CHRONIC NEUROLOGIC MANIFESTATIONS OF LYME DISEASE

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Abstract *Background and Methods.* Lyme disease, caused by the tick-borne spirochete *Borrelia burgdorferi,* is associated with a wide variety of neurologic manifestations. To define further the chronic neurologic abnormalities of Lyme disease, we studied 27 patients (age range, 25 to 72 years) with previous signs of Lyme disease, current evidence of immunity to *B. burgdorferi,* and chronic neurologic symptoms with no other identifiable cause. Eight of the patients had been followed prospectively for 8 to 12 years after the onset of infection.

Results. Of the 27 patients, 24 (89 percent) had a mild encephalopathy that began 1 month to 14 years after the onset of the disease and was characterized by memory loss, mood changes, or sleep disturbance. Of the 24 patients, 14 had memory impairment on neuropsychological tests, and 18 had increased cerebrospinal fluid protein levels, evidence of intrathecal production of antibody to *B. burgdorferi,* or both. Nineteen of the 27 patients (70 percent) had polyneuropathy with radicular pain or distal paresthesias; all but two of these patients also had encephalopathy. In 16 patients electrophysiologic testing showed an axonal polyneuropathy. One patient had leukoencephalitis with asymmetric spastic diplegia, periventricular white-matter lesions, and intrathecal production of antibody to *B. burgdorferi.* Among the 27 patients, associated symptoms included fatigue (74 percent), headache (48 percent), arthritis (37 percent), and hearing loss (15 percent). At the time of examination, chronic neurologic abnormalities had been present from 3 months to 14 years, usually with little progression. Six months after a two-week course of intravenous ceftriaxone (2 g daily), 17 patients (63 percent) had improvement, 6 (22 percent) had improvement but then relapsed, and 4 (15 percent) had no change in their condition.

Conclusions. Months to years after the initial infection with *B. burgdorferi,* patients with Lyme disease may have chronic encephalopathy, polyneuropathy, or less commonly, leukoencephalitis. These chronic neurologic abnormalities usually improve with antibiotic therapy. (N Engl J Med 1990; 323:1438-44.)

LYME disease, which is caused by the tick-borne spirochete *Borrelia burgdorferi,* is associated with a wide variety of neurologic abnormalities.[1-7] Early in the illness, many patients have episodes of headache and mild meningism.[8] Within several weeks, about 15 percent have objective neurologic abnormalities, most commonly lymphocytic meningitis, motor or sensory radiculoneuritis, or cranial neuropathy, particularly facial palsy.[2,3] A similar syndrome of meningoradiculitis occurs in Europe.[4,9,10] These early neurologic abnormalities can be cured with antibiotic therapy,[11,12] and even if untreated, they usually resolve within months.[4]

Chronic neurologic involvement, affecting either the central or peripheral nervous system, may also occur in Lyme borreliosis. In Germany, Ackermann et al. described 44 patients with progressive borrelial encephalomyelitis, a severe neurologic disorder characterized by spastic paraparesis or tetraparesis, ataxia, cognitive impairment, bladder dysfunction, and cranial neuropathy, particularly deficits of the seventh or eighth cranial nerve.[5] In all cases, the diagnosis was proved by the demonstration of intrathecal production of IgG antibody to *B. burgdorferi.* In addition, acrodermatitis chronica atrophicans, a late skin manifestation of Lyme borreliosis reported primarily in Europe, has been associated with a sensory polyneuropathy[13,14] and with mental disturbances.[15]

In the United States, Halperin et al. described two chronic neurologic syndromes associated with Lyme disease: one involved the peripheral nervous system and was characterized by paresthesias and electrophysiologic evidence of axonal polyneuropathy,[6] and the other involved the central nervous system and was manifested by encephalopathy with memory impairment.[7] The patients with central nervous system involvement usually had intrathecal production of antibodies to the spirochete, but those with abnormalities of the peripheral nervous system did not. A few patients have been described with other neurologic abnormalities thought to be due to Lyme disease, including encephalitis,[16-18] dementia,[18,19] psychiatric syndromes,[17] possible demyelinating disease,[17,19] stroke,[20,21] brain-stem abnormalities,[17] and extrapyramidal syndromes.[22] In some instances, however, the evidence linking these syndromes to infection with *B. burgdorferi* was incomplete.

The goal of the current study was to define further the chronic neurologic abnormalities of Lyme disease. We describe the clinical courses, diagnostic studies, and treatment responses of 27 patients in whom chronic neurologic syndromes developed months to years after the onset of Lyme disease.

METHODS

Neurologic Evaluation

From October 1987 through December 1989, we evaluated a total of 37 patients with chronic neurologic symptoms following well-recognized manifestations of Lyme disease. Eight of them had been entered previously into clinical studies of Lyme disease and had been followed prospectively for 8 to 12 years after the onset of infection. The 37 patients had detailed neurologic evaluations, including lumbar puncture, neuropsychological testing, electrophysiologic studies, and magnetic resonance imaging of the head. The antibody responses to *B. burgdorferi* in serum were determined by indirect enzyme-linked immunosorbent assay[23] and in serum and cerebrospinal fluid samples obtained simultaneously, by capture enzyme immunoassay.[24] If the patient was seronegative according to these methods, the serum was further tested by immunoblotting,[25] and peripheral-blood mononuclear cells were tested for reactivity with borrelial antigens by proliferative assay.[26]

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Neuropsychological tests were selected to provide measures of immediate and delayed memory, conceptualization, copying, perceptual discrimination, and language. These tests included the Wechsler Memory Scales, California Verbal Learning Test, Wisconsin Card-Sorting Test, Trailmaking Test, Rey–Osterrieth Complex Figure Test, Finger-Tapping Test, Benton Face-Discrimination Test, Hooper Visual Organization Test, Boston Naming Test, Token Test, and Oral Word-Association Test. In addition, intelligence quotient was estimated with either the Wechsler Adult Intelligence Scale–Revised or the Shipley Hartford Institute of Living Scale. Finally, symptoms of concurrent psychopathology, such as depression, were assessed by the Minnesota Multiphasic Personality Inventory. The test scores were transformed into standard scores that were calculated from published, age-corrected normative data. According to a previously described system,[27] evidence of memory impairment was defined as scores that were 2 SD below the normative mean on any one of the three tests of memory (Wechsler Memory Scales, California Verbal Learning Test, or Rey–Osterrieth Complex Figure Test) or more than 1 SD below the mean on two of the tests. A score of 70 or above on the Minnesota Multiphasic Personality Inventory was considered indicative of depression.

A detailed electromyographic examination of limb and paraspinal muscles was performed with concentric needle electrodes. Motor-nerve and sensory-nerve conduction studies of the median, ulnar, peroneal, and tibial nerves were performed with 10-mm surface recording and stimulating electrodes. For magnetic resonance imaging of the brain, T_1-weighted sagittal and axial images were obtained on a 1.0-tesla Siemens Magnetom with a repetition time to echo time of 650/20 msec, and T_2-weighted axial images were obtained with a repetition time to echo time of 3000/45 and 90 msec.

Criteria for Case Inclusion

Of the 37 patients, 5 who had memory difficulties, depression, or headache after erythema migrans were excluded because they had normal neurologic tests, negative or indeterminate antibody responses to *B. burgdorferi*, and no reactivity of mononuclear cells to borrelial antigens. Five additional patients who had dementia, demyelinating disease, or headache were excluded because Alzheimer's disease, multiple sclerosis, or brain tumor was the likely diagnosis. Four of these five patients still had antibody responses to *B. burgdorferi*. We believe that the remaining 27 patients had neurologic abnormalities caused by infection with *B. burgdorferi*. All 27 had previously had signs of Lyme disease, had neurologic symptoms lasting at least three months that could not be attributed to another cause, and had current evidence of humoral or cellular immunity to *B. burgdorferi*, as shown by an elevated serum IgG or IgM antibody titer of at least 1:400,[23] five or more IgG antibody bands to spirochetal polypeptides,[25] or a stimulation index of 10 or more in response to borrelial antigens.[26]

Treatment Regimen and Follow-up Examinations

The patients were treated with 2 g of ceftriaxone intravenously once a day for 14 days. Complete blood counts and liver-function tests were done on days 0, 7, and 14 to monitor the effect of therapy. Follow-up examinations were performed three and six months later. Serologic testing for *B. burgdorferi* was repeated at each follow-up visit, and all samples were tested again on a single plate to assess the change in titer. If possible, neurologic tests whose results had been abnormal in the initial examination were repeated at the six-month follow-up examination.

Results

Course of Lyme Disease

Of the 27 patients with chronic neurologic abnormalities due to Lyme disease, 23 (85 percent) had erythema migrans at the beginning of the illness and 2 others (7 percent) had an influenza-like illness without rash during the summer, days to weeks before the onset of early neurologic involvement (Table 1). The two patients who did not have symptoms of early infection did have arthritis followed by neurologic abnormalities. In 11 patients (41 percent), early symptoms included severe headache, mild neck stiffness, or spinal pain. Eight patients (30 percent) had early neurologic abnormalities consisting of facial palsy, sometimes with meningitis or thoracic radiculoneuritis, a median of one month after the onset of erythema migrans. These abnormalities resolved within one to two months except in one patient, who had mild residual facial weakness and a unilateral hearing impairment. A median of six months after the onset of disease, 19 patients (70 percent) began to have brief episodes of arthritis affecting primarily the knees. Arthritis occurred in all these patients before the chronic neurologic symptoms developed, and it was still present in 10 patients (37 percent) when the chronic neurologic abnormalities were noted.

Symptoms of chronic involvement of the peripheral nervous system developed a median of 16 months after the onset of infection, whereas symptoms of central nervous system involvement usually began later, a median of 26 months after the onset of disease (Table

Table 1. Course of Lyme Disease in the 27 Study Patients.*

Median age — yr (range)	49	(25–72)
Male/female	14/13	(52/48)
Early infection	25	(92)
Tick bite	10	(37)
Erythema migrans	23	(85)
Influenza-like summer illness without rash	2	(7)
Headache and neck stiffness or spinal pain	11	(41)
Oral antibiotics for early symptoms		
Doxycycline or tetracycline	4	(15)
Penicillin	2	(7)
Erythromycin	1	(4)
Early neurologic abnormalities	8	(30)
Median time from erythema migrans to early neurologic involvement — mo (range)	1	(0.5–2)
Facial palsy	8	(30)
Meningitis	2	(7)
Radiculoneuritis	1	(4)
Doxycycline for facial palsy	1	(4)
Oligoarticular arthritis	19	(70)
Median time from erythema migrans to arthritis — mo (range)	6	(1–57)
Antibiotics		
Oral tetracycline	1	(4)
Intramuscular penicillin V benzathine	1	(4)
Chronic neurologic abnormalities	27	(100)
Median time from erythema migrans to chronic peripheral nervous system involvement — mo (range)	16	(1–156)
Median time from erythema migrans to chronic central nervous system involvement — mo (range)	26	(1–168)
Duration of chronic neurologic involvement at time of evaluation — mo (range)	12	(3–168)
Intravenous antibiotics for arthritis and neurologic abnormalities		
Penicillin	3	(11)
Ceftriaxone	3	(11)

*Unless otherwise noted, values are numbers of patients, with percentages given in parentheses.

1). At the far end of the spectrum, these abnormalities began 10 or more years after the onset of disease, after long periods of latent infection (Fig. 1). At the time of the current evaluation, chronic neurologic involvement had usually been present for more than 1 year, and in several patients for 10 or more years. Fifteen of the 27 patients (56 percent) had already been treated with one or more courses of antibiotic therapy before this evaluation; in six cases, they had received two-week courses of intravenous penicillin or ceftriaxone.

Chronic Neurologic Abnormalities

Seventeen of the patients (63 percent) had abnormalities of both the central and peripheral nervous systems manifested as subacute encephalopathy and axonal polyneuropathy, seven patients (26 percent) had encephalopathy alone, two (7 percent) had polyneuropathy alone, and the remaining patient (4 percent) had leukoencephalitis.

Subacute Encephalopathy

Of the 27 patients, 24 had a mild encephalopathy. Twenty-two of them had difficulty remembering things (Table 2). They forgot names, missed appointments, or misplaced objects. To compensate, they often made daily lists. Ten patients had symptoms of depression, and three of them sought psychiatric help or received antidepressant medication. Eight patients had excessive daytime sleepiness, and seven had extreme irritability. They became angry over circumstances that previously caused only minor annoyance. Finally, five patients had subtle symptoms of a language disturbance, with difficulty finding words. No one had seizures, myoclonus, or a change in the level of consciousness. Although most patients were able to remain employed, three quit their jobs, three decreased their work hours to part-time, and two retired early.

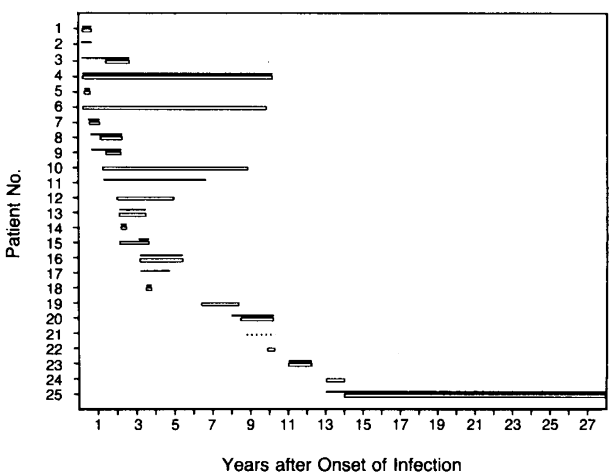

Figure 1. Interval between the Onset of Lyme Disease and the Occurrence of Encephalopathy, Polyneuropathy, or Leukoencephalitis and the Duration of These Complications in the 25 Patients in Whom the Onset of Infection Could Be Determined.

Chronic neurologic abnormalities began 1 month to 14 years after the onset of disease and lasted from 3 months to 14 years.

Table 2. Signs and Symptoms of Chronic Neurologic Abnormalities.

Signs and Symptoms	No. of Patients (%)
Encephalopathy	24 (89)
Memory loss	22 (81)
Depression	10 (37)
Sleep disturbance	8 (30)
Irritability	7 (26)
Difficulty finding words	5 (19)
Polyneuropathy	19 (70)
Spinal or radicular pain	11 (41)
Distal paresthesia	7 (26)
Sensory loss	12 (44)
Lower-motor-neuron weakness	2 (7)
Ankle hyporeflexia	2 (7)
Leukoencephalitis	1 (4)
Upper-motor-neuron weakness	1 (4)
Hyperreflexia	1 (4)
Increased muscle tone	1 (4)
Other symptoms	27 (100)
Fatigue	20 (74)
Headache	13 (48)
Hearing loss	4 (15)
Tinnitus	2 (7)
Fibromyalgia	4 (15)

All 24 patients had at least 12 years of education; they had intelligence quotients that were average or above, and none had a history of neuropsychological impairment. Of the 22 patients with symptoms of memory loss, 12 had evidence of memory impairment on neuropsychological tests, and the 2 with encephalopathy who did not notice any memory changes also had evidence of such impairment on these tests (Table 3). In only six patients was memory dysfunction marked enough to be apparent on neurologic evaluation at the bedside. On the Minnesota Multiphasic Personality Inventory, 9 of the 10 patients with symptoms of depression had scores indicative of depression. Only two patients scored 1 SD below the mean on any other neuropsychological test.

Of the 24 patients with encephalopathy, 21 had elevated serum IgG antibody responses to *B. burgdorferi* (Fig. 2). Of the remaining three patients, all of whom received antibiotic therapy for erythema migrans, one had only an IgM response (1:3200) to the spirochete; one had an IgG response in the indeterminate range (1:200), but the immunoblot showed antibody to six spirochetal polypeptides; and one had only a cellular immune response to borrelial antigens (stimulation index, 28). On analysis of the cerebrospinal fluid, 11 patients (46 percent) had evidence of slight intrathecal production of antibody to *B. burgdorferi:* 8 had only IgG antibody to the spirochete, 1 had both IgG and IgA antibodies, 1 had only IgA antibody, and 1 had only IgM antibody (Fig. 2, Table 3). In addition, 11 patients had increased cerebrospinal fluid protein levels, but only 1 had a pleocytosis of 7 lymphocytes per cubic millimeter. Thus, a total of

Table 3. Results of Neurologic Tests in 27 Patients with Chronic Neurologic Abnormalities.

TEST*	ENCEPHALOPATHY AND POLYNEUROPATHY (N = 17)	ENCEPHALOPATHY ALONE (N = 7)	POLYNEUROPATHY ALONE (N = 2)	LEUKOENCEPHALITIS (N = 1)	TOTAL (N = 27)
	number of patients (percent)				
CSF analysis					
Increased protein	8	3	0	1	12 (44)
CSF:serum ratio of antibody to *B. burgdorferi* >1	7	4	0	1	12 (44)
Increased protein or CSF:serum ratio >1	13	5	0	1	19 (70)
Pleocytosis	1	0	0	1	2 (7)
Neuropsychological testing					
Memory loss	12	2	0	1	15 (56)
Depression	6	3	0	0	9 (33)
Electrophysiologic testing					
Abnormal electromyogram	14	0	2	0	16 (59)
Abnormal nerve conduction	7	0	1	0	8 (30)
Magnetic resonance imaging scan of brain					
Small areas of increased T_2-signal intensity	3	1	0	1	5 (19)

*CSF denotes cerebrospinal fluid.

18 patients had increased cerebrospinal fluid protein levels, evidence of intrathecal production of antibody to *B. burgdorferi*, or both. Only one patient had an elevated IgG index and an increased rate of IgG synthesis in cerebrospinal fluid. None of the patients had low glucose levels in cerebrospinal fluid, oligoclonal bands, or a positive Venereal Disease Research Laboratory test. Four of the 24 patients, who were 34, 61, 64, and 72 years of age, had abnormal magnetic resonance imaging scans of the head. They had numerous small, rounded areas of increased T_2-signal intensity, primarily in the peripheral white matter (Fig. 3).

Overall, 23 of the 24 patients had objective evidence of memory impairment, abnormal cerebrospinal fluid findings, or both. Of the 10 patients in whom memory impairment could not be demonstrated on neuropsychological tests, 9 (90 percent) had abnormal cerebrospinal fluid analyses. All four patients with abnormal magnetic resonance imaging scans of the head had objective signs of memory loss, and three of them had abnormal cerebrospinal fluid findings.

Axonal Polyneuropathy

Of the 27 patients, 19 (70 percent) had polyneuropathy; all but 2 of these patients also had encephalopathy. Eighteen of the 19 patients had sensory symptoms: 11 had pain in the cervical, thoracic, or lumbosacral area of the spine, usually accompanied by tingling, burning, spasms, or shooting pain in the limbs or trunk, and 7 had only distal paresthesia, with intermittent tingling or "pins and needles" sensations in the hands or feet (Table 2). On examination, 12 patients had diminished sensation in response to light touch or pinprick within affected cutaneous areas, 2 had ankle hyporeflexia, and 2 had mild weakness of the limbs. The one patient who did not have sensory symptoms had "stocking" sensory loss (affecting the feet and areas of the legs usually covered by stockings) on examination. Sensory signs or symptoms were symmetric in 13 patients and asymmetric in 6.

On electrophysiologic testing, 16 of the 19 patients had evidence of an axonal polyneuropathy (Table 3). Electromyography showed that 9 of the 11 patients with spinal pain and 6 of the 7 patients with only distal symptoms had active or chronic denervation both in proximal paraspinal and in more distal limb muscles. In contrast, only 3 of the 11 patients with spinal pain and 4 of the 7 patients with distal paresthesia had slightly slow conduction velocities of the motor or sensory peroneal and tibial nerves or slightly prolonged motor latencies to the intrinsic muscles of the foot. The single patient with asymptomatic polyneuropathy had slight slowing of conduction velocities in the legs and denervation in the paraspinal and limb muscles. Of the three patients with normal electro-

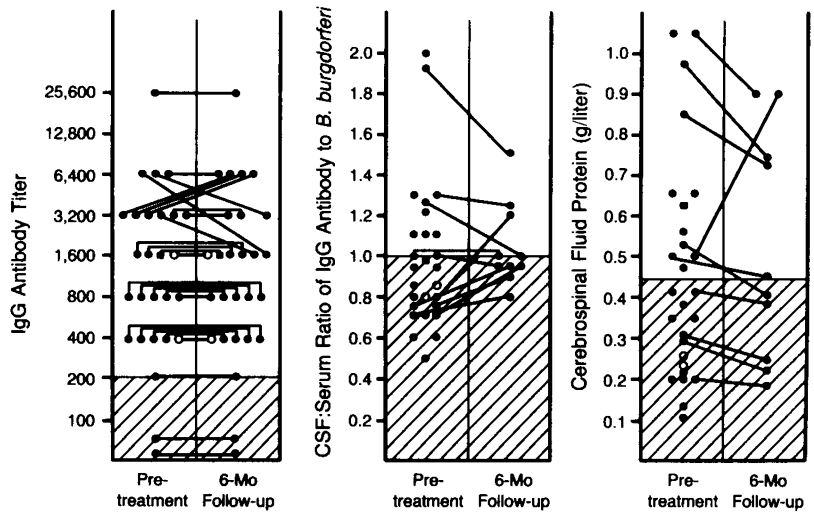

Figure 2. Pretreatment and Follow-up Serum IgG Antibody Responses to *B. burgdorferi*, Cerebrospinal Fluid (CSF):Serum Ratios of IgG Antibody to the Spirochete, and Cerebrospinal Fluid Protein Concentrations in the 27 Patients with Encephalopathy (●), Polyneuropathy Alone (○), or Leukoencephalitis (■). The hatched areas indicate the normal ranges.

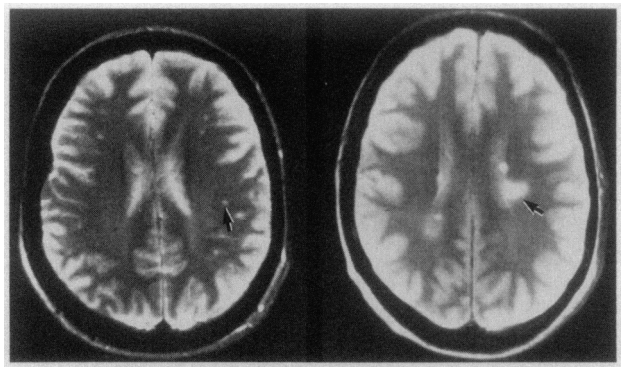

Figure 3. Magnetic Resonance Imaging Scans of the Brain of a 34-Year-Old Woman with Encephalopathy (Left Panel) and a 40-Year-Old Man with Leukoencephalitis (Right Panel).
Arrows indicate peripheral (left panel) and periventricular (right panel) lesions of the white matter.

physiologic studies, two had typical radicular pain and one had distal paresthesia.

Leukoencephalitis

Six years after the onset of Lyme disease, after erythema migrans and several brief attacks of arthritis that were treated with erythromycin and penicillin V benzathine, respectively, 1 of the 24 patients experienced progressive stiffness and then moderate weakness and increased tone in the muscles of his right arm and of both legs. His gait showed reduced arm swing on the right. Tendon jerks were diffusely brisk, with bilateral ankle clonus and Babinski signs. He had urinary urgency and frequency, with occasional episodes of incontinence.

Magnetic resonance imaging of the brain showed numerous small areas of increased T_2-signal intensity in the periventricular regions (Fig. 3). The scan of the spinal cord was normal, as were visual and brain-stem auditory evoked potentials. The serum IgG antibody response to *B. burgdorferi* was 1:12,800. The patient's cerebrospinal fluid showed 6 lymphocytes per cubic millimeter, an increased protein level of 0.64 g per deciliter, a cerebrospinal fluid:serum ratio of IgA antibody to *B. burgdorferi* of 4, and an IgG ratio of 0.98 (Fig. 2, Table 3). Analysis of the cerebrospinal fluid did not show a low glucose level, oligoclonal bands, myelin basic protein, or an increased rate of IgG synthesis. The patient scored 1 SD below the mean on two separate tests of memory. Electrophysiologic studies were normal.

Associated Symptoms

Of the 27 patients, 20 had marked fatigue, which was often a major symptom of their illness. Thirteen patients had mild-to-severe, episodic, non-pounding headache in a global, hemicranial, bifrontotemporal, or occipital distribution. They did not have nausea or visual or somatosensory aura. In two of them, headache was the primary symptom. Four patients, from 35 to 67 years of age, had mild-to-moderate unilateral hearing loss, sometimes accompanied by tinnitus. In all four, the hearing loss was apparent on physical examination, and in the two patients tested, audiometry confirmed a mild, high-frequency, sensorineural hearing loss. During the course of neurologic involvement, four patients had symptoms of fibromyalgia, a chronic pain syndrome associated with tender points in multiple locations, most commonly over spinal or paraspinal areas. However, all four of these patients had abnormal results of cerebrospinal fluid analyses or white-matter lesions on magnetic resonance imaging scans of the brain.

Treatment

The 27 patients were treated with 2 g of intravenous ceftriaxone a day for 14 days. Near the end of therapy, four patients had diarrhea and three had slightly elevated enzyme levels on liver-function tests. At the evaluation six months later, 17 patients (63 percent) were better, including the patient with leukoencephalitis. Improvement often did not begin until several months after the completion of therapy, and recovery was seldom complete. Of the remaining 10 patients, 6 (22 percent) improved but then relapsed, and 4 (15 percent) were no better. The response to treatment among patients with polyneuropathy was slightly better than that among patients with encephalopathy (68 vs. 58 percent).

In general, an improvement in symptoms was accompanied by an improvement in neuropsychological tests (five of six patients) and in nerve-conduction studies (five of seven patients). Regardless of the response to antibiotics, the cerebrospinal fluid protein levels often declined, and the serum and cerebrospinal fluid antibody responses frequently remained the same (Fig. 2). However, the one patient whose cerebrospinal fluid protein levels increased, the one in whom evidence of intrathecal antibody production subsequently developed, and two of the three whose serum antibody titers increased had recurrent symptoms. Although there was objective clinical improvement in the five patients with abnormal magnetic resonance imaging scans of the brain, the lesions showed no change. When pretreatment characteristics were analyzed according to the response to treatment, there was a trend toward a longer duration of infection, higher serum antibody titers, increased cerebrospinal fluid protein levels, and objective evidence of memory impairment in patients who did not respond, but these differences were not statistically significant.

Discussion

In this study of patients with chronic neurologic symptoms following well-recognized manifestations of Lyme disease, three neurologic syndromes emerged: encephalopathy, polyneuropathy, and leukoencephalitis, alone or in combination. These chronic neurologic abnormalities began months to years after the onset

of infection, sometimes after long periods of latency, as in neurosyphilis. In some cases, patients had erythema migrans during the summer followed within weeks by early neurologic abnormalities. Months later, arthritis often dominated the picture, and years later, chronic neurologic involvement became apparent, which often showed little progression for several years. In other cases, however, this chronology was condensed, the system involvement was incomplete or overlapped, chronic neurologic symptoms began early in the illness, or the neurologic abnormalities progressed more rapidly.

The most common form of chronic central nervous system involvement in our patients was subacute encephalopathy affecting memory, mood, and sleep, sometimes with subtle disturbances in language. Diagnosis of this condition may be difficult because the typical symptoms are nonspecific. In addition to evidence of immunity to *B. burgdorferi,* however, most of our patients had memory impairment on neuropsychological tests and abnormal results of cerebrospinal fluid analyses, frequently accompanied by axonal polyneuropathy and arthritis — a clinical picture that is very suggestive of Lyme disease. Although the anatomical and pathological basis for Lyme encephalopathy is not yet known, spirochete-like structures have been seen in brain-biopsy samples from two patients with apparent Lyme encephalitis.[17,28] By analogy with the general-paresis form of neurosyphilis, which may begin with impairment of memory and concentration, irritability, depression, sleep disorder, and fatigue,[29-31] we suspect that the pathologic process of Lyme encephalopathy may be mild, multifocal, and generalized, affecting both the gray and white matter. We excluded three elderly women from our series who had dementia several years after Lyme disease because we could not rule out the diagnosis of Alzheimer's disease. It remains possible that *B. burgdorferi,* like *Treponema pallidum,* may occasionally cause severe cognitive deficits.

In addition to encephalopathy, most of our patients had peripheral sensory symptoms, either distal paresthesias or spinal or radicular pain. Electrophysiologic testing, particularly in those with distal paresthesias, often showed an axonal polyneuropathy, with subtle abnormalities of distal motor-nerve or sensory-nerve conduction. Demyelinating features were not seen. Most of our patients, however, including those with only distal symptoms, also had extensive abnormalities of the proximal nerve segments on electromyography. The pathoanatomical basis for this symmetric or asymmetric polyneuropathy may be mononeuritis multiplex. In support of this idea, sural-nerve biopsies in affected patients have shown predominantly axonal injury with perivascular infiltration of lymphocytes and plasmacytes around epineural vessels.[6,32,33]

One patient in our series had an asymmetric spastic diplegia, upper-motor-neuron bladder dysfunction, subtle memory impairment, pleocytosis, and lesions of the periventricular white matter. This clinical picture is partially compatible with either European borrelial encephalomyelitis[5] or multiple sclerosis. Against the diagnosis of multiple sclerosis was the patient's progressive course involving only the motor system, normal evoked potentials, and the absence of myelin basic protein or oligoclonal bands in cerebrospinal fluid. Most important for the diagnosis of borrelial leukoencephalitis were the findings of lesions of the periventricular white matter and intrathecal production of antibody to *B. burgdorferi.* In two previous studies, patients with classic multiple sclerosis did not have antibody to *B. burgdorferi.*[34,35]

The typical response of our patients to antibiotic therapy supports the role of spirochetal infection in the pathogenesis of each of the syndromes described here. However, our results were not as good as those in previous reports.[6,7] Six months after treatment, more than one third of the patients either had relapsed or were no better. In addition, more than half had previously received antibiotic therapy thought to be appropriate for their stage of disease and still had progression of the illness. The likely reason for relapse is failure to eradicate the spirochete completely with a two-week course of intravenous ceftriaxone therapy. On the other hand, the patients whose conditions did not improve may have had irreversible damage to the nervous system, particularly since the response to therapy tended to be worse in patients with longer durations of disease. This is reminiscent of far-advanced neurosyphilis, in which the response to penicillin may be minimal.[36]

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CORTICOSTEROIDS AS ADJUNCTIVE THERAPY FOR SEVERE *PNEUMOCYSTIS CARINII* PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

A Double-Blind, Placebo-Controlled Trial

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Abstract *Background.* Preliminary reports suggest that patients with the acquired immunodeficiency syndrome (AIDS) and *Pneumocystis carinii* pneumonia may benefit from the addition of corticosteroid treatment to antibiotic therapy.

Methods. We conducted a double-blind, placebo-controlled trial to assess the efficacy of adjunctive corticosteroids in patients with AIDS and severe *P. carinii* pneumonia. Patients with marked abnormalities in gas exchange who had been treated with antibiotics for less than 72 hours were randomly assigned to receive either methylprednisolone (40 mg) or placebo every 6 hours for 7 days, in addition to treatment for 21 days with trimethoprim–sulfamethoxazole. The primary outcome measures were survival until hospital discharge and the development of respiratory failure.

Results. Twenty-three patients were enrolled in the study; there were no significant differences in base-line clinical or laboratory measures between the two treatment groups. Of 12 patients treated with corticosteroids, 9 (75 percent) survived until hospital discharge, as compared with only 2 of 11 placebo recipients (18 percent) ($P<0.008$). Respiratory failure developed in nine placebo recipients, as compared with only three patients treated with corticosteroids ($P<0.008$). No patient required the interruption or discontinuation of corticosteroid or antibiotic treatment because of toxicity or a complicating event. Because of the marked difference in survival, it was deemed unethical to continue the trial, and the study was terminated.

Conclusions. Early adjunctive corticosteroid therapy can improve survival and decrease the occurrence of respiratory failure in patients with AIDS and severe *P. carinii* pneumonia. (N Engl J Med 1990; 323:1444-50.)

PNEUMOCYSTIS CARINII pneumonia is the most common opportunistic infection associated with the acquired immunodeficiency syndrome (AIDS). In approximately 60 to 65 percent of patients with AIDS, it is the AIDS-defining diagnosis; another 20 percent of such patients acquire the disease over the course of their illness.[1] The death rate from *P. carinii* pneumonia approaches 25 percent, making it a major cause of mortality.[2-4] At present, standard chemotherapy consists of a prolonged course of either trimethoprim–sulfamethoxazole or intravenous pentamidine isethionate (pentamidine).[1,5-10] The predictors of a poor clinical outcome include extensive bilateral pulmonary infiltrates, concurrent pulmonary infections, recurrent *P. carinii* pneumonia, an elevated serum concentration of lactate dehydrogenase, a decreased serum concentration of albumin, a respiratory rate above 30 per

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