## Major Periods in the History of Lyme Disease

- **1976-1990** Discovery & Openness
- **1990-2008** Narrow Definitions, Conflict & Entrenchment
- **2008-** Renewed discovery & exploration
A brief history of Lyme disease...

3000 BCE

Ice Man: Lyme DNA 5,000 yrs old

Cluster of unexplained childhood arthritis

1980

Spirochete found in tick

"Lyme: The NEW great imitator"

1990

CDC 2-Tier Criteria


Persistence of Bb in Animal Models after Abx treatment

2000

Bb genome sequenced

Vaccine

Systems Biology – "-Omics"

2010

>300,000 new diagnoses/yr

Lyme, CT

CDC 2-Tier Criteria

Persistence of Bb in Animal Models after Abx treatment

"Lyme: The NEW great imitator"
Paradigm Shifts of last decade

- Recognition that Lyme Disease is not simple
  - Current blood tests are inadequate
    - Only 35-50% sensitive in early Lyme disease
  - Spirochetes can persist – even after standard antibiotic treatment – a new focus of research

- Recognition that chronic symptoms have biological correlates (in the brain, spinal fluid, & blood)
Paradigm Shifts of last decade

- **Recognition: an epidemic**
  - The geographic spread of ticks expanding

- **Discovery of new microbes**
  - Ticks

- **Recognition of the brain’s involvement**
  - Persistent symptoms.
Technology Advances: new assays & biomarkers - the power of OMICS
Borrelia spirochetes persist despite antibiotics. This has been shown in many species.

Often with minimal or No Disease

Slide courtesy of Stephen Barthold, UC Davis
Spirochetes can be visualized within tissue of a mouse at 12 months following antibiotic treatment.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0086907
Persistence of B burgdorferi in the Rhesus Macaque

Monica Embers, Tulane University
Xenodiagnosis to detect Borrelia in humans
(Marques et al, CID, 2014)

- Tick from 1 of 9 persons with previously treated Lyme Disease tested positive by PCR for DNA of the Lyme spirochete.
Advances in Diagnosis: Metagenomic Next Generation Sequencing enable rapid detection of All Microbes

Turn around time: hours to days (vs. days – weeks)

Slide courtesy of Charles Chiu
We no longer need a fishing pole/guess approach to microbial detection. We now can cast a wide net to detect all microbes – even without knowing what’s there.
Assesses cytokine response to Lyme protein stimulation of human T-cells (or macrophages)

In early Lyme Disease (EM) (Callister 2016):
- 69% sensitivity
- After treatment (2 months later) – 80% negative
**Advances in Diagnosis:** Metabolomics-based assay

Metabolic biosignature: sugars, peptides, lipids, nucleic acids

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**Early Lyme vs Controls** (Molins et al, 2015)

- 88% sensitive in early Lyme  (2x higher than 2-Tier assay)

- Differentiates Lyme from other diseases
  Correct differentiation 93% of Lyme from CFS & Fibromyalgia

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Next: study **Post-treatment Lyme disease** using Metabolomics

- To identify a biosignature of recovery and of PTLDS
- To suggest new treatments
Causes of Persistent symptoms under investigation

Persistent Bb infection

Unrecognized Coinfections

Neural Network dysregulation

Immune dysregulation

Advance: repeated antibiotic therapy can help persistent fatigue. Stonybrook & Columbia NIH Studies

<table>
<thead>
<tr>
<th>% Responders</th>
<th>Ceftriaxone</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Krupp 2003</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>All patients</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>Fallon 2008</td>
<td>75</td>
<td>25</td>
</tr>
</tbody>
</table>
Advance: Persister Borrelia require different approaches for eradication

Ying Zhang, MD (Hopkins)  
Kim Lewis, PhD (Northeastern)
Advance: ticks carry more than just the agent of Lyme disease

- Borrelia miyamotoi
- Borrelia mayonii
- Babesia Microti
- Anaplasma phagocytophylum
- Ehrlichia
- Powassan Virus

Tokarz et al, Scientific Reports, 2018
Advance: Recognition that patients with post-treatment Lyme disease have an altered Cerebrospinal Fluid protein profile (692 unique proteins)

- This proteomic CSF profile differentiated post-treatment Lyme disease from Chronic Fatigue
- Persistent symptoms are associated with an increase in immune proteins

Schutzer, Angel, Liu...Fallon, Natelson, PLoS-One, 2011
The chemokine CCL-19 remains elevated among patients with PTLDS

(Aucott et al 2016)
Advance: recognition that patients with post-treatment Lyme encephalopathy have objective brain changes: altered brain metabolism & blood flow. (Columbia Imaging studies)

The patient group showed a diminished ability to enhance blood flow compared to controls (8.2% for patients vs 28.1% for controls, p<.02) (Fallon et al, JAMA Psychiatry, 2009)
Current research: Do human post-mortem brains from LD harbor Lyme spirochetes?

- **Columbia**
  - Andrew Dwork
  - Gorazd Rosoklija
  - Jim Goldman
  - Brian Fallon

- **Microbiologists:**
  - Monica Embers (Tulane)
  - Timothy Sellati (SRI)

- **Other Collaborators**
  - Ken Liegner
  - New York Brain Bank

Monkey Brain Tissue
Current Research: Are the brain’s neural circuits or chemistry altered? A Columbia study of Post-treatment Lyme patients

Functional Magnetic Resonance Imaging
- Does the brain show central sensitization – hyperactivated pain circuits compared to healthy controls?

Magnetic Resonance Spectroscopy
- Is the brain neurochemistry different from healthy controls?

Alla Landa, PhD
What is the patient’s experience?

Eduard Munch: Sensory Hyperarousal  
William Blake: “Job Being Accused”
Reports & Case Series of Neuropsychiatric Manifestations

Clinical Series & Controlled Studies:
- Cognitive Problems (Keilp 2006)
- Depression/Irritability (Logigian 1990)
- Sensory Sensitization (e.g., Light, Sound) (Batheja 2013)

Less common manifestations (case reports):
- Psychosis, Paranoia (Hess, 1999)
- Tourettes Disorder (Riedel, 1998)

Need a large epidemiologic study to examine these associations.
357 Children age 9-17 had structured psychiatric evaluation.

15 of 16 children were treated within one month of infection; all recovered fully within 4 months. One of 16 was not diagnosed until 4 months after onset and she experienced 5 years of intermittent arthritis, severe fatigue, cognitive impairment, emotional problems, and school performance deterioration.

Conclusion: Among children, acute Lyme treated early is not associated with more psychiatric disorders than those without a Lyme history. Delayed treatment however may pose increased risk of neuropsychiatric & rheumatologic problems.
159 patients from an academic rheumatology Lyme Disease referral center were screened for psychiatric disorders. Which group had more psychiatric disease?

4 Groups of Patients:

1. **CLD: Post-Lyme Disease Syndrome** (n=31)
2. **CLD: Medically Unexplained Symptoms attributed to LD** but without evidence of Bb infection & > 90 days of antibiotics (n=46)
3. **Recovered from Lyme Disease** (n=40)
4. **Other medical disorder and not LD** (n=42)
Increased Depression is not due to “believing” you had Lyme disease

Hassett et al, Arthr & Rheum 2008

Depressive co-morbidity was much higher in patients with definite prior LD vs those with medically unexplained symptoms who did not have a good history of LD but self-identified as having chronic Lyme
Neuropsychiatric Symptoms among patients with acute or post-treatment Lyme disease

- Bb-triggered Neuropsychiatric Symptoms (Antibiotic Responsive)
- Bb-triggered Neuropsychiatric Symptoms (No longer antibiotic responsive)
- Bb-unrelated Neuropsychiatric symptoms
Jan 6, 2010
- Went to bed ok, woke up next day crying “something is wrong with my head & I can’t stop it”
- Sudden onset OCD with rituals taking 4-6 hrs/day

She was hospitalized in an inpatient psychiatry unit because she was so terrified & the rituals were so consuming
Sally’s Medical History

Numerous embedded ticks & from an endemic area
- 3-6 mos before:……more Tick bites (treated with Amoxil)

Did not recall a Lyme rash, joint pain, shooting pains
But she had did have:
- Mild paresthesias in feet & 3 months of fatigue.
- Trouble reading: her vision had deteriorated from 20/20 to 20/240

No history of movement disorders, strep throat or + titers.
Sally’s work-up & Treatment

- **Medical work-up**
  - Lyme tests in serum were positive:
    - C6 ELISA – very high positive (6.35)
    - Western blot: IgM WB (3/3) and IgG WB (6/10 bands).

- **Outpatient psychiatrist decisions**
  - Discontinue Psychiatric meds in favor of Lyme treatment.

- **Treatment:**
  - On antibiotics x 14 wks. Doxy 2 wks (initial worsening of anxiety) → Amoxicillin for 12 weeks
  - Weekly CBT
PANS – Pediatric Acute Onset Neuropsychiatric Syndromes

From Swedo 2014
Criteria for PANS

- Abrupt onset of OCD or food restriction
- Concurrent onset of 2 or more:
  - Anxiety (separation, GAD)
  - Emotional lability and/or depression
  - Irritability, aggression
  - Developmental regression
  - Deterioration in academic performance
  - Sensory or motor (e.g. dysgraphia) symptoms
  - Other (urinary freq, mydriasis, insomnia)
Did Case 1 meet Criteria for PANS?

- **Abrupt onset of OCD or food restriction**
- **Concurrent onset of 2 or more:**
  - Anxiety (separation anxiety, GAD)
  - Emotional lability and/or depression
  - Irritability, aggression
  - Developmental (behavioral) regression
  - Deterioration in academic performance
  - Sensory or motor (e.g. dysgraphia) symptoms
  - Other (urinary freq, mydriasis, insomnia)
Indications of cross-reactive Ab in neurologic Lyme

Serum from neurologic Lyme pts contains anti-Bb IgM antibodies autoreactive to human peripheral nerve axons

Bb flagellin IgG Ab reacts in vitro against:
- human nerve axons; HSP-60 of neuroblastoma cells

Bb OspA peptide Ab reacts in vitro against:
- Human brain neurons, spinal cord, dorsal root ganglia

Source: Sigal 1988, 1993; Fikrig 1993; Yu 1997; Alaedini & Latov 2005
Persistent symptoms are associated with increased antibodies against neural proteins.

Chandra et al, 2010
Ganglioside antibodies in Neuroborreliosis

~30% of Patients with NB develop Ab to gangliosides (GM1 in CSF & serum) –
>> than those with other Lyme manifestations, SLE, anti-phospholipid syndrome, normal controls

Reactivity is comparable to those with motor neuropathies with/without conduction blocks & in Guillain-Barre syndrome

Garcia-Monco, Seidman, Benach  Infection and Immunity, 1995
Anti-Neuronal Antibodies in Lyme Disease (Fallon, Cunningham)

- Is there evidence of Ab-mediated neuronal activation (ie, Cam Kinase)?
- Are specific anti-neuronal antibodies increased compared to community controls?

- Anti-lysoganglioside
- Anti-tubulin
- Anti-D1 receptor
- Anti-D2 receptor

Supported by a grant from the Lyme Disease Association, Inc.
Samples from Columbia Lyme Center Biorepository
Methods

Sera from patients vs community controls

Patient Groups (n=151 patients, 22 controls)
- Early Lyme EM with no prior LD (n=24)
- Early Lyme EM with prior LD (n=9)
- Persistent Symptomatic/Past LD (n=118)

- Community controls (n=22)
  - No history of prior LD
  - Negative on US ELISA, C6, and WB (IgM & IgG)
  - Negative on European ELISAs and WBs
Questions

Do these antibodies contribute to disease?

Or, are they unrelated to Bb infection or non-pathogenic secondary responses to Bb infection?

What role do immunomodulatory therapies play in Lyme disease?
- IV IG, Plasmapharesis, Antibiotics
Possible Mechanisms for persistent symptoms

- **Inflammation – Cytokines** (Strle 2014, Soloski 2014, Jacek 2013)
- **Neural excitation - Quinolinic acid** (Halperin 1992)
- **Central Sensitization** (Batheja 2013)
- **Altered Neurocircuitry/Metabolism** (Fallon 2009)
When should one suspect that neuropsychiatric sx may be Lyme-related?

Lyme History and Labs:
- Multi-systemic symptoms (CNS, PNS, muscles, joints, fatigue).
- Symptoms emerge after flu-like illness & exposure to a Lyme endemic area
- Seroconversion, increased titers or recent tick bite, abnormal spinal fluid

Psychiatric disorder is atypical
- Manifesting at an odd age
- Cognitive features (verbal fluency & memory)
- Lack of a personal or family history of psychiatric disorders
An open label report indicates IV Ig helps improve Lyme neuropathy (Katz, AAN, 2009)

26 patients with painful neuropathy attributed to either OspA vaccine or Lyme
- Serologic evidence of OspA Ab
- Either NCS confirmed neuropathy or diminished epidermal nerve fiber density

Open label treatment –
- Objective, quantitative & sig mean increase in epidermal nerve fiber density after IV Ig
- All pts reported clinical improvement. (Antineuronal Ab panel not available on these patients).
Case 2: Post-treatment Lyme, OCD, CIDP, Severe allergies

Antibiotics in this case weren’t the answer.

After 3-4 months of IV Ig
New Neurology-Psychiatry Pediatric Neuropsychiatric Focus

- Joining forces with Columbia Neurology
- Focus on infection-triggered and immune-triggered neuropsychiatric disorders

Shannon Delaney (Child Psychiatry), Wendy Vargas (Pediatric Neurology), Dritan Agalliu (Neurology, Pathology, Cell Biology), Tyler Cutforth (Neurology)
So… is there reason for hope?
Thank you from our team

Columbia Lyme & Tick-Borne Diseases Research Center
Addendum material
2. Behavioral Changes

Between 1982 and 1984, a 12-year-old boy had four attacks of swelling of the right knee; the diagnosis of Lyme arthritis was confirmed serologically. After the last attack, he was treated with doxycycline, 100 mg twice a day for 30 days. Two months later, the patient became withdrawn and depressed. He no longer interacted with his friends, spent most of this time alone, and would no longer do his school work. He ate very little and began to exercise compulsively. His weight dropped 14 kg. On admission to a psychiatric hospital, he was grossly depressed and uncommunicative. He was diagnosed as having anorexia nervosa.

Because of the history of Lyme disease, he was transferred to Yale-New Haven Hospital. Serum and CSF antibody titers to *B. burgdorferi* were elevated, but neurologic evaluation was normal. He was treated with intravenous penicillin, 20 million U a day for 14 days, and within several weeks he began to eat more, gain weight, and communicate. During the following several months, his behavior returned to normal, he went back to school, and has remained asymptomatic for the past 2 years.
Lyme Disease: A Neuropsychiatric Illness

Brian A. Fallon, M.D., M.P.H., and Jenifer A. Nields, M.D.

Ms. A, a previously healthy 18-year-old college freshman, suddenly developed severe and sustained anxiety, depersonalization, and panic attacks associated with insomnia and appetite loss. She consulted the university health services. After evaluation by both a psychologist and an internist, rest was recommended, under the assumption that these symptoms represented an adjustment reaction to being away from home. As her symptoms worsened, Ms. A began to fear that she was going crazy.

Two weeks later, Ms. A returned home on a medical leave of absence. An extensive medical workup revealed no abnormalities except for a positive Lyme ELISA titer. A Western blot for *B. burgdorferi* also came back positive. Ms. A insisted on getting a spinal tap. Although the cell count and total protein were normal, the CSF revealed IgG antibodies to *B. burgdorferi*. The diagnosis of CNS Lyme disease was made. The patient was treated with a 6-week course of intravenously administered antibiotics, and over the course of the following 3 months she felt 80% better.
One year later, Ms. A developed a return of anxiety with panic attacks and agoraphobia. In addition, she developed rare déjà vu episodes, repetitive musical hallucinations, and intrusive obsessional thoughts and images. Results of a repeat spinal tap were normal on routine testing with a nonreactive CSF ELISA for *B. burgdorferi* antibodies. An EEG after sleep deprivation revealed intermittent slowing in the right and left temporal areas with rare sharp waves. Ms. A was treated for 6 months with imipramine, with complete resolution of her panic attacks and agoraphobia. With time, the obsessional thoughts, déjà vu experiences, and musical hallucinations also resolved.

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