LYME DISEASE

OVERVIEW & REVIEW OF THE LITERATURE

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HISTORY

Allan C. Steere and associates from Yale University recognized Lyme Disease as a distinct entity in 1975. Steere was investigating an epidemic of what was originally believed to be Juvenile Rheumatoid Arthritis (JRA). An unusual cluster of arthritis in children and adults occurred, centered about the towns of Old Lyme and East Haddam, Connecticut. The incidence in young children was 100-10,000 times that expected for JRA. Twenty five percent of those afflicted recalled a characteristic rash preceding arthritic symptoms. The epidemiology of illness and location of rash suggested insect borne disease. One individual recalled being bitten by a tick.[17]

A similar rash had been described in 1909 by Swedish Physician Arvid Afzelius in patients who had been bitten by a tick of the Ixodes family. He named it Erythema Chronicum Migrans (ECM), meaning "chronic migrating red rash". Typically it begins as a red papule at the site of the bite, expanding irregularly radially, with reddish raised serpiginous margins and often with a concentric ring of clearing.[4,17,37]

The deer tick Ixodes dammini was identified as the vector of Lyme Disease. Identification and isolation of a treponema-like spirochete from Ixodes dammini was accomplished in 1982 by W. Burgdorfer[8] and demonstrated to be the cause of Lyme disease.[42] The organism was shown to be a newly recognized bacterium of the class Borrelia,and named Borrelia burgdorferi in honor of its discoverer.

Illnesses similar to Lyme Disease, occuring after a tick bite had been described in the European and British literature:[30]

1922 Garin & Bujadoux
1941 & 1944 Bannwarth
(Sometimes referred to as Garin, Bujadoux, Bannwarth Syndrome or GBB)

SPECTRUM OF ILLNESS

Early Lyme Disease:

Lyme Disease often presents as a flu-like illness occuring days to weeks after receiving a tick bite. Fever, may occur, sometimes as high as 104 degrees, along with malaise, myalgias, fatigue, headache, and arthralgias. Sometimes mild meningeal irritation may be present. Alternatively, sore throat & swollen lymph nodes may be prominent features. Twenty five

percent or more of affected individuals may not experience ECM. Rash may not be present at all, or may be atypical, hive-like, or indistinguishable from cellulitis. Symptoms, including rash if present, will usually resolve with time even without treatment.[12,17,35,36,37]

Intermediate Lyme Disease:

Weeks to months after entry of spirochete into body, an intermediate stage of the disease can occur, consisting chiefly of cardiac and/or early neurologic involvement. Arrhythmias and cardiac conduction abnormalities may occur.[32] The latter can rapidly progress to complete heart block requiring the placement of a temporary transvenous pacemaker. Myocarditis, pericarditis, and myopericarditis also have been frequently observed.[1,25,32,41] Neurologic involvement may include meningitis, encephalitis, meningoencephalitis, cranial neuritis (especially VII nerve palsy; bilateral VII or facial nerve palsy is <u>almost</u> pathognomonic of Lyme Disease.). Multiple cranial nerve involvement may be seen (eg. III,IV,V,VI,VII VIII,IX,X,XII in various combinations) in the same patient. Motor and sensory radiculopathies can occur with weakness, numbness, and/or painful paresthesias, and changes in reflexes. Neuropathies may occur in isolated nerves or dermatomes, or in motor and/or sensory branches of one or more roots of a major nerve plexus serving an upper or lower limb (eg. brachial or lumbosacral plexitis). Involvement may be bilateral or may affect upper and lower extremities in the same patient. Hence nerve involvement may present as mononeuritis or mononeuritis multiplex. Symptoms may be migratory. [9,17,18,26,27,30,36]

Late Lyme Disease:

Originally, the main focus in late disease was arthritis, occuring months to years after onset of infection.[38] It is now recognized that late and severe neurologic sequelae may dominate the clinical picture in this stage, or may co-exist with arthritic manifestations.[6,7,26,29,30,31] Also, as clinical experience is gained, additional organs and organ systems have been found to occasionally be affected.[2,33,40]

Arthritis is evidenced by intermittent attacks of joint swelling and pain primarily affecting large joints, with redness and signs of inflammation. Attacks are intermittent, usually lasting for weeks to months in a given joint, and recurring over a period of years. Advanced arthritis is in some cases poorly responsive to antibiotics, even in high dosage given intravenously. Ten percent of patients develop joint destruction with erosion of cartilage and bone.[17,38,39]

Severe late neurologic manifestations have been recognized including severe late encephalopathy with intellectual and personality deterioration, extensive demyelinating disease involving the subcortical cerebrum, dementia, psychotic states, or myelitis,and milder chronic fatigue states.[6,7,26,29,30,31] Some of these late neurologic manifestations of Lyme Disease have proven successfully treatable with appropriate parenteral antibiotic therapy. Others are recalcitrant to any treatment, reflecting the advanced and irreversible organic changes which have been produced by the spirochete and/or the immunologic reaction it initiates.

Other severe and late sequelae which have been described include reports of panophthalmitis with blindness[40], keratitis (inflammation of the cornea)[2], and severe late skin manifestations (acrodermatitis chronica atrophicans).[36]

Lyme Disease In Pregnancy:

It has been well documented that Borrelia burgdorferi is capable of transplacental passage and there have been several case reports of adverse fetal outcomes related to maternal Lyme Disease, particularly when contracted during the first trimester of pregnancy.[21,24,34] One case of stillbirth demonstrated the presence of the spirochete in fetal liver, heart, adrenal gland, sub-arachnoid space, and brain in association with a congenital heart defect (A-V canal type of ventricular septal defect). In a second case in which the infant died shortly after birth, the Lyme disease spirochete was found in the spleen, bone marrow, and kidneys of the fetus, which had multiple congenital cardiovascular abnormalities incompatible with long term survival. No definite conclusions could be drawn as to whether the spirochete CAUSED the heart abnormalities. In another series of 19 pregnancies during which Lyme Disease occurred, there were 5 adverse outcomes including intrauterine fetal demise, prematurity, and developmental delay with cortical blindness.

Simultaneous occurrence of Lyme Disease with Babesiosis:

Babesia are tiny protozoa which can parasitize red blood cells, destroying them and resulting in hemolytic anemia. Babesia also may be transmitted to humans by deer ticks and there have been a few case reports of simultaneous infection with Borrelia burgdorferi and Babesia microti.[16] One of these cases was fatal.[25]

PATHOLOGY OF LYME DISEASE:

The spirochete is introduced to the skin during the feeding of the nymphal or adult tick Ixodes dammini. Other species of Ixodes have also been proven to be vectors of the disease. The spirochete multiplies in the host and spreads out circumferentially from the site of the bite. Spirochetes have been identified in the skin in biopsies taken from Erythema Chronicum Migrans, usually at the leading edge or margin of the rash, using special stains (Warthin-Starry silver).[5] It is not known when the spirochete disseminates from the skin to other tissues, however the spirochete has been isolated from blood cultures when special media have been used (Kelly's media).[3] It is not known whether other vectors besides ticks can transmit the disease, however in areas endemic for Lyme other blood feeding insects such as deer flies, horse flies, and mosquitos have been shown to harbor the spirochete and there have been anecdotal reports of ECM occurring at the site of deer fly and or mosquito bites.[22] Manifestations of the disease seem to be particularly severe in persons bearing genetic marker DR-2 on their B cell lymphocytes.[17,42] Aside from the direct effects of the spirochete on tissues, it is also believed that the organism or its components initiate inflammatory and possibly immune mediated reactions which exacerbate the disease. Lipoprotein released from the cell membrane is thought to stimulate production of interleukin-1 (IL-1) by host macrophages and synovial cells which aggravates the inflammatory response by means of prostaglandin synthesis, all furthering the toxic and tissue destructive processes. It has been shown that injection of IL-1 or lipopolysaccharide into the skin can each produce a reaction mimicking Erythema Chronicum Migrans.[17]

The widespread and anatomically remote manifestations of Lyme Disease and the laboratory abnormalities found suggest an immunologically mediated disease with vasculitis, and parallels have been drawn to an entity called Serum Sickness.[19] Although the advanced stages of Lyme Disease are thought to occur in the presence of the spirochete, there is some concern that the immunologic processes initiated in the disease may be self-perpetuating even after the eradication of the spirochete.

DIAGNOSIS OF LYME DISEASE:

The diagnosis of Lyme Disease is based on clinical grounds although a variety of laboratory data MAY be helpful. Diagnosis may be quite straightforward but may be extremely difficult despite maintaining a high index of suspicion. It has been stated that Lyme Disease, like the prototypical spirochetal disease Syphilis, may fairly be called a Great Imitator.[42] The protean and often confusing manifestations of Lyme Disease, the

often non-specific initial flu-like presentation, and the fact that many victims relate a history of neither a tick bite nor rash further confound efforts to establish a diagnosis. Likewise, laboratory tests for Lyme are often unhelpful, especially early in the disease. Specific IgM and later IgG antibodies against Borrelia burgdorferi eventually develop in most but not all patients with intermediate and late Lyme Disease. The antibody response may be aborted by early antibiotic treatment. Once present, antibodies against the agent persist for years. Furthermore, these antibodies are not protective against re-infection with the spirochete from a new tick bite.[28] Other laboratory tests which may be helpful include the Erythrocyte Sedimentation Rate, a non-specific indicator of inflammation, which may be elevated, and cryoglobulins, which are thought to be caused by circulating antigen:antibody complexes occurring during the disease.[18] Residence in a Lyme endemic area, ownership of pets which go out of doors, and an out of doors life-style are important clues to the diagnosis.

TREATMENT OF LYME DISEASE:

Recommendations in recent years called for tetracycline, 250 mg., penicillin VK 250 mg., or erythromycin 250 mg. four times a day for ten days. Better understanding of the biology of the spirochete, and the recognition that treatment failures have occurred in early Lyme Disease with courses meeting or exceeding those recommendations[10] have led to different regimens. Because of the slow replication time of the spirochete, it is now recognized that high, sustained, and prolonged antibiotic levels are required in blood and tissues to reliably erradicate it. Current recommendations for early Lyme are doxycycline (a long-acting congener of tetracycline), 100 mg. orally twice a day for 21 days or amoxicillin 500 mg. three times a day along with probenecid 500 mg. three times a day for 21 days (the probenecid delays excretion of amoxicillin by the kidneys thus achieving higher blood levels of amoxicillin).[12]

Recommendations for the treatment of intermediate Lyme Disease are less standardized, some authorities recommending the same regimen as for early Lyme if the manifestations are mild (eg. isolated cranial or peripheral neuritis). For more severe manifestations such as meningitis or cardiac abnormalities parenteral (intravenous or intramuscular) antibiotics are felt to be mandatory. This is usually high dose penicillin in the order of 20 to 24 million units per day for 10 or more days. Another antibiotic which is gaining increased usage for intermediate and advanced Lyme Disease is ceftriaxone (ROCEPHIN) which has a very long half-life, readily achieving levels in the

body which kills the spirochete. Ceftriaxone penetrates into the central nervous system well, even in the absence of acute inflammation (unlike penicillin which will not penetrate uninflamed meninges) thus helping to assure eradication of the spirochete.[11] The recommended dosage of ceftriaxone is one or two grams once or twice a day intravenously or intramuscularly for 14 days. The cost of the drug for such a regimen is upwards of two thousand dollars.

For Late Lyme Disease high dose parenteral penicillin or ceftriaxone are recommended. Ceftriaxone, as well as another drug (chloramphenicol)[13] have proven effective in certain cases refractory to penicillin in the maximum recommended doses. Although a significant percentage of patients with late Lyme Disease do respond to antibiotics, some do not, probably reflecting the severe tissue damage already sustained before treatment is administered.

Patients undergoing antibiotic treatment for Lyme Disease may experience an apparent worsening of symptoms during the first 24-72 hours of treatment. As great numbers of spirochetes begin to be destroyed toxic bacterial components such as lipopolysaccharide endotoxin are thought to be released causing generation of interleukin-1 and other mediators of inflammation. As a result, fever and chills may worsen and the rash of ECM may intensify or reappear. This phenomenon, termed the Jarisch-Herxheimer reaction[23] is transient and may be treated with antipyretics such as aspirin or acetaminophen (TYLENOL). The Jarisch-Herxheimer reaction also occurs during the treatment of syphilis.

PREVENTION OF LYME DISEASE:

There appear to be no easy answers to preventing Lyme Disease. Avoidance of wooded areas and underbrush may minimize risk, however even suburban lawns in endemic areas may harbor deer ticks. An extreme reaction might be retreat to urban enclaves or virtual "silviphobia". As the white-tailed deer appears to play a crucial role in the life cycle of Ixodes dammini, elimination of deer in populated areas would likely solve the problem, however this would be morally and aesthetically objectionable to many people. Certainly wearing protective clothing and the use of tick-repellant sprays such as N,N-diethyl-meta-toluamide (DEET,' and others) may afford some protection.

Another approach which may prove practical, particularly on and about residential properties is the use of a product called Damminix. Taking advantage of the propensity of white-footed mice to hoard materials suitable for nest lining, biodegradable tubes containing cotton impregnated with a potent acaricide are placed strategically. The cotton is retrieved to to the burrows where it is highly efficient in killing larval

and nymphal ticks feeding on the mice.[43] (Call EcoHealth, (617) 742-2400 for information).

TICK REMOVAL:

As risk of transmission of the spirochete is related to the duration of attachment,[15] there is rationale to tick removal as soon as possible. If it can be removed entirely by means of gentle traction with a tweezers applied forward of the body, that is ideal. One should avoid squeezing the abdomen as this may result in inadvertent inoculation of spirochetes. Since the embedded mouth parts may be contaminated with spirochetes, it would seem logical to remove them along with the body. If mere traction is unsuccessful, I have found that commonly recommended techniques (e.g. use of vaseline, acetone, heat, etc.) generally will also fail. A technique that I have found to be effective is to carefully undercut the area of mouth part attachment with a sterile 18 guage needle while gentle traction on the cephalothorax is maintained. In that way the tick is removed in toto, with a tiny button of skin. Generally, a bandaid and bacitracin is the only local care necessary. Of course, antiseptic technique must be used and for patient comfort local anaesthesia with lidocaine is advisable. If the mouth parts are retained in the skin after earlier attempts, then removal requires a small excisional wedge biopsy. It is unclear whether removal of retained embedded mouth parts is advantageous in terms of reducing the rate of transmission of the spirochete.

PROPHYLACTIC TREATMENT OF LYME DISEASE:

This is a controversial subject. Some argue that antibiotic treatment after a mere tick bite in the absence of clinically evident disease is not justified, especially since not all ticks harbor the spirochete. On the other hand, since disease detection may be difficult or manifestations delayed and since the consequences of Lyme Disease can be quite serious there may be some rationale for prophylactic treatment for unequivocal bites by deer ticks. Decisions on whether, when, and how to treat are best made on an individualized basis between physician and patient, with consultation with an infectious disease expert when necessary. Most would feel that prophylactic treatment IS indicated during pregnancy. Studies are underway sponsored by New York Medical College to determine the optimal antibiotic regimen to prevent Lyme Disease after deer tick bites on a prophylactic basis.

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