Lyme Disease

Richard A. Jacobs, MD, PhD.

Outline

• History of Lyme disease
  – How the “new” disease was discovered
  – How the etiology of the disease was discovered
• Clinical manifestations
• Diagnosis
• Therapy
• Prevention
• Controversies

Case

• A 35 yo woman is being evaluated for a 6 month h/o fatigue, arthalgias without arthritis and memory loss manifest as word-finding difficulties and forgetfulness. The work-up has been thorough but frustrating for both you and the patient because answers have not been forthcoming. Finally, after an exhaustive internet search, she requests that Lyme disease serologies be performed. You reluctantly agree.
Case

- Serologies
  - CDC recommends 2-stage testing
    - Screening ELISA—very sensitive but not specific
      - If negative—no further testing
      - If positive—confirmatory test
    - Confirmatory Western Blot
      - IgM—can take several weeks to become positive
      - IgG—positive after the IgM

Case

- Serologies return:
  - ELISA screening test is equivocal
  - Confirmatory Western Blot is IgM (+) and IgG (-)

Questions

- How do you interpret the serologies?
- Does she have Lyme disease?

Definition

Lyme disease is a bacterial infection caused by the spirochete Borrelia burgdorferi in the US and Borrelia afzelii, and Borrelia garinii in Europe and Asia and is transmitted to humans by the bite of infected Ixodes ricinus complex deer tick. The clinical manifestations can be complex but affect primarily the skin, joints, nervous system and heart.
“Tick Biology 101”

- Hard ticks (over 700 species)
  - Ixodes ricinus complex
  - Different geographic distributions
    - Northeastern and upper midwestern states
      - Ixodes scapularis (also called Ixodes dammini)
    - Western states—Ixodes pacificus
    - Europe—Ixodes ricinus
    - Asia—Ixodes persulcatus

- Soft ticks (over 150 species)

“Tick Biology 101” (continued)

- Three stages:
  - Larval—feeds from August to September on white-footed mouse
  - Nymphal★★—feeds from May through July on white-footed mouse
  - Adult—feeds on larger mammals, especially deer in the spring and fall

★★ nymph primarily responsible for disease transmission “Summer Flu”
Tick Biology (continued)

Engorged Tick

History of Lyme Disease

• 1909 a Swedish dermatologist, Arvid Afzelius, presented a paper in Stockholm describing a patient with an expanding, circular, red rash following the bite of sheep tick that lasted several weeks
• The rash was named “Erythema (red) Chronicum (lasts weeks) Migrans (expands) of Afzelius” or ECM
Modern History of Lyme Disease

In November 1975 a mother from Old Lyme, Connecticut informed the SHD that 12 children from a small community of 5,000, 4 of whom lived on the same road, had a rare disease diagnosed as juvenile rheumatoid arthritis (JRA).

During the same month another mother from a neighboring community reported at the Yale Rheumatology Clinic that she, her husband, 2 children and several neighbors all had arthritis.

Polly Murray who first reported what would become to be known as Lyme disease. Author of “The Widening Circle: A Lyme disease Pioneer Tells Her Story”
Dr. Allen Steere, who at the time was a Rheumatology Fellow at Yale University, was sent to investigate along with Dr. David Snydman of the Connecticut SHD

LYME ARTHRITIS
AN EPIDEMIC OF OLIGOARTICULAR ARTHRITIS IN CHILDREN AND ADULTS IN THREE CONNECTICUT COMMUNITIES
ALLEN C. STEERE, STEPHEN E. MALAWISTA, DAVID R. SNYDMAN, ROBERT E. SHOPE, WARREN A. ANDMAN, MARTIN R. ROSS, and FRANCIS M. STEELE

Arthritis and Rheumatism 1977;20:7

Lyme Arthritis

• 51 residents (total population 5,400) had arthritis
  – Sudden onset
  – Large weight bearing joints (knee > ankle)
  – Lasted several weeks and resolved spontaneously
  – Many (70%) had recurrences
  – Often associated with fever, fatigue, headache, muscle aches (Flu-like symptoms)
Lyme Arthritis

- Other important observations:
  - A significant number recalled a red, expanding rash several weeks before the onset of arthritis
  - One person recalled a tick bite at the site of the rash
  - Most affected individuals lived on heavily wooded lots or on farms
  - Most cases of arthritis occurred from June to September
- Extensive studies on blood and joint fluid and could find no causative agent

Conclusions

- Clustering of cases suggested an infectious etiology — unknown at the time
- Clustering of cases in wooded areas and peak occurrence in the summer months led “the authors to believe that the epidemiology fits best with an illness transmitted by an arthropod vector”
- Noted the similarity of the rash to ECM of Afzelius that was transmitted by Ixodes ricinus

Willie Burgdorfer’s Discovery

- 1946 accepted as grad student at U. of Basel
  - Mentor interested in borrelia species transmitted by ticks causing disease in sheep
Willie Burgdorfer’s Discovery

1946 accepted as grad student at U. of Basel
- Mentor interested in borrelia species transmitted by ticks causing disease in sheep
- “For the next 3 years, I dissected thousands of ticks” and studied the replication of bacteria in the tick

1951 hired by Dr. Gordon Davis (“the world’s best known borreliologist”) at Rocky Mountain Laboratory in Hamilton, MT to continue his studies on borrelia

Funding for borrelia research dries up
Willie Burgdorfer’s Discovery

• 1951 hired by Dr. Gordon Davis (“the world’s best known borreliologist”) at Rocky Mountain Laboratory in Hamilton, MT to continue his studies on borrelia
• Funding for borrelia research dries up
• RMSF—another tick-borne disease caused by Rickettsia rickettsii transmitted by the dog tick, Dermacentor variabilis

Willie Burgdorfer’s Discovery

• 1975 collaborates with Dr. Jorge Benach of the NYSHD because of an outbreak of RMSF on Long Island

Willie Burgdorfer’s Discovery

• 1975 collaborates with Dr. Jorge Benach of the NYSHD because of an outbreak of RMSF on Long Island
• In 1981 after examining 100’s-1,000s of dog ticks and not finding the cause of RMSF he asks Dr. Benach to send other ticks from Shelter Island—Ixodes dammini
• Sees an unusual parasite in the endolymph of 2 of 44 ticks
• Dissects the mid gut and he doesn’t see parasites, he sees…..
Willie Burgdorfer’s Discovery

- Recalls paper from 1949 on ECM of Afzelius and the postulation of a spirochetal cause; and discussion with Steere that Lyme arthritis is associated with Ixodes dammini.
- Dissects 124 more ticks and finds spirochetes in 60%
- Examines Ixodes ricinus and Ixodes pacificus ticks (Dr. Robert Lane from UC Berkeley) and finds spirochetes in them as well
Spirochetal Etiology of Lyme Disease

• Able to isolate spirochetes from humans with Lyme disease
• Able to isolate spirochetes from Ixodes dammini ticks
• Able to demonstrate an antibody response to the spirochetes in patients with Lyme disease

Borrelia burgdorferi

• Scientific break through
• Serendipity
• An accident
• The result of 35 years of research into the complex relationship of ticks, the bacteria they harbor and their interaction with humans

Clinical Manifestations

• Early Localized Disease
  — Usually occurs 7-10 days after the bite
  — Range 3-30 days
• Early Disseminated Disease
  — Weeks to months after the bite
• Late Disease
  — Months to years after exposure

Spirochetal Etiology of Lyme Disease

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• Able to demonstrate an antibody response to the spirochetes in patients with Lyme disease
  — 94% of patients with late manifestations of Lyme disease had positive antibody titers
Early Localized Disease

- Erythema Migrans
  - Seen in 70%-80% of cases
    - With or Without
- Nonspecific systemic symptoms
  - Fatigue
  - Anorexia
  - HA
  - Myalgias/arthralgias
  - Fever
- About 40% of patients have spirochetemia

Early Disseminated Disease

- Cutaneous Manifestations
  - EM at sites other than the original bite
- Neurologic (15% of UNTREATED patients)
  - Lymphocytic meningitis
  - Cranial nerve palsies (especially the facial nerve)
  - Peripheral neuropathy (motor and sensory)
  - Radiculopathy
- Heart (5% of UNTREATED patients)
  - Atrioventricular block
  - Myocarditis (rarely)
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Late Disease

- Arthritis (60% of UNTREATED patients)
  - Large weight bearing joints
  - Often recurrent
- Neurologic (5% of UNTREATED patients)
  - Encephalopathy with mild cognitive dysfunction
  - Radiculopathy
  - Chronic encephalomyelitis with spastic paraparesis, cranial neuropathy and cognitive impairment (rarely seen in the US—caused by B. garinii)

Diagnosis

- Early Disease
  - Because of slow rise in antibody titers (IgM 1-2 weeks; IgG 2-6 weeks), diagnosis is made clinically
  - If repeat titers after 4 weeks almost all positive
Diagnosis

• Late Stages
  – CDC recommends 2-stage serologic testing
    • Screening ELISA—very sensitive but not specific (syphilis, gingivitis, LYMErix, etc)
      – If negative—>no further testing
      – If positive/equivocal—>confirmatory test
    • Confirmatory Western Blot

Diagnosis of Late Manifestations

• Sensitivity of 2-tier testing in late Lyme disease is 100% and specificity is 99%
• “Therefore, current thinking is that all patients with objective neurologic, cardiac, or joint abnormalities associated with Lyme disease have serologic responses to B. burgdorferi”

New Approaches to Serodiagnosis

• V1sE C6 ELISA (C6 test)—measures antibodies to a protein-like sequence expressed in the sixth invariant region
  – More sensitive in early disease than 2-stage testing
  – Equal sensitivity and specificity in late stage disease
  – More sensitive for European strains

Commonly Asked Questions

• Persistence of antibodies
  – 10-20 years after successful treatment IgM (10%-20%) and IgG (25%-60%) can remain positive
• Early treatment
  – May abort antibody response
• Isolated positive IgM
  – Previously treated disease
  – False positive
• Reinfection
  – Recurrent episodes of EM almost always reinfection NOT relapse
  – Reinfection not reported in patients with Lyme arthritis
Commonly Asked Questions

- Lyme disease and pregnancy
  - Does not predispose to congenital anomalies or fetal demise
- Asymptomatic Lyme disease
  - Uncommon ≤ 5%
  - Treatment is controversial
    - I would weigh in on side of therapy

Clues to Diagnosis

- EM occurs 3-30 days after bite—most commonly in 7-10 days
  - Early reactions that fade are due to the tick bite and are not EM
- Ticks must feed 24-36 hours to transmit organism
- Know prevalence in your area
  - East Coast 60-70% infected
  - West Coast ≤ 5% infected
Table 2. Recommended antimicrobial regimens for treatment of patients with Lyme disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage for adults</th>
<th>Dosage for children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>500 mg 3 times per day²</td>
<td>50 mg/kg per day in 3 divided doses (maximum, 500 mg per dose)³</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>500 mg twice per day⁴</td>
<td>30 mg/kg per day in 2 divided doses (maximum, 500 mg per dose)⁴</td>
</tr>
</tbody>
</table>

Alternate oral regimens

- For patients weighing > 50 kg: 2 g intravenously every 6 h⁵
- For patients weighing ≤ 50 kg: 1 g intravenously every 6 h⁵

Table 3. Recommended therapy for patients with Lyme disease.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment</th>
<th>Duration, days range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tick bite in the United States</td>
<td>Doxycycline, 200 mg in a single dose⁶ (6 mg/kg in children ≤ 9 years of age and/or observation)</td>
<td></td>
</tr>
<tr>
<td>Early neurologic disease</td>
<td>Early neurologic disease</td>
<td>14-16 days</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>Meningoencephalitis</td>
<td>14-16 days</td>
</tr>
<tr>
<td>Central nervous palsy</td>
<td>Central nervous palsy</td>
<td>14-16 days</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Cardiac disease</td>
<td>14-16 days</td>
</tr>
<tr>
<td>Bacterial lymphocytosis</td>
<td>Bacterial lymphocytosis</td>
<td>14-16 days</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Lyme disease</td>
<td>14-16 days</td>
</tr>
</tbody>
</table>

- Acute without neurologic disease:
  - Oral regimens
  - 20 days

- Recurrent arthritis after oral regimen:
  - Oral regimens
  - 20 days or parenteral regimens
  - 14-16 days

- Antibiotic-refractory arthritis:
  - Symptomatic therapy

- Central or peripheral nervous system disease:
  - Parenteral regimens
  - 14-16 days

- Acrodermatitis chronica atrophicans:
  - Oral regimens
  - 20 days

- Post-Lyme disease syndrome:
  - Consider and evaluate other potential causes of symptoms; if none is found, then administer symptomatic therapy

Prevention

- Light colored protective clothing with shirt tucked into pants and pants tucked into socks
- DEET
- Permethrin spray for clothes
- Tick checks with prompt removal
- Antibiotic prophylaxis—200 mg doxycycline
  - Ixodes tick; fed for 36 hours; tick infection rate >20%; antibiotics given within 72 hours of tick removal

Proper Tick Removal

[Image of tick removal process]
Prevention

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Back to the Case

- A 35 yo woman is being evaluated for a 6 month h/o fatigue, arthralgias without arthritis and memory loss manifest as word-finding difficulties and forgetfulness.

- Lab tests
  - ELISA—equivocal
  - WB—positive IgM and negative IgG
- NOTE—FALSE (+) IgM ANTIBODY TITERS ARE COMMON

Controversies in Lyme Disease

- IDSA (Infectious Disease Society of America)
- Alternate view of the disease
  - LLMDs—Lyme literate physicians
  - ILADS—International Lyme and Associated Disease Society in US
    - Own set of guidelines
    - Supported by powerful patient advocacy groups
  - European equivalents
    - German Borreliosis Society
    - Dutch Lyme Association

How Far Apart Are The Views?

- IDSA
  - Clinical Manifestations
    - Skin
    - Joints (arthritis)
    - Neurologic system
    - Heart
- ILADS/LLMDs
  - Clinical Manifestations
    - Fatigue
    - Headache
    - Joint pain
    - Nerve pain
    - Sleep disturbance
    - Irritability and mood swings
    - Depression
    - Back pain
    - Abdominal pain/nausea
    - Diarrhea
    - Sleep disturbance
    - Irritability
    - Mood swings
    - Depression
    - Back pain
    - Nerve pain
    - Sleep disturbance
### How Far Apart Are The Views?

**IDSA**
- **Diagnosis**
  - 2-tier testing
- 1983 study using "crude" (early) assay 94% had a positive test
- 2008 article by Steere 99% with late disease had positive test

**ILADS/LLMDs**
- **Diagnosis**
  - Since there is no definitive test for Lyme disease, laboratory results should not be used to exclude an individual treatment
  - Lyme disease is a clinical diagnosis and tests should be used to support rather than supersede the physicians judgment
  - Diagnosis of Lyme by 2-tier confirmation fails to detect up to 90% of cases

### How Far Apart Are The Views?

**IDSA**
- **Therapy**
  - Longest duration 28 days
  - May need to re-treat some with persistent arthritis

**ILADS/LLMDs**
- **Therapy**
  - Rather than an arbitrary 30-day treatment course, the patients clinical response should guide duration of therapy
  - Combination and sequential therapy that can last months

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### How Contentious Is It?

**Very**

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**Antiscience and ethical concerns associated with advocacy of Lyme disease**


Lancet Infect Dis 2011;11:713-719
Antiscience and Ethical Concerns

- Antiscience groups and pseudoscientific practitioners
- Using unvalidated laboratory tests
- Various specialty laboratories in CA and KS that have been investigated and fined
- List current and former ILADS officers sanctioned by state medical boards or reprimanded by federal agencies

Counterpoint

- World Wide Lyme Rally & Protest May 10, 2013 Union Square, NYC—comments by Dr. Kenneth Liegner

Counterpoint

- “Chronic Lyme disease does not exist”
- There are at least four possibilities to explain why a person might hold this view:
  - They can be “dumb as bags of rocks”
Counterpoint

• “Chronic Lyme disease does not exist”
• There are at least four possibilities to explain why a person might hold this view:
  – They can be “dumb as bags of rocks”
  – They can be character-disordered, with exceeding rigid thinking, impenetrable, circular logic
  – They can be corrupt
  – They can be sociopaths

• One thing is for damn sure:
Counterpoint

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  - They can be corrupt
  - They can be sociopaths
- One thing is for damn sure: they are truly lousy clinicians

How Contentious Is It?

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

How Contentious Is It?

Shortly after the guidelines were published, AG Blumenthal sued the IDSA saying the guidelines “severely constrict choices and legitimate diagnosis and treatment options of patients”.

In addition, he accused the IDSA:
1. Several panelist had conflicts of interest
2. Panel refused to consider information about CLD
3. Refused to appoint panelists with divergent views on CLD

Law Suit Against IDSA

- Blumenthal ended suit in 2008
- Blumenthal & IDSA agreed to appoint a new committee vetted by both sides to review the data in the recommendations
- All day open public hearing to offer a forum for alternative views of the diagnosis and treatment of Lyme disease
  - 3 from Lyme advocacy groups
  - 4 ILADS/LLMDs
The Final Report--2010

• The Review Panel finds that the 2006 Lyme Guidelines were based on the highest-quality medical/scientific evidence available at the time and are supported by evidence that has been published in more recent years.
• The Review Panel did not find that the authors of the 2006 Lyme Guidelines had failed to consider or cite relevant data and references that would have altered the published recommendations.

Two Common Scenarios

• Scenario 1
  – Patient has documented Lyme disease and after therapy continues to have nonspecific symptoms
• Post-Lyme disease Syndrome (<10%)
  – Antibiotics – 4 RDBPCS
    • 3mos of abx v placebo — no difference in symptoms
  – Xenodiagnosis
    • Unable to infect laboratory strains of ixodes ticks
  – Immunology
    • T N response with high levels of IL-23 v usual T N1 response

Two Common Scenarios

• Scenario 2
  – Patient has nonspecific symptoms and no evidence of exposure to Borrelia burgdorferi i.e. antibody tests are negative
• This is where most of the “philosophical divide” occurs
  – They may have some underlying infection...BUT
    • I don’t think it is Lyme disease
    • I have seen no evidence that the symptoms respond to antibiotics

Some Observations

• Spirochetal diseases that affect humans
  – Relapsing fever (Borrelia recurrentis and other Borrelia spp)
  – Leptospirosis (Leptospira species)
  – Syphilis (Treponema pallidum)
  – Lyme disease (Borrelia species)
• Diagnosed with antibody studies &/or direct visualization
  – Relapsing fever—70% by visualization
  – Leptospirosis—55% by serology
  – Syphilis—95%-100% by serology
• Duration of therapy
  – Relapsing fever—single dose to 10 days
  – Leptospirosis—up to 7 days for severe disease
  – Syphilis—depends on stage of disease; neurosyphilis 10-14 days
Some Questions

- With all of the patients with “chronic Lyme disease” treated by LLMDs with long term antibiotics, why has there never been a randomized, double-blinded controlled study to see if antibiotics are any more effective than placebo?

Poly-ticks: Blue State versus Red State for Lyme disease-2004

Poly-ticks: Blue State versus Red State for Lyme disease-2004

Bush/Cheney vs. Kerry/Edwards

Lyme Disease/leaves

Tick

Southern Tick-Associated Rash Illness—STARI/Amblyomma americanum (Lone Star Tick)