

Lyme Disease

- I Some important events in the development of Lyme disease
- A. 1977 Alan Steere and colleagues at Yale University described an epidemic of arthritis in 39 children and 12 adults living in eastern Connecticut.
 - 1. The illness was characterized by recurrent attacks of asymmetric swelling and pain in a few large joints, especially the knee.
 - 2. Though originally diagnosed with juvenile rheumatoid arthritis, many clinical and epidemiologic problems emerged with that diagnosis.
 - 3. An infectious etiology from an arthropod vector was suspected because:
 - a. Most cases lived in wooded areas rather than in town.
 - b. Peak occurrence was in summer.
 - c. 25% of patients had a unique expanding skin rash 1 to 24 wks before the onset of arthritis.
 - B. 1980 Alan Steere and colleagues showed that penicillin therapy could reduce the likelihood of arthritis in patients with EM, further implicating an infectious etiology.
 - C. 1982 Willy Burgdorfer and colleagues at the Rocky Mountain Labs isolated a treponema-like spirochete from *Ixodes dammini*, the tick thought most likely to carry the Lyme agent. Serum from patients with Lyme disease contained antibodies to the newly discovered spirochete.
 - D. 1983 Spirochetes were isolated from blood of 2 of 36 patients with Lyme disease. The organism was morphologically identical to that isolated by Burgdorfer from ticks.
 - E. 1984 The Lyme spirochete is defined as a member of the *Borrelia* genus, and is named *Borrelia burgdorferi*, after Willy Burgdorfer who first cultured it.
 - F. 1997 *B. burgdorferi* genome is sequenced.
 - G. 1998 FDA approves Lyme disease vaccine
- II Microbiology and pathogenesis
- A. Lyme disease is caused by *Borrelia burgdorferi*, which is related to other spirochetes such as *Treponema* (the agent of syphilis) and *Leptospira* (Leptospirosis).
 - B. After injection by an infected tick and 3 to 32 days incubation, the organism multiplies locally in the skin at the site of the bite. Within days to weeks it may disseminate to blood, CSF, other skin areas, myocardium, synovium and other sites. Congenital infection has been suggested but not well documented.
 - C. Immune response
 - 1. Initially there is immune suppression, which permits dissemination.
 - 2. Proinflammatory cytokines are produced, such as IFN γ .
 - 3. Specific IgM peaks within 3 to 6 weeks, and may be associated with polyclonal activation of immunoglobulin, circulating immune complexes, and cryoglobulins.
 - 4. IgG develops over months and IgM wanes.
 - D. All infected tissues show an infiltration of lymphocytes and plasma cells.

- E. Bacteria can be cultured from EM skin lesions, rarely from other sites.
- F. Despite the immune response, *B. burgdorferi* may survive for prolonged periods in untreated patients in joints, nervous system, or skin.

III Epidemiology and Ecology

A. Prevalence

1. Lyme disease is the most common vector-borne disease in the U.S.
2. Lyme occurs throughout the Northern hemisphere, with 4-5 times more cases in Europe/Asia than in North America
3. More than 10,000 new cases each summer.
4. Although cases have been diagnosed in all 48 lower states, Lyme disease occurs primarily in 3 geographic areas:
 - a. Northeast from Maryland to Massachusetts
 - b. Midwest in Wisconsin and Minnesota
 - c. West in California and Oregon
5. In California, the Department of Health Services recorded 145 cases in 1999; 73 cases were reported for 2000 as of August 30.
6. Most cases occur from May to October, especially June and July.

B. The vector ecology of *B. burgdorferi* is different in the Northeast and Midwest compared to the West. The differences explain why Lyme disease is so much more common in the East:

1. Northeast and Midwest
 - a. The tick vector in this area is *Ixodes scapularis* (*Ixodes dammini*), which feed on white-footed mice,
 - b. *B. burgdorferi* is transmitted from mouse to tick and tick to mouse and about 10 to 50% of the ticks are infected.
 - c. When *I. scapularis* feeds on humans, *B. burgdorferi* may be transmitted and Lyme disease may occur.
2. California and Oregon
 - a. The tick vector here is *I. pacificus*, which feeds primarily on lizards.
 - b. However, lizards cannot acquire *B. burgdorferi*. *I. pacificus* ticks only acquire infection when they feed on the woodrat, which they typically don't do. Therefore, only about 1 to 3% of *I. pacificus* are infected with *B. burgdorferi*.
 - c. The reservoir is maintained between the woodrat and another tick, *I. neotomae*, which doesn't feed on humans.
 - d. Only when *I. pacificus* feeds on the woodrat and then feeds on humans will *B. burgdorferi* be transmitted to humans.

IV Clinical Manifestations

A. Early Infection (Localized)

1. EM occurs at the site of the tick bite. It begins as a red macule or papule and slowly expands, often clearing in the center.

2. If the lesion is on the head, it may appear as only a linear streak that appears to emerge from the hairline.
 3. The lesion is warm to touch but not often painful.
 4. About 80% of infected patients will have this rash.
 5. Only about 30% of patients will recall a tick bite at the affected site.
- B. Early Infection (Disseminated)
1. Days
 - a. Secondary annular skin lesions
 - b. Malaise, fatigue, headache, myalgias, regional lymphadenopathy
 - c. Symptoms of meningeal irritation may occur early at the time of EM, but there is no associated CSF pleocytosis at this time.
 2. Weeks to few months
 - a. After several weeks to months, about 15% of untreated patients in the U.S. will develop neurologic abnormalities
 - i. Signs include meningitis, encephalitis, facial palsy, motor and sensory radiculoneuritis or myelitis.
 - ii. Bell's palsy frequently occurs alone and may be the presenting manifestation of the disease.
 - iii. At this stage, there is a CSF lymphocytic pleocytosis of about 100 cells/mm³.
 - b. About 5% of untreated patients develop cardiac disease.
 - i. Most common abnormality is fluctuating degrees of AV block (first degree, Wenckebach, or complete block).
 - ii. Duration is usually brief (3 to 6 wks); complete block rarely persists for more than a week and placement of a pacer is unnecessary.
 - iii. More diffuse cardiac involvement with myocarditis or pericarditis can occasionally be seen. Spirochetes have been demonstrated in myocardium by endomyocardial biopsy.
 - iv. Musculoskeletal pain is common in this stage, usually with migratory pain in joints, tendons, muscle or bone.
 - c. About 20% of patients will have evidence of mild hepatitis at this stage.
 - d. Unusual complications
 - i. Osteomyelitis and myositis
 - ii. Conjunctivitis, choroiditis, and keratitis.
- C. Late Infection (Months to years)
1. About 60% of untreated patients will have intermittent oligoarthritis.
 - a. Primarily large joints, especially the knee.
 - b. Affected joints are swollen, painful, but not red. Attacks last weeks to months. Joint fluid WBC ranges from 500-110,000 cells/mm³, most of which are PMNs in patients with high WBC.

- c. Organisms have only rarely been cultured from synovial fluid, but they can be routinely detected by PCR.
 - d. Number of patients with recurrent attacks decreases by 10 to 20% per year.
 - e. A small percentage of treated patients develop persistent joint swelling for months or years after therapy. Organisms cannot be found by culture or PCR in the joint fluid of these patients, who likely have immune-mediated disease.
2. Some patients will develop chronic neurologic sequelae, the most common of which is a subacute encephalopathy affecting memory, mood, sleep and sometimes with subtle language problems.
- a. Most of these patients will have elevated CSF protein and elevated antibodies to *B. burgdorferi*.
 - b. Cognitive impairment may be apparent on neuropsychological tests.
 - c. SPECT scanning may show decreased perfusion of frontal and subcortical structures.
 - d. Electrophysiologic testing frequently shows diffuse axonal polyneuropathy.
 - e. Borreliac encephalomyelitis, described primarily in Europe, is a severe disorder characterized by ataxia, cognitive impairment, bladder dysfunction, and cranial neuropathy (especially VII and VIII).
3. Acrodermatitis chronica atrophicans
- a. Observed primarily in the elderly in Europe, years after EM.
 - b. Begins with red violaceous lesions that become sclerotic or atrophic.
 - c. May last for years and still be culture positive 10 years after onset.
4. Fibromyalgia
- a. A small percentage of patients may develop a chronic pain syndrome similar to fibromyalgia.
 - b. Lyme patients usually do not have the anxiety, depression, difficulty with concentration and diffuse musculoskeletal pain that are characteristic of fibromyalgia. However, the distinction can be difficult.

V Laboratory diagnosis

- A. Diagnosis is based on a characteristic clinical picture, sufficient exposure in an endemic area, and an elevated antibody response to *B. burgdorferi*.
- B. Serodiagnosis
 1. Sensitivity of serodiagnosis is 60-70% 2 to 4 weeks after infection and 90% 4 to 6 weeks after infection.
 2. Antibody titers fall slowly after antibiotic therapy, but most patients with late manifestations of the disease have titers for years.

3. From 10 to 20% of patients will have asymptomatic infection, so a positive titer does not necessarily mean that a given symptom complex is related to infection with *B. burgdorferi* (ie, true, true, and unrelated).
 4. The CDC recommends two-tiered testing. An ELISA should be performed first, preferably with acute and convalescent sera, for both IgM and IgG. Positive or equivocal tests should be followed by western blot.
 5. An isolated positive IgM 1 month or more after onset of disease is common and is very likely a false positive.
 6. If the pretest probability of Lyme disease is less than 20% or greater than 80%, the serology is probably not helpful. While it is difficult to estimate pretest probability, a patient with no known tick bite, no EM rash, and no exposure to an endemic area will probably not benefit from Lyme serology.
 7. CSF/serum antibody ratio > 1.0 suggests intrathecal antibody production.
- C. Culture
1. Usually a research technique only
 2. Rarely positive except in skin.
- D. PCR
1. In one study, 75 of 80 (85%) synovial fluid samples from patients were positive, while 0 of 64 controls were positive.
 2. Sensitivity of PCR in CSF appears to be lower.
 3. PCR is commercially available (iGeneX, Palo Alto, CA) for whole blood, serum, urine and CSF. However, the company has no data regarding sensitivity or specificity on clinically confirmed cases. They only have data on how much DNA they can detect in spiked samples.
 4. Independent sources suggest that there is no role for PCR of blood or urine.
- E. Lyme urinary antigen test (LUAT)
1. Commercially available by iGeneX
 2. Reported by the company to be 70-90% sensitive and >90% specific.
 3. Only published literature is a paper in 1995 in the Journal of Spirochetal and Tick Biology, a journal that with very limited circulation.
 4. Reliability of this test is suspect.
- VI Treatment
- A. General
1. Oral therapy is effective for the large majority of cases.
 2. Fewer than 10% of treated patients fail to respond to appropriate therapy.
 3. One repeat treatment course may rarely be needed, but not more.
 4. Approximately 15% of patients may have a Jarisch-Herxheimer reaction during the first 24 hrs of therapy.
 5. The most common reason for apparent lack of response to appropriate antibiotics is misdiagnosis.
 6. There is no known indication for a treatment course to exceed 28 days.
- B. Guidelines for the treatment of Lyme disease

1. Oral therapy is appropriate for the following manifestations:
 - a. EM (14-21 days)
 - b. Cranial nerve palsy (14-21 days)
 - c. First or second degree heart block (14-21 days)
 - d. Arthritis (28 days)
 2. Parenteral therapy is appropriate for patients with:
 - a. Meningitis or radiculopathy (14-28 days)
 - b. Third degree heart block (14-21 days)
 - c. Recurrent arthritis (14-28 days)
- C. Antibiotic regimes for treatment of Lyme disease
1. Oral therapy
 - a. Amoxicillin 500 mg tid
 - b. Doxycycline 100 mg bid
 - c. Alternative
 - i. Cefuroxime 500 mg bid
 - ii. Macrolides are less effective than other agents.
 2. Parenteral therapy
 - a. Ceftriaxone 2 g iv qd
 - b. Alternatives
 - i. Penicillin G 18-24 MU iv/d divided into doses given q4h
 - ii. Cefotaxime 2 g iv tid
- D. Management of patients with chronic symptoms
1. Two studies were initiated under contract by the NIH to study patients
with

either

well-documented Lyme disease and long term symptoms, despite earlier treatment with antibiotics. Patients were randomly assigned to receive

placebo or 30 days of ceftriaxone iv followed by 60 days of doxycycline.
 2. On November 14, 2000, the Data and Safety Monitoring Board, an independent monitoring group, reviewed a planned interim analysis of of data from these two placebo controlled trials.
 3. The board unanimously recommended that the NIH terminate both trials because there were no significant differences.
 4. Another similar NIH funded study is ongoing at Columbia University (www.columbia-lyme.org; 212 543-6510).

VII Prevention

- A. Personal protection
 1. Avoid tick-infested areas.
 2. Tuck pants into boots or socks, shirt into pants.
 3. Use insect repellent.
 4. Check daily for ticks and remove them promptly.
 - a. Use forceps, grab the mouthparts near the skin, pull straight out.
 - b. Don't touch the tick with bare hands.
 - c. Clean the area.
- B. Environmental

1. Mow grass along trails, buildings.
2. Remove brush.
3. Area application of insecticides does not control ticks.

C. Immunization

1. History: The OspA story
 - a. Laboratory grown *B. burgdorferi* produces abundant amounts of a 31 kDa protein called outer surface protein A (OspA)
 - b. Because it was abundant and on the outer surface, OspA was a natural vaccine candidate. In 1990 it was shown to protect mice from experimental challenge with *B. burgdorferi*.
 - c. Clinical trials were begun, and in 1998 the FDA approved the first Lyme disease vaccine (LYMERix, SmithKline Beecham), which is recombinant OspA.
 - d. While the OspA vaccine work was well underway, it was discovered that *B. burgdorferi* expresses OspA when grown in culture and in the tick before feeding, but not after feeding. So when the bacteria are injected into the host, they are expressing OspC and very little OspA.
 - e. So why does the Lyme vaccine work? The bacterium is being killed in the tick!
2. Schedule
 - a. Vaccine is approved on a 0, 1, 12 month schedule.
 - b. 0, 1, 2 or 0, 1, 6 month schedules may be equivalent.
 - c. A 1-year booster may be needed.
3. Efficacy is 75% protection against definite disease, 88% if persons older than 65 years are excluded.
4. Indications
 - a. Approved for persons 15 to 70 years at high or moderate risk of Lyme disease.
 - b. In California, vaccine is indicated for persons with frequent or prolonged exposure to tick habitats in geographic areas known to have some or moderate risk of Lyme disease. These areas, in decreasing order of risk, include:
 - i. North coastal range (Mendocino area)
 - ii. Sierra foothills
 - iii. San Francisco Bay area, including Santa Cruz County
5. Limitations
 - a. Not studied in children < 15 years and not efficacious in the elderly.
 - b. Usefulness against the broad range of *B. burgdorferi* strains unknown, but probably does not protect against European and Asian genospecies that cause Lyme disease. A bioengineered OspA that confers broad immunity will begin Phase I clinical trials in the first quarter of 2002.
 - c. A protein found on blood and other human cells resembles the immunodominant epitope of OspA. This raises the theoretical possibility that OspA vaccine might, via molecular mimicry, cause

arthritis or other autoimmune disease. Although there was not an increased frequency of arthritis found among almost 11,000 vaccine recipients, these findings raise the theoretical possibility of vaccine-associated autoimmunity.

- D. Prophylactic therapy
1. Northeastern/Midatlantic and Midwestern United States
 - a. The probability of Lyme disease after a tick bite in an infected area is about 1%.
 - b. A cost benefit analysis suggested that prophylactic antibiotics may be useful when the likelihood of disease is greater than 1%.
 - c. A meta-analysis suggested that even in endemic areas the likelihood of disease is sufficiently low that prophylactic antibiotics are not warranted. However, they are frequently given.
 - d. Antibiotics may be appropriate when a documented tick bite has occurred and the tick has been attached for more than 24 hrs. Doxycycline or amoxicillin for 10 days is probably sufficient to prevent Lyme disease.
 2. Western United States
 - a. The prevalence of infected ticks is only 1 to 3% and the likelihood of disease from a tick bite is very low.
 - b. For these reasons, antibiotic prophylaxis is not indicated.

References

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