Lyme Neuroborreliosis: A Diagnostic Headache

Case 1: A 4-year-old girl presented to our emergency department (ED) during the height of summer with 5 days of left-sided facial droop, which spared the forehead. The patient also complained of severe fatigue, 1 week of frontal headaches, urinary retention, intermittent erythematous rash around her eyes and behind her knees, and an increase in night terrors. Three days before admission, she was seen by her pediatrician, who sent Lyme serologies and empirically started amoxicillin given that the patient lived in an endemic area. She notably had no known history of tick bite or rash. Lyme serologies returned negative, so the patient was referred into our ED.

The patient had 2 previous admissions to the neurology service 2 weeks and 3 weeks before the current presentation. The first presentation was for complaints of fever, urinary dribbling despite normal fluid intake, and bilateral lower extremity pain and weakness. Laboratory data including complete blood cell count (CBC) were within normal limits except for mildly elevated inflammatory markers of erythrocyte sedimentation rate of 32 mm/h and C-reactive protein (CRP) of 2.6 mg/dL. The patient improved overnight with supportive care, and the patient’s symptoms were attributed to a viral process. Outpatient lumbar magnetic resonance imaging (MRI) was scheduled to evaluate for tethered cord, and the patient was discharged. The next week, the patient presented for her second admission with cough, fatigue, intermittent urinary dribbling and retention, and an erythematous rash around her eyes. Inflammatory markers were slightly improved (erythrocyte sedimentation rate 27 mm/hr, CRP 0.8 mg/dL). Lumbar MRI was normal. The patient again improved with supportive care and was discharged with a diagnosis of a viral upper respiratory infection.

There was particular concern on the patient’s third presentation given her continued fatigue, urinary retention, and new-onset headaches and night terrors. Physical examination in the ED included a left peripheral cranial nerve VII paralysis with an otherwise nonfocal neurologic exam. Given reasonable concern for Lyme disease, Lyme serologies were again drawn and amoxicillin was restarted. Despite treatment, the patient’s symptoms continued. Given a strong family history of autoimmune disease, an expansive rheumatologic and neurologic workup was obtained, all of which returned negative. Infectious disease (ID) was also consulted. Because of the odd combination of symptoms and broad differential including multiple sclerosis, acute disseminated encephalomyelitis, viral meningitis, or an oncologic process, a brain MRI and lumbar puncture (LP) were obtained. MRI of the brain showed abnormal enhancement of the distal canalicul and labyrinthine segments of the facial nerves, asymmetrically more
enhancement on the left, consistent with the reported history of cranial nerve VII palsy. There was also notably abnormal enhancement of multiple other cranial nerves. LP was notable for elevated total white blood cell count (WBC) of 44 with 71% lymphocytes and 25% atypical lymphocytes, 1 red blood cell, normal glucose at 47 mg/dL, and elevated protein at 62 mg/dL. After these studies were completed, Lyme serologies returned with both Lyme immunoglobulin (Ig)M and IgG enzyme immunoassay (EIA) results positive. Confirmatory Western Blot returned positive for IgM with 2 of 3 bands but negative for IgG with 3 of 10 bands. The patient was started on a 14-day course of intravenous ceftriaxone for Lyme neuroborreliosis, and her symptoms rapidly improved overnight. The patient was discharged the next day and has remained asymptomatic since completing her treatment.

Case 2: A 4-year-old boy presented to our ED during the summer with severe abdominal pain and headaches. Symptoms initially started 15 days before admission after receiving routine vaccinations. He developed a persistent fever without other localizing symptoms. Five days after onset of fevers, he developed intermittent headaches. His pediatrician obtained a CBC, which had a normal WBC count but monocytosis of 21%, and a CRP, which was mildly elevated at 1.2 mg/dL. There was no recent history of a tick bite or rash. The patient lived on a farm in an endemic area, and his father was recently diagnosed with Lyme disease, prompting Lyme serologies to be sent. The EIA was positive for IgM and negative for IgG, and confirmatory Western blot was negative for both antibodies. The next day, the patient defervesced, but he developed severe intermittent periumbilical abdominal pain. An abdominal x-ray done at that time showed a significant stool burden; after an enema, abdominal pain was relieved, and headaches did not continue. However, his abdominal pain and headaches returned after 4 symptom-free days. His pediatrician then prescribed Cefdinir for presumed sinus infection, of which the patient took only 1 dose because of emesis. His symptoms continued to increase in severity over the next 3 days, so the patient presented to another hospital’s ED on day 14 of illness. Computed tomography of the abdomen and pelvis was done, which showed concern for intermittent ureteropelvic junction obstruction that was not felt to be consistent with the patient’s abdominal pain; head computed tomography showed no abnormalities. A urinalysis, complete metabolic panel and CBC were unremarkable. Lyme serologies were sent, he received a dose of intravenous ceftriaxone for possible Lyme neuroborreliosis, and he was transferred to our facility for additional workup and management.

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At our facility, physical examination was noted to be completely normal, including a bedside, undiluted fundoscopic examination. Repeat Lyme serologies were sent at our hospital per maternal request. Antibiotics were initially discontinued, and the patient had an extensive workup by urology, gastroenterology, neurology, and ID. Ophthalmology was also consulted in the setting of persistent headaches, who noted mild papilledema bilaterally. Patient then received an MRI brain and an LP per neurology and ID recommendations given the papilledema and persistent headache. MRI showed contrast enhancement of several cranial nerves, (Figures 1 and 2) and LP revealed elevated total WBC at 57 with 96% lymphocytes and 4% monocytes, glucose of 44 mg/dL, and protein of 22 mg/dL. The gram stain and cultures were negative. Lyme studies from cerebral spinal fluid were not sent. At this time, Lyme serologies completed at the outside hospital (OSH) and our hospital, done 10 days after initial testing, resulted. Both our results and OSH Lyme IgM and IgG EIA were reported positive. The OSH confirmatory Western blot was positive for IgM with 3 of 3 bands and negative for IgG with 4 of 10 bands; the results at our institution were similar having a positive IgM with 2 of 3 bands and negative IgG with 2 of 10 bands. He was started on intravenous ceftriaxone for Lyme neuroborreliosis to complete a 14-day course. Abdominal pain and headache resolved completely upon follow-up.

Question 1: What are the various presentations of Lyme neuroborreliosis, and how did these patients’ differing presentations fit into this diagnosis?

Discussion: Lyme disease is the most common tickborne disease in the United States and Europe. In the United States, it is caused only by the spirochete Borrelia burgdorferi sensu stricto, whereas in Europe, there are 5 Borrelia subspecies that may cause Lyme disease.1 The bacteria are passed through the hosped tick primarily during the summer months in endemic regions. Clinical findings include cutaneous manifestations, such as erythema migrans during the early stage and atrophic chronic acrodermatitis during the late stage, and extracutaneous manifestations affecting the heart, peripheral and central nervous systems, and joints during the early disseminated and late stages.2 These various stages can
present in a nonlinear fashion, making diagnosis difficult.

Neurologic manifestations of Lyme disease vary, but prompt recognition and diagnosis is important. In the United States, prevalence of Lyme neuroborreliosis with respect to all Lyme cases is <10%, whereas in Europe, prevalence is 35%. The most common presentations in children in the United States are facial palsy, headache, and aseptic meningitis. The meningitis can be difficult to distinguish from enterovirus meningitis given the same summer and fall seasonal predominance. It is reported that in children, however, papilledema is more common in Lyme meningitis. Cranial neuritis is also commonly seen in the United States, which most often affects cranial nerve VII peripherally, causing a unilateral or bilateral facial droop. All cranial nerves have been reported to be affected in Lyme neuroborreliosis except cranial nerve I. European Lyme neuroborreliosis more commonly presents as Bannwarth’s syndrome, which is a triad of lymphocytic meningitis, cranial neuritis, and radiculitis. Radicular pain is dermatomal and often characterized as a burning, neuropathic pain, and it is believed that the dermatomal distribution may be related to the location of the initial tick bite. The high European prevalence is likely due to the different Borrelia subspecies in Europe; however, this triad has been reported in the United States. It is unclear if the significantly lower prevalence of this syndrome in the United States is due to lack of recognition or true lack of prevalence, but it is notable that in a series of 96 children with Lyme disease in North America, only 2% of patients had peripheral nervous system symptoms. Other neurologic manifestations of early disseminated Lyme disease include transverse myelitis, plexopathies, mononeuropathy multiplex, and complex mononeuropathy multiplex. These syndromes, which can have such varying presentations as bilateral leg weakness, urinary retention, and sensory abnormalities, can mimic such diseases as Guillain-Barré, multiple sclerosis, and acute disseminated encephalomyelitis and lead to diagnostic difficulty for the clinician. History or presence of erythema migrans rash is helpful with diagnosis but is not always available. Because of the non-specific nature of symptoms that can present as Lyme neuroborreliosis, if an erythema migrans rash is not present, laboratory data are required to support the diagnosis of Lyme disease, which typically includes peripheral and/or intrathecal Lyme serologies.

Given the multiple presentations of Lyme neuroborreliosis, it was important...
to consider Lyme disease for our cases, particularly given the summer season and their living in an endemic area. Case 1 showed signs of some of the more rare manifestations of Lyme neuroborreliosis, including leg weakness with urinary retention. Weakness, fatigue, and general malaise are common and were present throughout Case 1’s presentation; however, Lyme disease was not high on the differential until she presented with a cranial nerve VII palsy and subsequently was found to have a lymphocytic meningitis and cranial neuritis on MRI. Interestingly, the waxing and waning symptoms with which she presented are not clearly delineated in the literature, and given a strong family history of autoimmune disease, as well as negative initial Lyme serologies, there was a concern that Lyme disease did not explain her clinical presentation. However, extensive rheumatologic and neurologic workup was negative, and the patient’s various symptoms resolved with treatment.

Case 2, in presenting with abdominal pain and headache, also had a large differential diagnosis, but his subsequent clinical findings suggest a picture of Bannwarth syndrome, including abdominal pain secondary to a radiculitis. It is notable that a description of the quality of pain in this patient was limited by his age.

**Question 2: What are the limitations of Lyme serology in diagnosing Lyme disease?**

**Discussion:** Our patients had several Lyme serologies drawn at different time points over the course of their illnesses that were initially negative and later became positive. This may have contributed to a delay in treatment, and it is important to understand the limitations of Lyme testing.

Diagnosis of Lyme disease without the classic erythema migrans rash or known history of a tick bite can be difficult. There is currently no gold standard for diagnosis, but general practice standards involve 2-tier testing of EIA followed by confirmatory Western blot as determined by the Dressler criteria. EIA tests for serum IgM and IgG titers to *B burgdorferi*, and if elevated, confirmatory Western blot identifies IgM and IgG that are responsive to certain spirochete proteins. A positive Lyme test requires 2 of 3 IgM bands to be positive and/or 5 of 10 IgG bands. EIA lends sensitivity to the test, whereas the Western blot adds specificity. Other tests that may be done include Lyme polymerase chain reaction and *Borrelia* cultures, which all have their own limitations and may not all be readily available at different sites.

Several factors can affect the outcome of Lyme serologies. As with many serologic tests, there is a window period before elevated Ig levels can be detected in the serum, and with Lyme disease, this window period can be anywhere from 2 to 6 weeks, although 1 study found that the IgM peak, whether in localized or disseminated disease, most often occurs at 8 to 14 days. Erythema migrans and even cranial nerve VII palsy can appear during the window period, but by the time symptoms of Lyme neuroborreliosis such as meningitis and peripheral neuropathy have appeared, patients typically have elevated serologies.

Per Infectious Diseases Society of America guidelines, repeat serologies should be completed 2 weeks after the initial acute-phase samples were sent if they returned negative. The majority of patients will have seroconverted by this point, but in the minority of patients who have not seroconverted, per Infectious Diseases Society of America and the Centers for Disease Control and Prevention, repeat EIA and Western blot testing should be completed after 30 days of initial symptoms. A negative test after 6 weeks of symptoms effectively rules out Lyme disease.

Many other factors can affect positivity and interpretation of Lyme serologies. Both of our patients received antibiotics during the course of their illness, which can affect production of IgG antibodies, although this does not seem to affect the production of IgM antibodies. Although Lyme neuroborreliosis is considered early disseminated disease, IgG levels may not be elevated at the time of diagnosis, or confirmatory Western blot may not reveal enough positive bands for IgG positivity. In addition, IgM levels can remain elevated for at least 1 year and sometimes longer after diagnosis, even after symptoms have resolved. False elevations in IgM and IgG levels can occur in relation to syphilis, relapsing fever syndromes, lupus, and other high immunoglobulin-producing syndromes, although typically Western blot testing rules out these syndromes. Additionally, in patients living in highly endemic regions, there can be up to a 4% background rate of seropositivity, which can result in false positives if Lyme serologies are sent in the setting of vague symptoms. All of these factors should be taken into consideration when obtaining Lyme serologies. It is important for clinicians to recognize the limitations of current Lyme testing, and if suspicion is high for Lyme disease, continued empirical treatment.
should be considered if serologies return negative or inconclusive, especially during the window period, and serologies should be repeated in 2 weeks.

Conclusions: Lyme disease occurs in stages and has a wide spectrum of presentations, which lends to difficulty in diagnosis. In patients living in an endemic area who present with varying central and/or peripheral neurologic symptoms of no clear etiology, and especially in patients who present with the triad of lymphocytic meningitis, cranial neuritis, and radiculitis, Lyme disease should be considered. It is important to recognize the limitations of Lyme testing as it stands at this time, however, and to recognize that Lyme serologies may evolve over time. Therefore, if the pretest probability is high in a particular patient, it is worthwhile to resend Lyme serologies if they were sent during the potential window period and initially return negative.

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