Systemic and Ocular Manifestations of Lyme Disease

Presented by:
Dr. Michael Cooper, OD
Solinsky EyeCare, LLC
West Hartford, CT
coopadre@gmail.com

Disclosures

• The content of this presentation was prepared independently by Michael Cooper, OD without input from members of the ophthalmic community.
• Dr. Cooper is affiliated with Allergan, Alcon Surgical, BiTissue, Shire, JUVC, TearScience, Glaukos, Bausch + Lomb/VAIant, Oculel, Mediplast, and TearLab as a consultant/speaker.
• There is no direct financial or proprietary interest in any companies, products or services mentioned in this presentation.
• The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service.

The Ancient Tick: Palaeoborrelia dominicana

This tick trapped in ancient amber from the Dominican Republic is between 15 million and 20 million years old. Before it died, it was carrying the type of bacteria that causes Lyme disease.

Credit: Photo by George Poiar, Jr., courtesy of Oregon State University

The Walking Dead Origin Story?

Historical Relevance

• The oldest documented case of Lyme disease in humans comes from the famous 5,300-year-old ice mummy dubbed Otzi, discovered in the Eastern Alps about 25 years ago.
• Initially thought to be an uncommon arthritis condition, the first cluster of adult and pediatric cases were noted in 1975 in Old Lyme, CT.
• By 1977, the first 51 (mostly pediatric) cases of “lyme arthritis” were described, and the babesiosis parasite (black-legged) tick was linked to the transmission of the disease.
• In 1982, Borrelia burgdorferi, was discovered and a brochure was distributed by the arthritis foundation for public health purposes.
• Serology testing began in 1984.
Across the Pond

- Illness consistent with Lyme disease was reported in Europe as early as 1883.
- Lyme disease is now recognized as the most common vector-borne disease in both Europe and North America.

Picking Up Steam

- In 1987, Lyme Disease became a reportable condition to the CT Department of Public Health.
- 1988 marked the beginning of national media attention to the disease as more serious cases emerged throughout the US.

Let's back up though for a moment and consider this...

Serendipity: The Long Island Connection

Snackable Bits

- More than 22 variants caused by tick bites
- B. Miyamotoi is resistant to doxycycline, but exceedingly rare in (0.0004%)
- Powassan Virus is a Flavivirus, the latest to see press time—no current treatment available.
- Babesia and Anaplasma have seen tremendous incremental increase in the past 5-6 years.

Case Report #1

45 year old Caucasian male presents with bilateral blurry red eyes for the past month. He has a previous medical history of hypertension, elevated cholesterol, and a history of left arm. Upon further questioning, the patient reveals a past social history of marijuana use with cessation approximately 10 years ago. His vision is 20/25 in the right eye and 20/20 in the left eye, but "blurry".

B burgdorferi Genome

Fraser and Canisius et al. sequenced the genome in 1997-2000
- Comprises a linear chromosome of 151 Mb.
- At least 21 linear and circular plasmids, with a combined size of ~0.5 Mb.
- Consil in nature, minimal ability for recombination or transfer of plasmids (~1 Mb).

High genetic diversity within Borrelia populations and the disparity in the genetic structure between Borrelia and its tick vector are likely consequences of strong balancing selection on host Borrelia clones.
- Evolutionary and ecological impact in the last ice age to modern times about 20,000 years ago.
- Times the shifting environment help shape the biodiversity of tick to host.
**Spirochete Tricks**

*Immune evasion:*
- Consistent with their genomic characterization as intracellular pathogens for which antibody, complement, and phagocytes are critical for host defense.

*Spirochete Binding:*
- A tick salivary protein to shield against host antibodies and complement. Lyme borreliosis also expresses proteins that bind host factor H to further inhibit complement-mediated lysis.
- Antigenic variation of outer surface protein OspE is required for long-term survival of the pathogen in mammals, subsets specific antibody-mediated clearance.
- As infection progresses, Lyme borreliosis may reduce surface lipoprotein expression to further impair immune clearance.

"*Spirochete trickery: Remember they conksworn into tissue, leading to the chronic "arthritic" effect."

**B microti: What is it?**

*Classified in the Phylum Apicomplexa*
- It's an obligate parasite of the genus Babesia using the I. scapularis vector for host transmission.
- Although more than 100 Babesia species have been reported, relatively few have caused documented cases of human infection; these include (but are not limited to) B. microti, B. divergens, B. duncanii, and a currently unnamed agent designated MC-1.
- It's Unique and Small
  - 3 nuclear, 1 mitochondrial, and 1 apicoplast chromosomes encoding 3500 prokaryotes; several of which are genes specific.
  - The size of the organism may be due to regressive evolution from an ancestral line.
  - Genome-wide phylogenetic analysis indicate that B. microti is significantly distant from all species of Babesiae and Plasmodia and defines a new clade.
  - Mitochondrial genome is circular; no other member of Apicomplexa illustrate this pattern.

**Anaplasma Phagocytophilum**

*Infecting classification:*
- Anaplasmataceae, in the order Rickettsiales, and they are classified as c-proteobacteria.
- Was referred to as Ehrlichias until early 2003, now called Anaplasmosis.
- Obligate parasite.

*Small Genome and Missing Parts:*
- 1.0-1.5 Mb
- Undergo many rounds of reductive evolutionary processes as they have lost redundant genes.
- Devel ox dependence on the host cell for necessary functions.
- Gram negative organism that lacks peptidoglycan and lipopolysaccharides.
- Makes up for this deficiency by using the host to derive cholesterol to bulk up the cell wall.
- Cholesterol-rich cell walls may also function as ligands for stimulation of innate and acquired immune responses.

**Life Cycles**

- R. burgdorferi (Lyme)
  - The life cycle of I. scapularis generally lasts 2 years, during which the tick takes 3 blood meals, one each as larva, nymph, and adult.
  - Ticks are sterilized when they hatch from eggs; they acquire R. burgdorferi by feeding on infected reservoir hosts, principally mice, shrews, other small mammals and various species of birds.
  - Infected ticks are able to transmit the pathogen during subsequent feedings to new reservoir hosts, thereby perpetuating the natural cycle. Unlike reservoir hosts, humans are incidental or dead-end hosts that do not sustain large numbers of spirochetes in either tissues.
  - Adult ticks feed preferentially on deer, which are immune to R. burgdorferi but play an important role in the ecology of disease by transporting ticks and supporting tick populations.
Life Cycles: Part 2

- *Borreliosis (Babesiosis):
  - Life cycle involves two hosts, which include a rooker, primarily the white-footed mouse and a tick in the genus *Ixodes*. During a blood meal, a Babesia-infected tick introduces sporozoites into the mouse host. Sporozoites enter erythrocytes and undergo asexual reproduction (budpling).
  - The definitive host is the tick. Once ingested by an appropriate tick, germinates once and undergoes a sporogonic cycle resulting in sporozoites. Transovarial transmission has been documented for "large" *Babesia* species but not for the "small" *Babesia*, such as *B. microti*.
  - Humans enter the cycle when bitten by infected ticks, by introducing sporozoites into the host.
  - Multiplication of the blood-stage parasites is responsible for the clinical manifestations of the disease. Humans usually are dead-end hosts. However, human-to-human transmission is well recognized to occur via contaminated blood transfusions.
  - Became a notifiable disease in 2011.

Life Cycles: Part 3

*Anaplasma phagocytophilum:
- 10% of patients have serologic evidence of coinfection with lyme disease or babesiosis.
- The reservoir for *A. phagocytophilum* is primarily small mammals such as the white-footed mouse, Dusky-footed Wood rats, or others such as *Apodemus*, *Microtus*, or *Gliricidia* species.
- 3 feeding stages (enymph, nymph, and adult); each developmental stage feeds only once. Trans-stadial (i.e., enymph-nymph-adult) transmission occurs during nymph and adult feeding stages because larvae are unaffected.
**Epidemiology**

- Most common reported vector-borne disease coming in at 30,000 reported cases per year in the US.
  **\*The true number is likely 10-fold higher at 300,000 cases\***

- Lyme disease has been a nationally notifiable condition in the United States since 1991.

- It is important to note that surveillance data are captured by county of residence, not county of exposure.

Case definitions are reviewed periodically, as in 1996 to clarify laboratory criteria and again in 2006 to allow reporting of probable cases.

**US Incidence**

- During 1992 to 2013, US states and territories reported 430,540 confirmed Lyme disease cases to the CDC.

- Annual case counts increased approximately 3-fold during the period, from 9908 confirmed cases in 1992 to 27,203 confirmed and 9104 probable cases in 2013.

**\*For Vermont, the incidence is the highest in the US (78.4). As of 2015, the CDC reported the number of cases confirmed is 491 and probable is 279.\***

- Dating back to 2005, there were only 54 reported cases.

**Fast Facts**

- In 2015, 55% of confirmed Lyme disease cases were reported from 14 states:

- Heavier concentration of cases are noted most in the Northeast and Upper Midwest.

- Areas of hyperendemicity with county-level rates in excess of 200 per 100,000 population include Windham (County in Connecticut, Where I practice).

  *Remember, this is just Borelia burgdorferi, not its 22 other brothers and sister variants globally.*

**Domestic and Global "Friends"**

<table>
<thead>
<tr>
<th>Genus</th>
<th>Name</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. burgdorferi</em></td>
<td><em>B. afzelii</em></td>
<td>Europe</td>
</tr>
<tr>
<td><em>B. burgdorferi</em></td>
<td><em>B. garinii</em></td>
<td>Europe</td>
</tr>
<tr>
<td><em>B. burgdorferi</em></td>
<td><em>B.idia</em></td>
<td>Europe</td>
</tr>
<tr>
<td><em>B. burgdorferi</em></td>
<td><em>B. valaisiana</em></td>
<td>Europe</td>
</tr>
<tr>
<td><em>B. burgdorferi</em></td>
<td><em>B. junnieri</em></td>
<td>Europe</td>
</tr>
<tr>
<td><em>B. burgdorferi</em></td>
<td><em>B. malayi</em></td>
<td>Asia</td>
</tr>
<tr>
<td><em>B. burgdorferi</em></td>
<td><em>B. miyamotoi</em></td>
<td>Asia</td>
</tr>
</tbody>
</table>

**Global Incidence**

- In Europe, ticks infesting in adult ticks tend to be higher in Eastern as compared with Western Europe, and the relative frequency of infection with the different genospecies seems to vary across regions.

- Ticks collected in the northern and eastern regions of Europe (e.g., Scandinavia, Baltic states, Czech Republic, Slovakia, Croatia, Bulgaria) are more likely to carry *B. garinii*, whereas those from Western European countries (e.g., Austria, Switzerland, United Kingdom) are more likely to be infected with *B. afzelii*.

- The distribution of species also extends into the northern reaches of Morocco, Algeria, and Tunisia, where they are most often infected with *B. afzelii*.

**\*Reporting practices vary throughout the EU and non-EU countries.\***
Global Incidence

Asia

- The distribution of *I. persulcatus*, the principal vector in Asia, extends from Western Russia, where it overlaps with *I. ricinus*, eastward through Mongolia and China to the Pacific Ocean and Japan. This species transmits *B. gibsoni* as well as Asian and European variants of *B. burgdorferi*. It is not known to transmit *B. afzelii*.

- In Russia, official records on Lyme borreliosis have been kept since 1992 with reported incidence in endemic areas generally ranging from 5 to 10 per 100,000 population. However, considerably higher rates are reported in areas northeast of Moscow in Kirovsk Oblast, in the Sverdlovsk (Sverd) region, and Western Siberia.

- *B. afzelii* strains have been isolated from rodents and ticks in at least 20 provinces in China, including Heilongjiang in the northeast, Xinjiang in the northwest, and Guizhou, Hunan, and Hejiang provinces in Southern China. *B. burgdorferi* is not known to infect any tick species in China. *B. afzelii* and *B. burgdorferi* are among the isolated strains, and human illness has been detailed among forestry workers in Heilongjiang Province.
Case Report #2

17-year-old Hispanic male presents for consultation at our office with “dry eyes” and lower leg extremity joint pain and stiffness for the past 6 months. Before leaving for vacation to Spain, his parents brought him in at a local ED who diagnosed joint pain associated with the rigors of his soccer training. Upon further questioning, the patient mentioned that he was very concerned about what was causing the pain and wanted further clarification. His vision was 20/20 in both eyes, but no voice was made that he was constantly thinking before reading the letters.

I. What other questions would you ask?
II. Are we the only providers she has seen?
III. What ophthalmological information is pertinent to collect?
IV. How would you manage and treat this patient?
**The Great Imitator**

Here are just some of the conditions that can be confused with Lyme:
- Acneiform disease
- Juvenile rheumatoid arthritis
- Viral meningitis
- Multiple sclerosis
- Bell’s palsy
- NLT
- Encephalitis
- Sarcoidosis
- Bipolar Disorder

---

**What I Order for Lyme**

- From my humble perspective, a Lyme filter even with a reflex is not helpful.
- Go for the Gold: The antibodies (IgG and IgM) (Lyme Disease) need at least 5 IgG bands to be a positive result.
- Babesiosis Reference Range:
  - Babesia microti Antibodies IgG: 1:64 Babesia microti Antibodies IgM: 1:20

---

**Babesiosis Treatment**

Atovaquone 750 mg tab bid po PLUS Azithromycin

On the first day, give a total dose in the range of 500-1000 mg orally; on subsequent days, give a total daily dose in the range of 500-1000 mg.

- OR
- Chloroquine 600 mg orally 2 times a day 500 mg intravenously 4 times a day

*PLUS* Quinine 40 mg orally 1 tab 12 hr

[this combination is the standard of care for severely ill patients.]

Treatment Time: 7-10 days

**New Drug Candidates:** Fosmidomycin and FR900098

---

**Special Note from CDC**

- Remember what I just said about the title?
- Still order the enzyme immunoassay (EIA).
- In CT, it’s automatic, but may vary by state.
- Conform to the CDC guidelines to stay within the appropriate practice pattern.
- Avoid ordering excessive bloodwork as this has been found to be insufficient in diagnosis and treatment.
**Anaplasmosis Treatment**

Doxycycline is the first line treatment for adults and children of all ages:

- **Adults:** 100 mg every 12 hours
- **Children under 40 kg (90 lbs):** 2.2 mg/kg body weight given twice a day
- **Treatment Time:** 14 days

In B. burgdorferi coinfections, children younger than 1 year:

- Doxycycline should be continued until the patient is afebrile for 3 days, with the remainder of the 14-day course completed with an alternative agent active against B. burgdorferi (eg, amoxicillin or cefuroxime axetil) to minimize the risk of relapse.
- Patients who fail to respond clinically to doxycycline monotherapy after 72 hours should be evaluated for an alternative diagnosis or the possibility of Relapsing Fever.

**Prevention**

1. **Clothing**
   - Tight-fitting clothes
   - Hats
   - Long sleeves and pants with elastic bands

2. **Permethrin (DEET)**
   - Be wary of herbal remedies

3. **Inspecting Pets**

4. **Respect Young Children**
   - Removing ticks promptly

**Secret Weapon: Guinea Fowls**

African Guinea Fowls have proven to be effective in removing ticks by consumption within the grass or weeds in your yard.

*They also "feralize" your lawn!

**Proper Tick Removal Technique**

*Removing the tick from the abdomen is incorrect since it will lead to the tick being more of the parasite into the wound site.*

**Be a Role Model**

1. **Techniques to share the progress with your patient**
   - Direct information is paramount

2. **Developing a relationship with a compounding pharmacy**
   - Periodically calls to ensure relationship is maintained.

3. **How to co-manage with infectious disease specialist and PCPs**
   - Always send letters.
   - Fill out appropriate paperwork

4. **Follow-up protocol in my practice**