Clinical Study

Lyme Neuroborreliosis: Preliminary Results from an Urban Referral Center Employing Strict CDC Criteria for Case Selection

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1. Introduction

Lyme disease is a multisystem infectious disease caused by the bite of the hard shelled Ixodes tick-borne spirochete B. burgdorferi sensu stricto (hereafter referred to as B. burgdorferi), which frequently affects the nervous system [1]. Heightened awareness of the spectrum of Lyme neuroborreliosis (LNB) has resulted in increased serological testing to detect antibodies to B. burgdorferi in patients with early and late infection, and in many, even without the typical clinical features, who may nonetheless be receiving empiric antibiotics for late disease [2]. With this in mind the first 50 patients with presumed LNB were screened and strict criteria were applied for case ascertainment of Lyme disease. Two patients with varying involvement of the central (CNS), peripheral (PNS), and autonomic nervous system (ANS) and varied duration of LNB emerged. A preliminary report has been published [3].

2. Methods

The records of 50 consecutive patients referred to the author (D.S.Y.) were selected for inclusion based upon conformity to strict criteria for clinical and laboratory case definition of Lyme disease of the Centers for Disease Control and Prevention (CDC) [4, 5]. The majority of patients were referred with the diagnosis of chronic Lyme disease [6] and had received, or were receiving, antibiotic therapy for persistent Borrelia burgdorferi infection. Altogether, 23 patients underwent two-tier serological testing for the diagnosis of Lyme disease at the single reference laboratory, Stony Brook University Laboratory, New York, employing a first-tier screening enzyme-linked immunoassay (ELISA) and second-tier IgG and IgM immunoblots performed on reactive or borderline results as recommended by the CDC [5]. The 27 patients that had laboratory studies for Lyme disease performed elsewhere were excluded from this analysis. Of the remaining 21 patients, 5 with nonreactive first-tier ELISA as well as 12 with reactive and 4 with borderline reactive screening serology, all with nonconfirmatory Lyme IgG or IgM immunoblots, were also excluded. Two patients described below met criteria for case selection.

Noncontrast magnetic resonance imaging (MRI) and nuclear medicine (NM) cerebral perfusion imaging with single-photon emission spectroscopy (SPECT) screened for
brain dysfunction, the main symptoms of which were
typically neurocognitive.

Quantitative sensory testing (QST) for heat pain per-
ception thresholds [7] and epidermal nerve fiber (ENF)
studies of the thigh and calf [8] screened for small fiber
sensory nerve (SFSN) dysfunction [9], the main symptom of
which was dysesthesia, often reported as tingling, pricking,
burning, deep aching, jabbing, or shooting sensations often
in association with numbness and coldness of the limbs.

Quantitative sudomotor axon reflex testing, beat-to-beat
blood pressure (BP), and heart rate responses to head-up
tilt, deep breathing, Valsalva maneuver, with calculation of
a composite autonomic scoring scale (CASS) using a WR
Electronics laboratory, Rochester, Minnesota, [10] screened
for ANS dysfunction, the symptoms of which consisted of
postural hypotension, palpitation, dizziness, headache, and
lightheadedness.

Electrodiagnostic studies including nerve conductions
and electromyography of the arms and legs defined PNS
dysfunction including distal polyneuropathy (DPN) [11]
and polyradiculoneuritis [12] in the two patients, the
symptoms of which included patchy radicular peripheral
nerve disturbances often with little or no motor involvement.

Cerebrospinal fluid (CSF) was not collected for diag-
nostic levels of IgM and IgG antibodies alone or in paired
analysis with serum, or for isolation of B. burgdorferi using
polymerase chain reaction studies, in either patient, and thus
was not available for retrospective analysis.

3. Patient Descriptions

3.1. Patient 1. A previously normal 38 year old woman
had lightheadedness, dizziness, palpitation, and headache
commencing 3 months after tick bite, fever, joint pain,
and erythema migrans (EM) rash in the summer of 2007
that prompted the clinical diagnosis of Lyme disease.
Neurological examination showed slight tandem imbalance,
slowing of cold temperature, and vibratory sensory loss with
otherwise normal cognition, cranial nerves, limb strength,
coordination, and reflexes. Laboratory testing showed reactive
Lyme serology with an optical density (OD) of .265
(reactive cutoff + 3 standard deviations (SD) .130), positive
IgM immunoblot comprised of 23 and 41 kDa bands, and a
negative IgG immunoblot. Noncontrast brain MRI was normal.
Quantitative sensory testing showed heat pain thresholds below the 5th
percentile in the left foot and normal in the left hand. Cere-
bral perfusion with SPECT showed decreased perfusion in the temporal lobes.
Autonomic testing showed mild phase IV
attenuation of the Valsalva maneuver with an overall CASS
of 1. She was not treated with further antibiotics. Sustained
subjective and objective neurological improvement on repeat
examination 3 months later paralleled improvement on repeat
autonomic neurophysiological studies and QST after
an empiric course of 2 grams per kilogram of intravenous
immunoglobulin (IVIg) in 5 successive days per month for 3
months for acquired autoimmune peripheral and autonomic
neuropathy.

3.2. Patient 2. A previously normal 48 year old woman was
diagnosed with Lyme disease following a tick bite and EM
rash and treated with oral followed by intravenous antibiotics
according to prevailing standards [13]. One year later
she noted cognitive impairment, imbalance, and sensory
disturbance in the legs. Lyme serological studies were reactive
with an OD of 1.201 (reactive cutoff .149), positive Lyme IgG
immunoblot comprised of 18, 28, 30, 41, 45, 58, and 93 kDa
bands, and negative IgM immunoblot. Neurological exami-
nation showed mild stocking vibratory and cold temperature
sensory loss with otherwise normal cognition, cranial nerves,
limb strength, coordination, and reflexes. Electrodiagnostic
studies including EMG/NCS showed a distal sensorimotor
neuropathy with mixed demyelinating and axonal features.
Neuropsychological studies revealed significant deficits in
semantic fluency, reading speed and comprehension, audi-
tory attention, visual and verbal memory, psychomotor
speed, and phonemic verbal fluency, without depression or
anxiety. Noncontrast brain MRI was normal. Quantitative
sensory testing showed heat pain thresholds below the 5th
percentile in the left foot and normal in the left hand. Cere-
bral perfusion with SPECT showed decreased perfusion in the temporal lobes.
Autonomic testing showed mild phase IV
attenuation of the Valsalva maneuver with an overall CASS
of 1. She noted cognitive impairment, imbalance, and sensory
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an empiric course of 2 grams per kilogram of intravenous
immunoglobulin (IVIg) in 5 successive days per month for 3
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neuropathy.

4. Discussion

Two patients met CDC criteria for the clinical and laboratory
diagnosis of Lyme disease, including one with symptomatic
polyradiculoneuritis, dysautonomia, and serological evi-
dence of early infection and the other with SFSN, DPN,
dysautonomia, and serological evidence of late infection. The
remaining 21 patients had negative or indeterminate lab-
atory evidence of Lyme disease indicating that symptoms
initially ascribed to Lyme disease were probably unrelated to
B. burgdorferi infection. The CDC [4, 5] has not determined
the sensitivity or specificity of the serological diagnosis of
Lyme disease in any given cohort, using diagnostic levels of
IgM and IgG antibodies to the B. burgdorferi spirochete in
serum. Thus, it is uncertain whether having 2 of 23 patients
(8.7%) with diagnostic serology for Lyme disease in a given
cohort with primarily chronic symptoms is representative of
our cohort. A two-tier test approach for active disease and
previous infection with the demonstration of a significant
change in IgM or IgG antibody response to B. burgdorferi
in paired acute- and convalescent-phase serum samples,
examination of diagnostic levels of IgM and IgG antibodies
to the spirochete in CSF, and isolation of B. burgdorferi from
CSF are recommended to improve the diagnostic accuracy of
serological testing in Lyme disease [4, 5], including LNB.
Unlike meningitis, cranial neuritis, polyradiculoneuritis [14], and encephalomyelitis [15] which have been ascribed to the direct effects of B. burgdorferi infection, the etiopathogenesis of encephalopathy, SFNS, DPN, and dysautonomia are less certain, and probably related to autoimmune factors, triggered by exposure to B. burgdorferi antigens. Two candidate antigens that cross-react with constituent peripheral nerve molecules, one against flagellin and the other against gangliosides experimentally, are found in the sera and peripheral nerve of affected patients [16–18]. Acquired autonomic neuropathy, in which autonomic fibers are selectively or disproportionately affected, is presumably also of autoimmune cause as suggested by the occurrence of autonomic neuropathy after Lymerix and the Connaught vaccination [19, 20], and the favorable response to IVIg therapy in Patient 2.

The management of LNB remains controversial as to the timing and duration of oral and intravenous antibiotics. The occurrence of peripheral neuropathy, dysautonomia, and encephalopathy years later after adequate antibiotic therapy underscores the selective vulnerability of the nervous system to the immunological effects of B. burgdorferi infection, although the exact mechanisms remain uncertain.

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