LATE-STAGE NEUROPSYCHIATRIC LYME BORRELIOSIS DIFFERENTIAL DIAGNOSIS AND TREATMENT

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Lyme borreliosis (Lyme disease) is a multisystem illness caused by the spirochete Borrelia burgdorferi. Although dermatologic, articular, cardiac, opthalmologic, and neurologic manifestations are well known, it is less well known that psychiatric disorders may also arise as a result of borrelial infection (1). Depression (2), panic attacks (3), schizophrenia-like psychotic state (4), bipolar disorder (3), and dementia (5) have been atributed to Lyme borreliosis. In this report, we present two patients in whom psychiatric symptoms represented the primary manifestations of their late-stage Lyme borreliosis. Specific dilemmas of diagnosis and treatment will be discussed.

CASE REPORTS

CASE 1. Mrs. A. was a 34-year-old, previously healthy married woman who presented with frontal headaches, slurred speech, distal paresthesias, fatigue, memory loss, and intermittent visual blurring and diplopia. A neurologic exam was normal. Brain magnetic resonance imaging (MRI) revealed multiple whilte matter lesions on T2-weighted scanning. The differential diagnosis included multiple sclerosis (MS), multi-infarct syndrome, or Lyme encephalitis. Blood tests were unremarkable except for a reactive antibody test for Lyme borreliosis. Because of the prominent headaches (uncommon in MS), treatment for presumed Lyme borreliosis was begun using intravenous ceftriaxone. Within 2 weeks, Mrs. A's speech became pressured and her mood became irritable. She refused further treatment.

Over the following months, Mrs. A's mood fluctuated from marked agitation to severe depression accompanied by suicidal threats. Auditory hallucinations and paranoid delusions emerged along with a full manic syndrome. She also became violent - slapping her son repeatedly and breaking furniture.

At this time, a spinal tap reevealed 11 white blood cells (86% lymphocytes and 14% monocytes) with an elevated cerebrospinal fluid (CSF) immunoglobulin G (IgG) index of 1.17. There were no oligoclonal bands. A lyme Ab test was negative in the CSF but positive in the serum. Other labs were all normal (including TFT's, RPR, ANA, ESR). A neurologist diagnosed probable MS, although Lyme borreliosis as a cause of these symptoms could not be ruled out. She was then promptly admitted to a psychiatric hospital. A sleep-deprived EEG was normal. She was treated with lithium, perphenazine, and valproic acid. Her thoughts became less paranoid and her behavior less impulsive, but intermittent illogical thinking and poor insight remained. After 2 months, she was discharged with the diagnoses of "bipolar disorder, manic, and psychosis - improved" and "MS".

During the following 8 months, Mrs. A's poor insight, illogical thinking, irritability, and headaches continued. In addition, she developed diffuse paresthesias, migratory large-joint arthralgias, a stiff neck, lancinating spine pain, and persistent severe fatigue. At this point, a rheumatologist elicited a history 2 years earlier of a circular red rash with central clearing followed by flu-like symproms and a stiff neck. Repeat serologic tests again revealed a positive Lyme antibody test. Repeat CSF tests, other than a mildly elevated protein, were normal [including cell count, Lyme Ab by enzyme-linked immunosorbent assay (ELISA), oligoclonal bands, and myelin basic protein]. Despite apparently normal CSF, Mrs. A. was re-diagnosed as having persistent Lyme borreliosis (not MS) because of symptoms suggestive of peripheral and cranial neuropathies, large joint articular symptoms, past lymphocytosis in CSF (meniogoencephalitis), continued positive Lyme serologies, and a history of probable erythema migrans rash. Mrs, A, was given 15 weeks of IV ceftriaxone. Her physical and psychiatric symptoms improved markedly by the 5th week of therapy, and she was asymptomatic by the 12th week. All medications, including the psychiatric ones, were discontinued. This remission was sustained for 1.5 years.

Four years after the initial rash, Mrs. A. had another episode of manic psychosis that required hospitalization. A repeat MRI showed one new white matter lesion. There were no physical symptoms suggestive of active Lyme borreliosis. A spinal tap revealed 10 lymphocytes. Although conventional indirect antibody tests for CNS Lyme disease were unremarkable (CSF Lyme ELISA at the upper limits of normal), more sensitive ELISA tests using immune complex dissociation methods (6) (Stony Brook University) revealed Borrelia-specific IgG complexes in the CSF at a level of 0.120 (cutoff = 0.067). The serum Lyme IgG was also reactive. Under the assumption that this manic episode was related to active CNS Lyme disease, Mrs. A. was given psychiatirc medication (lithium, valproic acid, and perphenazine) and 12 weeks of IV antibiotics followed by maintenance of oral antibiotics. She improved rapidly. her psychiatric medications were tapered at 10 months. Twelve months after the second manic episode, Mrs. A. remains completely well.

The illness imposed a marked strain upon Mrs. A's family. After her husband and children left her, she lived in a homeless shelter. Once the infectious cause of the manic episode was explained, the family reunited. Mrs. A. had no prior psychiatric problems and no family history of mania. When she developed the presumed erythema migrans rash, she was living in a Lyme-endemic rural area heavily inhabited by deer. Shortly thereafter, she moved to a suburban area. Between recurrences of Lyme disease, there was no known tick bite or reexposure to a wooded area.

CASE 2. Mrs. B. was a 22-year-old, previously healthy woman who in late summer developed a flu-like illness and headaches, followed months later by swollen glands and painful joints, low-grade fevers, severe fatigue, stuttering, and more severe occipital headaches. At times, she had hyperacusis and photophobia. Physical and neurologic exams were normal. Blood tests revealed an "indeterminate" Western blot for Lyme borreliosis (41 kDa, 83 kDa bands), a positive cytomegalovirus (CMV) IgG titer (1:16), and a positive Herpes IgG titer (2.60). Brain MRI was normal on two occasions.

there was no history of a tick bite or rash. She did however live in a Lyme-endemic area and 4 months prior to the onset of symptoms she worked in a veterinarian's office.

Nine months after onset of illness, a diagnosis of probable Lyme borreliosis was made based on the physical symptoms and the two reactive bands on the Western blot. Four weeks of oral antibiotics were of no help. A subsequent 8-week course of IV ceftriaxone led to marked improvement in her headaches and joint pain. Several months later, because of extreme fatigue and the possibility of a systemic CMV infection (IgG titer 1:64), Ms. B. was treated with acyclovir. The fatigue persisted, and the headaches and painful joints resumed. Fifteen months after illness onset, given the possibility of persistent Lyme borreliosis, Ms. B. was treated with a second course of IV ceftriaxone (7 weeks). This led to a resolution of the fatigue and physical symptoms.

Twenty-one months after illness onset, Ms. B developed irritability, a spontaneous panic attack, intrusive obsessional thoughts with checking, and depression. She was treated with clomipramine. This syndrome then developed into mania with rapid mood swings (from grandiosity to sudden tearfulness), suicial thoughts, paranoid delusions, and auditory hallucinations. Serologic and routine CSF tests for Lyme borreliosis were negative. She was hospitalized and diagnosed as having atypical bipolar disorder and possible obsessive compulsive disorder. Her manic state was partially controlled with lithium. After discharge, she continued to be severly depressed, and she had evidence of cognitive dysfunction - trouble in spelling, writing, and verbal fluency.

Over the course of the following year, Ms. B's depression worsened and culminated in a life-threatening suicide attempt for which she was hospitalized. Mania and panic attacks emerged, along with paranoia, verbal aggressiveness, violent impulses, irritability, and auditory hallucinations. Other symptoms returned: stuttering, hip and knee pain, blurred vision, concentration and memory problems, and occipital headaches. Serologic studies for Lyme borreliosis were negative. An EEG was normal. Additional courses of antidepressants were tried without success. Electroshock theraoy was considered. Because case reports have linked Lyme borreliosis with psychiatric disorders, an empiric trial of IV ceftriaxone was initiated. During the first 2 weeks, Ms. B's psychiatric symptoms worsened with a marked increase in agitation. Obsessive-compulsive symptoms, such as horrific images of killing others and excessive bathing, returned. After 2 week, Mrs. B's symptoms markedly diminished and she was discharged shortly thereafter. After 12 weeks of IV antibiotics, Ms. B's psychiatric and cognitive symptoms were nearly completely resolved. The arthralgias and headaches were less severe. On 5 month follow-up, Ms. B. remains stable. She continues on lithium and oral antibiotic. Although tests for Lyme borreliosis were negative throughout the hospitalization (2 Western blots and 1 ELISA), Lyme tests after the hospitalization revealed a Western blot that was equivocal for IgG (41 kDa band) but positive for IgM (25, 41, and 83 kDa bands).

Mrs. B's past psychiatric history is unreemarkable. Her family history is positive for migraines. A maternal aunt was hospitalized twice for "nervous breakdowns".

DISCUSSION

Mrs. A. and Ms B. were diagnosed as having disseminated, late-stage Lyme borreliosis. In both cases, psychiatric presentations were prominant and profoundly disruptive. In both cases, initially no relationship was thought to exist between the history of Lyme borreliosis and the psychiatric disorders. In both cases, treatment for Lyme borreliosis led to a marked improvement in both the psychiatric and systemic symptoms. In both cases, a return of symptoms occurred despite prior antibiotic treatment. In this discussion, different aspects of the diagnosis and management of Lyme borreliosis will be presented with illustrations fromt these two patients.

DIAGNOSIS. the Centers for Disease Control and Prevention (CDC) epidemiologic surveillance criteria for the diagnosis of Lyme disease require a history of exposure to a Lyme-endemic area and either 1) a physician-diagnosed erythema migrans rash, or 2) serologic evidence of exposure to B. burgdorferi and one of the following: arthritis, neurologic symptoms (peripheral neuropathy, meningitis, encephalitis, meningoencephalitis), or cardiac conduction defects. These criteria are unduly restrictive for clinical purposes because about one-third of patients do not recall an erythema migrans rash and because serologic testing may be unreliable (7), with both false positive and false negative results. The serologic tests most commonly used are the ELISA and the Western blot, but newer methods are being standardized such as the polymerase chain reaction (8) and the antigen capture assays (9). Further complicating diagnosis is that some patients with CNS Lyme borreliosis may have apparently normal EEG, MRI, and CSF Lyme studies (10). In these situations, physicians must rely on the patient's full clinical presentation in making the diagnosis.

Lyme borreliosis is known to have protean manifestations, some of which do not include any of the typical features outlined by the CDC. Some of the presentations are listed in TABLE 1.

TABLE 1
DISORDERS ASSOCIATED WITH
NEUROLOGIC LYME BORRELIOSIS

COMMON OR TYPICAL

'Aseptic meningitis
Encephalopathy
Meningoencephalomyelitis
Cranial nerve palsies (e.g., Bell's palsy, optic neuritis)
Radiculoneuropathy
Chronic fatigue-like syndrome
Depression
Insomina
Mood lability and behavioral disorders in children

LESS COMMON

Spastic paresis or hemiparesis
Transverse myelitis
Cerebellar syndromes
Extrapyramidal syndromes
Seizure disorders
Dementia
Pseudo-tumor-like syndromes in children
Tulio phenomenon
Cerebrovascular disease
Demylinating-like disorders (e.g., multiple sclerosis-like)
Anterior horn cell-like disease (e.g., ALS-like, diffuse motor neuropathy)
Guillain-Barre-like syndrome
Psychotic or anxiety disorders

Because of lyme borreliosis's ability to mimic other known disease, it has been dubbed the "new great imitator" (11). As was true for syphilis - the former "great imitator" - late-stage Lyme borreliosis psychiatric disorders may appear as the predominant symptom. When Lyme borreliosis is suspected but not proven, either because the clinical profile is not typical or because the diagnostic tests are negative, some physicians opt to use a trial of antibiotics as both a diagnostic and therapeutic tool. If the patient improves, the diagnosis is supported.

With the exception of AIDS, infectious causes of psychopathology are not commonly recognized in this country. TABLE 2 lists a variey of medical disorders, including infectious diseases, that should be considered in the differential diagnosis of any new psychotic disorder.

TABLE 2

SELECTED INFECTIOUS CAUSES OF PSYCHIATRIC DISORDERS

BACTERIAL INFECTIONS

ACUTE:
Group A Beta Hemolytic streptococcus,
Pneumococcus, Haemophilus,
Meningococcus

SUBACUTE:
Leptospira, Borrelia burgdorferi,
Treponema pallidum,

Mycobacterium tuberculosis,
Whipple's disease

VIRAL INFECTIONS:
Coxsackievirus, Cytomegalovirus,
Enterovirus, Epstein-Barr virus,
Herpes simplex virus,
Human immunodeficiency virus,
Influenza virus, Measles virus,
Papovavirus, Poliovirus, Rabies
virus, Toga virus

PROTOZOAL INFECTION:
Toxoplasmosis

FUNGAL INFECTIONS:
Cryptococcosis, Coccidiomycosis,
Histoplasmosis

PARASITIC INFECTION:
Cysticercosis

Different diagnostic issues are raised by the two cases presented here.

In the case of Mrs. A., doctors were initially uncertain whether the correct diagnosis was Lyme borreliosis or MS. These disorders share similiar features: fluctuating neurologic symptoms, demyelinating-like lesions or MRI scans, and CSF lymphocytosis. The diagnosis was made more difficult by the fact that routine CSF testing for Lyme antibody was negative. The rheumatologist linked this patient's mania, psychosis, and aggressive behavior to infection with B burgdorferi because of the clinical and laboratory constellation: a probable erythema migrans rash prior to the onset of illness, positive Lyme serologies, MRI lesions, central and peripheral neurologic symptoms, prominent headaches, migratory arthralgias, repeated CSF lymphocytosis, and the remission of articular and psychiatric symptoms after an extended course of antibiotics. Confirmation of B. burgdorferi's involvement in the CNS came when more sensitive techniques were used to isolate Borrelia-specific antibodies. Although there is significant overlap in the clinical phenomenology between Lyme borreliosis and MS, Lyme borreliosis is the most parsimonious diagnosis when extraneural disease is present (e.g., dermatologic, articular), when there is a history of an erythema migrans rash and/or positive serologic tests, and when CSF oligoclonal bands and/or myelin basic protein are absent.

The diagnosis of Lyme borreliosis in Ms. B. was made based on the presence of a multisystem illness that included severe headaches, fatigue, joint swelling and pain, insomnia, and memory problems. Ms. B's initial Lyme tests were negative except for a Western blot IgG that had two positive bands. A more recent Lyme test was positive; this

may represent a late-appearing IgM response as has been described (12) or, possibly, reinfection. Ms. B.'s psychiatric symptoms started 21 months after the presumed onset of infection. These symptoms included depression, paranoid delusions, bipolar disorder, panic attacks, and obsessive-compulsive disorder. Worth noting is that the influenza epidemic of the 1920's was also associated with obsessive-compulsive disorder in some patients (13). More recently, a theory has been proposed that links new-onset obsessive-compulsive disorder in children to neuroimmunological dysfunction; cross-reactive antineuronal antibodies in some children with obsessive-compulsive disorder are thought to have been triggered by infection with Group A Beta Hemolytic Streptococcus (14). Ms. B's psychiatric disorder was unresponsive to psychiatric medications. When IV antibiotics were instituted, the psychiatric disorders resolved rapidly. The presence of typical Lyme symptoms, suggestive serologies, excellent response to IV antibiotic treatment, and the exposure to a Lyme-endemic area all support the diagnosis of Lyme borreliosis.

TREATMENT

Guidelines for the treatment of Lyme borreliosis have been changing rapidly. Until recently, a 4-week course of IV antibiotics was considered curative for patients with symptoms of CNS Lyme borreliosis. Now it is recognized that some patients relapse after an initial good response and require additional courses of IV antibiotics (15). Patients who are not treated until later in the course of illness are thought to be more likely to develop a chronic, relapsing disorder. Such was the case with these two patients. Mrs. A.'s first antibiotic course was begun 1 year after the presumed onset of infection (rash), and Ms. B.'s first course was begun 9 months after the onset of symptoms. Despite extensive courses of oral and IV antibiotics (17 weeks), Mrs. A. experienced a second manic episode with evidence of persistent CNS infection. Similarly, Ms. B.'s first signs of psychiatric illness began after having received 15 weeks of IV antibiotics and 4 weeks of oral antibiotics.

The persistence of symptoms despite antibiotic treatment suggests several possibilities: Lyme borreliosis has nothing to do with the psychiatric disorder; Lyme borreliosis triggered a psychiatric disorder that is now unrelated to ongoing infection; the spirochete has an unusual ability to resist antibiotic treatment; much longer courses of antibiotic treatment are needed; or the patient was reinfected. As already discussed, in both cases we believe Lyme borreliosis was related to the psychiatric disorder. In the case of Mrs. A., it is unlikely that Lyme borreliosis triggered a psychiatric disorder that is now autonomously occurring. Mrs. A. had borrelial antibodies in her CSF, thus suggesting ongoing infection. However, because psychiatric medications and IV antibiotics were administered simultaneously to treat her second manic episode, we cannot be certain that the psychiatric medications alone would not have been sufficient to treat the psychiatric disorder. In the case of Ms. B., the psychiatric disorder was refractory to all psychiatric treatments. Although she was maintained on lithium throughout her hospital stay, the dramatic response to the IV antibiotic treatment supports the assumption of ongoing infection. Could these patients have been reinfected? Mrs A. had moved out of the Lyme-

endemic area where she contracted her initial infection, making reinfection unlikely. Ms. B. continued to reside in an endemic area and therefore may have been reinfected.

That B. burgdorferi is capable of resisting routine courses of antibiotic treatment has long been suspected on clinical grounds. Preclinical and clinical evidence is now emerging to support the need for long-term treatment in some patients (15). How does B. burgdorferi evade both the patient's immune system and antibiotics? Recent studies have identified B burgdorferi intracellularly in human fibroblasts (16) and endothelial cells (17). Because organisms with intracellular localizations are difficult to cure, these in vitro observations may explain how B. burgdorferi can persist in the human host. Patients' symptoms, including psychiatric oones, may worsen during the first few weeks of antibiotic treatment (1). This phenomenon has been compared to the Jarisch-Herxheimer reaction that occurs when antibiotic treatment for syphilis is initiated. Mrs. A.'s first manic episode actually may have been precipitated or hastened by the IV antibiotic treatment. Ms. B.'s clinical condition deteriorated dramatically during the first 2 weeks of IV antibiotic treatment only to improve thereafter. It is worth noting that, in the treatment of tertiary syphilis, the Jarisch-Herxheimer reaction has included new-onset psychosis (18).

CONCLUSIONS

The psychiatric presentations of Lyme borreliosis may be as diverse and as debilitating as occur with neurosyphilis. Primary prevention and early treatment are keys to the control of this epidemic. However, because neurologic symptoms may emerge months to years after the initial infection (2), Lyme borreliosis may not be considered in the diagnosis - especially if the patient has moved out of the Lyme-endemic area. Failure to recognize active Lyme borreliosis can allow the infection to progress, perhaps allowing a treatable acute infection to become a relapsing chronic one that is ultimately less reponsive to antibiotics. Therefore, psychiatrists need to keep in mind the diagnosis of Lyme borreliosis when evaluating a patient with a new onset of treatment-refractory psychiatric illness.

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