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Clinical Manifestations of Lyme Disease in the United States

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Introduction

LYME disease is a tick-borne infectious disease caused by the spirochete, *Borrelia burgdorferi*.¹ In Connecticut, and other states in the northeastern United States, the disease is most commonly transmitted by the tiny deer tick, *Ixodes dammini*. This tick typically feeds unnoticed for many hours allowing sufficient time to transmit spirochetes from its gut to human skin at the site of a bite. Spirochetes then migrate outwardly in the skin causing the unique expanding skin lesion, erythema migrans. Subsequent hematogenous dissemination of spirochetes to secondary sites may cause major organ system involvement.

Lyme disease often is described as occurring in three stages. The illness begins with erythema migrans and associated flu-like symptoms (stage 1). Weeks to months later stage 1 illness may be followed by acute neurologic and cardiac disease (stage 2), and then months to years later by arthritis and chronic neurologic disease (stage 3). Considerable overlap exists among these stages, however, such that Lyme disease is best characterized as an illness which evolves from early to late disease without reference to an arbitrary staging system.

Cutaneous Manifestations

The cutaneous manifestations of Lyme disease can be divided into early (erythema migrans), secondary (disseminated lesions and lymphocytoma), and late lesions (acrodermatitis chronica atrophicans). With the exception of the latter, these cutaneous manifestations generally resolve spontaneously over weeks to months. The early and secondary cutaneous lesions can be effectively treated with antibiotics, as can acrodermatitis chronica atrophicans.

Erythema Migrans and Early Disease

Erythema migrans, the unique skin lesion of early Lyme disease, develops several days to one month after infection with *B. burgdorferi* in approximately two-thirds of patients. This lesion first appears as a red papule

at the site of the tick bite. An expanding area of erythema around the bite develops over days to weeks, attaining a median diameter of 15 cm, although lesions with a diameter of up to 68 cm have been reported. Central fading within the erythema typically gives erythema migrans a ring-like appearance. The lesion is often flat and may be asymptomatic, but tender, warm, or pruritic lesions are also quite common. Although the bite (and subsequent erythema migrans) may occur anywhere, the tick has a predilection for the thigh, groin, or axilla. Facial erythema migrans is more common among children. Atypical forms of erythema migrans occur: early lesions may have indurated or vesicular centers, or mimic streptococcal or staphylococcal cellulitis. Central necrosis also may occur and be misdiagnosed as a bite of the brown-recluse spider.² Rarely, transient eruptions are seen in early Lyme disease, and include maculopapular rashes, urticaria, malar rash, septal panniculitis (erythema nodosum),³ and/or localized granuloma annulare. Although *B. burgdorferi* has been isolated from the perimeter of erythema migrans, skin biopsy for diagnosis is a low-yield procedure. Histologically, erythema migrans has a non-specific appearance with a perivascular infiltrate comprised of lymphocytes, plasma cells, eosinophils, and histiocytes.

In addition to erythema migrans, many patients with early disease will have a flu-like syndrome characterized by fatigue, fever, malaise, headache, arthralgias, myalgias, regional or generalized lymphadenopathy, and/or conjunctivitis.⁴ One-third of patients will have such symptoms in the absence of erythema migrans. These symptoms are typically intermittent and changing, with the exception of fatigue, which is often persistent and may be debilitating. Right upper-quadrant tenderness and a mild hepatitis may occur (hepatitis also has been reported in later disease)⁵, as well as rare cases of myositis⁶ and adult respiratory distress syndrome.⁷ During this early phase of disease, laboratory findings are nonspecific and typically may include elevated sedimentation rates, elevated serum IgM levels, and mildly elevated hepatic transaminases; the latter supports the notion that hepatitis may be a feature of early Lyme disease. Specific IgM or IgG antibodies against *B. burgdorferi* are usually not

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detectable in serum unless symptoms have been present for at least two to four weeks.

Secondary Lesions

Several days to weeks after onset of erythema migrans, nearly one-half of untreated patients develop secondary skin lesions. These annular lesions resemble erythema migrans, but they expand less, are generally smaller, and lack indurated centers. Secondary skin lesions usually number less than 10, but patients with more than 100 such lesions have been reported.⁴

Spirochetes have been isolated from these lesions as well.⁸ Although patients may be systemically quite ill during this phase of illness, most of these symptoms will resolve without treatment, and the skin lesions typically fade over days to weeks. Months later, approximately 5% of untreated patients have recurrences of secondary lesions.

Borrelia Lymphocytoma

A rare early cutaneous manifestation of Lyme disease is borrelia lymphocytoma,⁹ a tumor-like violaceous swelling or nodule at the base of the earlobe or the nipple caused by a dense lymphocytic infiltrate of the dermis. This lesion occurs at the site of a tick bite, is usually solitary, and may be associated with regional lymphadenopathy. In the setting of fever, fatigue, and adenopathy, borrelia lymphocytoma can be confused with a lymphoma. Untreated, this lesion may linger for 6-12 months before it disappears spontaneously.

Acrodermatitis Chronica Atrophicans (ACA)

ACA is a late skin manifestation of Lyme disease which is more prevalent in Europe than the U.S..¹⁰ ACA is an indurated plaque at a site distal to erythema migrans (e.g. hand, forearm, or foot) occurring after hematogenous spread of *B. burgdorferi* from a primary skin lesion. Untreated, this inflammatory phase of ACA may persist for years, followed by an atrophic phase in which affected skin acquires the appearance of crumpled cigarette paper. This change may be coincident with the development of Lyme arthritis or neurologic sequelae. Skin biopsy reveals epidermal atrophy with thinning and hyperkeratosis, and a chronic dermal infiltrate. Antibiotics are effective treatment for ACA, but 10% of such lesions progress to a sclerotic morphea-like appearance.¹¹

Cardiac Manifestations

Lyme carditis occurs in roughly 8% of untreated patients within two to six weeks following infection, and may be the initial manifestation of Lyme disease.¹² Fluctuating degrees of atrioventricular block, including first-degree heart block and Mobitz type I block, are the most common features of carditis, but may progress to complete heart block requiring a temporary pacemaker. The cardiac conduction abnormalities of Lyme disease are usually brief, lasting days to weeks, and generally do not require permanent cardiac pacing. However, one recently-described patient had residual Mobitz Type I block 16 months after removal of a temporary pacer-

maker for Lyme carditis.¹³

Less common cardiac manifestations have included arrhythmias (supraventricular tachycardia and premature ventricular contractions) and myopericarditis with transient cardiomegaly and left ventricular dysfunction. This latter problem may be mistaken for acute rheumatic fever when cutaneous and joint manifestations are also present. EKG changes in such patients may include diffuse T-wave flattening or inversion, and rarely ST segment depression. The diagnosis of Lyme disease should be considered in all cases of unexplained heart block, because it is treatable with antibiotics.

Neurologic Manifestation

Neurologic abnormalities, which occur in approximately 15% of untreated patients generally within two to eight weeks after disease onset, may include aseptic meningitis, cranial nerve palsies, peripheral radiculoneuritis, and peripheral neuropathy.¹⁴ Later neurologic sequelae, such as demyelinating conditions, cognitive impairment, and chronic fatigue occur less commonly and may not become evident until several years after acute infection.

The predominant symptoms of Lyme meningitis are severe headache and mild neck stiffness, which may fluctuate for weeks after a posterythema migrans latent period. The cerebrospinal fluid (CSF) typically has a lymphocytic pleocytosis (15-700 WBC), slightly elevated protein levels with oligoclonal bands, and normal glucose levels, and is easily mistaken for aseptic meningitis. A relatively normal CSF with a high opening pressure (greater than 200 mm) suggestive of pseudotumor cerebri (with or without papilledema) may be responsible for persistent, refractory headaches, especially among children with Lyme disease.¹⁵ Atypical cases of Lyme disease have included patients with purulent Lyme meningitis,¹⁶ and recurrent acute meningitis.¹⁷ Nearly one-half of patients with Lyme meningitis will have an associated mild encephalitis with concentration deficits, emotional lability, lethargy, or focal cerebral dysfunction.¹⁸ During this acute phase of illness, CT scanning of the head is normal, and electroencephalograms may show mild slowing with excess sharp-wave activity.

Neuropathy of the seventh cranial nerve (Bell's palsy) occurs in up to 10% of patients with untreated early disease, and may persist for weeks or months before complete resolution. Bell's palsy may be bilateral¹⁹ and is sometimes accompanied by pain around the ear or jaw.

Peripheral radiculoneuritis also may occur within the first weeks to months of illness. Radiculoneuritis is characterized by radicular pain or paresthesia of the extremities or thoracic dermatomes, and is associated with abnormal nerve-condition studies of affected nerve roots. Occasionally loss of muscle strength with diminished reflexes in the territory supplied by individual peripheral nerves may suggest mononeuritis multiplex. Several neurologic sequelae may occur in combination; for example,

meningitis with Bell's palsy is particularly common. Generally, IgM or IgG antibodies against *B. burgdorferi* are detectable in patients with peripheral radiculoneuritis or meningitis, particularly if the illness has been present for longer than four weeks.

Chronic neurologic symptoms have also been reported in Lyme disease. Although the frequency of such symptoms is unknown, chronic sequelae appear to be uncommon. Reported symptoms have included cognitive impairment, behavioral changes, seizures, ataxia, and chronic fatigue. Neuropsychiatric testing of these patients may reveal organic brain dysfunction, and MRI scanning of the brain may reveal demyelinating lesions, cerebral atrophy, or ischemic infarcts.²⁰ Neuronal destruction may result in a static encephalopathy which may be refractory to antibiotic therapy. Improved delineation of the spectrum of late neurologic sequelae of Lyme disease is of paramount importance if rational treatment decisions are to be made in the management of these patients.

Lyme Arthritis

Arthralgia and myalgia are common features of early Lyme disease, however, frank arthritis during erythema migrans is unusual. An interesting and diagnostically useful rheumatic symptom in early Lyme disease is temporomandibular joint pain, which is only rarely seen in other rheumatic disorders.²¹ Months to years after erythema migrans, 60% of untreated patients will develop joint manifestations ranging from migratory arthralgias to chronic destructive arthritis. The most common syndrome is an intermittent inflammatory arthritis of one or more large joints, particularly the knee; large joint effusions and Baker's cysts are common. Rarely, smaller peripheral joint involvement resembling seronegative rheumatoid arthritis may occur.²² Attacks of arthritis may last weeks to months and recur for several years; however, the prognosis of those with intermittent arthritis is generally good, with 10% to 20% spontaneously achieving long-term remission each year.²³ A minority of patients with arthritis will develop chronic, erosive disease, usually of a knee. Chronic arthritis is more prevalent among individuals with the class II HLA phenotypes DR3 and DR4.

Radiographs taken during an attack of arthritis are usually normal, with the exception of soft-tissue swelling. Additional radiographic changes later in the course of arthritis have included joint-space narrowing, subchondral sclerosis, osteophytes, enthesopathy, and erosions.²⁴ Synovial fluid analysis reveals a variable WBC count (500 to 100,000 cells; average 25,000 cells per cubic mm) with a predominance of neutrophils and rare eosinophils.²⁵

Protein levels may be modestly elevated (range 3.6 g/dl to 5.7 g/dl) with normal glucose and complement levels. Tests for serum antinuclear antibodies, rheumatoid factors, and VDRLs are generally negative. Anti-*B. burgdorferi* antibodies of the IgG class should be present in serum in patients with Lyme arthritis. Synovial biop-

ties are not helpful in diagnosis since the histopathology (villous hypertrophy, vascular proliferation, and mononuclear infiltration) is similar to that of rheumatoid arthritis, and the isolation of spirochetes from synovial tissue or from joint fluid is extremely difficult. Patients with long-standing arthritis with synovial proliferation and radiographic changes may be refractory to antibiotic therapy, and may require synovectomy.

The patient who complains of intermittent arthralgia and chronic fatigue, without objective findings, poses a particular diagnostic and therapeutic challenge. Although cases of seronegative Lyme disease have been reported,²⁶ physicians should hesitate in making a diagnosis of Lyme disease in such patients in the absence of objective evidence of inflammatory disease and anti-*B. burgdorferi* antibody titers. A search for other causes of arthralgia and fatigue, including depression, fibromyalgia, postviral neurasthenia, collagen vascular diseases, indolent infections, and neoplasms is indicated in such patients. Empiric antibiotic trials may be indicated in some patients with a clear history of exposure in an endemic area, a tick bite, and subjective symptoms, but in general, antibiotic treatment should be reserved for patients with objective findings on physical exam and positive serologic tests. Decision for treatment of such individuals should be made only after consultation by a clinician experienced in the treatment of Lyme disease and after properly informing the patient of the diagnostic uncertainty inherent when objective physical findings and positive serologies are lacking.

Ocular Manifestations

Ocular manifestations may occur in Lyme disease, and include cranial nerve palsies (sixth and seventh nerves), iritis, optic neuritis, panophthalmitis with loss of vision,²⁷ interstitial keratitis with potential corneal opacity,²⁸ and choroiditis with retinal detachment,²⁹ as in other spirochetal infections, high-dose systemic antibiotics are required when *B. burgdorferi* causes ocular symptoms.

Pregnancy

Adverse fetal outcomes due to maternal-fetal transmission of Lyme disease have been reported,³⁰⁻³² but a uniform pattern of congenital malformations has not been identified. Of equal importance, however, is that the majority of such pregnancies are normal.³¹ Adverse outcomes include fetal demise with abnormalities of the heart and great vessels,^{30,31} as well as autopsy reports of septal defects and coarctation of the aorta. If Lyme disease is contracted during the first trimester of pregnancy, coincident with cardiac organogenesis, an increased risk of fetal cardiac anomalies may be present. Other adverse outcomes, which occurred despite antibiotic therapy, have included syndactyly, cortical blindness, and fetal wastage.³¹

In a prospective study of abortuses in an area endemic for Lyme disease, four cases of fetal borreliosis were described with *B. burgdorferi* isolated from fetal liver.³³ This observation suggests that *B. burgdorferi* may be an

etiologic agent in fetal demise of uncertain cause. The risk to infants of asymptomatic women with positive serologies for Lyme disease has been explored through analysis of cord blood for anti-*B. burgdorferi* antibodies. No association was noted between the presence of anti-*B. burgdorferi* antibodies in cord blood and the occurrence of congenital malformations, although seropositive babies tended to have a lower birthweight by 150 grams. The development of these infants warrants further observation, especially since in another spirochetal infection, congenital syphilis, abnormalities are not always evident at birth.

Conclusion

In summary, Lyme disease usually begins during the summer months with erythema migrans and flu-like symptoms, followed weeks to months later by cardiac or neurologic complications in a minority of affected individuals. Arthritis occurs in many untreated patients weeks to years after disease onset. Early antibiotic therapy generally aborts the later manifestations of Lyme disease and aggressive antibiotic therapy is generally effective in eradication of infection during later stages of illness. Current clinical research efforts are being directed toward prevention of infection, improvement in methods of serologic diagnosis, further delineation of the clinical spectrum, and optimizing treatment of all stages of disease.

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