



Journal of Spirochetal and Tick-borne Diseases

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Special Editorial Lyme Disease: A Clinical Challenge
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Journal of Spirochetal and Tick-Borne Diseases

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Dedicated to:
“Science and Art in Spirochetal and Tick-Borne Diseases”

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The following guidelines are in accordance with the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” and International Committee of Medical Journal Editors (the “Vancouver Group”) statement, agreed at the January 1993 Meeting.

The *Journal of Spirochetal and Tick-Borne Diseases* publishes quarterly reviews and original work studies about any aspect of spirochetal and tick-borne diseases. The primary purpose is to broaden our understanding of spirochetal and tick-borne diseases. Special focus is given to Lyme borreliosis (also known as Lyme disease), as the most prevalent spirochetal and tick-borne disease. The clinical topics may involve all medical disciplines, nursing, and pharmacy, as well as the social, ethical, and biological features of spirochetal and tick-borne diseases.

The Journal is composed of two major sections. One section is devoted to the review of a specific topic that is established by the Associate Editors, and a special guest editor is invited to coordinate the development of up to six manuscripts relating to the specific topic. The second section of original works is composed of unsolicited manuscripts that are subsequently reviewed by the Review board, as well as external reviewers, depending upon the potential for conflict of interest within the editorial panel and the potential interest by the readership.

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December 1995

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Journal of Spirochetal and Tick-Borne Diseases

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GUEST EDITORIAL

Lyme Disease: A Lesson to Be Learned

Martina H. Ziska, M.D.

Lyme disease (LD) is the most prevalent vector-borne disease in the United States. It is also a major source of controversy. In some instances, LD is no longer viewed as a medical problem, but rather a social and political phenomenon. Polarity and inconsistencies exist in the medical community, as answers to some of the most fundamental questions about LD are lacking. On one hand, a group of academically based physicians conceptualize LD as an overdiagnosed and overtreated disease (1, 2). These academics believe that patients and the physicians are endangering themselves through the reckless management of presumed LD with extended antibiotic treatment. On the other hand, clinicians point to the deliberate suppression (3) of the numbers and facts that would show that there is a "silent epidemic of LD," with potentially long-term debilitating problems (4) for thousands of patients. Much of the controversy may be due to how LD was initially handled.

A history lesson

The history of LD is a lesson in how social and biological factors interact to help and/or hinder disease recognition and management. It also shows how our past and present beliefs—rather than having marginal influences on a fundamental biological reality—have shaped almost every aspect of medical practice. The social construction of LD as a new disease and its social consequences were discussed previously by Aronowitz, who offered a novel approach to the understanding of various aspects of LD (5).

I wish to argue that alternate conceptions were (and still are) possible but are deliberately not considered due to social factors. LD was defined as a new entity in the 1970s (6). However, manifestations of LD were known in Europe for almost 100 years. If such a connection had been made, this knowledge could have been extremely helpful in the search for the causative agent and the basis for the clinical management of LD. LD would most likely have been conceptualized differently, perhaps minimizing current controversies.

In 1910, the Swedish dermatologist Afzelius described an expanding rash after a tick bite. This is regarded as the first description of erythema chronicum migrans (ECM) (7). Further reports of ECM followed, most notably that of Austrian dermatovenerologist Lipschutz, in 1913 (8–10). A description of acrodermatitis chronica atrophicans, a clinical manifestation now recognized to be part of LD, dates back to 1883 (11).

Neurologic manifestations of LD were first described by the French scientists Garin and Bujadoux in 1922 (12), who reported a case of marked erythema after a tick bite with subsequent radiculoneuritis associated with severe radicular pain and meningitis symptoms. In 1930, Hellerstrom, from Sweden, described meningoencephalitis, which developed 3 months after the onset of an ECM (13). He stressed a relationship between neurological symptoms, tick bite, and ECM. In 1941, Bannwarth added "chronic lymphocytic meningitis" to the clinical syndrome of neuralgia or neuritis (14). Even though

he failed to elucidate the relationship between tick bite and erythema migrans, such a connection was made by a few others not much later (15). Further systemic manifestations were later described by Hellerstrom (16) and Hollstrom (17). Etiological speculations focused on an infectious agent carried by ticks. Binder et al. (18) provided dramatic evidence for an infectious etiology by injecting portions of the ECM rash into volunteers, who later developed ECM themselves. The clinical response to antibiotics (17) suggested that the causative agent was a bacterium. The first to posit that spirochetes were responsible for ECM was Lennhoff (19), although others were unable to confirm his hypothesis. The discovery of a causative agent did not come until 1982 (20).

There are few possible explanations as to why this knowledge was not utilized in the United States as the first cases of LD were recognized. European literature was easily accessible to the American Researchers. There were even a few reports in the U.S. literature that provide information about ECM. A standard dermatological textbook published in 1956 (21) provided a remarkably comprehensive discussion of ECM in a chapter titled "Dermatoses of Undetermined Cause." The first reported case of ECM in the United States, described in 1970 (22), did not get much attention; nor did the first case cluster in the United States, identified by dermatologists in Groton, Connecticut, during the summer of 1975 (23). The article, "Erythema Chronicum Migrans in the United States," described the same disease process, which was investigated the next year by Steere et al. One can only speculate why this report did not capture much attention. Was it because the disease was viewed as an obscure medical entity, known in Europe for numerous years? Or were other nonbiological factors involved?

Problematic discovery

In 1976, an epidemiologic investigation of an outbreak of "juvenile rheumatoid arthritis" (JRA) in Lyme and Haddam, Connecticut, was conducted. The investigation was requested by two concerned mothers. One mother was ill with a multisystem disease that had also affected other family members, including her children. The second mother pointed out the unusual clustering of JRA cases in the area. Numerous adults were also affected. The investigation was led by Dr. Allen Steere, a rheumatologist with a background in epidemiology, and was supervised by Dr. Stephen Malawista. A case definition of arthritis was selected to distinguish people who had the disease from those who did not. This made it so they ended up with a disease that fit their preconceived definition (5). Since the characteristics of the disease process they were investigating did not conform to the case definition of JRA, they described a new disease entity, called Lyme arthritis (6). Further investigation connected Lyme arthritis to a skin lesion, which was recognized to be ECM (24). Neurologic and cardiac manifestations, although described, were not considered common. This view prevailed for a decade, despite increasing recognition of numerous neurological manifestations as fairly common (25).

In fact, to reflect the multisystem nature of the disease, part of the medical community insisted that the name be changed to Lyme disease. Although the tick-bite connection was noted in the original report, viral etiology was suspected. It was not until 1982 that the causative agent, *Borrelia burgdorferi*, was identified by Willy Burgdorfer, and NIH researcher trained in Europe. He found a new organism while looking for rickettsiae. It is likely that his training, along with his interest and familiarity with the European literature, enabled him to make the discovery:

Thus, by 1955, clinical and epidemiological evidence was fully provided that ECM is caused by a penicillin-susceptible bacterial agent transmitted by the ixodid tick, *I. Ricinus*. Unfortunately, no one was interested in looking for spirochetes, and the puzzle about the etiology of ECM remained unsolved (26).

A disease is lost

Why was previous knowledge about ECM ignored or not applied to the new entity? Aronowitz has provided us with various explanations. Was it because there are biological explanations for historical and geographic differences in the identification and definition of Lyme disease and ECM, for example, differences in the tick species and spirochetes? Or was it because of the various nonbiological factors involved, such as the nationality of investigators (Americans versus Europeans), disciplinary background (rheumatology versus dermatology), methodological approach (prospective studies versus case reports), interpretation of biological evidence (possible differences between European and American spirochetes and ticks), intellectual or attitudinal features (skepticism toward research in past generations), ecological relations (divergent interactions among vectors, hosts, and demographic changes), or professional concerns (potential self-interest in promoting a new disease) (5)?

While we may never be certain of the answer, an important question remains. How different would current attitudes about LD in the United States be if medical, rather than social, factors were given priority in the process of conceptualizing LD?

Future direction

When nonmedical factors govern the perception of new diseases, such as LD, research efforts may be misdirected. With the passage of time and better understanding, perceptions of LD are changing. Basic biological properties of *B. burgdorferi*, including protein and genetic structure, are now well described (27). Its pathogenesis, with possible persistence of the organism and long-term clinical sequelae, as well as protean clinical manifestations, have earned LD the title of "Great Masquerader" (28). Reliance on positive serologic tests has been challenged by reports of variable laboratory performance (29) and the existence of seronegative LD (30). Questions are frequently raised about which laboratory and clinical measures should be utilized in diagnosis. Nonspecific symptoms of late stages of LD were recently ascribed to conceptualized post-Lyme syndrome (31). The ability to detect active infection is limited by the lack of direct detection testing.

Unfortunately, most questions about antibiotic treatment remain unanswered. The current recommended treatment for disseminated LD is 4 weeks of antibiotics, with retreatment of relapses. However, several reports show that this and other treatment recommendations are not followed by the medical community (32–34). Physician approaches vary, especially with regard to the length of therapy and choice of drug. We should remember that answers are not likely to come from criticizing those who are not following the "recommendations." Only well-controlled, randomized treatment trials will

validate suggested treatment protocols. Until data from these trials are available, researchers should view old data and literature from the above-described perspective. We can only hope that history will be corrected soon.

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SPECIAL EDITORIAL

Lyme Disease: A Clinical Challenge

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The controversies surrounding various aspects of Lyme disease reflect that our knowledge in these areas is incomplete. The papers presented in this issue of the Journal are indicative of the types of questions that are raised regarding the epidemiology, diagnosis, and treatment of the disease.

Central to most of the controversies is what constitutes an appropriate definition of Lyme disease. Although attempts have been made to define the disease in terms of objective physical findings, the nature of the illness suggests that, in many cases, perhaps most, the disease is manifested by neurosensory complaints such as arthralgias, myalgias or muscle stiffness, paresthesias, cognitive dysfunction, and fatigue. The fact that it is very difficult for both patients and physicians to objectify these complaints and to easily distinguish these symptoms from those described for other possible diagnoses is an intellectually humbling experience, which should make us more open-minded and less dogmatic about what is and what is not Lyme disease. It is currently not easy to distinguish some of the symptoms of Lyme disease from those of fibromyalgia, chronic fatigue, and perhaps multiple sclerosis. Fibromyalgia and chronic fatigue are also ill-defined disorders, and some clinicians and academicians question whether fibromyalgia exists as a distinct entity.

The attempts to solidify the clinical diagnosis of Lyme disease using serologic methods, while well intended, are simply inadequate with current methodology. It is syllogistically illogical to conclude with what has already been reported that a positive serology defines, and a negative serology excludes, Lyme disease. The current enzyme-linked immunosorbent assay (ELISA) methodology uses whole, sonicated organisms that produce too many cross-reactions and require raising the levels for a positive test above background reactivity so that it does not achieve the sensitivity required of any useful test. The current ELISA tests are not readily reproducible between laboratories that otherwise are capable of conducting serologic assays for a variety of different infectious and noninfectious disorders (1). ELISA reactivity following infection has been noted in animals who do not get arthritis, as well as in those who do (2). Similarly, there are individuals who have strong ELISA reactions without clinical symptomatology, while others with weak reactions may have disabling symptoms. The ELISA tests are acknowledged to be of little value in early infection, further limiting their utility. If a subset of patients is capable of strong immunoreactivity, what of those who are not, but who have been proven to have Lyme disease by culture or PCR-DNA technology? Is it duplicitious to diagnose and treat patients who have "seronegative rheumatoid arthritis" and not do the same for "seronegative Lyme disease"?

Western blotting substantially increases the specificity of the immunodiagnosis, but the sensitivity of this method is unknown, and the definition of a positive reaction is imprecise. Particularly intellectually dissatisfying is the arbitrary decision that a given number of reactions seen on the immunoblot con-

stitutes positivity, to the neglect of the significance of specific versus nonspecific reactions. It has been shown in early disease that the first reactions are to the 41 kd flagellar and 23/25 kd Osp C proteins (3), yet these results would be deemed negative by some current recommendations, with the unfortunate result of a loss of opportunity to treat patients in a stage of the disease in which treatment appears to be reasonably successful.

The role of PCR-DNA analyses of blood, urine, and cerebrospinal fluid (CSF) in the diagnosis of Lyme disease remains to be delineated. Some early reports appear promising (4), although other reports (5) and experience suggest that it may not be a routinely clinically sensitive test upon which the diagnosis of Lyme disease can be made or excluded. The Lyme borrelia are known to establish a chronic infection; if, like other chronic infections that establish intracellular loci, readily detectable DNA fragments of the borrelial gene may not be released into the general circulation or CSF.

As confounding as are the clinical and laboratory diagnoses of Lyme disease is the treatment of the disorder. It would appear that the earliest symptoms and signs are eradicated with relatively short courses (i.e., 2 to 4 weeks) of treatment. But despite some strongly stated opinions and theoretical cost-benefit analyses (6, 7), there has been no controlled study to evaluate the proper type and duration of antibiotic therapy in persistent Lyme disease. The presumption that 1 month of treatment should cure Lyme disease appears now to be incorrect, as many practitioners are finding that a longer duration of therapy is needed to achieve significant improvement or cure (8). With its slow *in vitro* replication time and its likely persistence as an intracellular infection, both longer duration of therapy and the use of intracellular-penetrating antibiotics, such as the tetracyclines and macrolides, would be predicted to be the optimal approaches to successful treatment. Properly designed clinical treatment trials are needed to address these issues.

Although there are many questions regarding the diagnosis and treatment of Lyme disease, a reasonable approach currently is to include Lyme disease in the differential diagnosis of patients whose primary complaints include musculoskeletal symptoms in combination with fatigue, paresthesias, and cognitive dysfunction that persist for more than a few weeks. Appropriate laboratory studies should be conducted to address the possibility of rheumatoid-type disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Some patients may require neurological evaluation for possible multiple sclerosis (MS), including tests of visual and auditory responses, oligoclonal bands in the CSF, and magnetic resonance imaging (MRI) study of the brain; although none of these tests is specific for MS and excludes Lyme disease, it nonetheless may be useful in some cases to get as complete a picture as possible to achieve the correct diagnosis. If Lyme serologies are positive or indicate reactions on western blots to any of the highly specific 23/25 kd (Osp C), 31 kd (Osp A), 34 kd

(Osp B), and perhaps the 39 kd and 83 kd proteins, a greater confidence can be placed in the diagnosis of Lyme disease.

Once a diagnosis of Lyme disease is achieved or presumed, a reasonable approach to further evaluate the diagnosis is a treatment trial, using tetracycline, 500 mg t.i.d. (or doxycycline 100 mg t.i.d.), or other antibiotics for a 3-month period of time. We and others have found that patients routinely require 4 to 6 weeks before they begin to respond, and by 3 months, they are significantly improved. Extending the course of treatment is a clinical decision, frequently resulting in a total of 6 months of treatment. There are numerous examples of infectious diseases (e.g., tuberculosis, leprosy, hepatitis B/C) in which prolonged therapy is needed to effect improvement or cure. Until controlled trials are conducted, this empiric approach to treatment does not seem unreasonable in light of our current knowledge.

It is to be hoped that, as with any disease in which information is incomplete and evolving, our energies can be directed toward improving our understanding of Lyme disease through more research into the pathogenesis and treatment of the illness. Lyme disease needs to be depoliticized, and the burden borne by all involved needs to be less dogmatic and more sensitive to various hypotheses until more knowledge can provide us with better approaches to the diagnosis and treatment of the disease.

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CASE REPORTS

Lyme Arthritis in British Columbia

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The first known locally acquired case of Lyme arthritis in British Columbia is described. The patient had frequent tick exposure where he lived, on a forested island on the south coast of the province. The diagnosis was established by a clinical picture compatible with Lyme arthritis and by multiple reactive bands for *B. burgdorferi* on IGG and IGM western blot analysis of serum. The arthritis, which had been intermittent for more than 6 months, responded quickly to 1 month treatment of oral doxycycline, with no recurrence after 2 years. Although tick exposure is common and *B. burgdorferi* has been isolated from two species of ticks and from rodents in many areas of British Columbia, cases of Lyme disease and Lyme arthritis seem to be rare for reasons that are not clear.

INTRODUCTION

Arthritis is a manifestation of Lyme disease (LD), a tick-borne disease caused by infection with *Borrelia* (*B.*) *burgdorferi*. Lyme disease is transmitted by ixodid ticks of several species. The disease occurrence in North America corresponds to the distribution of these species—usually *Ixodes* (*I.*) *scapularis*, in the eastern United States and southern Ontario, or *I. pacificus* in the western United States and Canada (1, 2). Sporadic cases have appeared elsewhere, and horse flies, deer flies, mosquitoes, and other species of ticks have been implicated as possible vectors (3, 7).

The disease is found also in Europe, the former Soviet Union, Japan, and China where the vectors are different species of ixodid ticks, while in Australia, the vector has not yet been identified.

I. pacificus and other ixodid ticks are found in British Columbia. *B. burgdorferi* has recently been isolated from juveniles and adults of two species of ticks, namely, *I. pacificus* and *I. angustus*, as well as from rodents, in many areas of the province (4, 7). The tick species found in the western United States are much less frequently infected with *B. burgdorferi* than those in other regions of the continent, possibly because of a different intermediate host (1).

Most of the locally acquired cases reported in Canada have occurred in Ontario. However, many other patients with LD in Canada have probably acquired the infection during travel to a known endemic area (6). There have been only 11 cases of locally acquired LD diagnosed in British Columbia and no cases of Lyme arthritis to date (4, 5, 7).

In the following, we describe a case of Lyme borreliosis with arthritis believed to have been acquired in British Columbia.

CASE REPORT

A retired lawyer presented in January 1993 with pain and swelling in the left knee. For more than a year, he had felt generally unwell, and the knee had become painful and swol-

len 6 months earlier. The knee improved, but he then experienced pain in the right knee and both shoulders, along with swelling and pain in finger joints. In December 1992, pain and swelling in the left knee recurred. He treated himself with several medications, and although his complaints improved, he continued to have multiple joint pains and tenderness.

He lived on a wooded island off the coast of British Columbia where he had frequent exposure to tick-infested deer when hunting every autumn. In the autumn of 1990, he had also hunted in eastern British Columbia, on the western slope of the Rocky Mountains, and had carried an elk out of the bush. He had frequently observed ticks on deer but did not recall any tick bites or skin rashes. Two years previously he had traveled to the Baja California of Mexico but had not been outside British Columbia since.

There was no recent history of diarrhea or genitourinary symptoms. He had never had hepatitis or been jaundiced.

His mother was said to have "back problems," but there was no history of arthritis or psoriasis in the family.

Physical Examination

Positive findings were confined to the musculoskeletal system. There was tenderness and swelling of the right ulnar styloid and tenderness of the right second metacarpophalangeal (MCP) joint. The left knee was painful on movement and had a small effusion. The metatarsophalangeal (MTP) joints on the right foot were tender. Movements of the spine were full and pain free. There were no cardiological or neurological abnormalities.

Within a week, patient developed more pain and an effusion in the right knee as well as increased swelling and redness of the second and third MCP joints of the right hand and the right wrist.

The hematology panel was normal, but the erythrocyte sedimentation rate (ESR) was elevated to 37 mm (Westergren). The urinalysis was normal, and the antinuclear antibody (ANA) and rheumatoid factor tests were negative. Chemistry studies were normal as was the serum electrophoresis. Hepatitis B and C serology was negative. Joint fluid was not analyzed.

Serology studies were carried out at the Provincial Laboratory, British Columbia Centre for Disease Control. The en-

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ERYTHEMA MIGRANS

All the following photographs represent patients who witnessed a tick bite at the location which subsequently developed bull's-eye lesions or erythema migrans or erythema chronicum migrans for up to 3 to 10 days after the witnessed bite and imbedded tick. This section was prepared and photographs provided by Philip Paparone, D.O.



FIG. 1. Large bull's-eye lesion with distinct, narrow, erythematous border, somewhat raised, with a large, more central cleared area surrounding minor punctate erythematous lesions in the central portion of the bull's-eye.



FIG. 2. Patient with a bull's-eye lesion that is slightly ecchymotic with some central clearing.



FIG. 3. Patient with an oval bull's-eye lesion over the lateral posterior aspect of the thigh, with a central ecchymotic to dark red area, enhancing clear ring and thickened peripheral erythematous accentuated area.

ERYTHEMA MIGRANS



FIG. 4. Patient with markedly irregular erythema migrans over the right flank with linear erythematous extensions at approximately 9 o'clock.



FIG. 5. Patient with a large bull's-eye lesion over the left iliac crest with a central erythematous area surrounded by a faintly erythematous area that is irregular, and a more homogeneous erythematous periphery along one portion of the border.



FIG. 6. Patient with a left axillary bull's-eye lesion with an accentuated central bite site and irregular clearing zone surrounded by an irregular, accentuated, widened, erythematous border.

ERYTHEMA MIGRANS



FIG. 7. Patient with a pretibial markedly irregular and punctate ECM with some central clearing that is extremely irregular in its border and in the central clearing area.



FIG. 8. Patient with a pretibial ECM with slight tendency toward ecchymosis and markedly irregular peripheral accentuation within some portions of the lesion.



FIG. 9. Patient with a tick bite in a scar with a markedly irregular border, a portion of which is accentuated and a central core erythema.

CHRONIC LYME-RELATED BELL'S PALSY RESPONSIVE TO PROLONGED ORAL ANTIBIOTIC TREATMENT



FIG. 1. (March 1995) Note paralysis of the right facial nerve evidenced by weakness of the right side of the face and flattening of the nasolabial fold.



FIG. 2. (April 1995) Note that the patient can now open the right eyelid and that the paralysis of the right side of the face has improved.



FIG. 3. (August 1995) Note the nearly complete resolution of the facial paralysis.

zyme immunoassay for *B. burgdorferi* was highly reactive (A.U. 281.1), the positive cut-off value being 25 A.U. The confirmatory western blot IgG was also reactive, showing the following bands: 17, 25, 31, 34, 39 (faint), 41, 62, 66, and 97 kd. Western blot for IgM was also reactive with bands at 31, 34, 41, and 66 kd. Cultures of blood and urine were negative, and polymerase chain reaction (PCR) test for *B. burgdorferi* Osp A gene was also negative in blood samples.

Radiographs showed degenerative changes in the hands and wrists but no erosions, effusion of the left knee with soft tissue swelling medially and poor definition of the right patellar and quadriceps tendons, and normal sacroiliac joints.

Patient was started on doxycycline 100 mg b.i.d. for 30 days. Within 2 weeks, he was feeling generally improved and his joints were no longer painful. Within 1 month, he claimed that he had not felt so well for more than a year. All joint swelling was gone, and there have been no further attacks of arthritis in the 2 years of follow-up to the present.

DISCUSSION

This patient had an arthritis that was compatible with the late stage of LD. He had been frequently exposed to deer ticks but did not remember tick bites or skin rashes. No other cause for arthritis was found, and when the laboratory studies confirmed exposure to *B. burgdorferi*, he was treated with antibiotics. He improved quickly, and within a month, the arthritis was resolved. This may be the first case of arthritis associated with LD confirmed in British Columbia.

Lyme disease is now the most common vector-transmitted disease in North America (1). Deer ticks are commonly found in British Columbia, and the organism has been isolated from two species of ticks and rodents in many areas of the province. Following the recognition of this case, ticks infected with *B. burgdorferi* have been found on several coastal islands of British Columbia, which is most likely where the disease was contracted in this patient (4, 7).

Arthritis was the presenting feature in the first cases of LD reported by Steere et al. in 1977 (8). This is a late manifestation occurring a mean of 6 months after the primary infection in approximately 50% of untreated LD patients (9). It may start as recurrent arthralgias and musculoskeletal pains, followed by intermittent episodes of arthritis that are usually asymmetrical and oligoarticular with a predilection for larger, weight-bearing joints, particularly the knee. Periarticular structures such as tendon and ligament attachments (enthese) may be involved. Although the attacks of arthritis usually remit in a few weeks, they tend to last longer as the disease progresses, and approximately 10% of patients with arthritis may develop chronic inflammation with erosions and joint damage, which may mimic rheumatoid arthritis (9).

The radiographic features of Lyme arthritis are those of inflammatory joint disease and are nondiagnostic. However, swollen joints may show periarticular soft-tissue swelling and a loss of musculotendinous planes. As a manifestation of enthesopathy, tendons around involved joints may be thickened, with a loss of definition, as noted in this case. In chronic cases, erosions and cartilage loss may be found (10).

The diagnosis of LD arthritis usually depends on the presence of a characteristic clinical picture supported by positive serology for *B. burgdorferi* confirmed by western blot analysis. As the organism has recently been isolated from ticks and rodents in several areas of the province, British Columbia may now be considered an endemic area (4). Thus this patient would be classified as a case of "definite" LD by current Canadian surveillance criteria (6). It is uncommon to be able to

find the *B. burgdorferi* organisms in tissue samples and difficult to culture them from body fluids. In this case, both culture and PCR analysis of blood and urine were negative for the organism.

As LD is potentially curable, early recognition and treatment is vital to prevent chronic arthritis and other long-term complications of *B. burgdorferi* infection. However, the treatment of different stages of LD is still not standardized, and evaluation is continuing. Rahn and Malawista have recently summarised recommendations to assist in decision making (11). For the treatment of Lyme arthritis, in patients who do not have neurologic involvement, they and Steere et al. (12) recommended oral antibiotics. Thirty days of oral doxycycline 100 mg twice daily was preferred, but amoxicillin 500 mg and probenecid 500 mg, each 4 times a day, had also been used. With the oral regimes, 80 to 90% of patients improved. Treatment failures should receive either a second course of oral antibiotics or intravenous ceftriaxone, 2 g daily for 2 to 4 weeks. Previous intra-articular corticosteroid application was suggested as a factor in antibiotic failure and, therefore, should be avoided prior to treatment if the diagnosis of LD is considered. Other factors associated with treatment failures included the presence of HLA DR4 specificity and Osp A reactivity in serum or low concentrations of interleukin-1 receptor antagonist and high concentrations of interleukin-1 beta in synovial fluid (12).

Lyme Arthritis in British Columbia

Tick infestation of humans is common in British Columbia because of the large areas of forest and a population that uses these areas extensively during work and recreation. Despite the demonstrated presence of *B. burgdorferi* in many areas of the province, it is strange that locally acquired LD and, in particular, Lyme arthritis have been so rarely recognized.

Perhaps the disease is not being recognized by physicians. However, a seroprevalence survey for borreliosis in children with chronic arthritis in British Columbia showed no significant differences among patients with arthritis and controls in the distribution of IFA antibody titers to *B. burgdorferi* (Lyme disease) and *B. hermsii* (relapsing fever) (13). All of the positive IFA tests found in this study were negative on confirmatory western blots. These results suggested that, in children at least, unrecognized *B. burgdorferi* infection is not the reason for the scarcity of cases.

The incidence of LD and LD arthritis has a geographical variation, occurring much more in the United States than in the United Kingdom or continental Europe (14). Thus, there may also be a geographic factor affecting the incidence of Lyme arthritis at work in British Columbia. Rees and Axford suggested that the regional variations of LD arthritis may be related to pathogenic differences in the causative organism (14). In any case, the apparent low incidence of LD in British Columbia merits further study.

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Lyme Disease, Initially Misdiagnosed as Rheumatoid Arthritis, Successfully Treated with Long-Term Azithromycin

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A 59-year-old white male with a 10-year history of migratory and fixed joint pains, was initially diagnosed and treated as having rheumatoid arthritis (RA). When the patient failed to respond to nonsteroidal anti-inflammatory drugs (NSAIDs), he was placed on hydroxychloroquine sulfate (Plaquenil) and maintained on this for 8 more years, despite nonimprovement. He was eventually diagnosed with Lyme disease and treated with 5 months of azithromycin (Zithromax). He has remained symptom free for 2 years.

Lyme disease is a multisystem disorder caused by the spirochete *Borrelia burgdorferi*. The organism is transmitted to humans and animals mostly by ticks of the *Ixodidae* complex (1–5). In the endemic areas of the northeast and north central United States, the vector is *Ixodes scapularis* (formerly *I. dammini*) (6). *Ixodes pacificus* is the vector in the western states and British Columbia (7–9).

Lyme disease (LD) is often characterized by an expanding skin rash (erythema migrans) and constitutional symptoms such as fever, headache, fatigue, and malaise (10).

If the disease is untreated or treated inappropriately, cardiac, neurologic or joint abnormalities may also occur (7, 10–12). There is also evidence that even properly treated cases can develop these complications.

The diagnosis of LD depends upon the physician's assessment of clinical findings, epidemiological data, and laboratory testing (10, 13). Laboratory confirmation may be difficult with present testing options (14, 15).

CASE REPORT

A 59-year-old white male presented with a 10-year history of migratory joint pain, which had started in the feet and progressed to the lumbar and cervical spines. Eventually, the knees and shoulders became involved. In the last 8 years, the hands had become swollen and painful. These symptoms were associated with fatigue, memory loss, sleep disturbances, and frontal headaches.

In 1984, despite negative serological testing for rheumatoid arthritis (RA), three different rheumatologists recommended treatment for RA. It is not known what clinical criteria were used for this diagnosis. After 2 years of nonresponse to nonsteroidal anti-inflammatory drugs (NSAIDs), the patient was placed on hydroxychloroquine sulfate (Plaquenil), with little response. He remained on Plaquenil and Naprosyn for an additional 8 years.

When first evaluated in our office in August 1992, the patient gave a strong history of tick exposure. He has been also living in an endemic area of Lyme disease (Princeton, NJ). He was unable to close his hands without pain and awoke frequently during the night because of hand, neck, and shoulder pain. Swelling of his fingers (interphalangeal (IP) and metacarpophalangeal (MCP) joints) and limited range of motion of

the cervical spine and shoulders were the only objective physical findings.

Laboratory studies showed a slightly elevated titer of *B. burgdorferi* antibodies (10.9 with neg. 0.0 to 9.0). He had evidence of antibody activity against proteins 39, 41, and 60 kd on western blot IgG.

Sedimentation rate, RA factor, C-reactive protein, and antinuclear antibody (ANA) were all negative. Complete blood count, chemistry profile and thyroid testing were all normal.

In September 1992, the patient was started on azithromycin (Zithromax) 250 mg daily. When evaluated 4 weeks later, the patient was sleeping through the night without pain. His morning stiffness and swelling were gone, and his pain had diminished by 50%. Antibiotics were continued for another month and then decreased to one capsule 3 times a week (Monday, Wednesday, and Friday). This dose was maintained for 3 more months.

The patient experienced no problems with the antibiotics and was able to discontinue both the Naprosyn and hydroxychloroquine sulfate shortly after starting the azithromycin.

The patient was symptom free on March 24, 1993, and remains so today, more than 2 years after stopping azithromycin.

DISCUSSION

Several recent articles have suggested that some physicians have a tendency to over-diagnose and over-treat Lyme disease (13, 15, 16). In May 1994, Schoen stated his opinion as "At the present time, most individuals presenting to physicians with complaints about late Lyme disease do not have Lyme disease!" He quoted a study published by Sigal evaluating the first 100 patients seen at a Lyme disease referral center in central New Jersey (16).

Is it not possible that since 1991, our diagnostic ability has improved to the point where we can better detect cases that were missed earlier?

In 1994, using cytological techniques, Schubert and Greengard identified the Lyme spirochete in the vitreous fluids of patients with choroiditis and vitritis despite the negative serology testing before and after treatment (17). This case would not have been counted by Sigal as a legitimate case of LD as it comes under the heading of argued "seronegative" LD.

Many physicians may not have treated this "rheumatoid arthritis" patient based on positive history alone. Fewer would

have treated him on physical findings alone. Even with a completely negative serology, this patient should be given the benefit of the doubt and given a short course of antibiotics.

The other question this case presents is the treatment for chronic Lyme arthritis.

Lyme arthritis is a late complication of Lyme disease. Chronic Lyme arthritis is defined as 1 year or more of continuous joint inflammation. This occurs in just 10% of Lyme arthritis cases, usually starting during the second or third year of the infection (18–21).

Steere et al. (20) recommended treatment of Lyme arthritis with oral amoxicillin (with probenecid) or oral doxycycline. They prefer the latter since the former does not cross the blood-brain barrier very well. They also state that the main drawback of oral antibiotic therapy is that patients with Lyme arthritis may have latent or active neuroborreliosis, which may be inadequately treated with oral antibiotics. The possible use of IV ceftriaxone for an additional 2 to 4 weeks is recommended in those patients who do not respond to the oral regimen.

CONCLUSIONS

It is frequently suggested that if patients with LD do not respond to conservative therapy, that the diagnosis is incorrect. This principle should apply to all diagnoses. We should not assume diagnosis correct if the patient does not respond after a reasonable trial period of treatment.

All alternative diagnoses should be considered, even if the suggestion comes from the patient. Egos and prejudice should not deter us from including all possible diseases in our differential diagnoses.

Macrolides such as azithromycin have had reported success in treating Lyme disease in Europe and in the United States. Formalized research should be conducted to determine their value in the treatment of LD in all stages.

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Persistent PCR Positivity in a Patient Being Treated for Lyme Disease

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A 30-year-old white female presented with worsening clinical symptoms suggestive of Lyme disease while on antibiotic therapy. Results of enzyme-linked immunosorbent assay (ELISA) and of western blot tests for IgG and IgM antibody were equivocal. However, *Borrelia burgdorferi* DNA detected by the polymerase chain reaction (PCR) was detected in whole blood on two separate occasions, 1 month apart, while the patient was on oral doxycycline, 100 mg b.i.d. This report questions the significance of persistent *Borrelia burgdorferi* DNA in a patient who is not responding to antibiotic therapy.

INTRODUCTION

Lyme disease is transmitted to humans by ticks infected with *Borrelia burgdorferi* (Bb) (1). Illness usually begins with the appearance of the erythema chronicum migrans rash (ECM) and flulike symptoms. Untreated multisystem complaints, including neurologic, cardiac, rheumatologic, and ocular, may occur soon after the bite or many months later (2). The characteristic onset of the disease may not be observed because of the absence of ECM. Failure to treat early may result in disseminated disease.

There is controversy in the medical community as to the length of initial therapy as well as the most appropriate antibiotic. This case report highlights the difficulty that primary physicians face in having to choose an antibiotic empirically. It also raises questions as to the significance of repeatedly reactive polymerase chain reaction (PCR) tests in a patient whose clinical course is worsening.

CASE REPORT

Before contracting a present illness, 30-year-old white female occupational therapist was healthy and active. She bicycled regularly in a Lyme endemic area. In early July 1994, she had 3 days of flu-like symptoms with a temperature of 101°F for three consecutive nights. At the end of August 1994, she developed fatigue, and could not ride her bicycle as long as she was used to. She did not recall either a tick bite or a rash. By the beginning of September 1994, she had trouble concentrating, experienced short-term memory problems, and was increasingly fatigued. She had bilateral knee pain without redness or swelling. She noted a lot of "crunching" in the joints. She went to see her primary physician. Tests for infectious mononucleosis and rheumatoid arthritis were all negative. Because she lived in an area endemic for Lyme disease and spent much time outdoors, the physician performed a Lyme disease antibody test in October 1994. The test was positive, and she was started on oral doxycycline, 100 mg b.i.d. for 30 days. Her symptoms persisted and antibiotic treatment was extended for a total of 3 months. At the end of this period, she felt better but reported that she was not "normal." Her physician felt that

additional treatment was unnecessary. In March 1995, the patient complained of recurrent frontal headaches, vertigo, shooting pains in her right ear, neck stiffness, pain near the paravertebral area of the upper thoracic spine, arthralgia, paresthesia of the right hand, and weakness in her thigh muscles. She felt heaviness in her chest and exertional dyspnea climbing a flight of stairs. She had memory problems, difficulty concentrating, and irritability when referred.

Her past medical history and physical examination were unremarkable. Lyme antibody tests were repeated at North American Clinical Laboratories. The IgG ELISA titer was 1:160, and the IgM < 1:160. The IgG test was interpreted as equivocal, and the IgM as nonreactive. The IgG western blot showed 50,41,23 Kda bands. The IgM blot showed a 31 Kda band. Both western blots were interpreted as equivocal. A PCR was done on whole blood (N.A.C.L.) and was positive. The PCR on whole blood utilized a 20 kb primer, which is a protein of the 350 kb Osp A sequence. Positive hybridization controls (HLA), DQ alpha negative controls, and inhibition controls were used in each PCR run. Amplified products were detected by both southern blotting and a nonradioisotopic DNA capture technique. Patient was restarted on oral doxycycline 100 mg b.i.d. The patient continued to have the same symptoms with exacerbations once a week while on the oral doxycycline. The PCR test on whole blood was repeated 1 month later while on doxycycline. It was again positive for Bb. After the second positive DNA-PCR test result, the patient was switched to intravenous Ceftriaxone 2 gm q.d. for 4 weeks. At the end of 2-1/2 weeks, she developed an allergic rash, and the I.V. therapy was discontinued. As of this writing, she is being continued on oral Biaxin (500 mg b.i.d.). The patient has improved significantly and is 95% better.

DISCUSSION

The patient described here received 100 mg of doxycycline orally twice a day for 30 days. Oral doxycycline has good absorption and good central nervous system (CNS) penetration due to its lipophilic affinity. However, the mean inhibitory concentration (MIC) of doxycycline in the CNS and other organs is not known and may not be high enough with the currently recommended dose to eradicate most strains of Bb (3, 4). It has been documented that the *in vitro* sensitivity of antibiotics to Bb does not correspond to treatment results (5). It has been

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previously reported that Bb may reside in privileged sites like macrophage (3) and fibroblasts (6, 7). The intracellular localization of Bb is believed (8) to make effective eradication of the organism very difficult (12, 13). In this case, extended doxycycline therapy did not eradicate the symptoms.

It has been reported that patients with arthralgia, myalgia, malaise, and evidence of dissemination, such as the patient in this case, were more likely to have recurrent symptoms after treatment (5). The longer the duration of Lyme disease before treatment the more frequent the residual symptoms may be (14). In one study, patients whose treatment was delayed had arthralgia, distal paresthesia, concentration difficulties, verbal memory deficit, and fatigue at a greater frequency than the control group (14) who received timely therapy.

The lack of response to therapy in a patient is very difficult to assess. It is hard to determine on clinical grounds alone when treatment has been adequate (12). Persistence of symptoms has been suggested to be caused by a mechanism other than chronic infection, and the lack of response to prolonged therapy has been attributed to permanent tissue damage, post Lyme disease syndrome, slowly resolving Lyme disease, or causes other than infection with Bb (14–16).

There have been few well-controlled clinical trials to determine the relationship between length of antibiotic therapy and adequacy of therapy. Similarly, little data are available on the choice of antibiotics and its relation to clinical outcome. It should not be assumed that failure to respond clinically to an antibiotic is a function of "post Lyme syndrome." It is possible that protracted symptoms may be a function of persistent infection due to Bb.

Preliminary results on 40 patients with late stage or post acute Lyme suggest that whole blood PCR is more sensitive than either serum or urine. Over 80% of patients with Lyme disease fitting the Centers for Disease Control (CDC) surveillance definition had at least one positive PCR (Tilton, RC, unpublished data). Other studies (17), however, reported that PCR positivity was usually restricted to the initial 7 to 10 days of infection. The detection of circulating DNA in this patient may indicate persistent infection or DNA released from lysed bacteria. The PCR in cerebrospinal fluid (CSF) is useful in identifying patients persistently keep infected with Bb as well as patients who may be refractory to antibiotic therapy (18, 19). At present, a reactive PCR should not be used to prove persistent infection nor a negative PCR considered a test of cure. However, this sensitive and specific test when positive indicates that Bb is present in the patient.

CONCLUSION

This case report points out the problems in choosing the appropriate antibiotic and the duration of therapy for LD. DNA

testing may be a useful laboratory test to determine either persistence of the bacterium in the host or the presence of lysed products from bacteria that were once viable. The duration of DNA positivity in a recovering patient or the frequency of DNA reactivity in a symptomatic patient is still unknown.

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Neuroborreliosis in Texas

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INTRODUCTION

Chronic persistent symptoms after treatment for Lyme disease (LD) are common. Early effective treatment is the only known way to avoid this possibility (1). Despite early recognition of the infection, patients still may not do well due to failure to eradicate the spirochete. Causes for antibiotic failure include its poor absorption or insufficient tissue levels, inappropriate route of administration (i.e., oral rather than intravenous), substandard dosage, inadequate duration therapy of, selection of a nonbactericidal drug, or poor compliance. When a patient's symptoms linger or other manifestations of borreliosis arise at a later date, the likelihood that initial treatment was noncurative should be addressed, and prompt retreatment should be considered. The following case is provided as an example of a patient who failed to return to his premorbid status despite early recognition of this infection.

Also addressed are issues of seronegativity, particularly as they apply to regions of the country where strain variation of borrelia is expected and its influence on standardized testing is unknown. It is anticipated that patients with LD who are seronegative have greater difficulty obtaining the diagnosis and adequate treatment. This patient is presented, not because he is a "textbook case", but rather because he is an example of an all-too-common clinical problem.

CASE HISTORY

This 28-year-old male carpenter was in excellent health until May 1992. He was hospitalized with a 2-week history of fever, rash, and headaches following a fishing trip in East Texas. A tick bite behind his left knee and erythema migrans was noted by an infectious disease doctor. He also had a diffuse erythematous papular rash on his arms and trunk. ANA, HIV, Lyme, typhus, Rocky mountain spotted Fever, hepatitis B, and Q fever titers were negative, but he had a weakly positive rheumatoid factor. Cerebrospinal fluid (CSF) revealed 46 WBCs (72% polymorphonuclear, remainder monos), protein 60, glucose 51, and a negative VDRL. He was treated with 1 week total of intravenous antibiotics, first ceftriaxone then doxycycline. During that week, a Bell's palsy developed that was treated with prednisone. Three weeks of oral doxycycline completed his therapy. He continued to have fatigue and headaches.

Six months later, he developed pain in the distribution of the first division of the left trigeminal nerve. A magnetic resonance image (MRI) showed a 5-mm hyperintense lesion on T2-weighted images in the left parietal white matter. His EEG had nonspecific slowing in the parieto-occipital region bilaterally, more marked on the left than right. His Lyme serology was negative. Repeat CSF analysis showed negative Lyme antibodies and viral cultures. He was treated with carbamazepine, and the neuralgia resolved. Two months later he developed severe pain in the frontotemporal area associated with vertigo, nausea, night sweats, and chills. He was rehospitalized with a

fever of 101°F and a pulse rate of 104. Erlichia, Lyme, HIV, and leptospira antibodies were negative. Repeat CSF for Lyme antibody, oligoclonal bands, IgG synthesis rate, and myelin basic protein were negative. The MRI lesion noted previously was not seen on a repeat scan. His doctors concluded he had a new febrile illness, possibly viral, with associated vascular headaches and labyrinthitis.

Several months later, he continued to have headaches, night sweats, and chronic fatigue. No treatment was given, and he was told to return as necessary. Two months later (20 months after the tick bite) the patient sought the consultation of this physician. He had returned to work but had to quit because of headaches and severe joint pains, including his knees and low back, accompanied by fatigue and confusion. The patient was forgetful, could not concentrate, and was cognitively impaired by bedside examination. Another lumbar puncture was remarkable for a protein of 50. Both CSF Lyme antigen and polymerase chain reaction (PCR) were negative.

Oral antibiotics did not effect improvement after 6 weeks, so cefotaxime at 3 g twice daily was given intravenously for 1 month. This reduced complaints of fatigue and confusion. He was maintained on oral antibiotics because attempts at withdrawing therapy were associated with subjective worsening. One year later he complained of worsened neuropsychiatric symptoms. Neuropsychology tests confirmed cognitive impairment. A SPECT scan of the brain showed pronounced decoupling between early and late phase images. Temporal lobes showed abnormal uptake with reduced level of uptake on the right compared with the left. Pulse therapy with cefotaxime 3 days per week was given over 6 weeks. He has had subjective improvement of the headaches, muscle aches, and joint pains, but cognitive difficulties remain 1 month after treatment.

CASE DISCUSSION

This patient's clinical course represents a classical presentation of LD and the complications of inadequate early treatment. He presented with erythema migrans associated with tick bite, a viruslike illness, and documented aseptic meningitis with Bell's Palsy, a clinical constellation typical for early disseminated LD (stage II). The patient also had secondary skin lesions consistent with hematogenous spread of the organism (2). Although he was correctly diagnosed with LD, he was treated for only 1 week with intravenous antibiotics and then oral antibiotics. Current duration of therapy for Lyme meningitis is 3 to 4 weeks of appropriate intravenous antibiotics (3), so it is probable this treatment was insufficient to effect bacteriologic cure. Subsequent development of a fifth then eighth cranial nerve dysfunction did not alert his physician to the development of mononeuritis multiplex, a known complication of Lyme infection, but rather they viewed it as two event unrelated to his initial disease, of unknown cause, and therefore untreatable.

The patient then presented to this physician with the insidious development of debilitating encephalopathy, generally referred to as stage III or chronic disseminated LD. The time line of his progressive symptoms and signs match that described previously, with peripheral nervous system disease beginning a median of 16 months from erythema migrans, and central nervous system involvement beginning a median of 26 months after the onset of infection (4). When the patient was retreated with antibiotics for central nervous system involvement, he improved, but not back to normal. Failure to regain full neurological recovery with retreatment is common with neuroborreliosis (4). He then had a relapse of encephalopathic symptoms a year later, and a recent SPECT scan was abnormal. One study suggests that the SPECT scan may be a useful tool to follow patients with Lyme encephalopathy pre- and postintravenous antibiotics (5). This patient's repeat scan shows improvement after retreatment.

It is possible that the first physician either did not know that relapses can occur with LD and retreatment is necessary, failed to suspect that the neurological complications were related to LD, or simply assumed ensuing symptoms were not due to LD because of seronegativity. Some degree of physician latitude in judgment is expected in assessing the need for retreatment, but criteria are not well defined (4, 6, 7). Unfortunately current laboratory testing may not always confirm the disease and therefore may mislead the uninformed physician. Most authorities recommend that the diagnosis of LD be based on clinical symptoms and signs, with laboratory tests used only to support that diagnosis (6, 8–10). This patient had erythema migrans following a tick bite in an endemic area and this satisfies Centers for Disease Control and Prevention (CDC) surveillance definition for the diagnosis of LD (11); positive serology is not required in this instance. Texas is an endemic area of LD, although questions regarding strain variance and epizootiology remain. *B. burgdorferi* has been isolated from *Amblyomma (A) americanum* (the lone star tick), *Ixodes scapularis* (the black-legged tick), *Rhipicephalus sanguineus* (the brown dog tick), and *Ctenophthalmus felis* (the cat flea). *Borrelia* spirochetes have been isolated from patients in Texas, and a clinical presentation similar to LD reported from other endemic areas has been described (12–14). Antibody negativity for LD has been present throughout this patient's illness. However, the absence of Lyme antibodies at the time of his disease presentation (2 weeks after the bite) is typical because it may take several weeks for a patient to mount a detectable antibody response (15). And then early subtherapeutic doses of antibiotics, as happened with this patient, may blunt or totally abrogate the antibody response, thus explaining his continued seronegativity (16). Immune complexes can also mask the serological response in otherwise well-documented cases of LD (17).

Another interesting cause of persistent antibody negativity in this case could be related to strain variations of the *Borrelia* causing LD in Texas. When sera of patients, from whom *B. burgdorferi* was isolated, were tested by the Texas Department of Health, only one-half of the specimens contained detectable antibodies to the spirochete, and even then, the titers were not always high enough to be diagnostic (13). Also, CSF PCR studies show that patients with clinically suspected neuroborreliosis had positivity in many instances where serologies of blood and CSF were nondiagnostic (18). A unique species of *Borrelia* has recently been identified by PCR in *A. americanum* (19). It is already known that LD is not caused by a single species *Borrelia*; at least three species responsible for human infection have been identified (*B. burgdorferi sensu stricto*, *B. garinii*, and *B. afzelii*) (20). Since there are no currently available antibody tests that are based on the strains known to cause LD in this area of the United States, standard serological tests

could be misleading when employed for out patients. Since variable immune reactivity occurs secondary to antigenic variation among *Borrelia* species (21), western blot testing based on local strains of *Borrelia* would, presumably, vastly benefit sensitivity and specificity.

Not only did this patient's CSF remain antibody negative but it became acellular despite clinical progression of his disease. However, it is not unusual to see an absence of both intrathecal antibodies and CSF cellularity in cases of mononeuritis multiplex, or even encephalopathy, due to North American LD (4, 6, 22). This is in contrast to European LD where marked CSF changes are typical. Variation in both clinical picture and laboratory confirmation of LD between North America and Europe have been well described (23) and probably reflect the different antigenic composition of *Borrelia* strains isolated from the two areas.

CONCLUSION

This case illustrates a poor outcome in a patient who was given early but noncurative antibiotics for Lyme meningitis and vii. cranial nerve palsy. The opportunity to retreat when the patient developed mononeuritis multiplex was missed and symptoms of developing encephalopathy were likewise ignored. Unfortunately, there is no test that reliably documents cure, relapse, or persistent infection (24). Even in patients who have been antibody positive, following titers is not helpful for monitoring their response to therapy; a decrease in serum antibody titers does not prove bacteriologic cure nor does persistence of elevated titers signal therapeutic failure. Anytime along the course of persistent infection, treatment should prevent further progression associated with later-stage disease. Also, treatment may not fully reverse neurological deficits once they have occurred. Better understanding by physicians regarding the importance of early aggressive treatment necessary to eradicate the spirochete, in conjunction with close follow-up for potential relapses, should improve prognosis for patients with LD. Seronegativity is a well-known phenomenon in LD, but its relative frequency is unknown. Special issues regarding strain variance of *Borrelia* in areas of the country where the epizootiology is less well understood, such as Texas, need to be resolved. Physicians who practice in areas where LD is less well characterized should be especially wary about relying on serological tests designed for identification of *Borrelia* isolated elsewhere. Thus far there are no available tests that are strain specific for LD acquired in Texas.

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Chronic Lyme-Related Bell's Palsy Responsive to Prolonged Oral Antibiotic Treatment

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INTRODUCTION

Lyme disease is a tick-borne spirochetal disease of increasing importance. Although there are a myriad of manifestations of Lyme disease, certain clinical syndromes seem more prominent. Initial infection with the causative agent, *Borrelia burgdorferi*, may cause a characteristic expanding erythematous rash, erythema migrans. Disseminated infections may cause syndromes consisting of arthritic and neurologic manifestations. Cranial nerve palsies are among the well-recognized manifestations of "defined clinical syndromes" associated with neuroborreliosis (1). Bell's palsy, or seventh cranial nerve palsy, has also been reported in Lyme disease (1). Usually, Bell's palsy conveys a good prognosis and is often treated with corticosteroids. When it becomes chronic, Bell's palsy is difficult to treat, and long-standing cases rarely improve. Herein, a case of chronic paralysis of the seventh nerve (facial) due to Lyme disease, which responded to oral antibiotic therapy, is presented. It is suggested that in Lyme endemic areas, cranial nerve palsies including Bell's palsy be considered a manifestation of a possible Lyme disease. Oral antibiotic treatment may be effective for cranial nerve palsies due to Lyme disease if given for a long enough period of time.

CASE REPORT

A 78-year-old, nondiabetic white male presented in October 1994 for evaluation of a chronic paralysis of the right side of his face as well as extreme fatigue and joint pains. The patient reported that his symptoms began 3 years earlier. He had been treated with corticosteroids without success and had seen several physicians including a neurologist and an infectious disease specialist. The patient recalled a possible tick bite preceding his illness but denied a rash. He also complained of marked fatigue and generalized arthralgias. He had inquired about Lyme disease but was told that his illness was not compatible with that diagnosis and was reluctantly tested for serologic evidence of exposure to *Borrelia burgdorferi*. A western blot at SmithKline Beecham Clinical Laboratories was reported as "nonreactive" in August 1994.

The physical examination revealed a pleasant elderly man in no distress. The blood pressure was 124/72. The pulse was irregular at 80. He weighed 176 pounds. Cranial nerve examination revealed marked weakness of the right side of his face with drooping of the right eyelid and flattening of the right naso-labial fold consistent with paralysis of the right seventh cranial nerve. The cardiac examination revealed an irregular rhythm consistent with atrial fibrillation. The pulmonary and abdominal examinations were normal. Orthopedic examination revealed pain on external rotation of both hips. The remainder of the examination was normal.

Laboratory evaluation revealed a normal chemistry profile, including blood glucose and complete blood count. The eryth-

rocyte sedimentation rate was 12 mm/h. The rheumatoid factor was negative. A Lyme enzyme-linked immunosorbent assay (ELISA) was negative, but the western blot was reported as positive with IgG bands detected at p54/58, p41, p34, and p30/32 at Roche Laboratories. Magnetic resonance imaging of the brain revealed multiple, bilateral cerebral hemispheric periventricular and white matter hyperintensities said to be due to small vessel disease. The patient would not consent to examination of the cerebrospinal fluid.

The patient was started on oral doxycycline therapy at 100 mg twice daily upon receipt of the positive serology 1 week after initial presentation in October 1994. Within 1 month, he reported subjective improvement with decreased arthralgias and fatigue. Because of the encouraging initial response to treatment, he was switched to clarithromycin 500 mg daily. He continued to notice subjective improvement. By March 1995, the patient began to show some noticeable improvement in his facial weakness. Photographic evidence documents progressive objective improvement. By April 28, 1995, the patient was able to voluntarily open his right eye for the first time and had regained partial movement of the right side of his face for the first time in 3 years. By August 1995, the patient had nearly complete resolution of his facial palsy (Photographs 1 through 3). He is continuing to derive both subjective and objective benefit from clarithromycin and remains on 500 mg daily.

DISCUSSION

Cranial nerve palsies may complicate many illnesses and may also occur idiopathically (2). In this case, a patient, seropositive for Lyme disease with chronic Bell's palsy, had an objective response to oral antibiotic therapy. Evaluation failed to reveal any other tenable explanation for his illness, and given his positive western blot, a trial of oral antibiotic therapy was considered reasonable. Although uncommon, there may be discordance between the Lyme ELISA and western blot at commercial laboratories. The positive western blot confirms infection with *Borrelia burgdorferi*. There was no history of trauma or herpes zoster infection. There was no evidence of glandular tuberculosis (scrofula), Wegener's granulomatosis, or sarcoidosis. Diabetes was excluded by routine blood chemistry analysis while intracranial and brain stem aneurysms and neoplasms were excluded by the magnetic resonance imaging.

Bell's palsy is usually transient, and the standard treatment includes corticosteroids. When long-standing, Bell's palsy is often unresponsive to treatment, and the patients may be left with a permanent facial paralysis. The response to oral antibiotic therapy in this case after 3 years of paralysis is striking and suggests that infection with *Borrelia burgdorferi* may be responsible. Furthermore, it suggests that oral antibiotic therapy may be effective for Lyme-related cranial neuropathies if taken long enough. It should be noted that 5 months of oral antibiotic treatment were given before any objective improve-

ment was noted. Lyme disease should be considered as a possible cause of cranial neuropathies including Bell's palsy, and patients should be offered treatment even if their paralysis is of long-standing duration. In highly endemic areas, cranial nerve palsies should mandate consideration of Lyme disease as a potential etiology.

CONCLUSION

Lyme disease is known to produce cranial nerve palsies as one of its defined clinical syndromes. Chronic seventh cranial nerve paralysis is usually refractory to treatment. Herein, a case of chronic Bell's palsy due to Lyme disease that re-

sponded to long-term oral antibiotic therapy is presented. It is suggested that Lyme disease be considered among the potential etiologies when evaluating cases of cranial nerve palsy, particularly in Lyme endemic areas. Long-term oral antibiotic treatment may be effective in treating chronic cranial nerve palsies including Bell's palsy due to Lyme disease.

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LETTERS TO THE EDITOR

Lyme-Related Relapsing Motor Neuron Disease

To the Editor: Motor neuron disease (MND), particularly amyotrophic lateral sclerosis, is generally considered to be a progressive nonremitting disease. Lyme neuroborreliosis is reported to cause various neurologic syndromes affecting both the central and peripheral nervous systems, including a rare association with amyotrophic lateral sclerosis (1). Relapsing MND is distinctly uncommon.

A 71-year-old woman presented in 1989 with symptoms of Parkinson's disease. She was treated with levodopa and improved. In May 1990, she presented with fulminant weakness, dyspnea, and shaking chills. Testing revealed an erythrocyte sedimentation rate (ESR) of 93 mm/h, negative antinuclear antibody (ANA), normal creatine phosphokinase (CPK), polyclonal increase on immunoelectrophoresis, positive Lyme immunoblot for the 41 and 55 kda bands, and Lyme enzyme-linked immunosorbent assay (ELISA) with IgM 1.63 normal (<0.8). Cerebrospinal fluid analysis was normal. Temporal artery biopsy was normal. Nerve conduction studies (NCV) were normal. Electromyography (EMG) revealed diffuse fasciculations, high-amplitude polyphasia, and giant motor unit action potentials with decreased recruitment pattern consistent with MND. Muscle biopsy revealed neurogenic atrophy. The patient was placed on ceftriaxone 2 g intravenously daily for 3 weeks. The patient's strength improved. Repeated EMG in October 1990 revealed absent fasciculations, improved insertional activity with continued decreased recruitment pattern. The patient continued to improve, and EMG in August 1990 showed normal motor unit potentials.

In September 1992, the patient presented again with diffuse weakness, hyper-reflexia with extensor plantar responses. Cerebrospinal fluid was normal. Western blot for Lyme disease was negative, and B₁₂ levels were normal. The ESR was ele-

vated. She was placed on ceftriaxone 2 g daily with rapid improvement. On switching to oral antibiotics, she lapsed in November 1992, becoming unable to ambulate across a room. Reinstitution of intravenous ceftriaxone resulted in marked improvement within 1 week.

On examination in June 1993, patient exhibited hyper-reflexia, left clonus with extensor plantar response, but well-maintained strength. EMG did not reveal any evidence of active denervation, but polyphasia was still present.

This patient exhibited a fluctuating course of relapse and remission of MND over a 3-year period. Repeat neurophysiologic studies appeared consistent with MND rather than a syndrome mimicking it (i.e., polyneuropathy and radiculopathy). Evaluation suggested an initial acute presentation of Lyme neuroborreliosis. The mechanism of repeated improvements or exacerbations is unclear. Previous explanations include an intrinsic beneficial effect of third generation cephalosporins (2).

Further study of Lyme neuroborreliosis as a cause of potentially reversible MND would be beneficial.

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Lack of Transplacental Transmission of Lyme Disease Spirochetes in a Mouse Model

To the Editor: Lyme disease is a widely distributed multisystem disorder caused by the tick-borne spirochete *Borrelia burgdorferi*. Transplacental transmission of other spirochetes such as *T. pallidum*, *Leptospira* sp., and *Borrelia recurrentis* is associated with a wide spectrum of adverse pregnancy outcomes including abortion and stillbirth (1). Consequently, we used a mouse model to test whether *Borrelia burgdorferi* crosses the placenta and behaves in a similar way to other spirochetes. Adverse outcomes during pregnancy have been linked with Lyme disease (2), but this has not been observed consistently (3).

Six- to eight-week-old female T/O mice were mated with 8- to 10-week-old male T/O mice. Mice were separated on the following day, and this was considered day 0 of pregnancy in the mice with copulatory plugs. *Borrelia burgdorferi* (NCH-1) P-10 isolated from an erythema migrans patient was used to infect mice (4). Five pregnant T/O mice were inoculated intradermally with 10^6 viable spirochetes in BSK-II medium. Two pregnant control mice were injected with 10^6 heat-killed spirochetes. Mice were sacrificed on days 17 or 18 of pregnancy, and fetal outcome was determined. The placenta, maternal hearts, spleens, and urinary bladders were removed aseptically, half of these tissues were macerated in BSK-II medium and then inoculated into BSK-II medium containing antibiotics (50- μ g/mL colistin sulfate, 50- μ g/mL rifampicin, and 100- μ g/mL 5-fluorouracil). Cultures were incubated at 34°C and examined by dark-field microscopy every week for 1 month. The remaining tissues were macerated separately and digested with proteinase K (100 μ g/mL) overnight, then phenol was extracted. Fetal samples were subjected only to PCR because of their small size. The PCR was carried out using a heminested set of primers that are complementary to conserved regions of the *osp A* operon. Amplification was performed in a 50- μ L reaction volume using a Perkin Elmer 9600 Gene amp thermal cycler (5). The PCR products were electrophoresed through a 2% agarose gel at 100 V for 1 hour and their identity confirmed by southern blot and hybridization using a probe generated from the *osp A* gene of *B. burgdorferi sensu stricto* (strain B31). An aliquot of each processed placenta and fetal tissue sample was "spiked" with 100 femtograms (fg) of total genomic DNA from *Borrelia burgdorferi* and amplified to demonstrate the absence of PCR inhibitors in the samples.

All tissues cultured for spirochetes were negative. Fetal death occurred in 3 (5%) of 62 fetuses as compared with none of 23 fetuses in the control mice ($\chi^2 = 1.15$; $p = 0.28$). The three fetal deaths came from three different pregnant mothers. *B. burgdorferi* DNA was detected in five hearts, four urinary bladders, and two spleens from the five pregnant test mothers, but it was not detected in the control mice. However, *B. burgdorferi* DNA was not detected in any fetus or placenta (including the three fetuses that were found dead). All the "spiked" samples were PCR positive, indicating the absence of PCR inhibitors. The detection limit of this PCR using control DNA was about 1 fg, corresponding to approximately one spirochete.

Transplacental transmission of *B. burgdorferi* did not occur in this model, and there was no significant fetal death associated with infection. The absence of transplacental transmission

of Lyme disease spirochetes in our mouse model correlates with the findings of Mather et al. (6), although one cannot exclude the possibility of occasional transplacental transmission of Lyme disease spirochetes (7). Since the fetal death in this experiment is not statistically significant, we examined the breeding records of T/O mice. These revealed that natural death occurred in 18 (2%) of 1051 fetuses—not significantly different from results in our experiment ($\chi^2 = 3.09$; $p = 0.08$).

These data do not support the concept that there is either transplacental transmission or increased fetal mortality as a result of *B. burgdorferi* infection, although the extent to which mouse models of *B. burgdorferi* infection reflect the pathology observed in human cases is debatable. It is also known that different species of *B. burgdorferi* show different tissue tropisms (8). Nevertheless, the use of an experimental model using a human fetal isolate of *B. burgdorferi* deserves further study.

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Ixodes Scapularis Larvae: A Possible Vector of Lyme Disease?

To the Editor: *Ixodes scapularis* larvae, like nymphs and adults widely distributed, are far and away the most abundant tick stage in nature (1). It has been assumed that because transovarial infection of larvae with *B. burgdorferi* has been estimated at only 0.9% (2), their importance as vectors in animal and human borreliosis is negligible. Yet in northern California, Lyme disease presents a definite public health problem with up to 25% of human inhabitants in certain areas testing seropositive,* in spite of the fact that only some 1 to 6% of *Ixodes pacificus* adults may harbor *B. burgdorferi* (2).

Field entomologists having repeated exposure to larvae are sometimes able to detect larval attachments when itching and local skin reactions develop. This indicates the deposition of tick saliva, and with it, the theoretic possibility of concurrent transmission of spirochetes. Transmission of but a single spirochete may suffice to infect a mammalian host and eventually result in clinical disease.

Larval attachments might be responsible for some of the atypical cases of human Lyme disease seen in endemic areas: those with long periods of clinical latency, a blunted immune response with T-cell anergy (3) due to the low antigenic stimulus presented by small inoculae of spirochetes (and hence seronegativity), and without recognized tick attachments or classic erythema migrans.

A role of ixodid larvae in the transmission of Lyme disease

to humans would have important implications and needs to be systematically studied. Since larval ticks are nearly undetectable by visual inspection, "tick checks" might confer little protection against them. The relative futility of conventional measures of personal protection against Lyme disease has been highlighted recently (4). More attention needs to be focused on vector control to prevent the spread of Lyme disease and other tick-borne illnesses (5, 6).

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*(Lane R, personal communication).

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