# Lyme Disease and MS: Fact and Fiction

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## Disclosures

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# Lyme Disease and MS

- 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?

| | Lyme Disease | MS |
|---|---|---|
| **Demographics** | ▪ M>F<br>▪ Ages 5-14, 40-50<br>▪ Tick exposure<br>▪ Seasonality | ▪ F>>M<br>▪ Ages 15-50<br>▪ Year round |
| **Clinical** | ▪ Systemic issues<br>▪ Skin, joint, heart, CNS/PNS | ▪ Limited to CNS |
| **Laboratory** | ▪ Lyme seropositive | ▪ Lyme seronegative |
| **MRI** | ▪ Generally normal | ▪ Almost always abnormal |
| **CSF** | ▪ ↑ Cells, protein<br>▪ Intrathecal Lyme antibody production | ▪ +Oligoclonal bands<br>▪ ↑ IgG index |
| **Therapy** | ▪ Appropriate antibodies | ▪ Appropriate DMT |

## Fact

- 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

## Fact

- 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

## Fiction

- 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

## Lyme Disease and MS

- Bacterial infection due to the spirochete *Borrelia burgdorferi*
- Responds to antibiotics
- Spirochetal infections share certain properties

# Spirochetal Infections*

- Human infections involve
  - syphilis (*Treponema pallidum*)
  - leptospirosis (*Leptospira interrogans)*
  - relapsing fever *(Borrelia recurrentis,* and other *Borrelial* species)
  - Lyme disease *(Borrelia burgdorferi*)
- Spirochetes produce infection in stages
- Relapsing, remitting illness
- Early blood stream invasion

**Infections Nerv Syst* 1987;43

# Spirochetal Infections*

- 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

# Demographics

- 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

# B. Burgdorferi*

- 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

# Demographics/Disease Transmission*

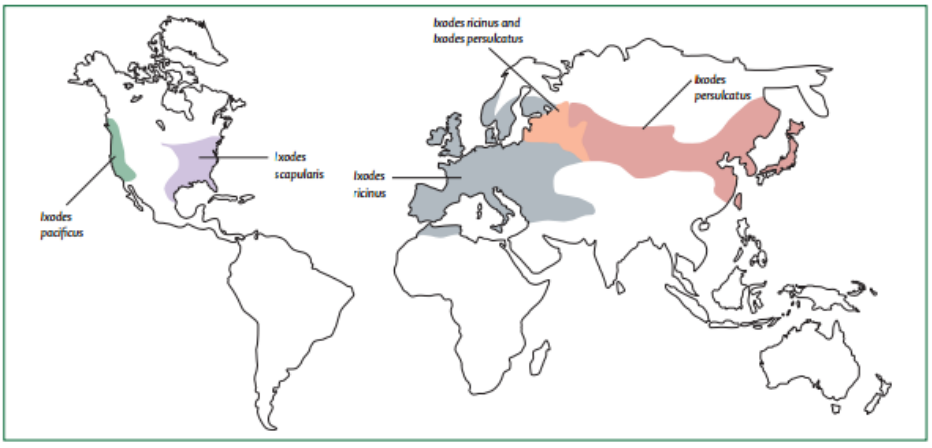
- Most common vector-borne infection
- CDC estimates 300,000 cases annually in United States
  - highest incidence ages 5-14 years, 40-50 years; males>females
- Virtually all human transmissions involve tick bite (? placental; ? blood transfusion; ? mosquito, fly, flea, lice bite)

*_JAMA_ 2013; 310:1110

# Demographics/Disease Transmission*

- 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

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

# 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/arthritis

## 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

# EM with Meningitis*

- 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

# EM with Meningitis*

- 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

**Clin Infect Dis* 2013; 57:501

## Neurologic Lyme Disease

- Late stage infection
  - encephalopathy (typically subtle)
  - chronic polyradiculopathy
  - encephalomyelitis (very rare)

## Unusual Neurologic Manifestations

- Intracranial hypertension in children/adolescents (with abnormal CSF)
- Psychiatric disease
- Stroke, vasculitis

## Lyme Disease Diagnosis

- 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)

## Lyme Disease Diagnosis

- 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

## Lyme Serology

- 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

## Lyme Serology

- 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

## Lyme Serology

- 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 Serology

- 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

| Event | Result | Ref. Range |
|---|---|---|
| Lyme Serology Pair, Fluid # | 42514 | |
| Lyme Serology Pair, Fluid Interpretation | * (a) REACTIVE | (NR - ) |
| Lyme Serology Pair, Fluid Patient O.D. | 0.287 | |
| Lyme Serology Pair, Fluid Brdln Cutoff | 0.118 | |
| Lyme Serology Pair, Fluid Reac Cutoff | 0.151 | |
| Lyme Serology Pair, Serum Interpretation | * (a) REACTIVE | (NR - ) |
| Lyme Serology Pair, Serum Patient O.D. | 0.236 | |
| Lyme Serology Pair, Index | * H 1.22 | (<1.1 - ) |
| Lyme Western Blot, # | 167 | |
| Lyme Western Blot, IgM Serum | (a) INDETERMINATE | (NEG - ) |
| Lyme Western Blot, IgM Bands (Kda), Ser | * 41 | |
| Lyme Western Blot, IgG Serum | (a) POSITIVE | (NEG - ) |
| Lyme Western Blot, IgG Bands (Kda), Ser | * 18,28,39,66,93 | |
| Lyme Western Blot, Serum Comment | * Lyme Western Blot, Serum Comment | |
| Lyme Western Blot, Fluid # | 167 | |
| Lyme Western Blot, IgM Fluid | * NEGATIVE | (NEG - ) |
| Lyme Western Blot, IgG Fluid | (a) POSITIVE | (NEG - ) |
| Lyme Western Blot, IgG Bands (Kda), Fld | * 18,28,39,41,58,66,93 | |
| Lyme Western Blot, Fluid Comment | * Lyme Western Blot, Fluid Comment | |

# Brain SPECT

- ↓ 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

## Lyme Disease Therapy

- 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

## Lyme Disease Therapy

- 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
- Counselled 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

## Neurologic Lyme Disease Pathophysiology

- 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)
- *Ehrilichia-muris* agent
- *Bartonella henselae*
- *Rickettsia* species

## Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome*

- 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

**Joint Bone Spine* 2014; 81:110-111

## Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome*

- 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

**Joint Bone Spine* 2014; 81:110-111

## 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?

# Gaps/Future Issues

- 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?