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Lyme Disease Associated with Alzheimer's Disease

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Abstract. This case report discusses a patient with co-occurring neuroborreliosis and Alzheimer's disease (AD). Although no claim is made for causality nor is there objective evidence that spirochetes are involved in AD, co-infection may exacerbate the symptoms of either neuroborreliosis or AD. Much is to be learned about the role of spirochetes in degenerative central nervous system disease.

Lyme borreliosis is a multisystem disease caused by infection with the spirochete, *Borrelia burgdorferi* sensu lato. Neurologic complications of Lyme disease (LD), also known as neuroborreliosis, include encephalitis, meningitis, and dementia as well as a broad range of peripheral neuropathies, including single or multiple cranial neuropathies, diffuse polyneuropathies, and painful radiculopathies. The many symptoms of LD may mimic multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS). Although there is no evidence that any of these diseases are caused by spirochetal infections, diagnosis of each must rule out the possibility of neuroborreliosis. Halperin et al. [5] reported that *Borrelia burgdorferi* antibodies were present in patients with motor neuron disease and speculated that all of the peripheral nerve disorders observed appear to be manifestations of a mononeuropathy multiplex.

LD remains a clinical diagnosis and laboratory tests continue to be supplements to clinical impression. However, there are laboratory tests that may be very helpful, especially for differential diagnosis. Such tests include the detection of specific DNA in body fluids such as cerebrospinal fluid, tissue, and blood by the polymerase chain reaction (PCR), single peptide recombinant antibody tests such as the C6 Lyme peptide (C6LPA) antibody test on both cerebrospinal fluid (CSF) and serum, as well as the Western immunoblot [6]. The C6LPA is available on CSF for investigational use only, but is approved by the Food and Drug Administration for the testing of serum and plasma samples.

Culture of *B. burgdorferi* from CSF specimens is technically difficult with a very low yield on patients with neuroborreliosis and is not readily available. This case report describes a patient with LD and AD.

Case Report

MR is an 83-year-old woman who had resided in Switzerland for more than 30 years. Her health history is remarkable for a car accident in 1956 in which she sustained multiple injuries. She has hypertension, which has been controlled by diuretics.

In August 1993, she complained of a rash on her entire right leg resembling the erythema migrans of LD, but did not recall a tick bite. She was treated with tetracycline 200 mg daily for 10 days, and the rash resolved. At the time that she was evaluated by the physician, her *B. burgdorferi* IgG (IFA) titer was 1:256 (negative < 1:64), the IgG enzyme-linked immunosorbent assay (ELISA) was 146 (negative < 100), the IgM capture ELISA was negative, and her TPHA for syphilis was also negative. A Western blot was not performed.

During the winter of 1996–1997, MR complained of flu-like symptoms, evening febrile episodes, weakness, fatigue, both short-term and long-term memory loss, and

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depression with anxiety. She lost 7 kg of body weight. Physical examination revealed an enlarged thyroid, blood pressure of 140/80 mm Hg, muscle and joint stiffness, and neuropsychiatric deficits such as irritability, short-term and long-term memory loss, inability to select appropriate vocabulary, disorientation, depression, and anxiety. Her neurologic examination was normal. When tested in June 1997, all of her laboratory tests were normal except the thyroid-stimulating hormone (TSH) was 6.99 mU/mL (normal, 0.2–3.77 mU/mL), antithyroglobulin antibody was 374 IU/mL (normal < 120 IU), and antinuclear antibody was 320 (normal < 8). Tests were again performed for LD. IgG ELISA was 146 (negative < 100), IgG IFA was elevated at a titer of 1:256, and IgM capture ELISA was 2+ positive. Both the IgG and IgM antibody titers were confirmed with positive IgG and IgM Western blots. The TPHA continued to be negative. The patient declined a lumbar puncture.

A thyroid scan indicated decreased thyroid uptake suggestive of Hashimoto's disease (hyperthyroidism). Treatment for hyperthyroidism was initiated, and some improvement in energy level was observed with a decrease in TSH to normal levels.

Antibiotic therapy for LD was initiated in June 1997 and consisted of deoxytetracycline (doxycycline) 200 mg bid for 3 weeks in September of 1997, an additional course of doxycycline for 3 weeks in January 1998, and 2 g intravenous ceftriaxone for 21 days during May 1998. Although MR reported less fatigue and weakness and no fever or flu-like symptoms after the antibiotic treatment, her neuropsychiatric condition continued to deteriorate. These included more severe memory loss, an inability to concentrate, depression, anxiety, and progressive loss of activities associated with daily living. A magnetic resonance scan of the brain revealed white matter defects in the frontal–temporal-parietal area and atrophy of the cortical and subcortical frontal temporal area bilaterally. The family decided at this point to discontinue intravenous antibiotic therapy.

Based on both laboratory and clinical evidence, a provisional diagnosis of LD and AD was made.

From July 1999 to November 2001, she had a series of problems including adult rotavirus gastroenteritis, bacterial pneumonia, and oral HSV-1 infection. She was relocated to a skilled-care facility and continued to deteriorate until she died in August 2003.

From her initial evaluation in 1993 through her death a decade later, MR's Lyme disease tests remained strongly positive for antibodies to *B. burgdorferi* sensu lato. An autopsy performed at the University of Lausanne revealed general debilitation, moderate cardiac hypertrophy, diffuse atherosclerosis with 80% stenosis of the intraventricular arteries, benign nephrosclerosis, and lymphocytic thyroiditis, consistent with Hashimoto's disease. There was physical evidence of malnutrition resulting in a 30-kg weight loss over a period of 2 years.

Postmortem examination of the brain revealed moderate atrophy of both hemispheres affecting all lobes, with slight hydrocephalus without focal lesions (weight 1090*g*, normal 1250*g*). No evidence of meningitis or encephalitis was observed microscopically. Numerous neurofibrillary tangles, spirals, threads, neuritic (amyloid) and diffuse plaques were observed throughout the hippocampus, parahippocampus, temporal, parietal frontal, and occipital cortex fulfilling the CERAD (Consortiom to Establish a Registry for Alzheimer's Disease) criteria for AD(A1). Slight amyloid angiopathy was present without vasculitis.

Three brain tissue samples (parietal, frontal, occipital), bladder, liver, spleen, heart, and cerebrospinal fluid were sent to Medical Diagnostic Laboratories (Mt. Laurel, NJ) for PCR tests. All specimens were extracted and the amplified DNA was probed for *B. burgdorferi* sensu lato, *Bartonella henselae*, *Babesia microti*, and *Mycoplasma fermentans.*

All three of the brain samples were positive by PCR for *B. burgdorferi* DNA. The parietal segment of the brain was also positive for *B. henselae* DNA. Cardiac tissue samples were positive for *B. burgdorferi* DNA. All other tissue and fluid samples were PCR negative for all of the microorganisms tested.

There are several interesting observations to be made in this case report. The patient had laboratory-confirmed neuroborreliosis as evidenced by the three brain tissue samples that were positive by PCR for *B. burgdorferi* DNA. She was treated for LD with at least three courses of an appropriate antibiotic on three separate occasions. However, a 3-week course of ceftriaxone may not have been adequate. Current treatment guidelines are controversial, but consensus experience justifies that at least 1 month of intravenous antibiotics is necessary (Estanislao and Pachner [3]). In spite of this treatment, there was continuing degradation of her neurologic condition, and ultimately spirochetal DNA was found in the brain and the heart.

Although the involvement of spirochetes such as *B. burgdorferi* in AD has been proposed by several groups, there is little evidence aside from co-infections or associations that these microorganisms are causative agents of this neurodegenerative disease or others such as AD, ALS, or MS. Gutacker et al. [4] analyzed brains from 10 patients with AD for *B. burgdorferi* DNA by PCR. Serology was also performed on serum samples from an additional 27 patients with AD. There was no evidence of *B. burgdorferi* infection in any of these

cases. In another study, however, Chmielewska-Badora et al. [2] found a significant relationship between Polish patients with MS and serologic evidence of LD.

Cassarino et al. [1] reported the first case of striatonigral degeneration in a patient with LD of the central nervous system and PD. Also of importance is the recognition that both diseases, LD and AD, may be present concurrently. Such co-infection, or co-occurrence, may exacerbate the symptoms of either neuroborreliosis or AD. This case report does not show causality nor is there objective evidence that spirochetes are involved in AD. No sure link is established between these two disease states, but their coincident occurrence in this patient is noted. Co-infection with other microorganisms such as *Babesia* and *Anaplasma* are known to exacerbate the symptoms of LD. Such may be the case for LD and AD. Although it is interesting to speculate on the presence of *Bartonella* DNA in the brain, this observation remains isolated, because there was no evidence of bartonellosis premortem.

There is much to be learned about the role of *B. burgdorferi* in infection of the central nervous system. This case report demonstrates our collective ignorance on the role of spirochetes in degenerative central nervous system diseases. It also demonstrates the need for pathologists, infectious disease physicians, and clinical microbiologists to work very closely on these complex cases involving multiple possible etiologies and complicated pathology.

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