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.

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

<table>
<thead>
<tr>
<th>NHS</th>
<th>Jan 09: Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biomerieux Vidas ELISA</td>
</tr>
<tr>
<td></td>
<td>Immunetics CE ELISA</td>
</tr>
<tr>
<td></td>
<td>Trinity Biotech Lyme+Vise Immunoblots IgM + IgG</td>
</tr>
<tr>
<td>May 09: Negative</td>
<td>Repeat tests</td>
</tr>
<tr>
<td></td>
<td>DiasoningG+H+M EIA</td>
</tr>
<tr>
<td></td>
<td>CSF IgG immuno</td>
</tr>
<tr>
<td></td>
<td>CSF C6 BA</td>
</tr>
<tr>
<td>Nov 09: Not done</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Private</th>
<th>'Weak indeterminate'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb 09:</td>
<td>Igenex Immunoblot</td>
</tr>
<tr>
<td></td>
<td>IgM p83-93kDa</td>
</tr>
<tr>
<td></td>
<td>IgG p23-25kDa, p31, p34, p39</td>
</tr>
<tr>
<td></td>
<td>Igenex Immunoblot +ve bands</td>
</tr>
<tr>
<td></td>
<td>IgM p41kDa</td>
</tr>
<tr>
<td></td>
<td>IgG p41kDa</td>
</tr>
<tr>
<td></td>
<td>Igenex PCR serum Negative</td>
</tr>
</tbody>
</table>

Netherlands June 2012

| IgM and IgG ELISA | Negative |
| IgM Immunoblot | Negative |
| IgG Immunoblot | p23,p30,p39 |
The Neuropsychiatry of Lyme disease

The Journey
- Shock
- Disbelief
- Fear
- Self-blame
- Loss
- Abandonment
- Entrapment
- Betrayal
  - Realisation
  - Recovery

What is Lyme Disease?
An infectious disease caused by the bacterium *Borrelia burgdorferi* – a spirochaete.

Transmitted to humans by ticks:

Borrelia vs Syphilis
Similarities
- Spirochaete → 'New Great Imitator' ¹
- Stages of illness - latency, dissemination – but early CNS seeding is recognised ²
- Multisystem: Skin, Nervous system, Joints, Eyes, Cardiovascular + other organs.
- Persistence despite immune activation ³
- Difficult to culture - fastidious
- Treated with antibiotics

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

Borrelia vs Syphilis
Differences ³

<table>
<thead>
<tr>
<th>Borrelia</th>
<th>Syphilis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Borrelia burgdorferi sensu lato</em> - 1981</td>
<td><em>Treponema pallidum</em> pallidum - 1905</td>
</tr>
<tr>
<td>Humans: Inadvertent hosts</td>
<td>Obligate human pathogen</td>
</tr>
<tr>
<td>Zoonosis - Complex Life cycle</td>
<td>Sexually transmitted</td>
</tr>
<tr>
<td>Complex Genome - Linear DNA 910,725 bp</td>
<td>Genome – Circular DNA 1,138,006 bp</td>
</tr>
<tr>
<td>12 linear + 9 circular plasmids</td>
<td>No plasmids</td>
</tr>
<tr>
<td>610,694 bp → lipoproteins</td>
<td>25% smaller than <em>Borrelia</em></td>
</tr>
</tbody>
</table>

¹. Blaser et al 2001

Neuropsychiatry - Borrelia spp.⁴

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

Accounts for some of the varying presentations

4. Stanek G et al 2011
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

Neuroborreliosis in Context

• Lyme disease
• Immune Response
• Neuroborreliosis
• Human Context
• Co-infections

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'

Human Nervous System 2

Human Nervous System 3

Early Neuroborreliosis: Symptoms

- 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
Early Disseminated Neuroborreliosis

< 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)

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

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

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 2⁰ gain

Comorbid Psychiatric conditions may occur in LNB

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

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......?
Neuroborreliosis: Lumbar puncture

- In very early or late-stage LNB the CSF may appear normal.
- LP may show monocytic pleocytosis, mildly elevated protein and in some cases ↑IgG index or oligoclonal bands.
- 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.
- Despite these various findings, most guidelines require evidence of CSF pleocytosis + intra-thecal antibody production for diagnosis.
- PCR insensitive – 30% sensitivity CSF.

EFNS Guidelines: Neuroborreliosis

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.

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)

EFNS Guidelines: Neuroinflammation

- 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 astroglialosis)
- Induction of neurotoxins (Nitric Oxide, quinolinic acid →NMDA agonist)
- Autoimmune: Ab against flagellin cross reacts with neural tissue.

EFNS Guidelines: Treatment

- ‘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.’
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

BMJ Letters 11; 16 July 2012