Lyme Disease and MS: Fact and Fiction

P K Coyle, M.D.
Professor and Vice Chair (Clinical Affairs)
Director, MS Comprehensive Care Center
Stony Brook University Medical Center, Stony Brook, NY

Disclosures

Consultant: AbbVie, Accordant, Acorda, Bayer, Biogen, Genentech/Roche, Genzyme/Sanofi, Novartis, Serono, Teva

Research: Actelion, Novartis, Opexa
These are 2 distinct and very different disorders
- Usually they are easy to tell apart
- More difficult is what to do with the neurologic patient with unexpected positive Lyme serology
- Can infection be a trigger for MS?

<table>
<thead>
<tr>
<th></th>
<th>Lyme Disease</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>M&gt;F</td>
<td>F&gt;&gt;M</td>
</tr>
<tr>
<td></td>
<td>Ages 5-14, 40-50</td>
<td>Ages 15-50</td>
</tr>
<tr>
<td></td>
<td>Tick exposure</td>
<td>Year round</td>
</tr>
<tr>
<td></td>
<td>Seasonality</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>Systemic issues</td>
<td>Limited to CNS</td>
</tr>
<tr>
<td></td>
<td>Skin, joint, heart, CNS/PNS</td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Lyme seropositive</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Generally normal</td>
<td>Almost always abnormal</td>
</tr>
<tr>
<td>CSF</td>
<td>↑ Cells, protein</td>
<td>+Oligoclonal bands</td>
</tr>
<tr>
<td></td>
<td>Intrathecal Lyme antibody production</td>
<td>↑ IgG index</td>
</tr>
<tr>
<td>Therapy</td>
<td>Appropriate antibodies</td>
<td>Appropriate DMT</td>
</tr>
</tbody>
</table>
Lyme disease cases can be seronegative
Spirochetes have been isolated from normal CSF
Lyme disease responds to appropriate antibiotics
You can get reinfected
A minority of patients will remain IgM seropositive

Most Lyme disease patients are seropositive
First tier tests have 20-25% false positive rate
There is no precedent for human infection requiring prolonged antibodies
Following the Lyme antibody titer will tell if the patient is responding to therapy
Suspected EM must be confirmed by positive serology
Negative serology rules out Lyme disease
Persisting atypical, biofilm, cystic forms cause infection
Lyme CSF PCR is helpful

Bacterial infection due to the spirochete *Borrelia burgdorferi*
Responds to antibiotics
Spirochetal infections share certain properties
Human infections involve:
- syphilis (*Treponema pallidum*)
- leptospirosis (*Leptospira interrogans*)
- relapsing fever (*Borrelia recurrentis*, and other *Borrelia* species)
- Lyme disease (*Borrelia burgdorferi*)

Spirochetes produce infection in stages:
- Relapsing, remitting illness
- Early blood stream invasion

*Infections Nerv Syst 1987;43

Limited organisms following dissemination

Damage to blood vessels/vasculopathy

Infection may not lead to clinical illness; may be contained naturally

Neurotropism (early CNS invasion, with latency and persistence)
- typically asymptomatic, with later symptoms in a subset

No precedent to require long term antibiotics

*Infections Nerv Syst 1987;43
Lyme disease caused by 30 distinct species

*B. burgdorferi* sensu stricto causes all neurologic cases in North America

*B. garinii* causes most neurologic cases in Eurasia, *B. afzelii* causes some cases

Neurotropic strains (species, subtypes) recognized

---

*B. Burgdorferi*

*B. burgdorferi* sensu stricto (North American species), and *B. afzelii, B. garinii, B. burgdorferi* sensu stricto, *B. spielmanii, B. bavariensis* (European species)

*B. afzelii* (skin), *B. garinii* (neurotopic), *B. burgdorferi* (arthritogenic)

Organism shows almost complete lack of biosynthetic pathways (depends on environment for nutrition)

*Lancet* 2012; 379:461
Culture requires special media, and takes several weeks

Dissemination, tropism may relate to species, genotypic issues, inoculum size, virulence, host immune factors

*Lancet 2012; 379:461

Most common vector-borne infection

CDC estimates 300,000 cases annually in United States

- highest incidence ages 5-14 years, 40-50 years; males > females

Virtually all human transmissions involve tick bite (placental; blood transfusion; mosquito, fly, flea, lice bite)

*JAMA 2013; 310:1110
95% (of 2013 cases) from 14 states (Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, Wisconsin)

Tick involves blacklegged (deer) tick, *Ixodes scapularis* (Northeast, Mid-Atlantic, North Central United States) and Western blacklegged (*I. pacificus*) tick (Pacific coast)

Dog ticks, lone star ticks, Rocky Mt. wood ticks do not transmit

*JAMA* 2013; 310:1110
### North American vs. Eurasian Lyme Disease

<table>
<thead>
<tr>
<th>Features</th>
<th>US</th>
<th>Eurasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major genospecies</td>
<td>B. burgdorferi sensu stricto; neurotropic subtypes</td>
<td>B. garinii, occ B. afzelii</td>
</tr>
<tr>
<td>Extraneural involvement</td>
<td>Arthritis common</td>
<td>Unique skin lesions (lymphocytoma, ACA)</td>
</tr>
<tr>
<td>Neurologic involvement</td>
<td>Less common; 15%</td>
<td>More common; 35%+</td>
</tr>
<tr>
<td>Major neurologic syndrome</td>
<td>Facial nerve palsy</td>
<td>Acute painful radiculoneuritis; most chronic encephalomyelitis cases</td>
</tr>
<tr>
<td>CSF findings</td>
<td>Much less inflammatory</td>
<td>Very inflammatory</td>
</tr>
<tr>
<td></td>
<td>Intrathecal anti-B. burgdorferi antibodies ≤60%</td>
<td>Intrathecal anti-B. burgdorferi antibodies, in close to 100%</td>
</tr>
<tr>
<td></td>
<td>Oligoclonal bands, intrathecal immunoglobulin production ≤20%</td>
<td>Oligoclonal bands, intrathecal immunoglobulin production in most</td>
</tr>
<tr>
<td>Antibiotic responsiveness</td>
<td>Intravenous cephalosporin</td>
<td>Oral doxycycline reported as effective</td>
</tr>
<tr>
<td></td>
<td>(ceftriaxone) preferred; generally for 4 weeks</td>
<td>as intravenous antibodies</td>
</tr>
</tbody>
</table>

### Clinical Lyme Disease

**Early local infection (≤30 days post tick bite)**
- erythema migrans (EM)
- summertime flu (fatigue, chills, fever, headache, arthragias/myalgias, lymphadenopathy)

**Early disseminated infection (≤90 days post tick bite)**
- multifocal EM
- neurologic
- rheumatologic (pain and swelling of large joints)
- cardiac (palpitations, dizziness, heart block)
Clinical Lyme Disease

- Late state infection (≥90 days after tick bite)
  - neurologic
  - rheumatologic/arthritic

Neurologic Lyme Disease

- Early local infection
  - CNS seeding can precede notable EM

- Early disseminated infection
  - aseptic/viral meningitis
  - Bell’s palsy
  - acute intrascapular pain, spine pain with dermatomal/myotomal features
  - acute cerebellar syndrome, meningoencephalitis
Evaluated N=161 European patients with EM and moderate/severe neurologic signs and symptoms who underwent LP

- N=31 (19%) had CSF ↑ WBCs

CSF pleocytosis/meningitis associated with radicular pain, larger EM, meningeal signs, peripheral facial palsy, sleep disturbances, low back pain

- not distinguished by headache, cognitive issues, vertigo, paresthesias, fatigue/malaise

*Clin Infect Dis 2013; 57:501

CSF cultures + in 6/127 (4.7%) without antibiotics, 0/34 with antibiotics

- + 5/31 (16.1%) with CSF pleocytosis, 1/130 without

CSF + intrathecal borrelial antibodies in 19/28 (67.9%) with CSF pleocytosis, 10/123 (8.1%) without
Late stage infection
- encephalopathy (typically subtle)
- chronic polyradiculopathy
- encephalomyelitis (very rare)

Intracranial hypertension in children/adolescents (with abnormal CSF)
- Psychiatric disease
- Stroke, vasculitis
Ultimately a clinical decision
Based on suggestive signs and symptoms
- spine pain
Possible exposure to infected ticks
EM considered pathognomonic clinical feature (no laboratory testing required)

Single most valuable laboratory test is positive serology (to document exposure)
- culture is not practical
- PCR not approved (? help in synovial fluid)
- no established antigen test
Can be done on blood, CSF (synovial fluid considered unvalidated)

Two step process (first tier ELISA; second tier immunoblot)

First tier test has false positive rate as high as 20-25%

Second tier western/immunoblot has much higher specificity
  - false + rate 1.5-8%
  - CDC only recommends IgM for first 4-6 weeks of illness

IgM western blot becomes positive first (2 weeks)

Subset of patients show persistent IgM positivity

Typically evolves to positive ELISA and IgG western blot

No standardization for first tier ELISA
Immunoblot standardized based on bands that are counted

- IgM 2 of 3: 23, 39, 41 kD
- IgG 5 of 10: 18, 23, 28, 30/31, 39, 41, 45, 58, 66, 93 kD

CDC considers IgM immunoblot only meaningful in first 4-6 weeks; they do not recommend blot unless first tier test positive, or borderline/equivocal

Lyme C6 peptide antibody test (based on reactivity to recombinant protein, variable major protein-like sequence expressed lipoprotein (C6VlsE) has ↓ specificity vs. 2 tier testing; better for European strains

Lyme antibodies can persist for many years (cannot follow for therapeutic response)

Seronegative cases can occur (early abortive antibiotics)
**Unvalidated Tests**

- LUAT (discredited – Igenix)
- Cell wall deficient/cystic, biofilm, L- forms of *B. burgdorferi* (by culture, staining, cell sorting)
- Quantitative CD57 lymphocyte assays (NK cells)

*CID 2014; 58:663

---

**Neurologic Lyme Disease**

- CSF: intrathecal Lyme antibody production, pleiocytosis, ↑ protein
- MRI: abnormal 25%; nonspecific
- Electrophysiologic: evidence for polyradiculoneuropathy
- Cognitive function testing: objective deficits
Cerebral perfusion (blood flow) reported in neurologic Lyme disease

- frontal, temporal, parietal
- global
- periventricular

Improvement post antibiotics

Similar patterns reported in CFS, depression, trauma, ischemia, narcotic use
Bacterial infection that responds to appropriate antibiotics

EM therapies (10-21 days) involve

- doxycycline 100 mg twice a day; cannot use under age 8 or during pregnancy; also treats anaplasmosis
- amoxycillin 500 mg three times daily
- cefuroxime axetil 500 mg twice a day

Neurologic Lyme disease

- ceftriaxone 2 grams daily IV for 14-28 days

Lyme arthritis, carditis

- oral or parenteral antibiotics for 14 (carditis) or 28 (arthritis) days
**IV Antibiotic Therapy**

- Consider mid or PICC line
- Infused over 30 minutes once a day
- Acidophilus recommended to ↓ *C. difficile* colitis
- Counselling on line infection/clotting, GI issues, gall bladder drug biliary sludge
- No routine bloods done
- Personal preference for 28 days
- Peripheral facial palsy, late encephalopathy considered CNS infection

**Neurologic Lyme Disease Pathophysiology**

- Organisms extracellular but tissue tropic, often extracellular collagen
- Neuropathology relatively mild
  - CNS: mild meningeal, perivascular inflammation; occasional spirochetes; microglial nodules; mild spongiform changes (rare obliterative vasculopathy, demyelination, granulomatous changes)
  - PNS: axonal injury; inflammation; angiopathy
  - Muscle: focal myositis; interstitial inflammation; focal necrosis; rare spirochetes
 Spirochete neurotropism, neurovirulence

* B. burgdorferi* produces host immune system activation, some autoreactivity

**Other Ixodid Tick Borne Diseases**

- Anaplasmosis
- Babesiosis
- *Borrelia miyamotoi* (fever, headache, myalgias)
- Powassan disease (virus; encephalitis and meningitis; 10% mortality, 50% morbidity rates)
- Tick-borne encephalitis virus (Eastern Europe, Asia)
- *Ehrlichia-muris* agent
- *Bartonella henselae*
- *Rickettsia* species
About 10-20% of treated Lyme disease patients experience prolonged fatigue, pain, joint/muscle aches
- delayed treatment; ↑ symptoms/signs; incomplete recovery at 4 months
- Can last >6 months in small minority
- This has been seen with other infections

Cause is unknown (may be multifactorial)
- immune mediated vs. persistent infection
- Recent study suggested high Th17-associated response, ↑ IL-23 with autoantibodies, ↑ IFNα associated with chronic issues
Case 1. Amy

Amy is a 21 year old college student. She presents with 3 days of right eye pain and ↓ vision. Exam is consistent with an optic neuritis. Blood work shows positive Lyme ELISA and IgM western blot. Brain MRI shows enhancement of the right optic nerve, and 3 periventricular ovoid lesions 4-6 mm in size.

- Does Amy have Lyme disease?
- What further tests would you do?
- How would you treat Amy?

Case 2. Fred

Fred is a 45 year old man with PPMS. He is not on any DMT, but several symptomatic therapies.

Fred has just noticed a rash on his torso that expanded in size dramatically over 3 days. It is a bull’s eye, diagnosed as EM. He is having mild headache and stiff neck.

- Does Fred have Lyme disease?
- What further tests would you do?
- How would you treat Fred?
Definitive diagnosis of neurologic infection
- CSF proteomal studies
- *B. burgdorferi* strains

Optimized therapy
- ? penetrating regimen

Persistent symptoms
- etiology/best management

Resolve: If there is possibility of CNS infection, is it best to give definitive penetrating antibiotic IV course?