Delayed Diagnosis of Neuroborreliosis Presenting as Bell Palsy and Meningitis

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Lyme disease is most prevalent in the northeast and upper Midwest regions of the United States. While early symptoms may be mild (eg, rash, flu-like symptoms, joint pain), late or persistent infection can cause chronic neurologic impairments. Because of this range of symptoms, physicians can have difficulty diagnosing Lyme disease, especially in the absence of erythema chronicum migrans. We report a case of a woman who initially presented with severe vertigo and vomiting and later with fever, headache, and facial droop. After more than 3 weeks of misdiagnosis, the patient tested positive for Lyme disease and was diagnosed as having neuroborreliosis presenting as Bell palsy and meningitis. The authors review the history, diagnosis, and management of Lyme disease.

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Report of Case
In October 2008, a 63-year-old white woman presented to our emergency department in Watertown, New York, and described various symptoms she had during the past 3.5 weeks. Her chief concern was a right-sided facial droop.

Patient Medical History
In September 2008, 3.5 weeks earlier, the patient presented to our emergency department complaining of severe vertigo and vomiting. She was treated with meclizine hydrochloride after a head computerized tomography scan yielded normal results. The patient followed up with her primary care physician 2 days later, at which time her symptoms were nearly resolved.

Three days after seeing her primary care physician, the patient presented to our emergency department again with a fever. She was diagnosed as having a urinary tract infection and was prescribed a 10-day course of orally-administered ciprofloxacin. At a 2-day follow-up with her primary care physician, the patient described severe headaches that felt like “bombs going off in her head.” The physician told the patient that she did not have a urinary tract infection and diagnosed temporal arteritis and prescribed prednisone. The physician did not confirm this diagnosis with a biopsy.

Two weeks after beginning doxycycline therapy, the patient awoke and noticed that the right side of her face was drooping, with her right eyebrow approximately 0.5 inches lower than her left eyebrow. The patient had difficulty closing her right eye, and saliva drooled from the right corner of her mouth. The patient also described severe pains shooting down her neck and blurred vision in her right eye.

Later that day, the patient visited an ophthalmologist, who suggested that she had Bell palsy. The ophthalmologist sent the patient to our emergency department for further evaluation.

Presentation
At our emergency department, we performed a lumbar puncture and consulted an infectious disease specialist. Results of cerebrospinal fluid testing showed lymphocytosis (>85% lym-
phocytes) and an elevated protein level (166 mg/dL). In light of these findings and the positive Lyme titer blood test results, the patient was admitted to our hospital with a diagnosis of neuroborreliosis presenting as Bell palsy and meningitis.

During hospitalization, the patient received a peripherally inserted central catheter (PICC) line and was administered ceftriaxone sodium intravenously at a dosage of 2 g/d and a tapering course of prednisone. Findings from magnetic resonance imaging and magnetic resonance angiography scans of the patient’s brain were normal.

The patient was discharged from our hospital 6 days later and followed up with an infectious disease specialist. Her right-sided facial droop had improved and her meningeval symptoms resolved.

Four days after being discharged, however, the patient developed new symptoms. That evening, the patient had difficulty moving her lips, and the next morning she noticed that she also had a left-sided facial droop. Due to these new symptoms, that patient was concerned that she might have had a stroke and she presented again to our emergency department.

At presentation, the patient was weak on both sides of her face and had difficulty swallowing liquids. The patient also complained of occasional headaches and difficulty speaking. She denied any vertigo, nausea, diplopia, or blurred vision and was able to chew without much difficulty despite some numbness to her tongue. The patient’s hearing was normal, and she did not describe arthralgia, rashes, or joint swelling. Her neck was supple, and she did not have any meningeval signs on examination.

Initial laboratory and diagnostic evaluations at this time included an electrocardiogram, complete blood cell count, bone morphogenetic protein, and plain chest radiograph, all of which revealed normal findings. The patient continued ceftriaxone sodium therapy via the PICC line and began a tapering course of prednisone starting at 40 mg/d.

During this second hospitalization, a neurologist was consulted. Other than the patient’s previously identified symptoms (ie, facial droop), results of the patient’s neurologic examination were normal. While the neurologist thought the patient’s facial diplegia was secondary to neuroborreliosis, blood tests were ordered to rule out other causes such as sarcoidosis, vasculitis, myasthenia gravis, and idiopathic polyneuritis. Erythrocyte sedimentation rate, antinuclear antibodies, rheumatoid factor, lupus anticoagulant, angiotensin converting enzyme, rapid plasma reagin, acetylcholine receptor antibody, vitamin B<sub>12</sub>, and folic acid level test results were normal.

The patient was also examined by a speech therapist during her second hospitalization. The patient had no intrinsic problem swallowing—just difficulty with facial muscle paralysis, which improved greatly during this second admission. The patient continued to have a mild right-sided facial droop, however.

The patient was discharged to home 2 days after second hospital admission. She was prescribed the same tapering course of prednisone and continued ceftriaxone sodium therapy via a PICC line.

After discharge, the patient continued to follow-up with the infectious disease specialist. By January 2009, she had achieved near complete resolution of her symptoms except for mild right facial palsy and droop with some weakness when she attempted to pucker her lips. She was instructed to follow up with her primary care physician and the infectious disease specialist as needed.

The patient, an avid gardener, was advised to wear long sleeves and long pants when outside the home and to use DEET in the summer. She was also given information on how to carefully examine herself and remove ticks when going indoors.

**Comment**

**Background**

Lyme disease is a vector-borne illness transmitted to the human host via *Ixodes scapularis* and *Ixodes pacificus* ticks harboring the spirochete *Borrelia burgdorferi*. It is the most common vector-borne disease in the United States, accounting for more than 90% of such illnesses. Lyme disease is most prevalent in the northeast and upper Midwest, with the majority of cases occurring during late spring, summer, and early autumn. *Ixodes* ticks feed on a variety of animals, most commonly white-footed mice and white-tailed deer. Lyme disease is not often found in the southeastern and western United States because, in those areas, *Ixodes* ticks prefer to feed on lizards, which are not prone to *Borrelia burgdorferi* infection. Although Lyme disease is not known to develop in wild animals, the ticks can feed on domesticated animals such as cattle, horses, and even dogs.

As ticks mature, they go through larval, nymph, and adult stages. At each stage, they require a blood meal for survival. The ticks hatch as larvae from eggs in the ground during the late spring and summer months. After hatching, the larvae attach themselves to the skin of animals on which they feed. It is during the next stage of tick development—the nymph—that ticks are most hazardous to humans. Nymphs are miniscule (<2 mm), making them exceedingly difficult to spot. *Ixodes* ticks in the nymph stage cause most cases of Lyme disease for this very reason, despite the fact that the larger adult ticks are more likely to carry *Borrelia burgdorferi*.

Humans contract *Borrelia burgdorferi* via the tick bite. The spirochete resides in the guts of *Ixodes* ticks and is transferred to the bloodstream of the host through saliva and regurgitated contents. Approximately 24 hours or more of feeding are necessary to transmit the spirochete to the human host.

**Stage 1**—In nearly 80% of cases, Lyme disease begins as erythema chronicum migrans, a red rash at the site of the tick bite that is pathognomonic for the disease. Erythema chronicum migrans indicates stage 1, or localized infection, developing after an incubation period ranging from 3 to 32 days.
The rash, classically 5 to 6.8 cm in diameter, often appears with a central clearing or center of purpura, giving it a “bull’s eye” appearance that may be mistaken for ringworm by the uneducated eye. On darker-skinned individuals, the rash may simply appear as a bruise.

In endemic areas of the United States, homogeneous red rashes may be more frequent. Though not often painful, the lesions may sometimes be hot to the touch and elicit a burning and itching sensation. The lesions may also become vesicular and necrotic. Common sites include the legs, groin, and axilla.

**Stage 2**—The second stage of the disease, disseminated infection, occurs within days or weeks after onset of the rash. Lymphatic or hematogenous spread may affect many different bodily sites, making diagnosis particularly challenging. At this stage, neurologic sequelae including meningitis, photophobia, confusion, altered consciousness, ptosis, facial paralysis, paresthesias, dysarthria, and even hallucinations may ensue. Although these symptoms can resolve, they may lead to chronic disease without treatment.

The second stage of the disease is also frequently characterized by flu-like symptoms such as fatigue, lethargy, myalgia, arthralgias, stiff neck, headache, nausea, sore throat, fever, and chills. Many of these symptoms become less severe or disappear within several weeks, even in untreated patients. Migratory joint pains also commonly occur in the second stage. In a small minority of patients (about 8%), cardiac complications may arise, including atrioventricular nodal block, myopericarditis, cardiomegaly, and pancarditis. Although these symptoms last for only a few weeks, they may recur in untreated patients.

During disseminated infection, *Borrelia burgdorferi* can be found in the blood, cerebrospinal fluid, myocardium, retina, meninges, brain, bone, spleen, and liver. The spirochete is thought to spread by binding to plasminogen and its activators as well as a number of host receptors.

It is also during the disseminated infection stage that adaptive B- and T-cell responses produce antibodies against the organism. An IgM response is associated with polyclonal activation of B cells, including heightened amounts of cryoglobulins, circulating immune complexes, and serum IgM.

In response to nonprotein antigens and spirochetal polypeptides, an IgG response develops slowly over weeks to months.

Despite this active immune response, *Borrelia burgdorferi* can survive for years within the skin, joints, and nervous system through lipoprotein antigenic variation and down-regulation of surface proteins. In neuroborreliosis and Lyme arthritis, patients’ CD4+ helper T cells preferentially produce interferon gamma-1b, a pro-inflammatory cytokine.

**Stage 3**—Months after the initial onset of symptoms, late or persistent infection (stage 3) can affect the nervous system, the musculoskeletal system, and the skin. Arthritis, typically oligoarticular arthritis of the large joints, develops in as many as 60% of untreated patients. While less common, memory loss, mood changes, and sleep disorders secondary to subtle encephalopathy may also occur during this phase of the disease.

Even after years of latent infection, chronic neurologic impairments may occur in about 5% of untreated cases. In addition to those previously mentioned, impairments may include axonal polyneuropathy marked by spinal radicular pain or distal paresthesia. These chronic neurologic impairments may resemble those of another spirochetal infection, tertiary syphilis.

**Diagnosis**

*Borrelia burgdorferi* may be cultured in Barbour-Stoenner-Kelly medium early in the disease—primarily from skin lesions—for a definitive diagnosis. However, Lyme disease is usually diagnosed by the previously discussed characteristic clinical presentations (eg, rash) in combination with serologic testing.

The diagnostic approach may vary depending on disease probability and severity of symptoms. If a patient presents with a clear-cut case of erythema chronicum migrans, the physician may diagnose Lyme disease solely on clinical findings and initiate appropriate treatment. In the absence of such a clear-cut finding, however, the Centers for Disease Control and Prevention recommend a 2-step approach in which equivocal or positive enzyme-linked immunosorbent assay (ELISA) testing is followed by the more specific Western blot.

A lumbar puncture may need to be performed if the patient presents with neurologic complications. In such instances, results of cerebrospinal fluid testing will be abnormal, exhibiting lymphocytosis and an elevated protein level. Cerebrospinal fluid isolates are not found in patients with chronic neuroborreliosis. *Borrelia burgdorferi* DNA has only been detected in a small sample of patients.

Results of ELISA testing are best interpreted in light of patients’ epidemiologic histories. Because serologic reactions are insensitive during roughly the first 2 weeks of infection, only 50% of patients with early-stage Lyme disease have positive serology test results. IgM antibodies appear 2 to 4 weeks after the onset of erythema chronicum migrans. IgG antibodies appear 4 to 6 weeks after the onset of erythema chronicum migrans. IgG antibody levels will remain low even with successful treatment, while IgM usually drops off to very low levels 6 months after disease onset.

After 4 weeks, most patients with active Lyme disease infection will have a positive IgG antibody response. Because of the persistence of IgG and IgM antibodies for many years after treatment, a positive IgM test alone is likely a false-positive after 1 month of active infection and likewise should not be used to diagnose Lyme disease after this period. Although ELISA testing may reveal intrathecal production of IgM, IgG, or IgA antibodies to *Borrelia burgdorferi*, positive test results are less common in chronic cases of neuroborreliosis.
During the early stage of Lyme disease, ELISA testing has 59% diagnostic sensitivity and 93% diagnostic specificity. During late stage disease, ELISA testing has 95% sensitivity and 81% specificity. Serology plus Western blot testing has a diagnostic sensitivity range of 50% to 75% and a specificity of 99% to 100%.[11]

Neither ELISA nor Western blot testing is able to distinguish active from inactive infection. Consequently, other tests that detect Borrelia burgdorferi directly are being investigated. As previously mentioned, the spirochete may be cultured from skin lesions, but cultures from other sites have been less successful. Borrelia burgdorferi DNA has been detected by polymerase chain reaction in synovial fluid samples. This type of test may replace culture testing in cases of Lyme arthritis. One study showed a sensitivity of 85% in such cases. Polymerase chain reaction—sensitivity was much lower, however, in cerebrospinal fluid obtained from patients with neuroborreliosis.[8]

**Treatment**

Oral antibiotic therapy (e.g., doxycycline, amoxicillin, cefuroxime, erythromycin) will suffice for most cases of early localized or disseminated Lyme disease infection. Neuroborreliosis, however, typically requires intravenous therapy, except in cases where a facial palsy is the sole presenting symptom. In such cases, oral regimens may be adequate.[4]

A typical intravenous regimen for treating neuroborreliosis includes a daily dose of ceftriaxone (2 g/d) for 14 to 28 days. Alternatively, a dosage of penicillin G at 20 × 10⁶ U/d, divided into doses of 5 × 10⁶ four times per day for 14 to 28 days may be used to treat patients with neuroborreliosis. For patients allergic to penicillin, a dosage of orally-administered doxycycline at 100 mg 3 times daily for 2 to 4 weeks is recommended.[14] However, some authorities find this regimen ineffective.[4] Among patients with disseminated infection, about 15% experience a Jarisch-Herxheimer reaction within 24 hours after the initiation of therapy.[4]

LYMERix vaccine (recombinant OspA) was available from 1998-2002 but was withdrawn from the market because of concerns of neurologic impairments among vaccinated patients. Adverse effects also included arthralgias, myalgias, and sores at the injection site. In addition, the vaccine caused false-positive tests and Lyme disease in some recipients.[15]

Evidence of relapsing neuroborreliosis is rare after appropriate intravenous antibiotic therapy with ceftriaxone. A postinfectious syndrome, however, has been described. It includes subjective neurocognitive difficulties that may last for years, as well as musculoskeletal pain and fatigue similar to chronic fatigue syndrome and fibromyalgia.[4] Prolonged antibiotic coverage is not warranted in these cases and may even be dangerous. Supportive and symptomatic treatment is advised.

**Conclusion**

The present case illustrates the difficulties in diagnosing Lyme disease, especially when neurologic symptoms predominate. Because Lyme disease produces a variety of symptoms, diagnosis can be challenging without the tell-tale sign of erythema chronicum migrans. This difficulty in diagnosing the disease can be distressing to the patient and costly to the healthcare system. We encourage physicians to maintain a high level of clinical suspicion for Lyme disease, especially in endemic areas. In addition, physicians should be aware that the disease may present without the rash and as neurologic complications, as demonstrated in the present case.

**References**