LYME DISEASE

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Introduction

The increasing incidence of cases of Lyme Disease in the United States, together with increased national media attention, has made Lyme Disease a potential concern for insurance underwriters. A recent cover story in Newsweek (May 22, 1989) educated the public about potential risks of Lyme Disease and epitomized this concern. The extreme of public hysteria was reported in Time Magazine (News report, August 14, 1989). A man in Detroit who was convinced he had Lyme Disease killed his family and himself because of his misconceptions of the disease.

In spite of relatively recent medical and news media attention, Lyme Disease was originally described in the early 20th century. A skin rash known as erythema chronicum migrans was originally reported in Europe in 1909. This rash was known to follow the bite of Ixodes ricinus ticks. Also in the early 20th century, neurologic symptoms including brain and spinal cord inflammation were linked to tick bites. These were probably early forms of our present Lyme Disease. The first cases in the United States probably occurred only 25 years ago in residents of Cape Cod and Connecticut. It wasn’t until 1975 that these signs and symptoms were linked to an infectious disease. Twelve cases of juvenile rheumatoid arthritis were reported in Lyme, CT, a town of approximately 4000. Dr. Alan Steere, then at Yale University, postulated these arthritis cases might have an infectious etiology.

Epidemiology

Lyme Disease was eventually found to be caused by a spirochete now known as Borrelia burgdorferi, named for its discoverer Willie Burgdorf. The spirochete is a coiled type of bacterium which is similar to that which causes syphilis. This organism is carried predominantly by ticks of the Ixodes species, especially Ixodes dammini. Other species of ticks are potential carriers and they may be important causes of Lyme Disease in non-endemic areas. Borrelia burgdorferi is widespread in the animal kingdom. The nymph (young) form of the tick is most important for transmission. The frequency of Lyme Disease depends on the population of Ixodes ticks and the potential degree of tick parasitism. There is a two year seasonal tick life cycle which involves a complex interaction between deer, the white-footed deer mouse and Ixodes ticks. In general, casual contact with a tick is inadequate for transmission of the spirochete. The spirochete lives in the salivary glands and intestine, and the tick needs to feed for several hours on human or animal blood to transmit infection. A tick found crawling in a bed, when there is no skin bite, is probably inadequate to transmit the disease.

The spirochete has worldwide distribution but in the U.S. there are three distinct endemic areas of infection: the northeastern U.S., the mid-western states and the western Pacific states. There have been sporadic cases reported in Ohio and other states. In 1988 there were 34 Ohio cases, but the overall accuracy is uncertain because the reporting is not required in Ohio. There are now 34 states which require the reporting of Lyme Disease to their health bureaus. Nationwide, the number of cases of Lyme Disease reported is estimated at 8,000. In 1987 there were 2300 cases reported. In 1988, 4800 cases were reported, a doubling of cases in a one year period. Individuals from other states who visit the endemic areas are at risk of Lyme Disease.

Clinical Manifestations

The clinical aspects of Lyme Disease can be divided into four stages. The first (Stage 0) is really an asymptomatic infection. Some patients with tick bites that may have been exposed to the organism will have antibodies to the spirochete and develop no sequelae of Lyme Disease. In the Massachusetts area, approximately 5-10% of all patients studied had antibodies to the spirochete and developed no symptoms mimicking viral meningitis. Spirochetes are actually found in these skin lesions. There are atypical forms of ECM, and “satellite” lesions may appear near the main lesion. Eighty-five percent of patients with Lyme Disease have ECM; 15%, however, do not. The rash is usually self-limited and the rash does not usually progress to other immediate sequelae. Non-cutaneous manifestations may occur in addition to ECM in Stage I illness; i.e., a flu-like illness with malaise and fatigue, low-grade fever and headache. There may also be migratory muscle and joint aches, but not destructive joint disease.

Stage II which represents a disseminated form of the spirochete, begins four weeks to several months after the bite and is usually manifested by neurologic and/or cardiac symptoms. Fifteen percent of untreated Stage I patients may progress to neurologic symptoms. The most predominant manifestation is “aseptic” (non-bacterial) meningitis: an inflammatory response seen in the spinal fluid and clinical symptoms mimicking viral meningitis. Spirochetes are actually found in the central nervous system. They are so few in number, however, that isolation is difficult. Another neurological manifestation may be a Bell’s palsy, where the 7th facial
nerve develops paralysis on one side. A patient with a Bell's palsy in an endemic area should be suspected of having Lyme Disease. Other second stage manifestations may relate to the heart and blood vessels. Eight percent of untreated Stage I patients develop either an atroventricular block or myocarditis that may cause heart failure. Eye involvement may occur in Stage II in a small percentage of patients and is usually self-limited; however, a rare case of blindness from eye involvement with the spirochete has occurred. Stage III illness represents persistent infection and occurs weeks, months, or years later; the individual response is quite variable. One of the major manifestations of late illness is arthritis. 60% of untreated patients may develop this complication. In general, the arthritis usually involves one large joint or a few nonsymmetric large joints. Ten percent of all untreated patients develop chronic disease with erosive joint damage. There seems to be a genetic predisposition for this arthritis which may resemble juvenile or adult rheumatoid arthritis. HLA-D4 histocompatibility antigen-positive patients are at a higher risk for the development of this erosive joint damage. Occasionally the organism is isolated from the synovial fluid or synovial tissue of these joints. Recurrent attacks of arthritis are common in untreated or unrecognized patients. Another manifestation of Stage III illness is a spectrum of neurologic symptoms occurring in an unknown percentage of untreated patients. A demyelinating illness resembling multiple sclerosis has been described, as well as dementia, encephalopathy and peripheral neuropathies. Finally, Stage III may lead to a chronic skin condition known as acrodermatitis chronica atrophicans which generally has no long-term sequelae.

There may be considerable overlap in these stages; ECM stands out in Stage I alone, but manifestations of Stage II may blend into Stage III. Arthritis, cardiac and central nervous system complications can occur anytime after the first few months of exposure.

Laboratory Diagnosis
There are a variety of laboratory tests for Lyme Disease. The routine tests include indirect immunofluorescent assay (IFA), and enzyme-linked immunosorbent assay (ELISA). Under further investigation is a western blot test and a lymphocyte blast transformation test.

For the IFA, Borrelia organisms are mixed and patient's serum and a labelled antibody; positive results are titered. The ELISA test probably has the best sensitivity and specificity. IFA is being abandoned in favor of ELISA. However, even the ELISA is fraught with variability in standardization, causing difficulty in establishing a diagnosis, especially if a history of ECM is absent and the patient is from a non-endemic area. Physicians may see many referrals for chronic fatigue syndrome and non-specific complaints and a few may have positive titers for Lyme Disease. "There is a risk that the assay may be falsely positive if large numbers of patients with a low a priori possibility of having Lyme borreliosis are examined. The decision to treat should be made with reference to the patient's clinical presentation and the predictive value of the diagnostic assay". A variety of conditions can cause false positive results by ELISA as well. "False positive results are not as troublesome as borderline or low-level positive titers in some patients with rheumatologic or neurologic disorders which cannot be clinically identified as being due to Lyme Disease. Because of increased professional and lay awareness of Lyme borreliosis, testing is often requested for defensive reasons to rule out that diagnosis. In this situation, the ratio of persons with false positive reactions compared to those who actually have the disease will predictably rise. Thus seropositive patients with disorders other than Lyme Disease may be subjected to long and potentially hazardous courses of antibiotics or other tests. Until Western blot and ELISA methods using elective, pathogen-specific Borrelia burgdorferi are generally available, the clinician is left with a helpful, but imprecise serologic test being offered. This test should not be used indiscriminately; it should be used solely to confirm a diagnosis based on epidemiologic and clinical findings".

Treatment
Treatment for Lyme Disease varies by stage of the disease. Therapy has been shown to shorten the duration of ECM and prevents the development of later illness in most cases. In Stage I the treatment of choice is generally a tetracycline or doxycycline or amoxicillin or erythromycin. In general, tetracycline has been most effective in preventing the late sequelae. If a patient with recognized ECM is treated, the chance of developing the later complications of Lyme Disease is less than 5%. Treatment of mild Stage II or III illness may utilize oral antibiotic therapy with the above antibiotics. However, more severe manifestations of illness require intravenous therapy with high-dose penicillin or a long-acting cephalosporin antibiotic known as ceftriaxone. In general, this treatment can be initiated in the hospital and followed-up at home as outpatient therapy.

Disease in Pregnancy
Lyme Disease can be transmitted in pregnancy. When this occurs, fetal death ensues in about 25% of cases. For infants born of mothers with Lyme Disease some have developed congenital cardiovascular abnormalities similar to congenital syphilis.

Morbidity and Mortality
There is some potential chronic morbidity or even mortality from Lyme Disease. The chance of an exposed patient having any chronic morbidity or mortality from Lyme Disease is unpredictable. There is an individual predisposition towards developing chronic arthritis relating to HLA-D4 but screening for this genetic antigen type seems impractical. The percentage of individuals insured who may develop Lyme Disease is small. The chance of a false positive test in areas with a low incidence of Lyme Disease creates a real risk for overinterpreting test results. In terms of chronic morbidity, destructive arthritis occurs in approximately 10% of patients with untreated Lyme Disease. Treatment in the early or even middle stage of illness does not necessarily guarantee a cure of the arthritis. A small percentage of patients, even with therapy, may develop destructive arthritis. This probably relates to the
pathogenesis of the illness; there is more immunologic mediated responses (similar to an “auto-immune” disease) rather than destruction by replicating spirochetes.\textsuperscript{19} Longterm neurological deficiencies may include brain and spinal cord inflammation that may decrease cognitive function and functional ability.\textsuperscript{11,12} A few cases of unilateral blindness due to Lyme spirochetes have been reported.\textsuperscript{9}

There has been one death from myocardial involvement with the Lyme spirochete.\textsuperscript{20} There have been several patients with either first, second or third degree heart block due to an indirect response to Lyme spirochetes.\textsuperscript{21,22} One patient required a permanent pacemaker for irreversible heart block.\textsuperscript{21} Recently, a chronic cardiomyopathy has been linked to the invasion of heart muscle by the organisms.\textsuperscript{23} Finally, one patient with unrecognized Lyme Disease developed fatal adult respiratory distress syndrome that was thought to be due to multisystem involvement with Lyme spirochetes.\textsuperscript{24}

In summary, therefore, Lyme Disease will continue to be an important infectious disease problem in endemic areas. However, the evidence suggests that although there is a significant risk for long-term disability and health impairments, the mortality risk from Lyme Disease is minimal.

REFERENCES