


The Neuropsychiatry of Lyme disease


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My Job Description


The Medical Director is primarily responsible for providing medical input to strategy and information products:

- reviewing medical information before publication;
- delivering content for information products as required;
- maintaining knowledge of relevant medical developments;
- cascading medical information as appropriate;
- medical consultancy role.




The Neuropsychiatry of Lyme disease: Case presentation

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History of Illness : First Six Months

- **Tick bite:** July 2008 - early antibiotics
- Flu-like illness/double vision/ noise sensitivity/malaise
- **EM rash** August 2008: Back of Left knee → persisted
- Insidious **Neurological symptoms ++** 6 months
- Cranial 6th nerve palsy → double vision
 Confirmed by ENG
- Ataxia = Unsteady gait, dizziness
- Memory Problems + Confusion
- Cognitive slowing + Inattention = ‘Brain Fog’
- Jan 2009 → GP → A&E ? Encephalitis
Lyme serology : Negative (ELISA , WB)
- Sensory abnormalities/ ↓ reflexes
- ↑CRP ↑viscosity
- MRI : T2 areas of high signal



History of Illness 2

- **Jan 2009:** Headache & pain++, fevers/chills, visual hallucinations, insomnia, nightmares, sleeps ++, mood swings
- **Doxycycline** →
- Feb 2009: ? Autonomic dysfunction - ? POTS (↑pulse>30/min on standing)
- May 2009: 1:80 IFAT **Babesia** → Atovaquone + Azithromycin
- May 2009: All differentials excluded.LP ①
- May 2009: Uveitis
- May 2009 → AF (1st episode)
- Sep 09 - Jan 2010: Gradual relapse off antibiotics
- Nov 2009 → Q Square → LP ② (↑ pressure and protein), POTS, Cognitive inefficiency,
- April 2010 IV Ceftriaxone → **Good response** 90-95%



Serology Test Results

NHS	Private
Jan 09: Negative • Biomerieux Vidas ELFA IgM+IgG • Immunetics C6 ELISA • Trinity Biotech Lyme+VlsE Immunoblots IgM + IgG May 09: Negative • Repeat tests • Diasorin IgG+IgM EIA • CSF IgG immunoblot • CSF C6 EIA Nov 09: Not done	Feb 09: ‘Weak indeterminate’ • Igenex Immunoblot IgM p83-93kDa IgG p23-25kDa, p31. p34, p39 • Igenex Immunoblot +ve bands • IgM p41kDa • IgG p41kDa • Igenex PCR serum Negative
	Netherlands June 2012 • IgM and IgG ELISA Negative • IgM Immunoblot Negative • IgG Immunoblot p25,p30,p39

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The Journey

- Shock
- Disbelief
- Fear
- Self-blame
- Loss
- Abandonment
- Entrapment
- Betrayal



- →Realisation
- →Recovery

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Striving for the prevention and treatment of Lyme disease and associated tick-borne diseases


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What is Lyme Disease?

An infectious disease caused by the bacterium *Borrelia burgdorferi* – a spirochaete.



CDC Public Health Image Library



LDA Image Library

Transmitted to humans by ticks:

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Borrelia vs Syphilis Similarities

- Spirochaete → ‘New Great Imitator’¹
- Stages of illness - latency, dissemination – but early CNS seeding is recognised²
- Multisystem: Skin, Nervous system, Joints, Eyes, Cardiovascular + other organs.
- Persistence despite immune activation³
- Difficult to culture - fastidious
- Treated with antibiotics

1. Pachner AR et al 1988
2. Halperin JJ et al 1995
3. The mechanisms for persistence probably vary (Blaser et al 2001)

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Borrelia vs Syphilis Differences³

Borrelia	Syphilis
<ul style="list-style-type: none"> • <i>Borrelia burgdorferi sensu lato</i> - 1981 • Humans: Inadvertent hosts • Zoonosis - Complex Life cycle • Complex Genome - Linear DNA • 910,725 bp • 12 linear + 9 circular plasmids • 610,694 bp → lipoproteins 	<ul style="list-style-type: none"> • <i>Treponema pallidum pallidum</i> - 1905 • Obligate human pathogen • Sexually transmitted • Genome – Circular DNA • 1,138,006 bp • No plasmids • 25% smaller than <i>Borrelia</i>

3. Blaser et al 2001

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Neuropsychiatry - Borrelia spp.⁴

Borrelia burgdorferi sensu lato

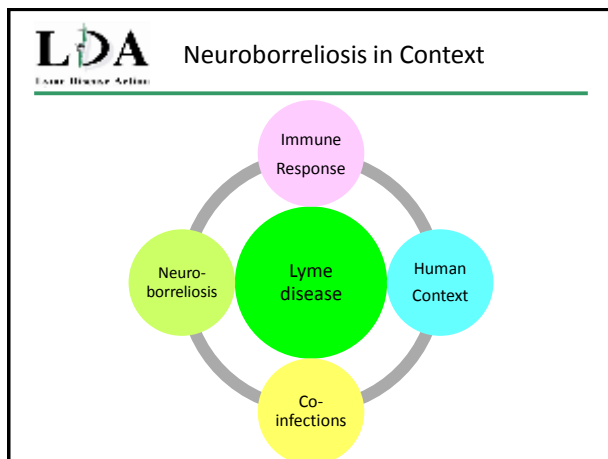
- *Borellia burgdorferi sensu stricto* (USA + Europe)
- *Borellia garinii* (Europe) ↓
- *Borellia afzelii* (Europe) ↓
- *Borellia spielmanii* (rare) (Europe) ↓

Accounts for some of the varying presentations

4. Stanek G et al 2011

LDA Lyme Disease Action **Neuroborreliosis: History**

- 1909: Afzelius : Tick-bite → Erythema chronicum migrans
- 1922: Garin & Bujadoux → Tick Paralysis
- 1930: Hellerstrom → EM → Encephalitis
- 1941: Bannwarth → Lymphocytic meningoradiculitis (Polyneuritis often with facial palsy)
Bannwarth syndrome → LNB
- Late 1970s: Lyme disease → Tick bite, EM + Juvenile arthritis
- 1981: Willy Burgdorfer → Borrelia burgdorferi



LDA Lyme Disease Action **Human Nervous System 1**

Central Nervous System: Enveloped by Meninges + Cerebrospinal Fluid

- Brain
- Spinal cord
- Cranial nerves

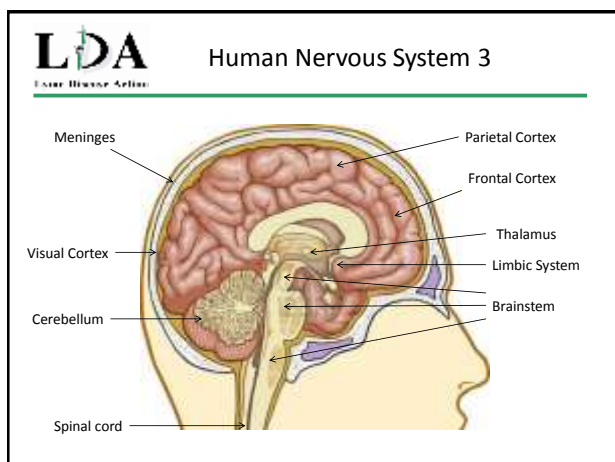
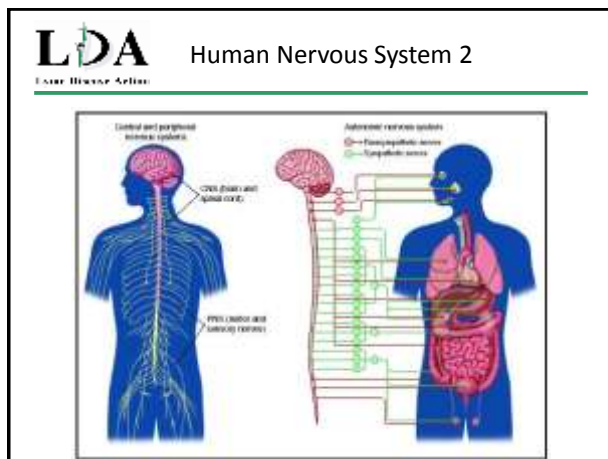
Peripheral Nervous system:

- Sensory nerves
- Motor nerves

Autonomic nervous system:

- Sympathetic
- Parasympathetic

Blood-brain-barrier → 'Immune privileged site'



LDA Lyme Disease Action **Early Neuroborreliosis: Symptoms ⁵**

- Patients may not recall a tick bite or rash
- **Neurological symptoms may be the presenting sign**
- Headache
- Flu-like illness
- Myalgia
- Fleeting arthralgia (joint pains)
- Photophobia
- Dizziness

5. Fallon B et al 1994

LDA Early Disseminated Neuroborreliosis ⁶

< 4 - 6 months

- Meningitis – ↓ signs of meningism
- Cranial neuritis – Facial palsy, double vision
- Sensory and Motor Radiculitis → neuropathic pain + weakness = **Bannwarth Syndrome**
- Encephalitis – fluctuating disturbances of mood, sleep, concentration + memory
- Myelitis
- Cerebral vasculitis
- Peripheral neuropathy – numbness, paraesthesia, weakness (↓ reflexes, vibration sense)

6. Fallon BA 2009

LDA Late Disseminated Neuroborreliosis

>6 months.....**Fluctuating course**

- **Encephalomyelitis** – severe, said to be rare → spastic paresis, transverse myelitis, cerebellar syndrome, hemiparesis
- **Encephalopathy** – subtle severe cognitive changes → ‘brain fog’, word-finding difficulties, dyslexia, memory problems, spatial disorientation, sleep disturbance, irritability, mood swings, anxiety, noise sensitivity, tinnitus, seizures, tremor.
- **Autonomic Neuropathy** – POTS,
- **+ Profound fatigue and malaise**

LDA Differential Diagnosis : LNB

- Multiple Sclerosis (demyelination)
- Stroke
- Bell's Palsy
- Parkinson's disease
- Dementia
- Delirium
- ALS-like syndrome
- Guillain-Barre
- CFS/ME*
- Various Psychiatric Disorders: Depression, Bipolar Affective Disorder, OCD, Psychosis, GAD, Panic, Hypochondriacal*, Somatoform*, Dissociative disorders*

* = Diagnoses of exclusion

LDA Diagnostic Cautions: LNB/Fallon

- ? Markers of non-psychiatric disease
- ? Atypical presentation
- ? Older patient > 50 years
- ? No personal or family psychiatric history
- ? Poor response or excessive side-effects to medication
- ? No psychological precipitants or 2^o gain

• **Comorbid Psychiatric conditions may occur in LNB**

LDA Differential Diagnosis: LNB Children

- Attention Deficit Disorder (ADD)
- Attention Deficit Hyperactivity Disorder (ADHD)
- Autism-like Disorder
- Behavioural Problems
- → Problems attending School
- → May Affect Educational and Social Development
- → Parental/ Family strain
- → Children also may be affected indirectly if parent has Lyme disease

LDA Neuroborreliosis: General Tests

- Inflammatory markers may be normal eg. ESR, CRP or plasma viscosity
- Nerve Conduction studies may be normal
- Nerve biopsy: peripheral small fibre damage
- EEG: Diffuse slowing or epileptiform activity
- MRI brain scan: T2 white matter hyperintensities
- SPECT/PET scan: Hypoperfusion → Frontal lobes
- Cognitive neuropsychological testing
- Tilt-table testing: Autonomic neuropathy
- Serology tests.....?

LDA Neuroborreliosis: Lumbar puncture

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- In very early or late-stage LNB the CSF may appear normal
7. Coyle PK et al 1992
- LP may show monocytic pleocytosis, mildly elevated protein and in some cases ↑IgG index or oligoclonal bands
5. Fallon et al 1994
- Lymphocytic pleocytosis (↑WBC), as well as several other CSF abnormalities, were frequent among patients with *B. garinii* isolated from CSF but were rare among patients in the *B. afzelii* group.
8. Strle et al 2006
- Despite these various findings, most guidelines require evidence of CSF pleocytosis + intra-thecal antibody production for diagnosis
- PCR insensitive – 30% sensitivity CSF

LDA Neuroborreliosis: Neuroinflammation ⁹

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- Dissemination via bloodstream or PNS/Lymphatics?
- Bb attaches to endothelial lining + ?platelets
- Penetration of BBB?
- Immune activation → Pro-inflammatory cytokines and chemokines eg CXCL13
- Direct cytotoxicity (apoptosis and astrogliosis)
- Induction of neurotoxins (Nitric Oxide, quinolinic acid →NMDA agonist)
- Autoimmune: Ab against flagellin cross reacts with neural tissue

9. Rupprecht et al 2008

LDA EFNS Guidelines ¹⁰: Neuroborreliosis

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Criteria for Diagnosis of Neuroborreliosis:
(3= Definite ; 2= Possible)

- Neurological symptoms
- Cerebrospinal fluid(CSF) pleocytosis
- Bb-specific antibodies produced intrathecally

PCR and CSF culture may be corroborative if symptom duration is <6 weeks, when Bb antibodies may be absent. PCR otherwise not recommended

10. Mygland A et al 2010

LDA EFNS Guidelines: Neuroborreliosis

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Treatment Recommendations Adults:

Acute LNB: Symptom duration < 6 months
Symptoms confined to PNS including meningitis→
Single 14 day course of antibiotics

- Oral Doxycycline 200mg per day or
- IV Ceftriaxone 2g per day

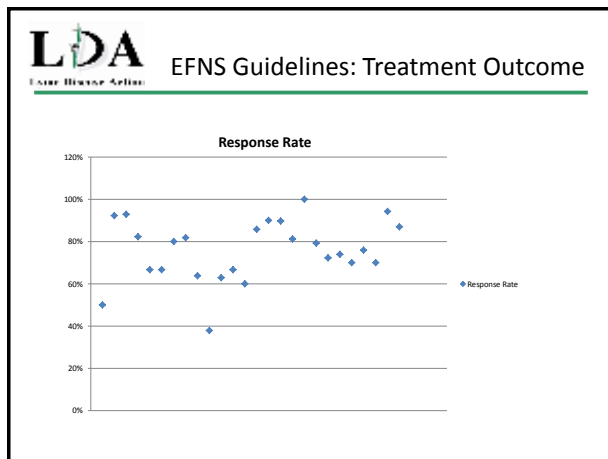
But CNS and Late LNB (symptoms>6 months)→

- IV Ceftriaxone 2g per day 21 days ←(GPP)

LDA EFNS Guidelines: Treatment

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- ‘The choice of the best antibiotic, the preferred mode of administration, and the duration of treatment are the still debated issues.’
- ‘There are no randomized treatment studies of European late LNB.’



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NICE Guidelines?

- Depression, Bipolar Affective Disorder, GAD.
- Depression in Adults with a Chronic Physical Health Problem (↑ suicide risk)
- Delirium
- Dementia
- Neuropathic pain
- HPA Protocol Encephalitis
- HPA Protocol Meningitis
- →→ **Doctors need accredited information on Lyme borreliosis**

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BMJ Letters ¹¹: 16 July 2012



11. Pearson S, Huyshe-Shires S BMJ 2012;345:e4727 doi: 10.1136/bmj.e4727 (Published 16 July 2012)