgdorferi* infection. On the other hand, a slightly less restrictive basis may be appropriate for diagnosing an individual patient in whom failure to treat a probable, but not definite, infection might have significant adverse consequences (*Neurology* 1996;46(3):619-627). (See sidebar, Diagnostic Criteria for Nervous System Lyme Disease.)

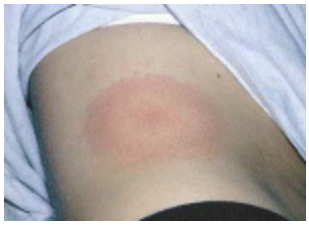

Figure. The bull's-eye erythema migrans is typically an indicator of possible Lyme disease.

Figure. Often, those with suspected Lyme disease do not recall exposure to the tick bite or resulting rash. Typically, the deer tick measures less than 1.5 cm.

Because the chronic symptoms of Lyme disease are thought to mimic other diseases - including rheumatoid arthritis, peripheral neuropathy, multiple sclerosis, and systemic lupus erythematosus - it is sometimes called the great imitator.

In the acute phase, Lyme disease is characterized by a localized erythematous, annular rash - the bull's eye rash - and sometimes flu-like symptoms. Without early, adequate antibiotic therapy, it may progress to a disabling multisystem illness, affecting the musculoskeletal system, CNS, and, rarely, the cardiovascular system.

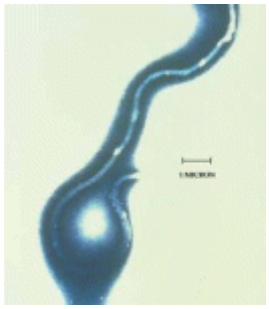

Figure. This is a photomicograph of *Borrelia burgdorferi*, the bacterium that causes Lyme disease.

Up to 50 percent of infected patients do not recall the tick bite or rash, so neurologic problems may be the first symptoms. Estimates of the incidence of neurologic complications of Lyme disease range from 15 to 40 percent. Patricia K. Coyle, MD, Professor of Neurology and Acting Chair of the Department of Neurology at the State University of New York at Stony Brook, thinks the figure may be somewhat lower - more like 10 percent or less.

Figure. Dr. Patricia Coyle: I think the incidence [of neurologic complications of Lyme disease] is decreasing, primarily because of raised awareness among the public and clinicians that early, adequate antibiotic therapy can prevent long-term complications in most cases.

In fact, Dr. Coyle told *Neurology Today*, I think the incidence is decreasing, primarily because of raised awareness among the public and clinicians that early, adequate antibiotic therapy can prevent long-term complications in most cases.

Nevertheless, she added, neurologic manifestations continue to be a problem for some patients. Diagnostic uncertainty and inadequate initial antibiotic therapy are contributing factors.

MAKING THE DIAGNOSIS

Initial diagnosis of Lyme disease is based on clinical and serologic findings. In patients with the typical rash and supportive serological results, the diagnosis is relatively straightforward. In addition to a history of exposure in an endemic area and a physician-diagnosed erythema migrans rash of at least 5 cm, the Centers for Disease Control and Prevention (CDC) criteria for a diagnosis of Lyme disease include positive serologic results based on enzyme-linked immunabsorbent assay (ELISA) and Western blot findings. However, in those patients without the rash and no memory of a tick bite, the picture is less clear.

According to Brian Fallon, MD, Associate Professor of Psychiatry and Director of the Lyme Disease Unit at Columbia University in New York, NY, ELISA is 64 percent sensitive in patients with later stage disease (*J Infect Dis* 1996;174:346-353). The Western blot offers considerably more information, Dr. Fallon said. The CDC criteria require two bands on the IgM and five on the IGG for a positive diagnosis. Three or four bands on the IgG are considered suggestive of Lyme disease.

However, the CDC criteria should not be regarded as definitive, according to Carolyn Barley Britton, MD, Associate Professor of Neurology at Columbia University. The criteria should be used to include, but not to

exclude patients, Dr. Britton said. If clinical symptoms and an epidemiologic risk are present and no other diagnosis can be made, clinicians should have a high index of suspicion for Lyme disease and treat the patient accordingly. By relying only on CDC criteria, some patients with Lyme disease go unrecognized and untreated.

Figure. Dr. Carolyn Barley Britton: If clinical symptoms and an epidemiologic risk are present and no other diagnosis can be made, clinicians should have a high index of suspicion for Lyme disease and treat the patient accordingly.

VARIED TESTING RESULTS

Results of laboratory testing for neurologic Lyme disease vary depending on the stage of the illness. The CSF may appear normal in patients with early CNS involvement or late-stage infection (encephalopathy), according to Dr. Fallon. In the presence of clinical signs of meningitis or encephalitis, spinal tap may reveal a mononuclear pleocytosis, mildly increased protein, and occasionally an elevated IgG index or oligoclonal immunoglobulins.

Figure. Possible exposure in areas considered endemic to the tick-borne spirochete that causes Lyme disease is considered when diagnosing the disease. The most recent US estimates show Lyme disease is mostly localized to states in the northeastern, mid-Atlantic, and upper north-central regions, and to several counties in northwestern California.

However, one third of patients with neurologic Lyme disease are thought to have misleadingly negative CSF results, Dr. Fallon said. Lyme disease is rarely diagnosed by culturing the organism. *B. burgdorferi* has been cultured from skin, CSF, blood, and joint fluid, but the yields are low. Polymerase chain reaction [PCR] has also been used to identify genetic material from *B. burgdorferi* but it is uncertain whether finding genetic material means that the organism is still viable and causing current infection. It is also uncertain whether DNA identification means there is antigen stimulation of the host, which may itself cause a 'reactive' inflammatory syndrome, even without actual infection. Thus, PCR in CSF is not reliable for diagnosing neurologic patients.

TREATMENT

In the acute phase, a three-week course of doxycycline or amoxicillin is recommended. In most cases, one course is sufficient to eliminate symptoms and prevent progression of the disease. In patients with neurologic symptoms in whom a diagnosis of Lyme disease is suspected, standard therapy is a four-week course of intravenous ceftriaxone or cefotaxime. Because laboratory testing does not always confirm the diagnosis, clinicians are faced with the dilemma of whether to treat a seronegative patient.

LYME ENCEPHALOPATHY

Some patients report continued symptoms after antibiotic treatment, however. This has been called the post-Lyme syndrome, chronic Lyme disease, or Lyme encephalopathy (*Ann Intern Med* 2002;136:413-419). There is no currently agreed upon definition of Lyme encephalopathy. Early definitions included fatigue, memory loss, depression, inability to concentrate, sleep disturbance, irritability, and difficulty finding words. However, these symptoms are totally subjective and overlap with those of independent depression. Laboratory signs of CNS involvement or objective evidence of impairment in cognitive testing are likely to be equivocal at best.

In one study, patients continued to report memory problems three to 12 months after antibiotic therapy. Although they performed significantly worse on measures of verbal fluency and memory than healthy controls, they did not differ on tests of attention, psychomotor skills, and executive functioning (*Arch Neurol* 1991;48:1125-1129).

In another study, patients with Lyme disease who continued to report problems after treatment demonstrated no performance abnormalities on neuropsychological testing (*Appl Neuropsychol* 1999;6:19-26).

According to the panel of experts that developed clinical guidelines for the treatment of Lyme disease for the Infectious Diseases Society of America, there is no such diagnostic entity as chronic Lyme disease (*Neurology* 2000;60:1888-1889). This may be in part due to the fact that studies to date on the use of antibiotics to treat the problem have had mixed results.

DURATION OF THERAPY

In the latest studies, Lauren Krupp, MD, and colleagues studied the effects of intravenous antibiotic therapy or placebo in 55 patients with Lyme disease with persistent fatigue attributed to chronic Lyme disease for at least six months after antibiotic therapy (*Neurology* 2003;60:1916-1922). To enter the study, one had to meet a predetermined severity level of fatigue. Compared with the placebo group, those treated with ceftriaxone showed improvement in disabling fatigue, but no beneficial effect was observed for cognition or laboratory measures of persistent infection, such as CSF levels or outer surface protein-A (OSP-A), a biological marker for *B. burgdorferi* (*Neurology 2003*; 60:1923-1930).

The problem is that the results of that study have been widely misinterpreted, Dr. Fallon said. "The main finding was that on the fatigue measure for which patients were recruited with a specific severity level, patients given IV antibiotics were 3.5 times more likely to have improved at the six month evaluation than patients given IV placebo.

Although there was no improvement in cognition or on detection of OSP-A, this is not surprising given that patients who entered the study were not required to have abnormalities in these areas at the start of the study.

In another study, Richard Kaplan, MD, enrolled 129 patients with a documented history of Lyme disease and examined the impact of 30 days of IV ceftriaxone treatment followed by 50 days of oral doxycycline therapy on cognitive function, pain, role functioning, and mood (*Neurology* 2003;60:1916-1922). They found that additional antibiotic therapy was not more beneficial than administering placebo.

In an editorial commenting on the studies by Drs. Kaplan and Krupp, Israel Steiner, MD, of the Department of Neurology at Hadassah University Hospital in Jerusalem, wrote: Although these studies do not provide credence to the possibility that PLD [post Lyme disease] is due to an infective process, at present the interpretation of the data does not prove that the condition does not exist, that there is no ongoing infection, or that the treatment protocols are or are not the appropriate ones. Most importantly, without an objective surrogate (preferably biological) marker to enable recruitment of homogenous study groups, every attempt to address clinical questions in the realm of PLS is doomed, almost by definition, to leave these questions unsettled (*Neurology* 2003;60(12):1888-1889).

Dr. Coyle agrees with that observation, adding that results of studies to date indicate that patients with persistent symptoms of Lyme disease do not respond to antibiotics in any meaningful clinical way, nor is there a response in biologic markers. But, she observed: This perhaps suggests that patients who are believed to have chronic Lyme disease have a syndrome that is not antibiotic-responsive.

Thus the use and duration of antibiotic therapy in Lyme encephalopathy remains controversial. Dr. Coyle noted that in some areas of the country, patients are being treated for months to a year or more with daily parenteral or oral antibiotics.

To date, no scientifically controlled study reported in the medical literature has demonstrated added efficacy from extending therapy longer than four to six weeks, Dr. Coyle said. Added expense and toxicity are often the only proven results of extended therapy.

There is a mistaken assumption that persisting seropositivity equates with persisting infection, she added. In some cases, the chronic symptoms may result from an immune inflammatory syndrome or concomitant infection

with another pathogen transmitted by the tick at the time of infection with Lyme disease. Also, it may have been acquired independently or could be a psychogenic disorder, she said.

Ticks are dirty reservoirs and can carry multiple strains of *B. burgdorferi* and multiple different types of organisms, such as parasites, rickettsial-like agents, and viruses.

In an effort to shed light on the efficacy and duration of antibiotic therapy, Dr. Fallon and Dr. Britton are involved in an NIH-sponsored, randomized, placebo-controlled study of brain imaging and treatment of persistent Lyme encephalopathy. Patients are being treated with intravenous ceftriaxone for 10 weeks, with a 14-week antibiotic-free follow-up period. At the end of the six-month study, patients randomized to placebo receive six weeks of antibiotic therapy. PET and neuropsychiatric testing are being used to evaluate patients at baseline and at 12 and 24 weeks.

We are using sophisticated PET techniques to study both cerebral metabolism and cerebral blood flow to assess benefits associated with treatment, Dr. Fallon said. We hope to be able to report the results in 2005.

TAKE HOME MESSAGES

Current knowledge of Lyme disease remains incomplete in two major areas - diagnosis and optimal treatment for patients with persistent symptoms. The absence of reliable laboratory tests makes it impossible to definitely exclude a diagnosis of Lyme disease, Dr. Britton said.

It is important not to overly rely on the presence of a rash or a patient's memory of a tick bite. Lyme disease should always be considered, particularly in patients presenting with a flu-like illness in the summer, because it is a treatable condition.

Although the prevalence of seronegative patients with Lyme disease is not known, these patients, though rare, clearly exist, she commented. Physicians should also be aware that patients with a seronegative illness may be infected with another pathogen transmitted by a tick.

Experts agree that prospective microbiologic and clinical studies are needed to identify risk factors that may predispose certain patients to develop Lyme encephalopathy and to distinguish those patients who will benefit from prolonged or repeated antibiotic therapy.

ARTICLE IN BRIEF

✓ Nearly 20 years after Lyme disease was first linked to the tick-borne spirochete *Borrelia burgdorferi*, there is a lack of consensus about the diagnosis and best treatment for patients with persistent neurologic symptoms.

✓ Experts are divided as to whether patients with neurologic symptoms who are seronegative for Lyme disease should be treated with antibiotics and how long that therapy should continue.

DIAGNOSTIC CRITERIA FOR NERVOUS SYSTEM LYME DISEASE

1. Possible exposure to appropriate ticks in an area where Lyme disease occurs.

2. One or more of the following:

* Erythema migrans or histopathologically proven *Borrelia lymphocytoma* or acrodermatitis

* Immunologic evidence of exposure to *B. burgdorferi*

* Culture, histologic, or polymerase chain reaction proof of the presence of *B. burgdorferi*

3. Occurrence of one or more of the neurologic disorders described below, after exclusion of other potential etiologies. Additional testing may be necessary. CSF analysis for cells, protein, and intrathecal production of specific antibody is indicated if CNS infection is suspected.

A. Causally related neurological disease:

* Lymphocytic meningitis with or without cranial neuritis, painful radiculoneuritis, or both

* Encephalomyelitis

* Peripheral neuropathy

B. Causally related syndrome:

* Encephalopathy

C. Causal relationship asserted but highly unlikely:

* Multiple sclerosis

* Amyotrophic lateral sclerosis

* Dementia

4. Based on a literature review and expert opinion, the following recommendations are supported as options.

* Localized disease is usually responsive to oral antimicrobial regimens (e.g., doxyclycline or amoxicillin for three weeks).

* CNS infection probably requires parenteral antimicrobial therapy (for example, ceftriaxone or cefotaxime for two to four weeks), although limited data suggest oral regimens may be efficacious in acute meningitis.

Source: Neurology 1996:46(3):619-627.

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