SHORT REPORT

ABSTRACT: Lyme disease is sometimes part of the differential diagnosis for amyotrophic lateral sclerosis (ALS). Herein we report on 414 individuals with ALS at the Massachusetts General Hospital who underwent laboratory testing for Lyme disease. Twenty-four (5.8%) were seropositive, but only 4 (0.97%) had confirmed past immunoreactive infection. Two of these patients received ceftriaxone for 1 month without clinical improvement. Lyme disease was rare in 414 patients with ALS and is not likely to be causative.

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LYME DISEASE SEROLOGY IN AMYOTROPHIC LATERAL SCLEROSIS

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Lyme disease is the leading arthropod-borne infection in the USA and is caused by *Borrelia burgdorferi*, a spirochete transmitted to humans by infected *Ixodes scapularis* and *Ixodes pacificus* ticks.[1] The incidence in the USA is 1 in 2719, although the illness is likely underreported, and the rate is much higher in hyperendemic areas such as the northeastern part of the country.[2,3] The 15-year mean annual rate for all states ranges from less than 0.01 cases per 100,000 population in Montana and Colorado to 74 cases per 100,000 population in Connecticut.[2] Neurological involvement can occur in up to 20% of those with confirmed infections.[4] The infection can be occult, resulting in long periods of latency before neurological symptoms are manifest. It has been reported that chronic symptoms may clinically resemble other neurological disorders, including amyotrophic lateral sclerosis (ALS).[5,6]

We studied the occurrence of Lyme disease in a large cohort of patients with ALS and assessed the clinical significance of laboratory testing and treatment of Lyme disease in patients with ALS.

METHODS

The American Academy of Neurology has established practice guidelines for the diagnosis of neurologic Lyme disease.[7] It is a clinical diagnosis, based on history and physical examination, best supported by laboratory data. Serologic testing involves a two-tier system: an enzyme-linked immunosorbent assay (ELISA) test for titer of antibodies to *Borrelia* followed by Western blot testing for immunoglobulin G (IgG) antibodies to *Borrelia burgdorferi*–specific proteins in blood.[8,9] This approach to diagnosing a past infection with Lyme disease was established by the Centers for Disease Control and Prevention (CDC) and the Association of State and Territorial Public Health Laboratory Directors.[10]

We conducted a chart review of 1760 patients with ALS who were at the who were Massachusetts General Hospital (MGH) from January 1984 to December 2007. Approval for the study was obtained from the MGH institutional review board. All participants with a diagnosis of ALS were identified using the computerized MGH Research Patient Data Registry (RPDR). The RPDR query generated a list of all patients with a diagnosis of ALS who

Abbreviations: ALS, amyotrophic lateral sclerosis; CDC, Centers for Disease Control and Prevention; ELISA, enzyme-linked immunoassay; IgG, immunoglobulin G; MGH, Massachusetts General Hospital; RDPR, Research Data Patient Registry

Key words: amyotrophic lateral sclerosis; Lyme disease; motor neuron disease; neuromuscular disease; neuroborreliosis; borrelia burgdorferi; serology

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Table 1. Profile of 4 patients with ALS and with past occurrence of Lyme disease (positive ELISA and Western blot).

Patient no.	Gender	Date of birth	Year of ALS symptom onset*	Date of diagnosis of ALS	Suspected date of Lyme infection†	ELISA date	Western blot date	Year of death	Treatment for Lyme disease
1	Male	8/30/31	2001	December 2006	Not known	11/24/2006	11/24/2006	2008	None
2	Female	11/23/47	Data not available	1999	Not known	9/28/1999	10/5/1999	2000	None
3	Male	2/26/45	2003	May 2004	Summer 2003	5/13/2004	5/13/2004	2005	Ceftriaxone: 5 weeks in winter 2003
4	Male	1/26/45	2002	February 2006	Summer 2005	11/21/2005	11/21/2005	2006	Ceftriaxone: completed 4 weeks in January 2006

**Approximate year based on data from medical records.*
†Obtained from medical history records.

presented to the hospital between 1984 and 2007, including those suspected of having ALS. A total of 414 patients had at least one laboratory test for Lyme disease performed. Laboratory tests ordered for detection of Lyme disease were attending physician dependent, and no particular clinical criteria were followed. Antibodies to *Borrelia burgdorferi* were determined in serum by ELISA run at the MGH Pathology Laboratory. The IgG Western blot was also performed at the MGH Pathology Laboratory, and a result was considered positive only if more than five of the following bands were present: 18, 23, 28, 30, 39, 41, 45, 58, 66, and 93 kDa.[9]

RESULTS

At least one laboratory test to evaluate the past occurrence of Lyme disease was performed in 414 patients (23.5%) with ALS. Of these 414 individuals, 24 (5.8%) had serologic evidence of past exposure to *Borrelia burgdorferi* with a positive ELISA test. However, only 4 (0.97%) had a positive Western blot test that confirmed past infection with Lyme disease. The Western blot test was negative for the other 19 seropositive patients. The clinical characteristics of these 4 individuals are summarized in Table 1. Among these 4 patients, 2 reported occurrence of clinical symptoms in the recent past and recalled exposure to ticks. Both patients received 4–5 weeks of intravenous ceftriaxone at the MGH; however, the use of ceftriaxone did not alleviate the neurologic symptoms, which included progressive decline in strength. The remaining 2 patients did not recall erythema migrans or any previous treatment for suspected Lyme disease. They may have suffered from a past subclinical Lyme infection.

None of these 4 patients had a positive family history of ALS. The onset of ALS symptoms in 1 seropositive patient occurred a number of years before the onset of suspected Lyme infection. All 4 patients died from ALS (see Table 1).

DISCUSSION

We found a prevalence rate of 0.97% for a confirmed previous Lyme infection in a large cohort of patients with ALS. The prevalence rate is comparable to the occurrence of Lyme disease in endemic areas of the USA.

The prevalence of Lyme disease is highly variable. Approximately 5–10% of patients in endemic areas have false-positive antibody results without any history of symptoms, and it may be possible for patients to not have any clinical history but to have serum samples with antibodies against *Borrelia burgdorferi*.[11] More than 90% of the cases in USA are reported from endemic areas in the northeast and upper midwest. The estimated prevalence rate is 6 per 100,000.[12] In highly endemic areas, the attack rate often reaches 2–3% of the population, and the asymptomatic infection rate may be as high as 20%.

Two previous studies have suggested an association between Lyme disease, indicated by immunoreactivity to Lyme, and ALS,[6,13] whereas a third has opposed the finding.[14] The investigators in one of these studies suggested that the observation of increased immunoreactivity to Lyme in their ALS

population could reflect the high background rate of seropositivity in a hyperendemic area (New York) where the study was conducted.[6] We have shown that the prevalence of a past infection of Lyme disease in a cohort of 414 patients with ALS was approximately 0.97%, which is comparable with the occurrence of Lyme disease in endemic regions of USA. The 4 patients with confirmed Lyme infection resided in the endemic northeastern USA. Two of the patients recalled exposure to ticks. Treatment for Lyme disease with ceftriaxone in 2 of our 4 seropositive patients did not improve signs or symptoms of their motor neuron disease.

Our study has some limitations. Massachusetts General Hospital is a tertiary care center, and it is possible that individuals with an ALS-like syndrome due to Lyme infection may have been treated and experienced improvement at outpatient facilities other than MGH. We also do not have data on the presence of a family history of ALS in the entire cohort of 414 patients who were evaluated for Lyme testing. There is a possibility that some patients among the 414 may have a familial form of ALS, and thus Lyme disease would be an even less likely explanation for their findings. It may be possible that some results of laboratory tests were false positive or some patients with subclinical Lyme infections were seronegative.

We conclude that the prevalence of Lyme disease in patients with ALS is similar to that found in epidemiological data available from the CDC and is not likely to be either an etiological factor or of significance in the differential diagnosis of motor neuron disease. Based on our data it is plausible that, unless clear symptoms of Lyme infection are present, such as erythema migrans, testing for past occurrence or subclinical Lyme disease in patients with ALS is not indicated.

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