

The Overdiagnosis of Lyme Disease

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Objective.—To analyze the diagnoses, serological test results, and treatment results of the patients evaluated in a Lyme disease clinic, both prior to referral and from current evaluation.

Design.—Retrospective case survey of prescreened patients.

Setting.—Research and diagnostic Lyme disease clinic in a university hospital.

Patients.—All 788 patients referred to the clinic during a 4.5-year period who were thought by the referring physician or the patient to have a diagnosis of Lyme disease.

Main Outcome Measurements.—Symptoms and signs of disease, immunodiagnostic tests of Lyme disease, and tests of neurological function.

Results.—Of the 788 patients, 180 (23%) had active Lyme disease, usually arthritis, encephalopathy, or polyneuropathy. One hundred fifty-six patients (20%) had previous Lyme disease and another current illness, most commonly chronic fatigue syndrome or fibromyalgia; and in 49 patients, these symptoms began soon after objective manifestations of Lyme disease. The remaining 452 patients (57%) did not have Lyme disease. The majority of these patients also had the chronic fatigue syndrome or fibromyalgia; the others usually had rheumatic or neurological diseases. Of the patients who did not have Lyme disease, 45% had had positive serological test results for Lyme disease in other laboratories, but all were seronegative in our laboratory. Prior to referral, 409 of the 788 patients had been treated with antibiotic therapy. In 322 (79%) of these patients, the reason for lack of response was incorrect diagnosis.

Conclusions.—Only a minority of the patients referred to the clinic met diagnostic criteria for Lyme disease. The most common reason for lack of response to antibiotic therapy was misdiagnosis.

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LYME DISEASE is a tick-borne spirochetal infection with protean clinical manifestations.¹ In the United States, the illness usually begins with localized infection of the skin, erythema migrans, followed by dissemination of the spirochete to many sites.² Manifestations of early disseminated infection include secondary annular skin lesions, meningitis,

facial palsy, painful radiculoneuritis, atrioventricular nodal block, or migratory musculoskeletal pain.²⁻⁴ Weeks to months later, intermittent attacks of oligoarticular arthritis may occur especially in large joints, sometimes followed by the development of chronic arthritis in the knees.⁵ Months to years later, chronic encephalopathy manifested primarily by memory impairment or sensory polyneuropathy with spinal pain or distal paresthesias may develop often accompanied by cerebrospinal fluid (CSF) or electromyographic abnormalities.⁶⁻⁹

Current recommendations for the antibiotic treatment of Lyme disease include 10-day to 30-day courses of oral doxycycline, amoxicillin, or amoxicillin

plus probenecid for early infection,¹⁰⁻¹³ and 30-day courses of these antibiotics for Lyme arthritis.¹⁴ Except for patients with facial palsy alone, patients with neurological involvement often require treatment with intravenous ceftriaxone sodium or sodium penicillin G for 2 to 4 weeks.^{6-9,15,16} In a small percentage of patients, infection with *Borrelia burgdorferi* seems to trigger immune-mediated or parainfectious syndromes that do not respond to antibiotic therapy. Patients with chronic arthritis of the knees, particularly those with the HLA-DR4 specificity and antibody reactivity to the outer-surface proteins A and B of the spirochete,^{17,18} may have immune-mediated phenomena that persist after spirochetal killing. Infection with *B burgdorferi* may also trigger fibromyalgia, a chronic musculoskeletal pain syndrome that does not appear to respond to antibiotic treatment.^{19,20}

The diagnosis of Lyme disease is based primarily on the presence of a characteristic clinical picture, exposure in an endemic area, and an elevated antibody response to *B burgdorferi*. Although serological testing for Lyme disease can be performed with a high degree of sensitivity and specificity,²¹⁻²³ the testing is not standardized, and false-negative and more commonly, false-positive results have been a considerable problem.^{24,25} Even in patients with Lyme disease, seronegative results are common during the first several weeks of infection,²⁶ and a small percentage of patients who are incompletely treated with antibiotics early in the infection are seronegative later in the illness.^{27,28} A greater problem is the fact that seropositive patients usually remain seropositive for years after adequate antibiotic treatment, and asymptomatic infection with *B burgdorferi* may occur in some individuals.^{29,30} If seropositive patients develop another illness, particularly with

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Table 1.—Age and Sex Distribution According to Diagnosis

Diagnosis	Age, y, Mean±1 SD	No. of Patients, M/F	Sex Ratio, M:F
Active Lyme disease	38±20	100/80	1.25 to 1
Previous Lyme disease and another current illness			
Prominent subjective symptoms	36±13	37/46	1 to 1.2
Prominent objective symptoms	46±21	37/36	1 to 1
Other diseases			
Prominent subjective symptoms	37±14	81/167	1 to 2
Prominent objective symptoms	42±18	88/116	1 to 1.3

joint or neurological symptoms, the positive test for Lyme disease may cause diagnostic confusion.

In a summary of the first 100 patients seen at a Lyme Disease Referral Center in New Jersey, only 37 had active Lyme disease and 25 had fibromyalgia, which was sometimes associated with Lyme disease.¹⁹ Approximately half of the courses of antibiotic therapy given to these 100 patients before referral were probably unwarranted. In our experience as well, Lyme disease has become an overdiagnosed and overtreated illness. We report here the diagnoses, serological test results, and treatment results in all 788 patients referred to the Lyme Disease Clinic at New England Medical Center, Boston, Mass, during the past 4.5 years.

METHODS

The Lyme Disease Clinic at New England Medical Center, which functions both as a research and diagnostic clinic, was begun in July 1987. Most patients were referred to the clinic by physicians, and all referrals were prescreened by a physician or research assistant in the clinic. Questions were asked about past or present erythema migrans, tick exposure, joint swelling, mental status, serological test results, and any abnormal laboratory findings. Although no one was excluded from the clinic because of the absence of a particular finding, an effort was made to provide advice or to make an alternate referral if the presumptive diagnosis was fibromyalgia, chronic fatigue syndrome, or psychosomatic illness. Referrals were drawn primarily from New England, but also from other parts of the country.

The diagnosis of Lyme disease was based on the presence of one or more of the characteristic clinical manifestations of the illness, a history of exposure in an area where *B burgdorferi* has been recovered from ticks, and in almost all cases, a positive serological test result for Lyme disease. The clinical criteria were as follows: erythema migrans was defined as a red macule or papule that expands over a period of days to weeks to form a large annular lesion, at least 5 cm in size, often with partial central

clearing, frequently accompanied by fatigue, fever, headache, mild stiff neck, arthralgia, or myalgia.² Lyme arthritis was defined as recurrent, brief attacks of objective joint swelling in one or a few joints, especially the knees, sometimes followed by chronic arthritis in these joints.⁵ Early neurological involvement included lymphocytic meningitis, cranial neuritis, or radiculoneuropathy, often accompanied by a CSF pleocytosis.³ Chronic neuroborreliosis included encephalopathy with memory impairment often accompanied by CSF abnormalities⁶; polyneuropathy with radicular pain or distal paresthesias frequently accompanied by electromyographic evidence of an axonal polyneuropathy^{6,8}; or leukoencephalitis with spastic parapareses and areas of increased T₂ signal intensity on magnetic resonance imaging scans of the brain.⁶ Lyme carditis was defined as fluctuating degrees of atrioventricular nodal block that resolved in days to weeks, sometimes associated with myocarditis.⁴ In patients with neurological, joint, or cardiac abnormalities, other possible causes of these syndromes, to the extent possible, had to be excluded.

Evidence of immunity to *B burgdorferi* was sought with the following series of tests. In all patients, the IgM antibody response to the spirochete was determined by capture enzyme-linked immunosorbent assay (ELISA) and the IgG response was determined by indirect ELISA, as previously described.²³ In patients with indeterminate responses by ELISA, the response was clarified by Western blotting.²³ In seronegative patients who met clinical criteria for Lyme disease including a history of erythema migrans, the cellular immune response to the spirochete was determined by proliferative assay.²³ Patients with neurological symptoms were evaluated by lumbar puncture, electrophysiological studies, magnetic resonance imaging of the brain, or neuropsychological tests, as previously described.⁵ When CSF analyses were done, the CSF/serum ratio of specific antibody responses to the spirochete was determined by capture ELISA.³¹ In none of the patients was the diagnosis made by

Table 2.—Patients With Active Lyme Disease

Manifestation	No. of Patients (%) (n=180)
Early disease	
Erythema migrans	5
Meningitis, cranial neuritis, or radiculoneuritis	9
Total	14 (8)
Late disease	
Intermittent arthritis (attacks lasting weeks or months)	71
Chronic arthritis (more than 1 y of continuous joint inflammation)	15
Chronic encephalopathy/polyneuropathy and active arthritis	12
Chronic encephalopathy or polyneuropathy	63
Acrodermatitis chronica atrophicans	1
Interstitial keratitis of the eye	1
Total	163 (91)
Asymptomatic seropositive infection	3 (1)

culture or visualization of the spirochete in patient specimens.

Patients with Lyme disease were treated according to treatment protocols that were approved by the Human Investigation Review Board at New England Medical Center. Briefly, patients with intermittent episodes of Lyme arthritis were randomized to receive 100 mg of doxycycline twice a day or 500 mg of amoxicillin and probenecid four times a day, in each instance for 30 days.¹ Patients with persistent Lyme arthritis or neurological abnormalities or both were treated intravenously with 2 g of ceftriaxone per day for 2 or 4 weeks.^{6,8} Similarly, patients with fibromyalgia following Lyme disease were usually treated with ceftriaxone for 2 or 4 weeks.²⁰ Patients with other manifestations of Lyme disease received recommended antibiotic regimens.¹ For this analysis, charts were reviewed on all 788 patients evaluated in the clinic from July 1987 through December 1991. Information was recorded regarding diagnosis, serological testing, and treatment, both prior to referral and from our evaluation.

RESULTS

Patients With Active Lyme Disease

Of the 788 patients referred to the Lyme disease clinic, only 180 (23%) met criteria for active Lyme disease. The mean age of the patients was 38 years (range, 5 to 72 years), and the sex ratio was slightly in favor of men (Table 1). The most common referral (71 patients) was for the primary treatment of Lyme arthritis (Table 2). An additional 15 patients were referred because of persistent Lyme arthritis in one or both knees despite previous treatment with oral or intravenous antibiotic therapy. Seventy-five patients had symptoms compatible with chronic encephalopathy or polyneuropathy following characteristic earlier manifestations of Lyme disease, and 12 also had active arthritis. The treat-

ment courses of 33 of these patients have been reported previously.^{6,8} Of the 75 patients with chronic neurological abnormalities, 51 had an elevated CSF protein level, intrathecal antibody production to the spirochete, electromyographic evidence of an axonal polyneuropathy, or areas of increased T₂ signal intensity on magnetic resonance imaging scan of the brain; nine did not have these abnormalities; and 15 declined the evaluation. Half of these patients had previously received courses of oral or intravenous antibiotic therapy for Lyme disease. One patient each was thought to have other late manifestations of Lyme disease—acrodermatitis chronica atrophicans or interstitial keratitis of the eye. Several patients were referred for the primary treatment of erythema migrans, early neurological involvement of the disorder, or asymptomatic seropositive infection.

Of the 180 patients with active Lyme disease, 176 (98%) had serological evidence of infection with *B burgdorferi*. The four seronegative patients, three of whom had positive test results indicating cellular immunity to the spirochete, had erythema migrans followed by mild arthritis, encephalopathy with an elevated CSF protein, or polyneuropathy documented by electromyography. These four patients have been described previously.²⁸ Altogether, 179 of the 180 patients who met clinical criteria for Lyme disease had evidence of immunity to *B burgdorferi*.

Patients With Previous Lyme Disease and Another Current Illness

We thought that 156 (20%) of the 788 patients had previously had clinical manifestations of Lyme disease and currently had symptoms of another illness. These patients had similar age and sex distributions as those with active Lyme disease (Table 1). Of the 156 patients, 84 (54%) had subjective symptoms consisting primarily of musculoskeletal pain and fatigue (Table 3). Twelve of these patients had minor arthralgia or fatigue soon after antibiotic-treated erythema migrans, and these symptoms resolved within several months without further treatment. Another 49 patients developed chronic fatigue syndrome or fibromyalgia within a few weeks or months after Lyme disease. Their symptoms included some combination of diffuse musculoskeletal pain, headache, paresthesias, sleep disturbance, difficulty with concentration, or chronic fatigue, sometimes accompanied by multiple symmetrical tender points on examination. A report of 15 of these patients who had fibromyalgia following soon after Lyme disease has been published.²⁰ The other

Table 3.—Patients With Previous Lyme Disease and Another Current Illness

Current Diagnosis	No. of Patients (%) (n=156)
Illnesses with prominent subjective symptoms	
Brief arthralgia or fatigue after erythema migrans	12
Chronic fatigue syndrome or fibromyalgia following soon after Lyme disease	49
Chronic fatigue syndrome, fibromyalgia, headache, or depression following 1 y or more after Lyme disease	23
Total	84 (54)
Illnesses with prominent objective findings	
Rheumatic diseases	
Osteoarthritis	18
Regional pain syndromes	11
Chondromalacia patellae	8
Rheumatoid arthritis	3
Gout	3
Other	7
Total	50 (32)
Neurological diseases	
Peripheral neuropathy, diabetic or idiopathic	4
Cervical or lumbar radiculopathy	2
Seizure disorder	2
Vertigo	2
Cerebellar tumor	1
Other	4
Total	15 (10)
Other illnesses with prominent objective findings	
Infectious diseases	
Acquired immunodeficiency syndrome	1
Viral respiratory infection	1
Cardiac disease	
Atrial fibrillation	2
Endocrine disorder	
Hypothyroidism	1
Gastrointestinal illness	
Crohn's disease	1
Eye disease	
Idiopathic anterior uveitis	1
Total	7 (4)

23 patients had musculoskeletal pain or fatigue, fibromyalgia, headache, or depression that began more than 1 year after objective manifestations of Lyme disease had resolved.

Fifty (32%) of the 156 patients were evaluated because they developed joint symptoms months or, in most instances, years after Lyme disease. The most common picture was that of an elderly patient who had degenerative arthritis in the finger joints, lower spine, hips, or knees. Most of the other patients with rheumatic symptoms had noninflammatory regional pain syndromes, such as subacromial bursitis or chondromalacia patellae. In most cases, the joints with degenerative changes were not those affected by attacks of Lyme arthritis, but in some patients, previous Lyme arthritis may have been a factor in the development of chondromalacia patellae or degenerative arthritis of the knees. A few patients had other types of inflammatory arthritis after Lyme disease, such as rheumatoid arthritis or gout.

Fifteen additional patients were eval-

Table 4.—Patients With Other Diseases

Diagnosis	No. of Patients (%) (n=452)
Illnesses with prominent subjective symptoms	
Chronic fatigue syndrome	142
Fibromyalgia	84
Subjective neurological symptoms	25
Total	251 (56)
Illnesses with prominent objective findings	
Rheumatic diseases	
Rheumatoid arthritis	28
Osteoarthritis	20
Spondyloarthropathy	13
Inflammatory monoarthritis, undifferentiated	15
Other	47
Regional pain syndromes	18
Hypermobile joints	2
Total	143 (32)
Neurological diseases	
Multiple sclerosis	7
Demyelinating disease	6
Amyotrophic lateral sclerosis	3
Peripheral neuropathies or radiculoneuropathies	17
Other	8
Total	41 (9)
Other illnesses with prominent objective findings	
Dermatologic diseases	
Chronic urticaria	3
Other	4
Infectious diseases	
Viral exanthem	4
Other	2
Eye diseases	
Chronic uveitis	1
Other	2
Cardiac disease	
Viral myocarditis	1
Total	17 (3)

uated for neurological symptoms that developed 1 year or more after Lyme disease. For the most part, these patients had illnesses of unknown cause, such as a seizure disorder or vertigo, but neurological test results for Lyme disease were negative. In one patient, detailed neurological evaluation led to the diagnosis of a cerebellar tumor rather than neuroborreliosis. The remaining patients had disorders affecting other systems. Of the 156 patients with previous Lyme disease and another current illness, 134 (86%) had a positive antibody response to *B burgdorferi* in our laboratory at the time of our evaluation; the remaining 22 had a history of erythema migrans.

Patients With Another Illness

We thought that 452 (57%) of the 788 patients had another illness rather than Lyme disease. They had had symptoms for a mean duration of 3 years (range, 1 month to 22 years) at the time of our evaluation. More than half of these patients had chronic illnesses with prominent subjective symptoms, such as chronic fatigue syndrome or fibromyalgia (Table 4). The sex ratio among these patients was 2 to 1 in favor of women, but the age distribution was similar to that in patients with past or current

Lyme disease (Table 1). Although psychiatric disorders such as anxiety, depression, or somatization clearly played a role in the illness of some of these patients, we did not attempt to make psychiatric diagnoses. Approximately 30% of the patients had other rheumatic diseases, including rheumatoid arthritis or osteoarthritis, or regional pain syndromes. The remaining patients had neurological diseases, such as multiple sclerosis, or disorders affecting other systems, such as chronic urticaria or chronic uveitis.

Most of the 452 patients had had multiple serological tests for Lyme disease done in multiple laboratories. Of the 452 patients, 203 (45%) had previously had at least one positive result in another laboratory, often in a borderline-positive range. In our laboratory, none of these patients was seropositive.

Results of Retreatment in Previously Treated Patients

Prior to referral, 409 of the 788 patients had received recommended treatment courses of oral or intravenous antibiotic therapy for Lyme disease, and some had been retreated multiple times. Of the 409 patients, 31 (8%) had chronic encephalopathy or polyneuropathy of Lyme disease, and 25 of these patients had improvement or resolution of their symptoms within 2 to 6 months after retreatment with 2 g of ceftriaxone per day for 14 or 30 days. Another 42 patients (10%) had chronic fatigue syndrome or fibromyalgia following soon after Lyme disease. Of the 22 patients with these syndromes whom we retreated, only one, whose only symptom was fatigue, improved after ceftriaxone therapy and did not relapse. Fourteen patients (3%) had chronic Lyme arthritis of one or both knees. Of the eight patients in this category whom we retreated, none responded. The remaining 322 patients (79%) had another illness, and we did not recommend further antibiotic therapy for these patients.

COMMENT

The greatest diagnostic problem demonstrated in this study was distinguishing Lyme arthritis, encephalopathy, or polyneuropathy from chronic fatigue syndrome or fibromyalgia. The most common picture in Lyme arthritis is marked swelling of one or both knees. Lyme encephalopathy and polyneuropathy, which probably result from direct infection of the nervous system with *B burgdorferi*, are usually associated with subtle memory deficit, localized radicular pain, or distal paresthesias.⁶⁻⁹ These symptoms, which are often accompanied by CSF or electromyographic abnormalities, improve gradually over a period of months

following intravenous antibiotic therapy.⁶

In contrast, chronic fatigue syndrome or fibromyalgia, which may be variants of the same disorder, tend to produce more generalized and disabling symptoms. They include marked fatigue, severe headache, widespread musculoskeletal pain, multiple symmetric tender points in characteristic locations, pain and stiffness in many joints, diffuse dysesthesias, difficulty with concentration, and sleep disturbance.³²⁻³⁵ These patients lack evidence of joint inflammation; they have normal neurological test results³⁶; they usually have a greater degree of anxiety and depression^{37,38}; and their illness is not cured by antibiotic therapy. We did not find age, sex, or duration of symptoms to be of help in distinguishing neuroborreliosis from fibromyalgia, but the presence of tender points on examination and lack of response to antibiotic therapy were important clues in diagnosing fibromyalgia.

The problems in distinguishing neuroborreliosis from fibromyalgia are compounded by the fact that some patients develop fibromyalgia in association with or soon after Lyme disease, suggesting that *B burgdorferi* is one of the infectious agents that may trigger this chronic pain syndrome. When the syndrome develops years after Lyme disease, we suspect that it is due to the chance occurrence of two diseases. In many ways, the development of fibromyalgia as a consequence of infection with *B burgdorferi* is now the worst complication of this disorder since, in our experience, the pain syndrome does not respond to antibiotic therapy.²⁰ Although some patients with fibromyalgia noted improvement while on antibiotic therapy, they invariably relapsed within several months after treatment was stopped. We suspect that such improvement may be due to the potential placebo effect of therapy. Regardless of whether Lyme disease is the triggering cause, the safest and most effective approach to the treatment of fibromyalgia includes low-dose tricyclic medications, analgesic agents, an exercise program, and stress reduction techniques.^{39,40}

The remaining patients who had illnesses other than active Lyme disease usually had other rheumatic or neurological diseases for which specific diagnostic tests are lacking. Several common problems were distinguishing degenerative arthritis or regional pain syndromes from Lyme arthritis. Determining the correct diagnosis was more problematic in patients who had neurological syndromes after Lyme disease, such as vertigo, seizure disorder, or idiopathic peripheral neuropathy. Although we sometimes decided to treat

these patients with antibiotic therapy, their symptoms did not improve.

The limitations of laboratory testing in Lyme disease include the insensitivity of culture methods, the inability of serological tests to distinguish active from inactive infection, and the marked interlaboratory and intralaboratory variability in test results.^{24,25} Of the 452 patients referred here with presumptive Lyme disease in whom we diagnosed another illness, 45% had had a positive serological test result for *B burgdorferi* in another laboratory, but were seronegative in our laboratory. Discrepant serological results, particularly if only one test result is positive, must be interpreted with caution. Physicians should also be aware that more and more of the population in endemic areas are becoming seropositive due to past or asymptomatic infection with *B burgdorferi*. A positive serological test result in these patients is often interpreted as evidence of active Lyme disease rather than as seropositivity due to past infection. If these patients develop another illness, which was the case in 20% of the patients referred to the clinic, it may be attributed incorrectly to Lyme disease. In the future, tests that detect antigen, such as the polymerase chain reaction, may help to distinguish active from inactive infection; these tests are currently being researched.

Patients were usually referred to the clinic because of persistent or recurrent symptoms following standard antibiotic regimens for Lyme disease.^{1,12,13} Although persistent or recurrent symptoms in Lyme disease may result from incomplete eradication of spirochetes, only the current patients with Lyme encephalopathy or polyneuropathy responded to retreatment with intravenous antibiotic therapy, and they accounted for a small percentage of the patients referred to the clinic. Another small percentage of the current patients seemed to have immune-mediated chronic arthritis or a parainfectious fibromyalgia syndrome triggered by infection with *B burgdorferi*, but they did not respond to additional antibiotic therapy.

The most important point of this report is that misdiagnosis, either by the physician or the patient, was by far the most common reason for the apparent lack of response to antibiotic treatment. Before retreating a patient with persistent or recurrent symptoms who is thought to have Lyme disease, the physician should first reconsider whether the diagnosis is correct.

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