LYME DISEASE

Lijing Yao, MD

Definition

Lyme disease is a multi-system disorder caused by the spirochete *Borrelia burgdorferi (B. burgdorferii*) that is transmitted to humans by the bite of a tick with symptoms ranging from a rash, fever, and headache to joint pain.

ETIOLOGY AND PIDEMIOLOGY

Lyme disease is caused by B. burgdorferi,[1] a type of bacterium called a spirochete that is a member along with treponema and leprospira of the spirochaetaceae family. The disease is transmitted via tick vector *Ixodes dammini* (deer tick) in the American Northeast and the Upper Midwest and by the California black-legged tick, *Ixodes pacificus* in the American West.[1-5] In Europe, erythema migrans had been recognized in the early of the century and attributed to bites by *Ioxdes ricinus* ticks.[6,7] Intermediate tick hosts for B. burgdorferi include deer, mice, cats, dogs and horses. The bacterium can be transmitted to humans by the bite of an infected tick and travel through bloodstream to various body tissues, where it causes a number of symptoms, some of which are severe.

The disease was first identified in 1975 in Lyme, Connecticut, in the United States of America.[8,9] Since then, it has been increasingly reported in the United States and other countries including Europe, Australia, and Asia.[10,11] In 1996, the overall annual incidence in the United States was 6.2 cases per 100.000 population,[12] with a high distribution in the Northeast, the upper Midwest, California, and certain areas of the Pacific North-West and Midwest.[12-14] However, sporadic cases have also been reported from 48 of the 50 states. Lyme disease can affect individuals of all ages. The incidence is the highest in children under 15 and adults with age range from 30 to 59 years.[11,15] It has been reported that the disease is somewhat more common in males than females.

CLINICAL FEATURES

Lyme disease is a disorder associated with multi-system abnormalities whose most prominent manifestations affect skin, nervous system, musculoskeletal system and heart. A wide spectrum of eye involvement has also been reported. The disease has three defined clinical stages.[1,3,16,17] However, some patients may not present all stages.

Stage I begins within 1 month of an infected tick bite, usually in the summer, and is manifested by an oval or annular skin rash of varying severity, often with a clear center at the area of the bite: erythema migrans (Picture 1).[17-19] The lesion may itch or be painful, but is often asymptomatic. Only approximately 30% of persons may recall being bitten. Other symptoms including headache, malaise, fatigue, fever, and arthralgias; lymphadenopathy may also occur at the early stage.

Stage II follows several weeks to months after infection and is characterized by potential involvement of nervous system and heart. The neurological symptoms may include severe headache and stiff neck, meningitis, peripheral radiculopathy, and cranial nerve palsies. The symptoms of headache, nausea, photophobia and vomiting often indicate meningeal involvement.[17,20] Cranial nerve palsy may be unilateral or bilateral, and most often affecting the facial nerves (Bell's palsy).[21] Both sensory and motor radiculopathy can occur. Cardiac

involvement more commonly presents with atrioventricular block of varying degree.[22] Other conduction system defects, arrythmias, myocarditis and pericarditis can also occur.

Stage III may occur up to 2 years after the initial infection and is characterized by prolonged episodes of migratory oligoarthritis and chronic neurologic syndromes.[17]Neurological features include ataxia, chronic encephalopathy, seizure, dementia, myelitis, spastic paraparesis, and psychiatric disturbances. Other symptoms include fatigue, lymphadenopathy, splenomegaly, sore throat, dry cough, nephritis, hepatitis, or orchitis.[17,18]

Table 1. Systemic and ocular features of Lyme disease in different stages of the disease.

	Systemic Manifestations	*Ocular Manifestations*
Stage I *(Local)*	Bull's-eye rash (Erythema migrans) Headache, malaise, and fatigue myalgias, and/or arthralgias Swelling of lymph glands near tick bite	Conjunctivitis Episcleritis
Stage II *(disseminated)*	Migrating pains in joints/tendons Severe headache Meningitis, Stiff, or Aching neck Encephalitis/myelitis Cranial neuropathy (facial palsy) Tingling or numbness in extremities Abnormal pulse Atrioventricular block Myopericarditis	Optic neuritis Perineuritis Papilledema Optic nerve atrophy Retinal hemorrhages Retinal vasculitis Choroiditis Blepharitis Exudative retinal detachments Cystoid macular edema Anterior or Posterior uveitis Intermediate uveitis Panuveitis Endophthalmitis

Stage III *(Persistent)*	Oligoarthritis Encephalopathy Seizure, dementia, disorientation sizziness, confusion Spastic paraparesis, myelitis Psychiatric disturbances and Ataxia Lymphadenophathy Sore throat, dry cough, or fatigue Nephritis or Hepatitis Testicular swelling	Chronic intraocular- inflammation Keratitis Episcleritis

Ocular manifestations of Lyme disease may occur at any stage but are more common in the last two stages.[17] The most common ocular finding in stage I is conjunctivitis.[19] During the second and third stages, ocular involvement includes anterior, intermediate, and posterior uveitis, endophthalmitis, keratitis (stromal opacities, punctuate superficial keratitis or peripheral ulcerative keratitis), and conjunctivitis. Neuroophthalmic features can also occur, including involvement of third, sixth, and seventh cranial nerves (Bell's palsy, most common),[21] optic nerve (optic neuritis and perineuritis, papilledema, ischemic optic neuropathy, optic nerve atrophy). Other possible ocular involvement includes retinal hemorrhages, exudative retinal detachments, cystoid macular edema,[20] blepharitis, scleritis and episcleritis.[17,21] The most commonly reported ocular syndromes in stage II are conjunctivitis and uveitis.[21] Bilateral interstitial keratitis has been described as a characteristic feature in the late stage of Lyme diseses.[22-26]

PATHOGENESIS

A primary infection occurs at the site of the tick bite. B. burgdorferi entries through a break in skin or mucous membrane and disseminates to all parts of the body via spirochetemia. The direct invasion by B. burgorferi may cause mechanical tissue damage. The bacterium itself and its outer surface protein A (OspA) is a strong antigen that stimulates natural, humoral and cell immunologic responses of the host, subsequently causing intense inflammation in the different involved parts of the host body.

Diagnosis

Erythma migrans is the typical clinical marker for Lyme disease and is present in 60% to 80% of patients.[18,19] When a patients with a history of a tick bite develops erythema migrans, the diagnosis of Lyme disease can be made. However, history of a tick bite is recalled in only about 50% of cases and a skin rash and early symptoms may be undetected or may be ignored. Because B. burgdorferi is difficult to culture, currently, the diagnosis of Lyme disease is primarily based on clinical presentations and laboratory testing from serologic examination.[27-32]

About 40 to 60% of patients with Lyme disease have elevated antibody titers (IgM and IgG) to B. burgdorferi several weeks after infection. At present, both immunosorbent assay (IFA) and

enzyme-linked immunosorbent assay (ELISA) tests are used to detect antibody titers for the diagnosis of Lyme disease. However, the ELISA test is more sensitive in all stages of the disease, especially in stage 2 (approximately 90%) and stage 3 (almost 100%),[17] and is the most specific of the routinely available tests in the clinical setting. False negative results can occur when patients with chronic Lyme disease may not have antibodies against B. burgdorfer if there was earlier inadequate oral antibiotic treatment or if patients are immunosuppressed.[17] False negative results can also occur during the first few weeks of infection, when antibody titers may be low and missed by serologic tests of lower sensitivities. Usually positive or equivocal ELISA results must be confirmed by both IgG and IgM Western blots. Western blot is a qualitative test and is generally more sensitive and specific than the ELISA. The test is also helpful in differentiating a false positive result that can occur in patients with syphilis, Rocky Mountain spotted fever, autoimmune disease, or other neurological disorders.[17] Both tests are considered more reliable and accurate when performed at least a month after initial infection, although no test is 100% accurate.

Polymerase chain reaction (PCR) is a very specific and sensitive assay in amplifying and detecting both genomic and plasmid B. burgdorferi specific DNA. If patients have neurological symptoms or swollen joints, a PCR test is recommended via a spinal tap or withdrawal of synovial fluid from an affected joint. This test amplifies the DNA of the spirochete and will usually indicate its presence.

In general, diagnosis of Lyme disease is primarily based on clinical presentations and serologic finding. In endemic areas, the diagnostic criteria usually include erythema migrants or at least one late manifestation involving musculoskeletal, or nervous or cardiovascular system involvement with positive serologic test. In nonendemic regions, erythema migrans with positive ELISA or erythema migrans with two-organ system disease is request for establishing diagnostic.[27-30]

DIFFERENT

Diagnosis

Lyme disease is a disorder with multiple organ involvement. Therefore, the diagnosis must always be considered in diseases that have multiorgan system involvement with constitutional, arthritic, neurologic, and ocular symptoms. Systemic diseases, such as syphilis, tuberculosis, and sarcoidosis, are the major disorders that should be ruled out in the differential diagnosis of Lyme disease. Diagnosis and differential diagnosis of Lyme disease based on laboratory testing is displayed in Table 2. Usually, history, physical examination, clinical presentation, and laboratory testing can help distinguish these different disorders.

Table 2. Diagnosis and Differential diagnosis of Lyme Disease Based on Laboratory Testing

SYSTEMIC DISEASE	LABORATORY TESTING
Lyme disease	Lyme IgM/IgG ELISA or IFA IgM/IgG; Western blot test for IgM/IgG titer. PCR
Syphilis	VDRL; FTA-ABS; TPTA
Sarcoidosis	Chest X-ray; ACE; Serum calcium and phosphorus; Serum lysozyme

Tuberculosis	Chest X-ray; PPD
TICK-BORNE DISEASES	LABORATORY TESTING
Babesiosis	Early infection: Blood smear FISH (Fluorescent In-Situ Hybridization) IFA IgM; PCR Later Infection: IFA IgG; PCR
Erlichiosis	Early Infection: Blood smear; IFA IgM; PCR Later Infection: IFA IgG; PCR
Tick-borne relapsing fever	Blood smear; IFA IgM/IgG; PCR
Tick-borne Mountain Spotted fever	Blood smear; IFA IgM/IgG; PCR

Other tick-borne diseases, including human babesiosis, human granulocytic erlichiosis, Rocky Mountain Spotted fever, and tick-borne relapsing fever, can also transmit some infectious diseases other than B. burgdorferi. Human babesiosis is caused by an intra-erythrocytic parasite, Babesia microti. Early in the infection, parasites are present in the red blood cells. Later there is an antibody response in about 70% of the patients. The disease has the same area of distribution where B. burgdorgeri is found. This disorder is characteristized by fever, chills, sweats, arthralgias, headache and fatigue.[33] Ocular involvement is rare, but retinal nerve fiber layer infarcts has been reported.[34,35]

Human granulocytic ehrlichiosis (HE) presents as a flu-like illness with fever, chills, malaise, headaches, myalgia, sweats, nausea, and vomiting.[36,37] Leukopenia, thrombocytopenia, and hepatic involvement are typically found associated with this disease in laboratory testing. In rare instances, infection may result in multiple organ failure and death, particularly in the elderly and immunosuppressed patients.[36-38] Patients considered with HGE should also be tested for Lyme disease, since the disease is transmitted by the same tick and coinfections have been reported.

Tick-borne relapsing fever is transmitted by several species of Ornithodoros tick. The disease presents with an acute fever, followed by an afebrile period, and then recurrence of the fever. The differential diagnosis of all these diseases described above is primarily based on clinical presentation and blood smear, as well as serology and PCR testing.

TREATMENT

Early **infection** or nonspecific symptoms with positive Lyme titers in the adult may be treated with oral doxycycline (100 mg twice daily for 4 to 6 weeks) or tetracycline (500 mg four times a day for 4 to 6 weeks). Children may be given oral penicillin V potassium (50 mg/kg per day in four divided doses) or oral amoxicillin (125 to 250 mg three times a day), or erythromycin (40 mg/kg per day in four divided doses) for 3 to 4 weeks.[17]

Severe **infection** in adults with definitive ocular, neuroophthalmic, neurological, or cardiac involvement may be treated with penicillin G (24 million units, intravenous, daily in four divided doses for 21 days) or intravenous ceftriaxone (2 g/day in two divided doses for 21 days.[39] Therapy for children includes intravenous penicillin G (250,000 units/kg per day in four divided doses for 21 days) or intravenous ceftriazone (100 mg/kg per day in two divided doses for 21 days).[17] Topical steroids and cycloplegics in conjunction with antibacterial agents is recommended for ocular inflammation.[17]

COMPLICATIONS AND PROGNOSIS

Erythema migrans and early clinical signs of Lyme disease can resolve without treatment after several weeks.[40] With early diagnosis and appropriate antibiotic therapy, most cases can be cured with no long-term sequelae. About 10 to 40% of patients with untreated erythema migrans will progress to second stage Lyme disease.[41] Three percent to ten percent % of patients will develop chronic arthritis, chronic skin involvement (i.e. acrodermatitis chronic atrophicans), or neurologic disease.[41] Chronic neurologic symptoms and arthritis may be persistent or reappear despite antibiotic treatment.

CONCLUSION

Lyme disease is a multi-system disorder caused by *B. burgdorferi*. It is a tick-borne spirochetal disease and is transmitted to humans by the bite of a tick with symptoms ranging from a rash, fever, and headache to joint pain. The disease may affect skin, nervous system, musculoskeletal system and heart. A wide spectrum of eye involvement has been also reported. A self-limiting conjunctivitis may be associated with early infection. With dissemination of the disease, intraocular inflammation and neuro-ophthalmic signs may occur. The disease is primarily based on careful history, thorough ocular and physical examination, as well as laboratory testing. Early diagnosis with appropriate antibiotic therapy is curative. Late sequelae involving the skin, joints and nervous system can occur and be resistant to antibiotic treatment.