Lyme neuroborreliosis: Alien invasion

Dr Sandra Pearson, MB ChB, MRCPsych
Consultant Psychiatrist and Medical Director
www.LymeDiseaseAction.org.uk
Out with the Old in with the New

Previous leaflet

LDA003
Lyme neuroborreliosis
Autonomic neuropathy: POTS

Venous Pooling
What is Lyme Disease?

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

- Transmitted to humans by the bite of an infected tick.
Lyme borreliosis: Bacterial cause

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

Different genospecies may account for variations in disease profile.

Borrelia

- *Borrelia burgdorferi* identified - 1982
- Zoonosis - complex life cycle
- Opportunistic pathogen → adaptation → persistence
- Small genome – mainly linear DNA
  910,725 bp
- + Plasmids - 12 linear + 9 circular
  610,694 bp
- Humans: inadvertent hosts

Borrelia and Syphilis
Similarities

• Both pathogenic spirochaetes/ obligate parasites
• Borrelia = ‘The New Great Imitator’ ¹
• Multisystem disorder: skin, nervous system, joints, eyes, cardiovascular + other organs
• Persistence despite immune activation ²
• Difficult to culture - fastidious
• Treated with antibiotics

LNB Dissemination

- Direct tissue penetration
- Blood-stream
- Migration along peripheral nerves
- Via lymphatic system?

- Early localised
- Early disseminated LNB: less than 6 months
- Late LNB : more than 6 months
- Evidence suggests these stages may not be clear-cut
- Host-pathogen relationship is important

Mygland A et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis 2010;17(1):8–16.
Lyme neuroborreliosis: Immune evasion

- Immune evasion and dysregulation
- Penetrates blood/brain into immune privileged site
- Persistence of atypical forms (Miklossy J. Open Neurology Journal 2012;6:146-57)

Armin Kübelbeck: Schematic diagram of blood brain barrier / Cc-by-3.0
Human Nervous System

Central Nervous System (CNS)  Enveloped by meninges + cerebrospinal fluid
- Brain
- Spinal cord

Peripheral Nervous system (PNS)
- Cranial nerves
- Sensory nerves
- Motor nerves

Autonomic nervous system (CNS & PNS)
- Sympathetic
- Parasympathetic
Human Nervous System

Central and peripheral nervous systems

CNS (brain and spinal cord)

PNS (motor and sensory nerves)

Autonomic nervous system

Parasympathetic nerves

Sympathetic nerves
The cranial nerves

Patrick J. Lynch, Medical illustrator Cc-by-2.5
Erythema migrans

- Not all patients remember a tick bite or EM rash:
- In LNB only 40-50% recall a tick-bite
- European LNB studies show only 20-30% remember an EM rash

Mygland A et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis 2010;17(1):8–16.

Lovett JK et al. Epidemiology and infection 2008;136(12).
Lyme neuroborreliosis

- Lyme neuroborreliosis (LNB) occurs when the disease affects the nervous system

- Neurological symptoms may begin early: 1-12 weeks (mainly 4-6 after tick bite) July-Dec

- Neurological symptoms may precede the EM rash or be the first sign later on – may be subtle/ atypical

Mygland A et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis 2010; 17(1):8–16.
Early Lyme borreliosis: General symptoms

First days and weeks of infection:

- Headache
- Flu-like illness
- Fever
- Fatigue
- Myalgia
- Fleeting arthralgia (joint pains)
- Neck ache/ mild neck stiffness

Lyme neuroborreliosis: ‘typical’ symptoms

- In Europe: symptoms which affect the nervous system are thought to develop in 15-20% of people days to months after infection.

- **Radiculitis** – inflammation of motor and/or sensory nerve roots.

- **Cranial neuritis** – inflammation of the cranial nerves

- **Meningitis** – inflammation of the membrane which surrounds the brain and spinal cord.

- Referred to as ‘Bannwarth’s syndrome’ (Lymphocytic meningoradiculitis)

Mygland A et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis 2010;17(1):8–16.
Lovett JK et al. Epidemiology and infection 2008;136(12).
Early Disseminated Neuroborreliosis

< 4 - 6 months

- Meningitis – minimal neck stiffness, ‘aseptic’
- Cranial neuritis – Facial palsy (VII), double vision (VI)
- Sensory and Motor Radiculitis → neuropathic pain + weakness
  = Bannwarth's Syndrome
- Encephalopathy (‘brain fog’)
- Encephalitis (confusion, drowsiness, seizures, behaviour etc.)
- Myelitis
- Cerebral vasculitis
- Peripheral neuropathy – numbness, paraesthesia, weakness
  (↓reflexes, vibration sense)

Late Disseminated Neuroborreliosis

- >6 months.....
  - Late LNB: Central nervous system: said to be rare
  - **encephalitis** (inflammation of the brain)
  - **myelitis** (inflammation of the spinal cord)
  - **vasculitis** (inflammation of blood vessels)
  - Late LNB: Peripheral nervous system
    - **peripheral neuropathy** +/- ACA, mononeuritis multiplex
    - **autonomic neuropathy** eg. POTS (postural orthostatic tachycardia syndrome)

Mygland A *et al.* EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis, 2010;17(1),8–16.
<table>
<thead>
<tr>
<th>Unusual Bannwarth’s</th>
<th>Unusual CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other cranial nerve palsies</td>
<td>Acute transverse myelitis</td>
</tr>
<tr>
<td>Diaphragmatic paralysis</td>
<td>Chronic meningitis</td>
</tr>
<tr>
<td>Urinary retention/constipation</td>
<td>Progressive encephalitis</td>
</tr>
<tr>
<td>Complex regional pain syndrome</td>
<td>Stroke-like syndromes</td>
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<tr>
<td></td>
<td>Optic neuritis</td>
</tr>
<tr>
<td></td>
<td>Pseudotumor cerebri (mainly children)</td>
</tr>
<tr>
<td></td>
<td>Dementia (+/- NPH)</td>
</tr>
<tr>
<td></td>
<td>Psychiatric syndromes</td>
</tr>
<tr>
<td></td>
<td>Motor neurone disease-like syndromes</td>
</tr>
<tr>
<td></td>
<td>Extrapyramidal syndromes (Parkinsonism, chorea etc)</td>
</tr>
<tr>
<td></td>
<td>Opsoclonus-myoclonus syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unusual PNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA associated peripheral neuropathy</td>
</tr>
</tbody>
</table>

(ECCMID 2013, EW19 Diagnosis & management of Lyme neuroborreliosis.
W79: Kristoferitsch W)
Lyme neuroborreliosis: ‘typical’ symptoms

- In Europe: symptoms which affect the nervous system are thought to develop in 15-20% of people days to months after infection.

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Lovett JK *et al.* Epidemiology and infection 2008;136(12).
Lyme neuroborreliosis: SW England

(Lovett JK et al. Epidemiology and infection 2008;136(12).)

- 25% (22/88) had significant neurological problems other than headache
- 91% had one of Bannwarth’s syndrome triad, only 9% had all three
- 58% male, 41% children (age range 5 years – 82 years)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial palsy (unilat + bilat)</td>
<td>64%</td>
</tr>
<tr>
<td>Bilateral facial palsy</td>
<td>14%</td>
</tr>
<tr>
<td>Isolated facial palsy</td>
<td>27%</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>50%</td>
</tr>
<tr>
<td>Radiculopathy</td>
<td>23%</td>
</tr>
<tr>
<td>Bannwarth’s syndrome</td>
<td>9%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>9%</td>
</tr>
<tr>
<td>Sixth nerve palsy</td>
<td>9%</td>
</tr>
</tbody>
</table>
Lyme neuroborreliosis: manifestations/ frequency
(Hansen K, Lebech M. Brain 1992;115 pt2,339-423)

- Meningoradiculitis: 61%
- Radicular pain only: 4.3%
- Meningoradiculomyelitis: 4.8%
- Subacute meningitis: 3.7%
- Chronic meningitis: 24.6%
- Chronic encephalitis/encephalomyelitis: 1.6%

Lyme neuroborreliosis manifestations/frequency chart.
Facial palsy, headache + fever predicts early LNB (May- Oct ‘Lyme season’) 

Aseptic meningitis more common than in adults 

Painful radiculopathy less common 

Neurological examination may be normal 

Weight loss, gastro-intestinal symptoms, malaise, fatigue.


Lyme neuroborreliosis: Children

(Christen HJ et al. Acta Paediatr Suppl. 1993;386,1-75.)

Facial palsy: 55%
Aseptic meningitis: 4.8%
Recurrent headaches: 3.6%
Bannwarth's syndrome: 3.5%
Meningoencephalitis: 4.1%
Guillan-Barré syndrome: 1.8%
Other neurological conditions: 27.2%
The Anatomy of the Facial nerve (VII Cranial nerve)

Figure VII–1 Overview of facial nerve components (parotid gland removed).

From “Cranial Nerves in Health and Disease” 2002. © Wilson-Pauwels, Akesson, Stewart, Spacey, B C Decker Inc.
• Weakness or paralysis on one or both sides of the face

• Called Bell’s palsy if cause unknown

• Distressing

• Hyperacusis/noise sensitivity if nerve to stapedius affected

www.neuroanatomy.ca/index.html
Lyme neuroborreliosis: diagnosis

 Diagnosis should be clinical and take account of test results

- Thorough history – with account of close relative/carer
- Full physical and neurological examination
- Search for ‘typical’ signs of Lyme disease
- Borrelia antibodies: serum, CSF
- Biopsy affected tissue (skin, nervous, heart, eyes)
- Alternative diagnoses may need to be excluded
### EFNS criteria for case definition of Lyme neuroborreliosis

<table>
<thead>
<tr>
<th>Definite LNB*</th>
<th>Possible LNB**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All 3 criteria</strong></td>
<td><strong>2 Criteria</strong></td>
</tr>
<tr>
<td>Neurological symptoms suggestive of LNB without other obvious reasons</td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid pleocytosis</td>
<td></td>
</tr>
<tr>
<td>Intrathecal Bb antibody production</td>
<td></td>
</tr>
</tbody>
</table>

*Except for Late LNB with polyneuropathy I) Peripheral neuropathy II) ACA III) Bb specific antibodies in the serum.

**After 6 weeks, there have to be Bb IgG antibodies in the serum.

Lyme Neuroborreliosis: General Tests

- Inflammatory markers may be normal: ESR, CRP, plasma viscosity
- Nerve conduction studies may be abnormal
- Nerve biopsy: peripheral small fibre damage
- EEG: Diffuse slowing or epileptic activity
- MRI brain scan: T2 white matter hyperintensities
- SPECT/PET scan: reduced blood flow late LNB
- Cognitive neuropsychological testing
- Tilt-table testing: autonomic neuropathy
- Serology tests
- Lumbar Puncture


ELISA and immunoblot (Western blot) are indirect tests

Confirm presence of antibodies in serum/CSF

Serology has limitations, negative result does not exclude a diagnosis of LNB

Eg: Diasorin Liaison Borrelia burgdorferi IgG, IgM Quant ELISA: Sensitivity

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>IgG % positive</th>
<th>IgM % positive</th>
<th>IgG &amp; IgM % positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema migrans n=45</td>
<td>80</td>
<td>55.6</td>
<td>88.9</td>
</tr>
<tr>
<td>*Neuroborreliosis n=57</td>
<td>93</td>
<td>57.9</td>
<td>96.5</td>
</tr>
</tbody>
</table>

* Case definition includes positive serology. Specificity of IgM = 96.6 % and IgG = 98%
Early LNB may show signs of inflammation:

- ↑ white blood cells (lymphocytic pleocytosis)
- ↑ protein
- +/- oligoclonal IgG bands
- ↑ opening pressure

In late LNB the lumbar puncture may be normal, or show only increased protein and pressure.

Infections caused by *B. afzelii* and those solely in the PNS may result in an inconclusive LP result.


Comparison of findings for *B. garinii* & *B. afzelii* isolated from CSF


- n = 48 culture positive (9.9%) – 12 did not grow well enough for LRFP
- n = 36 ↓
- 23 *B. garinii*
- 10 *B. afzelii*
- 3 *B. burgdorferi*

*Majority of *B. afzelii* did not fulfil typical LNB criteria*
Antibody Index [AI]: (Europe)

\[
\text{CSF/serum index [AI]} = \frac{\text{ELISA units in the CSF} \times \text{total IgG in the serum}}{\text{ELISA units in the serum} \times \text{total IgG in the CSF}}
\]

- Positive AI is proof of intra-thecal antibody production
- Sensitivity may be only 55-80%
- AI of 2.0 is considered significantly elevated (EUCALB http://www.eucalb.com/)

**Culture:** Difficult, 4-6 weeks

**PCR:** Sensitivity in CSF 30% due to low numbers of Borrelia

**Microscopy:** Low numbers of spirochaetes
Differential Diagnosis: LNB

- Multiple Sclerosis
- Bell’s Palsy
- Stroke
- Polio-like syndrome
- Parkinson’s disease
- Dementia
- Delirium
- Motor neurone disease, transverse myelitis
- Guillain-Barré syndrome
- HIV, syphilis
- SLE, sarcoidosis
- CFS/ME
- Depression, bipolar disorder, anxiety disorder, panic disorder, OCD, manic psychosis, schizophrenia-like /organic psychosis, hypochondriacal, somatoform, conversion & dissociative disorders
Lyme neuroborreliosis: Pointers to non-psychiatric illness

- Symptoms & signs of physical illness
- Atypical features
- New onset, especially > 40 years
- Absence of psychological factors
- No personal/family history of psychiatric illness
- Poor response/sensitivity to side-effects of psychotropic medication

- 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
Most people with LNB respond to antibiotics

Requires prompt treatment:

a) To avoid late stage LNB – persistent infection
b) To prevent late complications

Most effective drug and treatment length currently unknown

Antibiotics with good tissue and CSF penetration

Oral doxycycline 100mg bd, IV ceftriaxone 2g od, IV penicillin

Doxycycline failure is well documented

• Research in Europe has mainly studied early LNB

• Guidelines for late LNB extrapolate from early LNB and a small number of US trials of variable quality

• 2 UK studies suggest re-treatment and longer treatment may be beneficial\(^1,2\) (1. Dillon R et al. Clinical medicine 2010; 10, no. 5: 454-7. 2. White B et al QJM: 2012; 1–6.)

• Treatment of Late LNB is uncertain

• Polarisation of Expert opinion: (Easy vs. Hard)
<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early LNB - PNS</td>
<td>Oral doxycycline 200mg, IV ceftriaxone 2g</td>
<td>Oral doxycycline*, IV ceftriaxone 14 days</td>
</tr>
<tr>
<td>(meninges, cranial</td>
<td>IV Penicillin, IV Cefotaxime 14 days Level B</td>
<td>EFNS: not &lt; 8 years</td>
</tr>
<tr>
<td>nerves, nerve roots,</td>
<td></td>
<td>*BNF: not &lt; 12 years</td>
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<tr>
<td>peripheral nerves</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Early LNB – CNS</td>
<td>IV ceftriaxone 2g</td>
<td>IV ceftriaxone 2g</td>
</tr>
<tr>
<td>(encephalitis,</td>
<td>14 days GPP</td>
<td></td>
</tr>
<tr>
<td>myelitis,</td>
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<tr>
<td>vasculitis)</td>
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<td></td>
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<tr>
<td>Late LNB – PNS</td>
<td>Oral doxycycline 200mg, IV ceftriaxone 2g</td>
<td></td>
</tr>
<tr>
<td>(peripheral neuropathy</td>
<td>21 days GPP</td>
<td></td>
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<td>+ ACA)</td>
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EFNS Guidelines: Treatment Outcomes

Response Rate

0% 100% 200% 300% 400% 500% 600% 700% 800% 900% 1000% 1100% 1200%

Response Rate


Currently no test of cure

Recovery may take months.

Residual symptoms (12-50%) if delay in treatment or CNS symptoms

Other treatments may help

Unclear if persistent symptoms are due to:
  a) persistent infection
  b) immune dysfunction
  c) tissue damage........................or a combination of the three

What remains?
Lyme disease: NICE Guidelines?

- Depression in Adults with a Chronic Physical Health Problem CG 91
- Delirium CG103
- Neuropathic pain CG96
- HPA Protocol Encephalitis
- HPA Protocol Meningitis
- Clinical Knowledge Summaries http://cks.nice.org.uk/lyme-disease#!topicsummary
- Map of Medicine (currently in process of revision)
• Self-blame
• Fear
• Losses → Grief
• Abandonment
• Isolation
• Entrapment
• Resolution
• Reconciliation
• Carer’s issues
Lyme neuroborreliosis: Summary

- can be difficult to diagnose if symptoms not typical
- can affect any part of the nervous system
- is a treatable cause of a wide range of neurological and psychiatric disorders
- varies in symptom pattern and disease course from patient to patient
- has no gold standard test that can be relied upon for diagnosis
- can be successfully treated if treatment starts early