Disclosure

- Commercial: none

- Consultant:
  - Legal expert testimony defending health care providers in ‘failure to diagnose nervous system Lyme disease’ cases

- Commercial products:
  - Antimicrobials, generic name only
Lyme disease: A neurologist’s perspective

John J. Halperin MD

October 9, 2015
In the beginning...

Charles Lutwidge Dodgson
– 19th century English mathematician, logician & writer

(Lewis Carroll)

When I use a word, it means just what I choose it to mean, neither more nor less.
Daniel Cameron, MD, MPH, the upcoming president of ILADS and the chief author of the ILADS Lyme treatment guidelines, charged that the IDSA and AAN guidelines don't take into account evidence-based medicine. He described that as a treatment approach that allows physicians to take into account their own values, clinical expertise, and patient values in addition to published research from level 1 studies.


- class 0: things I believe
  - class 0a: things I believe despite the available data
- class 1: RCCTs that agree with what I believe
- class 2: other prospective data
- class 3: expert opinion
- class 4: RCCTs that don’t agree with what I believe
- class 5: what you believe that I don’t

Bleck BMJ 2000;321:239
Lyme disease: reality, misconceptions, tensions

Clinical/ Patient symptoms
- Specific + non-specific
- Non-specific / MUS

Physician thought process
- Evidence Based Medicine
- Anecdotal observation

Contextual bias
- Science
- Advocacy/Non-scientific

Neurology
- Neurophobia/ agnosia
- Neuro-behavior
Lyme disease – *History, Geography*

**Europe:**
- 1910: ECM (Afzelius)
- 1922: Garin, Bujadoux: tick & meningoradiculitis
- 1941: Bannwarth: meningoradiculitis & rheumatism
- 1980’s: Ackermann: encephalomyelitis
- 1984: *Borrelia burgdorferi*

**US:**
- 1950’s: Montauk knee
- 1970: Scrimenti: ECM
- 1975: Lyme arthritis
- 1979: Reik: Neuro-LD
- 1982-3: *Borrelia burgdorferi*
Organism

- *Borrelia burgdorferi sensu lato*
  - *B. burgdorferi sensu stricto* (US & Europe)
  - *B. garinii* (Europe)
  - *B. afzelii* (Europe)
  - *(B. spielmanii* (Europe))

Courtesy, CDC
Ixodes (Scapularis) & friends

Courtesy, CDC
Lyme disease - Geography

Europe:
- Max incidence: 130/100,000 (Austria)
- Neuro: 10-12%
- EM: 65-75%
- Arthritis: 8%
- Facial palsy: 5%
- Radiculitis: 5%
- Meningitis (alone): 4%

US: (MMWR 2004; 53:365-9)
- Max incidence: 133/100,000 (CT)
- Neuro: 12%
- EM: 68%
- Arthritis: 33%
- Facial palsy: 8%
- Radiculopathy: 4%
- Meningitis or encephalitis: 1%
- Heart block: 1%

Reported Clinical Findings for Lyme Disease Cases
United States, 1992-2004

Note: Percentages represent clinical findings among 119,955 patients for whom at least one symptom was reported. These total more than 100% because more than one clinical finding was reported for some patients.
Common misconceptions about Lyme disease

- Role of testing vs. Clinical Diagnosis
- What is (is not) nervous system involvement?
- Treatment
- Case definition: CDC vs clinical
Lyme disease - Clinical

- **Skin**
  - Erythema migrans
  - acrodermatitis chronica atrophicans, borrelia lymphocytoma

- **Cardiac**
  - Conduction abnormalities, otherwise unexplained

- **Rheumatologic**
  - Relapsing large joint oligoarthritis

- **Neurologic**
  - ......
Two tier testing (US):

+ ELISA:
  - Quantitates total Ab to *Bb*
  - Very sensitive
  - Fairly specific
  - False positives evaluated by Western blot

+ Western blot:
  - Measures Ab to *Bb*’s constituent proteins
  - Very specific
  - To be used primarily with + or borderline ELISA
Western blot criteria (US):

- IgM:
  - 2 of 3
  - 23, 39, 41 kD
  - Defined in seropositive individuals
  - ONLY used in 1st 2-6 weeks of infection

- IgG:
  - 5 of 10
  - 18, 23, 28, 30, 39, 41, 45, 58, 66, 93 kD
  - Defined primarily in seropositive individuals
**Lyme disease - Laboratory**

+ **“False” negatives - biologic:**
  + In any infection, antibody-based tests are initially negative, until sufficient antibody generated.
  + *Old hypothesis:* Can early incomplete treatment with antibiotics permanently blunt antibody response? (No)

+ **“False” positives - biologic:**
  + Related infections (lues, relapsing fever)
  + Nonspecific B cell expansion
  + Once +, unaffected by treatment - i.e. usually remains + after cure

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**Seronegative Lyme disease. Dissociation of specific T- and B-lymphocyte responses to Borrelia burgdorferi**

*RJ Dattwyler, DJ Volkman, BJ Luft, JJ Halperin, J Thomas, and MG Golightly*
Interpreting lab tests - statistics (1)

Screen: sensitivity only, or virtually dichotomous

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Applies to</td>
<td>Lab Samples</td>
</tr>
<tr>
<td>Assumption</td>
<td>Healthy</td>
</tr>
<tr>
<td>Statistic</td>
<td>Mean+/− 3SD</td>
</tr>
<tr>
<td>Positive</td>
<td>0.1% of nl samples</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Warning, lTed specificity</td>
</tr>
</tbody>
</table>
Interpreting lab tests - statistics (2)

Diagnostic: sensitivity vs specificity: ROC

<table>
<thead>
<tr>
<th>Applies to</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumption</td>
<td>Ascertainable risk</td>
</tr>
<tr>
<td>Statistic</td>
<td>ROC: Sensitivity/specificity</td>
</tr>
<tr>
<td>Positive</td>
<td>83%/95%-&gt;99%/ca 90%</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Diagnostic specificity</td>
</tr>
</tbody>
</table>

Receiver operating characteristic/curve (ROC): true +/all +(TPR = true positive rate=sens) vs. false +/all -(FPR = false positive rate), at various threshold settings.
Interpreting lab tests - statistics (3)

Diagnosis: Bayesian statistics

<table>
<thead>
<tr>
<th>Applies to</th>
<th>Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumption</td>
<td>Varying <em>a priori</em> risk</td>
</tr>
<tr>
<td>Statistic</td>
<td>Bayesian</td>
</tr>
<tr>
<td>Positive</td>
<td>( f(a\ priori\ risk) )</td>
</tr>
</tbody>
</table>

Bayes' theorem links the degree of belief in a proposition before and after accounting for evidence.

Statistical + \( 1/1,000 \)
Incidence \( 1/10,000 \)
Common misconceptions about Lyme disease

- “Lyme disease is a clinical diagnosis”

- Testing:
  - Seronegative Lyme disease
  - Effect of concurrent antibiotics on test results
  - Western blot interpretation:
    - With vs without ELISA
    - Surveillance vs clinical
    - Basis for criteria
  - IgM seropositivity
  - Post treatment seropositivity
Common misconceptions about Lyme disease

+ “Lyme disease is a clinical diagnosis“ – Not exactly

+ Testing:
  + Seronegative Lyme disease – ONLY VERY EARLY!!!!
  + Effect of concurrent antibiotics on test results – NOT!!!!
  + Western blot interpretation:
    + With vs without ELISA – WITH, PLEASE!!!!
    + Surveillance vs clinical – CLINICAL!!!!
    + Basis for criteria – Statistical, not individually diagnostic bands!
  + IgM seropositivity – EARLY ONLY!!!!
  + Post treatment seropositivity – Just like any other infection
Is identification of nervous system infection important?

- To the public, neurologic disease, particularly loss of cognitive function, is among the most feared of all illnesses.
- The specter of a progressive, brain damaging, difficult to treat infection is terrifying.

What constitutes neurologic disease?

- Nervous system Lyme disease: How is infection manifest?
- “Lyme encephalopathy”: What is it? Is it brain infection?
- Lyme disease & psychiatry: Do they interact?
- “Post Lyme disease syndrome”: Is this a brain infection?
What is nervous system disease?

- Peripheral Nervous System (PNS)
- Central Nervous System (CNS)
- Not NS (Medicine)

Neurobehavior
What is neuroborreliosis?

**Basic neurology assumptions (1):**

1. Diseases of the nervous system cause:
   - Objectively demonstrable changes in neurologic function *with*
   - Damage to nervous system

2. Systemic disease can have neurobiologic effects:
   - Objectively demonstrable changes in neurologic function, typically fluctuating in space & time *with*
   - No damage to NS *(if cognitive changes, = encephalopathy)*

3. Psychiatric disease is neurobehavioral, not neurologic:
   - Spares cognitive function; affects behaviour/concentration
   - Not associated with demonstrable nervous system damage
What is neuroborreliosis?

Basic neurology assumptions (2):

- **Infections** of the central nervous system almost always elicit a local inflammatory response, generally reflected in abnormalities of the cerebrospinal fluid.
What is Neuroborreliosis?

Conclusions:

1. Patients with nervous system Lyme disease should have:
   - Objectively demonstrable neurologic deficits, observable on clinical examination & confirmed by laboratory testing
   - Abnormal CSF, if the CNS is infected

2. Absent such findings, infection unlikely
Lyme disease: "the great imitator"

We expect tests to provide answers. In this case, many of those answers were confusing rather than illuminating. The patient had pain that suggested a pinched nerve, and an M.R.I. showed he had spinal stenosis — but that wasn’t the problem. He had a fever, and a chest X-ray suggested a lung infection — but that wasn’t the problem either. Lyme disease is an infection that can take many forms.

Perhaps it, too, should be known, like its cousin syphilis, as “the great imitator.”

The 62-year-old engineer struggled as he put on his pants. His left arm, which had hurt for the last couple of days, now felt weak, and his left hand hung limp and useless, as if it were somehow paralyzed. When he went to brush his teeth, he noticed that the foamy toothpaste was pouring from his mouth. He glanced up at the mirror and was startled
Is Lyme disease “a great imitator”?

<table>
<thead>
<tr>
<th>PNS: Clinical</th>
<th></th>
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<tbody>
<tr>
<td>Cranial nerves (III-XII)</td>
<td></td>
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<tr>
<td>Radiculopathy</td>
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<tr>
<td>Plexopathy</td>
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<tr>
<td>Plexopathy</td>
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<tr>
<td>Diffuse</td>
<td></td>
<td></td>
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<tr>
<td>Multifocal</td>
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</tbody>
</table>
Neurophysiology (human):
- Multifocal
- Peripheral > root
- Mononeuropathy through confluent mononeuropathy multiplex
- Rarely demyelinating changes (> chance?)

Rhesus macaque monkey:
- Virtually all have mononeuropathy multiplex
- Epineurial perivascular infiltrates ≠ vasculitis

Median nerve, rhesus monkey; Roberts et al; JID 1998;178:722-32
**Intrathecal antibody**

Y = IgG molecule  
Y = anti-Bb IgG

Lab assumes about 1/250 IgG crosses BBB & dilutes serum 1:500, CSF 1:1, comparing CSF to serum normals.

NOTE: elevated specific Ab from serum will be above cutoff & interpreted as elevated (‘positive’) but CSF:serum = 1.0
**Intrathecal antibody**

<table>
<thead>
<tr>
<th></th>
<th>Leaking Blood Brain barrier</th>
<th>Now 5x usual crosses</th>
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<tbody>
<tr>
<td>Y= IgG molecule</td>
<td>Y=anti-Bb IgG</td>
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<td>YYYYYYYYYYYYYYYYYYY</td>
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<td>YYYYYY</td>
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</tbody>
</table>

Lab assumes about 1/250 IgG crosses BBB & dilutes serum 1:500, CSF 1:1, Final [Ab] now 5x higher in diluted CSF than expected, so observed OD 5x actual

Result: Ab assay OD 5x higher, & “positive”

But if CSF, serum both diluted to same final [IgG], CSF:serum still 10%/10%=1.0
Intrathecal antibody

Y = IgG molecule
Y = anti-Bb IgG

Assume normal total crosses:

Blood Brain barrier

Assume B cells enter CSF, targeting organism

10% = specific

Now much more = specific
CSF:Serum >> 1.0
# Neurology, neurobiology, other

<table>
<thead>
<tr>
<th>CNS: Clinical</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudotumor cerebri (children)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemispheres</td>
<td></td>
<td></td>
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<tr>
<td>Cerebellar</td>
<td></td>
<td></td>
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<tr>
<td>Brainstem</td>
<td></td>
<td></td>
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<tr>
<td>Spinal cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td></td>
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<tr>
<td>Psychiatric</td>
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</table>
# Neuroborreliosis - Diagnosis

## AAN (1996)

- **Possible exposure**
- **Erythema migrans** (or histologically proven ACA, b. lymphocytoma)
  - OR + serology, culture, PCR
- **Specific neuro:**
  - Meningitis
  - Cranioradicular neuropathy
  - Encephalomyelitis
- **ITAb w active CSF sufficient but not necessary** (e.g. PNS)

## EFNS (2010)

- **Definite (3/3); possible (2/3)**
  - Neurological symptoms
  - Cerebrospinal fluid (CSF) pleocytosis
  - Bb-specific antibodies produced intrathecaally
    - if symptom duration <6 wks, Bb antibodies may be absent

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Mygland et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol 2010; 17:8-16
Neuroborreliosis - Treatment

- IDSA recommendations (2000, 2006)
  - Ceftriaxone 2 g IV qd x 14-28 days or
  - Cefotaxime 2 g IV q8hr or
  - Penicillin 20-24 MU/d (q4hr dosing)

  or, in selected circumstances

- Doxycycline 100-200 mg po bid x 30 d
  (not in children <8 or pregnant/nursing mothers)
Ratio of response rate to doxycycline vs parenteral penicillin or ceftriaxone; RR of 1.0 indicates identical response rates with the agents being compared; in eight studies, and in aggregate.
AAN & EFNS Guidelines

Prolonged courses of antibiotics:
1) Do not improve the outcome of Lyme or post-Lyme syndrome,
2) Are potentially associated with adverse events, and
3) Are not recommended (Level A recommendation).

Guidelines on Trial: AAN Subpoenaed as Part of Investigation into Treatment Parameters for Lyme Disease

By Lisa Phillips

Common misconceptions about Lyme disease

+ Treatment:
  + Response
    + Nonspecific symptoms rarely respond rapidly & often persist a while after successful treatment (just like pneumonia etc)
  + Duration
    + “Treat until symptoms & tests resolve”
    + “Bacteria hide and are treatment resistant”

+ ILADS Trifecta:
  + Improve immediately=good=treat more
  + Worse immediately='Herxheimer'=treat more
  + No response=resistant=treat more
Objectively evident cognitive, memory difficulty in patients with active Lyme disease

Originally 2 populations:

- Rare individuals with mild encephalitis (MRI & CSF) manifest only as cognitive slowing, with non-focal exams
- Individuals with apparent systemic inflammatory disease, & cognitive symptoms, but normal imaging & CSF (toxic metabolic encephalopathy)

“Chronic Lyme disease’ : is inclusive of persistent symptomatologies including fatigue, cognitive dysfunction, headaches, sleep disturbance and other neurologic features”

ILADS Guideline, 2004
# Neurobehavioral syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clin/Lab evidence of Bb infection</th>
<th>Objective evidence active Bb infection</th>
<th>Neuro-behavioral abnormalities</th>
<th>Antibiotic responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalitis</td>
<td>Req’d/req’d</td>
<td>Req’d</td>
<td>Focal</td>
<td>Yes</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Req’d/req’d</td>
<td>Req’d</td>
<td>Cognitive</td>
<td>Yes</td>
</tr>
<tr>
<td>PTLDS</td>
<td>Req’d/req’d</td>
<td>No</td>
<td>Cognitive</td>
<td>No</td>
</tr>
<tr>
<td>“Chronic Lyme Dis.”</td>
<td>No</td>
<td>No</td>
<td>Variable</td>
<td>No</td>
</tr>
</tbody>
</table>

**Post treatment Lyme disease syndrome:**
- any of: widespread musculoskeletal pain, cognitive complaints, radicular pain, paresthesias, or dysesthesias interfering with function within 6 months after initial diagnosis and treatment, persisting for at least 6 months

**“Chronic Lyme disease”:** (not formally defined but):
- “persistent symptomatologies including fatigue, cognitive dysfunction, headaches, sleep disturbance and other neurologic features”
A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy

Prolonged Lyme disease treatment - Enough is enough
John J. Halperin, MD

Neurology 70 (13), March 25, 2008
Fallon, NIH-funded, 10 wks ceftriaxone

20 Healthy Controls
Test-retest NPsych

Goal: 45 subjects
Advertised nationally, 4 years
Screened 3,368

1,439
inadequate prior Rx

37 subjects

1,316 - not CDC criteria
512 Western blot -
64 other

23
Ceftriaxone x 10 wks

Neuropsych aggregate
12 wks, cfx>placebo p=0.053

Neuropsych aggregate
24 weeks, cfx=placebo

Complications
3 withdrew
+3 comps->term drug
+1 cholecystectomy

Complications
2 withdrew
1 comp->term drug
Neuropsychologic Index (Fallon et al)

-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8

Baseline
12 wk
24 wk

Ceftx
Placebo
Normal

\( \Delta = 0.34 \)

\( \Delta = 0.35 \)

IV (wks 1-10)
Is isolated chronic cognitive difficulty Lyme encephalopathy???

Cognitive slowing, fatigue:
1/3 of population
Severe in 2%
(200/10,000)

Medical illnesses (inflammatory, infectious, metabolic, etc.)

Lyme disease (1/10,000 incid.)

Post Lyme disease syndrome (?1-3% of Lyme disease pts.)

All with objectively demonstrable abnormalities of memory & cognition
Post treatment Lyme disease

- Symptom complex occurs in 2% of general population
- 30+% of patients treated for Lyme disease have persisting symptoms at 6 months+
  - same frequency in matched not-Lyme controls over same time
  - more subjective sx than controls at f/u but no objective correlate (anchoring bias)
- Incidence: Fallon screened 3,368->37; <0.1% of incident cases
- If recent CDC statement that only 10% of cases reported...
Post treatment Lyme disease

- If it exists, what causes it:
  - Not microbiologic as not antimicrobial responsive
  - Antibody mediated? No correlation between [Ab] & Sx
  - Persisting bacteria or detritus, hidden from host immunity, yet action at a distance:
    - If hidden, cannot have immune mediators
    - No evidence for exotoxin
  - Behavioral – i.e. response to stressors:
    - Not depression
    - Resilience: + vs – affect = best predictor
The sociobiology of a disease

“The greater the ignorance, the greater the dogmatism”
Sir William Osler
Thank you for your attention
PNS Neuroborreliosis

Mechanisms:

Observations:

- Dermatomal involvement vs. site of bite (Europe) (?CNS access route)
- Resolves after antimicrobial therapy
- No evidence of spirochetes in nerves (in rhesus model Bb in dorsal root ganglia)
- No evidence of spirochetal antigens or immune complex deposition in nerve
Lyme Neuroborreliosis

Pathophysiology of CNS neuroborreliosis:

Clinical observations:
- Early entry of *B. burgdorferi* into CNS
  - PCR+
  - then \(\uparrow[CXCL_{13}]_{CSF}\) (\(\uparrow\) before serum)
    - B cell-attracting chemokine produced in monocytes & dendritic cells
  - \(\rightarrow\) High [B cells]_{CSF} and ITAb
- Symptoms resolve with antimicrobial therapy
- Duration ITAb >> illness >> CSF PCR/culture positivity

While clinical presentation quite variable, represents either:
- Meningitis
- Multifocal disease, white matter-predominant, (not demyelinating) presumably infectious with immune amplification, analogous to mononeuropathy multiplex
- Remote effect of systemic infection, i.e. altered CNS function without CNS infection/damage