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Abnormalities of the Nervous System in Lyme Disease: Response to Antimicrobial Therapy

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Objective measures of neurologic function were used to assess response to treatment in patients with late Lyme borreliosis. Neurophysiologic evidence of peripheral neuropathy was present in 64 of 137 patients tested. Measures of distal axon function (sensory amplitude and conduction velocity, motor terminal latency) were most affected. Repeat studies following 60 patients receiving antimicrobial therapy demonstrated significant improvement in these values. Before and after therapy 17 patients with late Lyme borreliosis and prominent subjective cognitive dysfunction underwent neuropsychologic tests of memory, conceptual ability, concentration, psychomotor function, overlearned intellectual abilities, and mood. Significant abnormalities were evident before treatment; all reversed with antimicrobial therapy. Many patients with this encephalopathy had specific abnormalities revealed by magnetic resonance imaging of the brain and had evidence of intrathecal synthesis of antibody to *Borrelia*. These findings indicate that late Lyme borreliosis commonly causes nervous system abnormalities that are reversible with appropriate antibiotic therapy.

Several specific neurologic syndromes have been described in Lyme disease [1, 2] and may be virtually pathognomonic. When a patient presents with a recent history of erythema chronicum migrans (ECM), positive Lyme serology, and Bell's palsy, the diagnosis is self-evident. However, in endemic areas, patients who are seropositive may present with any of a large number of other neurologic disorders. Since 5%–10% of the population in such areas may be seropositive [3–5], proving a causal relationship between Lyme disease and the neurologic abnormality may be quite difficult.

When other organ systems are infected with other agents, one can obtain biopsy tissue and either visualize or culture the causative organism. However, performing biopsies of the nervous system carries significant risk. Moreover, it is usually quite difficult to culture *Borrelia burgdorferi* from affected patients [6]. Therefore, one must use more inferential methods to conclude that a particular type of neurologic dysfunction has been caused by infection with *B. burgdorferi*. Good epidemiologic studies may reveal statistically significant associations. Alternatively, demonstration of a local immune response to the causative organism may be used to conclude that nervous system infection is present. This method, widely used in other infectious diseases of the CNS, has been shown to be useful in Lyme borreliosis as well [7, 8]. The concentration of antibody to *B. burgdorferi*, normalized for immunoglobulin concentration, is measured in both the CSF and serum. If there is more specific antibody in the CSF than in serum (ratio of CSF to serum titer ≥ 1.0), active CNS infection with *B. burgdorferi* may well be present.

Yet another approach is to detect a quantifiable abnormality that would not be expected to remit spontaneously and to assess its severity before and after specific antimicrobial therapy in a population receiving no other form of treatment. We have used this strategy for the past 2 years to focus on several particularly common aspects of Lyme neuroborreliosis [9, 10]. All patients studied had "late" Lyme borreliosis, i.e., they had (*1*) immunologic evidence of *B. burgdorferi* infection (either by ELISA or by an assay of specific cell-mediated immunity to this organism [11]) and/or ECM, (*2*) multiple organ-system involvement, and (*3*) disease of at least 4 weeks' duration.

Peripheral Neuropathy

Many patients with Lyme neuroborreliosis describe sensory symptoms. At one extreme, they may suffer severe radicular-type pain [1, 2]. Far more frequently, they describe intermittent limb paresthesias. The lat-

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ter symptom is frequently indicative of a mild underlying neuropathy, which can be reproducibly assessed with neurophysiologic techniques.

Neurophysiologic Testing

Conduction studies were performed by standard techniques [9] with the use of surface electrodes and with the limb temperature maintained at ≥32°C. Sensory conductions are performed by applying electrical stimuli to sites such as the digits, in which no muscles are present, and recording from nerve trunks. Conduction velocities are calculated by measuring the time required for the impulse to reach the recording electrode and the distance between stimulating and recording electrodes. Motor conductions are performed by applying the stimuli to peripheral nerves while recording from innervated muscles. The time for the impulse to propagate from the distal site of stimulation to the muscle is referred to as the terminal latency. By subtracting this from the time required for an impulse to reach the muscle from a more proximal stimulation site and measuring the distance between the two stimulation sites, a conduction velocity (CV) can be calculated. At the same time, late response latencies can be measured. The applied electrical stimuli always propagate both peripherally to the innervated muscle and centrally to the spinal cord. The centrally directed impulses can produce a secondary volley (arising from spinal cord neurons), which then travels back to the periphery, giving rise to a second, later contraction in the same muscle. If the centrally directed volley is conveyed by sensory fibers, the response is known as an H reflex and is roughly analogous to a tendon jerk reflex. If it travels in motor axons, the response is called an F response. Measurement of the latencies of these late responses is particularly useful in neuropathies, since the recorded impulses must travel the entire length of peripheral nerves, making them sensitive to mild but diffuse abnormalities or to abnormalities in proximal regions that could not otherwise be easily assessed.

Finally, since cranial nerve involvement has been said to be particularly common in Lyme disease [1], we recorded blink reflexes. This is performed by electrically stimulating the supraorbital nerve (at the eyebrow) and electronically recording the reflex contraction of the orbicularis oculi. This permits quantitative assessement of the function of the sensory trigeminal and motor facial nerves bilaterally.

Patients. Eighty-two patients meeting the above criteria for late Lyme disease were referred for neurophysiologic evaluation since they had symptoms or physical findings thought to be suggestive of a peripheral neuropathy (ranging from severe radicular-type pain to mild intermittent paresthesias). An additional 55 patients were evaluated as part of a prospective neurophysiologic study of patients with definite late Lyme disease, regardless of whether they had symptoms or findings indicative of a peripheral neuropathy.

Test results. Of the 137 patients with definite late Lyme disease, 64 had neurophysiologic evidence of a peripheral neuropathy (i.e., two or more abnormal nerves). The presence of a neurophysiologically demonstrable neuropathy correlated well with the patients' perceptions of intermittent limb paresthesias ($P = .0001$, Fisher's exact test) (table 1). In those with paresthesias, the mean number of abnormal nerves was 2.45, as compared with a mean of 1.05 in those without such symptoms ($P < .0005$, Stu-

Table 1. Characteristics and results of neurophysiologic studies among patients with late Lyme disease.

Characteristic	Symptom group: Paresthesias ($n = 93$)	Symptom group: No paresthesias ($n = 44$)	P value
Mean age in years (range)	43.5 (16–77)	37.5 (9–64)	<.0125
Mean duration of symptoms (mo)	25.5	29.08	NS
Mean (SD) no. of abnormal nerves	2.45 (2.02)	1.05 (1.45)	<.0005
No. of patients with ≥2 abnormal nerves	55	9	<.0001
No. of patients with <2 abnormal nerves	38	32	
No. of patients with carpal tunnel syndrome	29	4	

NOTE. NS = not significant.

dent's two-tailed *t* test). It is interesting that ~25% of our patients also had neurophysiologic evidence of carpal tunnel syndrome.

Sensory potential amplitude and CV and motor terminal latency were the most sensitive indicators of peripheral nerve dysfunction in these patients. These three measures all reflect function in the distal axon; each was abnormal in about one-third of the entire patient population. Late-response latencies, which can be affected by abnormalities either proximally or distally, were also frequently prolonged. In contrast, motor CV, which reflects conduction in nerves in more proximal segments of the limbs, was affected in only 7% of patients. Evaluation of blink reflexes never detected any abnormalities that were not clinically evident. (Thus, subclinical involvement of these cranial nerves appears to be infrequent in Lyme disease.)

Three patients underwent sural nerve biopsies. All had evidence of mild axonopathy, with mild perivascular round cell infiltrates in the perineurium and epineurium. In none could *B. burgdorferi*, complement, or antibody be demonstrated by immunocytochemical techniques.

Sixty patients were restudied 2–6 months after completion of parenteral antimicrobial therapy with either penicillin or ceftriaxone. No other therapeutic interventions were undertaken in these patients. Sensory CV and amplitude and motor terminal latencies, all of which had been most consistently abnormal before treatment, showed the greatest degree of improvement.

In summary, neurophysiologic testing, which provides consistent, reproducible, and well-standardized measures of peripheral nerve function, has proven to be highly useful in diagnosing and monitoring neuropathies in patients with Lyme neuroborreliosis. Our findings indicate that a substantial proportion of patients with late Lyme borreliosis have symptomatic abnormalities of the peripheral nerves. This neuropathy appears to affect the distal axons preferentially and reverses with appropriate antibiotic treatment.

Cognitive Function

Many patients with late Lyme borreliosis describe chronic fatigue, memory impairment, and difficulty in thinking. Although these patients are not severely impaired, they find their daily activities and job performance significantly affected. Seventeen such patients, selected because they described particularly marked difficulties with cognitive function and memory, underwent neuropsychologic evaluation (mean age, 39 years; mean years of education, 15). Neurologic examinations demonstrated slight dysarthria in one patient and Bell's palsy in another but no other focal abnormalities. One patient had acute meningoencephalitis [12]; most had chronic headaches. Lumbar punctures were performed in nine. Except for the one patient with meningoencephalitis and a second patient with 16 lymphocytes/mm^3, all CSF findings were normal. The electroencephalogram (EEG) in the patient with meningoencephalitis demonstrated diffuse slowing; the EEGs of the other patients revealed no significant abnormalities.

Neuropsychologic testing. Before and 2–4 months (mean, 11 weeks) after appropriate antimicrobial therapy, each patient underwent an extensive battery of neuropsychologic tests selected to measure memory, conceptual ability, attention/concentration, psychomotor function, and overlearned abilities [10] (table 2). Wherever possible, alternative forms were used for follow-up studies to limit practice effects. Since depression can artefactually lower scores on this type of testing, we also assessed mood with a Beck Depression Inventory in each patient. No patient had evidence of clinically significant depression before or after treatment. One patient was treated with chloramphenicol [12], 12 received ceftriaxone, and four received penicillin.

Scores on the California Verbal Learning Test (a sensitive test of memory) and the Booklet Categories Test (a difficult test of conceptual ability) were both abnormal before treatment. Performance on a somewhat simpler test of similar function (the Wechsler Memory Scale [WMS]) was initially in the low normal range, although these results were probably low for such a well-educated population. Similarly, performance on the Symbol Digits Modalities Test (a test of attention, concentration, and speed) and the Block Design Subtest of the Revised Wechsler Adult Intelligence Scale (WAIS-R) (which assesses psychomotor and perceptual motor function) were in the low normal range but were probably low for this group of subjects. Performance on all of these tests improved significantly after antimicrobial therapy. In contrast, performance on the WAIS-R information subtest and the WMS information, mental control, and orientation subtests (which test overlearned intellectual abilities and are typically resistant to deterioration in encephalopathies) were ini-

Table 2. Mean values of neuropsychologic measures in 17 patients with late Lyme borreliosis.

Test, characteristic measured	Mean value at indicated time		*P* value
	Pretreatment	Posttreatment	
Wechsler Memory Scale			
Logical memory (total score)	16.65	21.12	<.01
Logical memory (30-min delay)	11.44	16.06	<.025
Digits total	10.88	11.47	
Visual reproduction	9.53	12.24	<.001
Visual reproduction (30-min delay)	8.44	10.24	<.025
Associate learning	20.12	22.82	<.025
Memory quotient	102.35	118.65	<.01
California Verbal Learning Test			
Immediate recall (trial 5)	10.25	13.06	<.001
Free recall (2-min delay)	9.00	11.76	<.01
Cued recall (2-min delay)	10.00	12.47	<.01
Free recall (30-min delay)	8.75	11.94	<.01
Cued recall (30-min delay)	9.69	12.65	<.01
Recognition list	14.19	14.56	
Attention/concentration/speed			
Symbol-Digit Modalities Test			
Written	48.71	55.35	<.001
Oral	53.18	63.41	<.001
Trailmaking Test, part A	29.29	25.24	
Controlled Oral Word Association	44.71	44.88	
Conceptual Ability			
Trailmaking Test, part B	68.29	58.47	
Booklet Categories Test	52.85	33.20	<.01
Psychomotor and perceptual motor			
Purdue Pegboard			
Dominant hand	13.81	14.93	<.025
Nondominant hand	13.37	14.73	<.01
Simultaneous	11.69	12.47	
Block Design Subtest (WAIS-R, scaled)	11.00	12.37	<.01
Orientation/overlearned intellectual abilities			
Information Subtest (WAIS-R, scaled)	12.00	12.00	
Information, Wechsler Memory Scale	5.88	6.0	
Mental Control, Wechsler Memory Scale	7.06	7.94	
Orientation, Wechsler Memory Scale	4.88	5.00	
Beck Depression Inventory	7.63	4.42	

tially normal and did not change significantly with treatment. These findings indicate that patients with chronic Lyme borreliosis frequently have specific deficits of cognitive function. Such deficits are readily quantifiable and can be demonstrated to improve with appropriate antimicrobial therapy.

Magnetic resonance imaging (MRI). In an effort to understand the pathology underlying these cognitive deficits, 23 patients underwent MRI scanning of the brain. Sixteen of these patients were selected because they had particularly severe encephalopathy; the other seven were scanned for evaluation of either severe headaches or cranial neuropathies. A 1.5-Tesla General Electric scanner was used. Proton-, T1-, and T2-weighted images were obtained, with use of the spin-echo technique. Seven of the 16 patients with cognitive difficulties had focal white-matter abnormalities (i.e., regions of increased resonance on both proton- and T2-weighted images [figure 1]). None of the seven without encephalopathy had such lesions ($P = .047$, Fisher's exact test).

Specific antibody synthesis in CSF. In 22 patients we measured the amount of antibody to *B. burgdorferi* in both serum and CSF. These patients underwent lumbar puncture to evaluate either particularly marked cognitive difficulty ($n = 11$) or peripheral neuropathy ($n = 11$). Among the 11 patients with encephalopathy, the ratio of antibody in

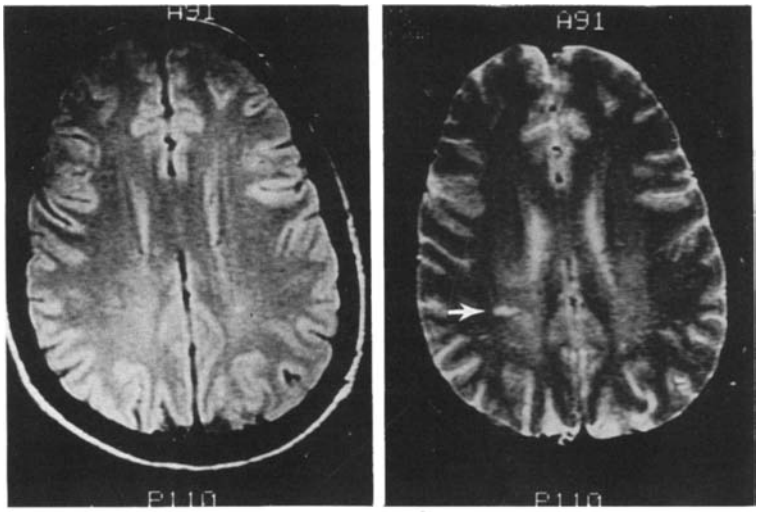

Figure 1. MRI scan of the brain (horizontal section; proton-weighted image on the left, T2-weighted on the right) of 28-year-old woman with a history of ECM who developed a febrile illness with joint swelling, fatigue, headache, and mental confusion 1 week after receiving a tick bite. Arrow indicates a hyper-resonant lesion in the deep cerebral white matter.

CSF to that in serum was >1.0 in nine, a finding that indicates intrathecal antibody synthesis. Among the 11 patients without encephalopathy, the ratio was >1.0 in only one ($P = .001$, Fisher's exact test). While the sample population was small and these data can only be considered preliminary, these findings (and those obtained by MRI scanning) suggest that the encephalopathy seen in chronic Lyme neuroborreliosis may, in some cases, be due to a low-grade meningoencephalitis.

Summary

While the earlier literature reflects a broad range of dramatic neurologic abnormalities in a small percentage of patients with late Lyme borreliosis [1, 2, 13, 14], we have been able to demonstrate the much more frequent occurrence of more subtle neurologic abnormalities in a far greater proportion of these patients. Using sensitive, quantitative, and reproducible neurophysiologic techniques, we have shown that the frequent occurrence of mild sensory symptoms, such as intermittent limb paresthesias, reflects the presence of low-grade distal axonal damage in the peripheral nerves. Similarly, using sensitive neuropsychologic methods, we have shown that the mild confusional state described by many of these patients does represent a mild encephalopathy. Our preliminary MRI and CSF studies suggest that this encephalopathy is due to a low-grade encephalitis. Most important, we have been able to demonstrate that the abnormalities of both the peripheral and the central nervous systems appear to be reversible with appropriate antimicrobial therapy.

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