LDA

Lyme Disease Action

Lyme neuroborreliosis: Alien invasion

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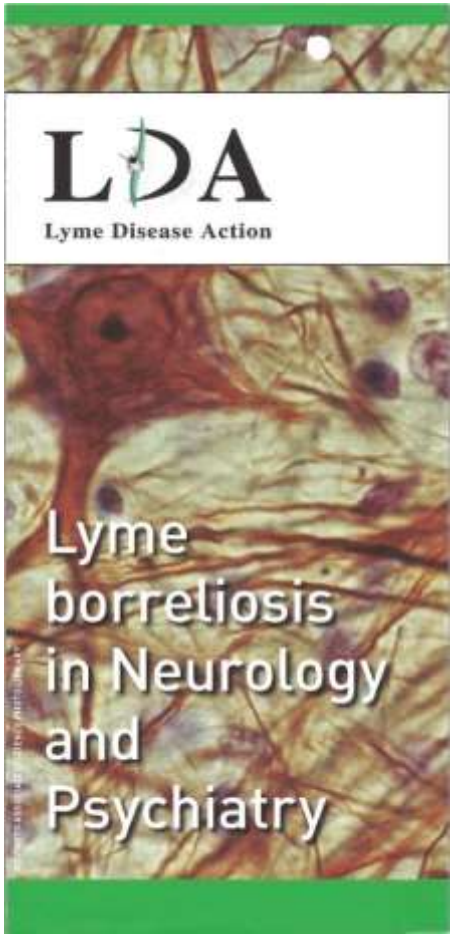
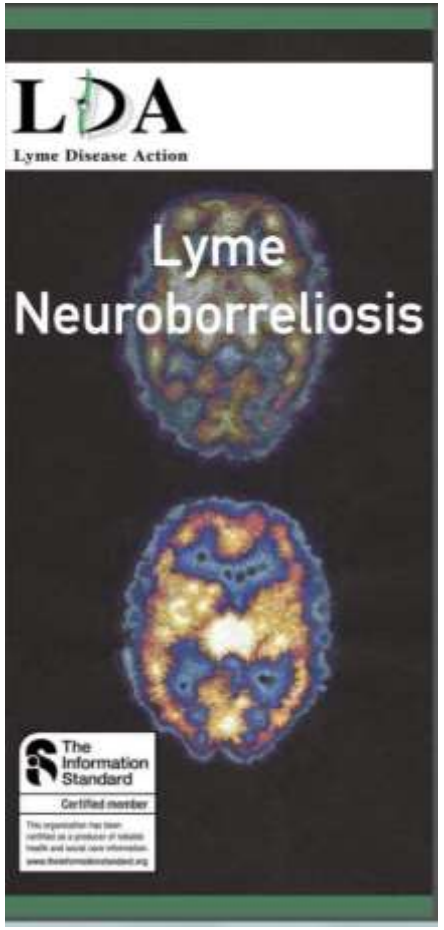
Out with the Old in with the New

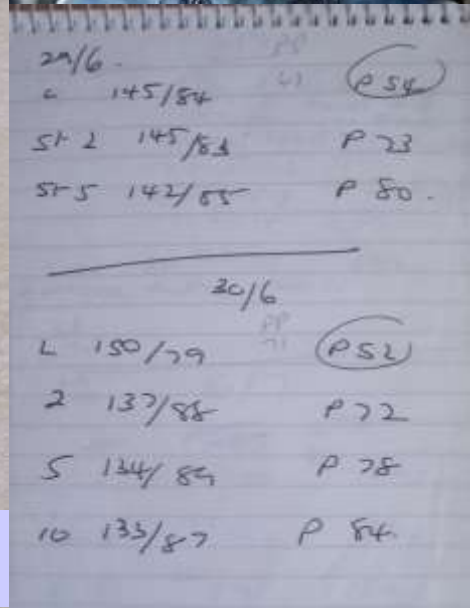
Previous leaflet	LDA003





Lyme neuroborreliosis
Autonomic neuropathy: POTS

Venous Pooling



What is Lyme Disease?

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

CDC Public Health Image Library

- Transmitted to humans by the bite of an infected tick.

LDA Image Library

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.

Stanek G, Wormser GP, Gray J & Strle F. Lancet 2011; 6736(11): 1–13.

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

Blaser MJ *et al*. Journal of Clinical Investigation 2001;107(6):651–656.

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

1.Pachner AR *et al*. Ann N Y Acad Sci 1998;539:56-6.
2.Blaser MJ *et al*. Journal of Clinical Investigation 2001;107(6):651–656.

LNB Dissemination

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

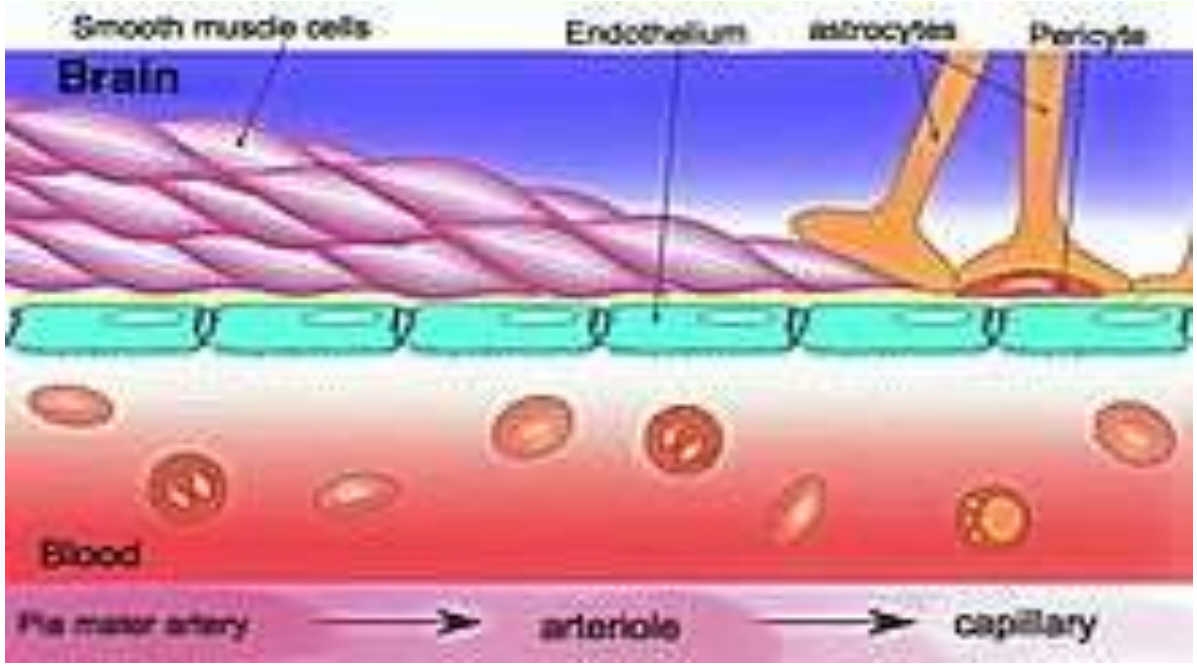
- Early localised
- Early disseminated LNB: less than 6 months
- Late LNB : more than 6 months
- Evidence suggests these stages may not be clear-cut
- Host-pathogen relationship is important

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

Rupprecht TA *et al*. Molecular medicine 2008;14(3-4):205–12.

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)



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

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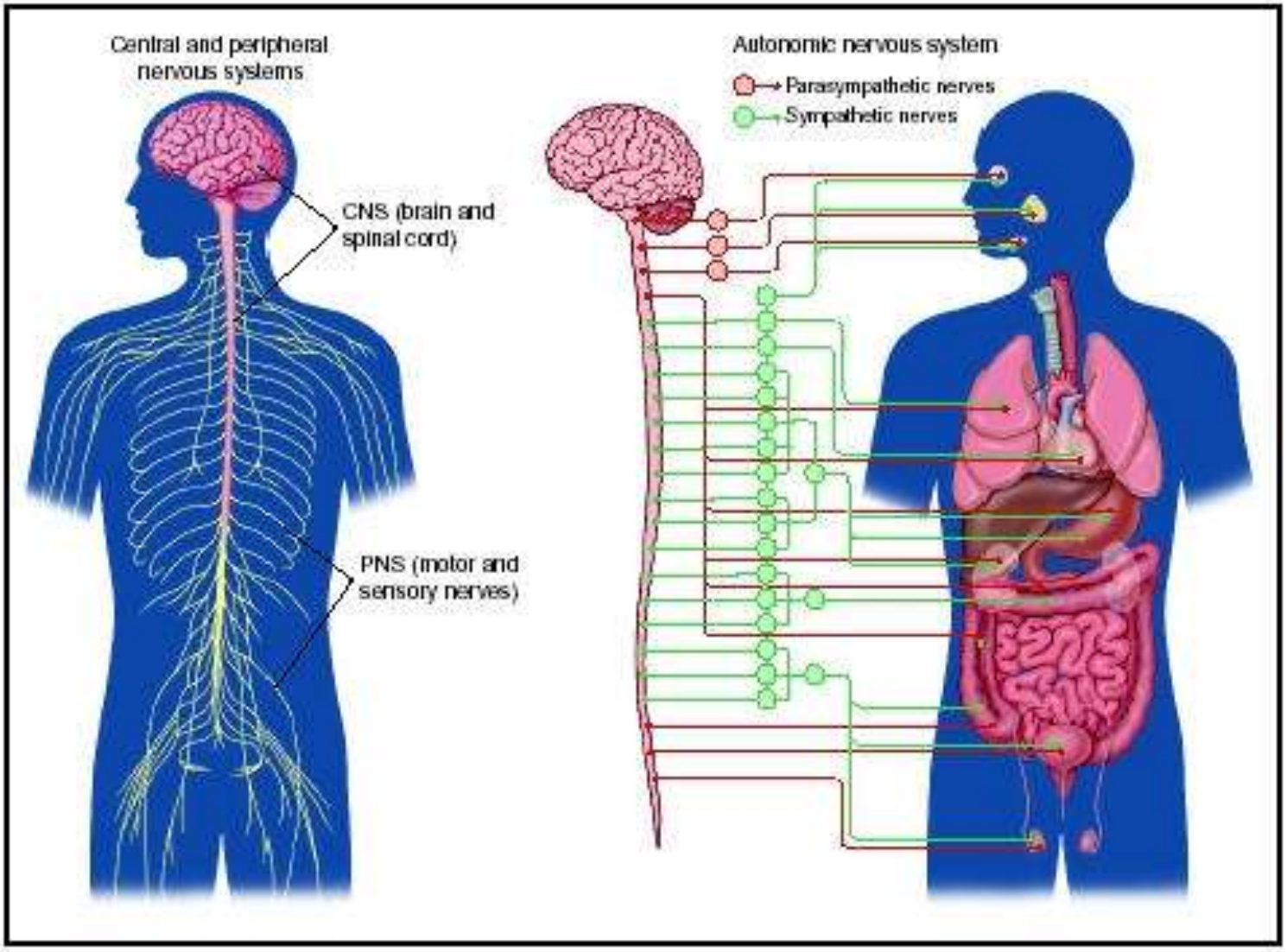
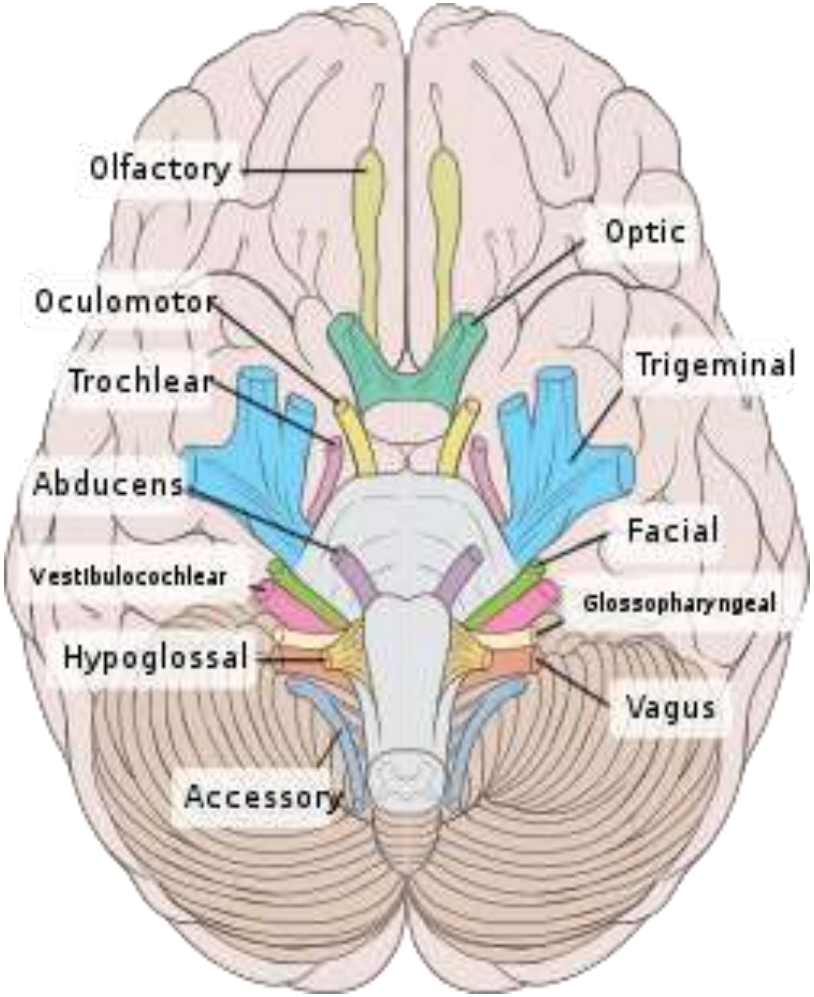
Human Nervous System



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

Stanek G *et al.* Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2011;17(1):69–79.

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)

Fallon B et al. Inflammation and central nervous system Lyme disease. Neurobiol Dis. 2010 Mar; 37(3):534-41.

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.

Kanjwal K *et al.* Cardiology journal 2011; *8*(1), 63–6. http://www.ncbi.nlm.nih.gov/pubmed/21305487

Unusual presentations of LNB

Unusual Bannwarth's

Other cranial nerve palsies
Diaphragmatic paralysis
Urinary retention/constipation
Complex regional pain syndrome

Unusual PNS

ACA associated peripheral neuropathy

Unusual CNS

Acute transverse myelitis
Chronic meningitis
Progressive encephalitis
Stroke-like syndromes
Optic neuritis
Pseudotumor cerebri (mainly children)
Dementia (+/- NPH)
Psychiatric syndromes
Motor neurone disease-like syndromes
Extrapyramidal syndromes (Parkinsonism, chorea etc)
Opsoclonus-myoclonus syndrome

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

Lyme neuroborreliosis: 'typical' symptoms

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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: SW England

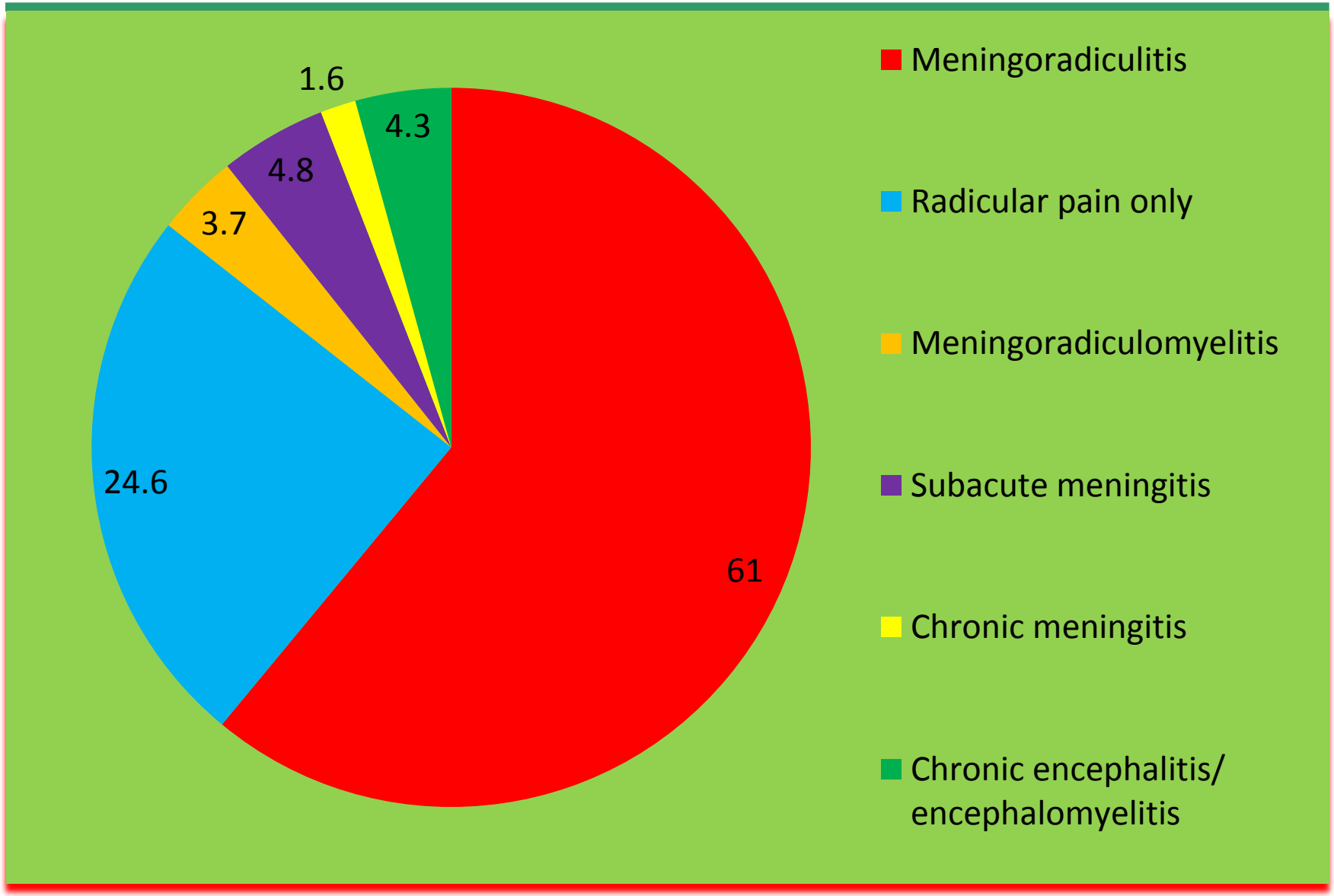
(Lovett JK *et al*. Epidemiology and infection 2008;*136*(12).)

- 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)

Characteristic	Patients %
Facial palsy (unilat + bilat)	64%
Bilateral facial palsy	14%
Isolated facial palsy	27%
Meningoencephalitis	50%
Radiculopathy	23%
Bannwarth's syndrome	9%
Peripheral neuropathy	9%
Sixth nerve palsy	9%

Lyme neuroborreliosis: manifestations/ frequency

(Hansen K, Lebech M. Brain 1992;115 pt2,339-423)



Lyme neuroborreliosis: Children

- 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.

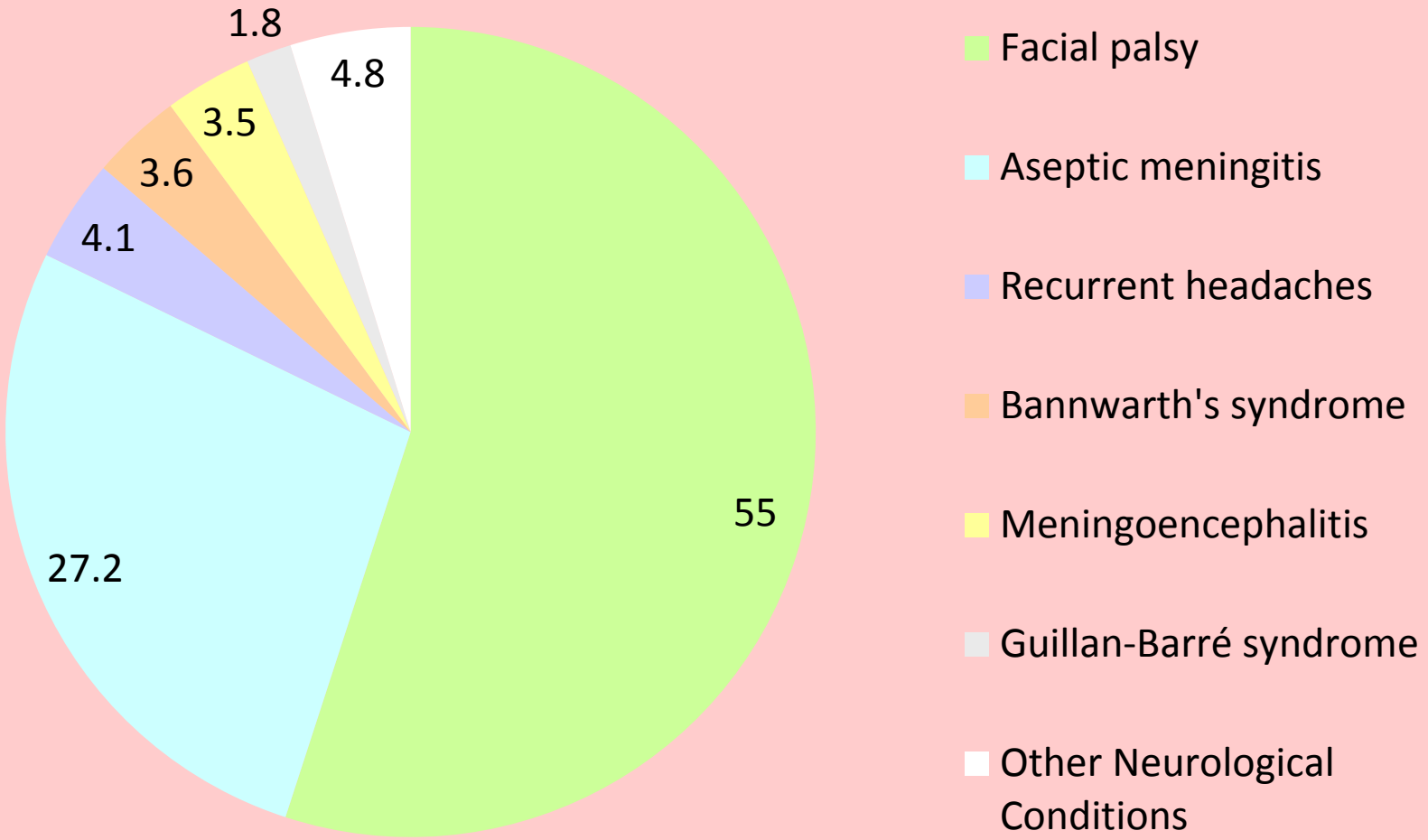
Nigrovic LE *et al.* Pediatrics 2008; 122(5): e1080–5.

Broekhuijsen-van Henten DM *et al.* Archives of disease in childhood 2010; 95(11),:910–4.

Tuerlinckx D & Glupczynski Y. Lyme neuroborreliosis in children. Expert review of anti-infective therapy 2010; 8(4): 455–63.

Lyme neuroborreliosis: Children

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



The Anatomy of the Facial nerve (VII Cranial nerve)

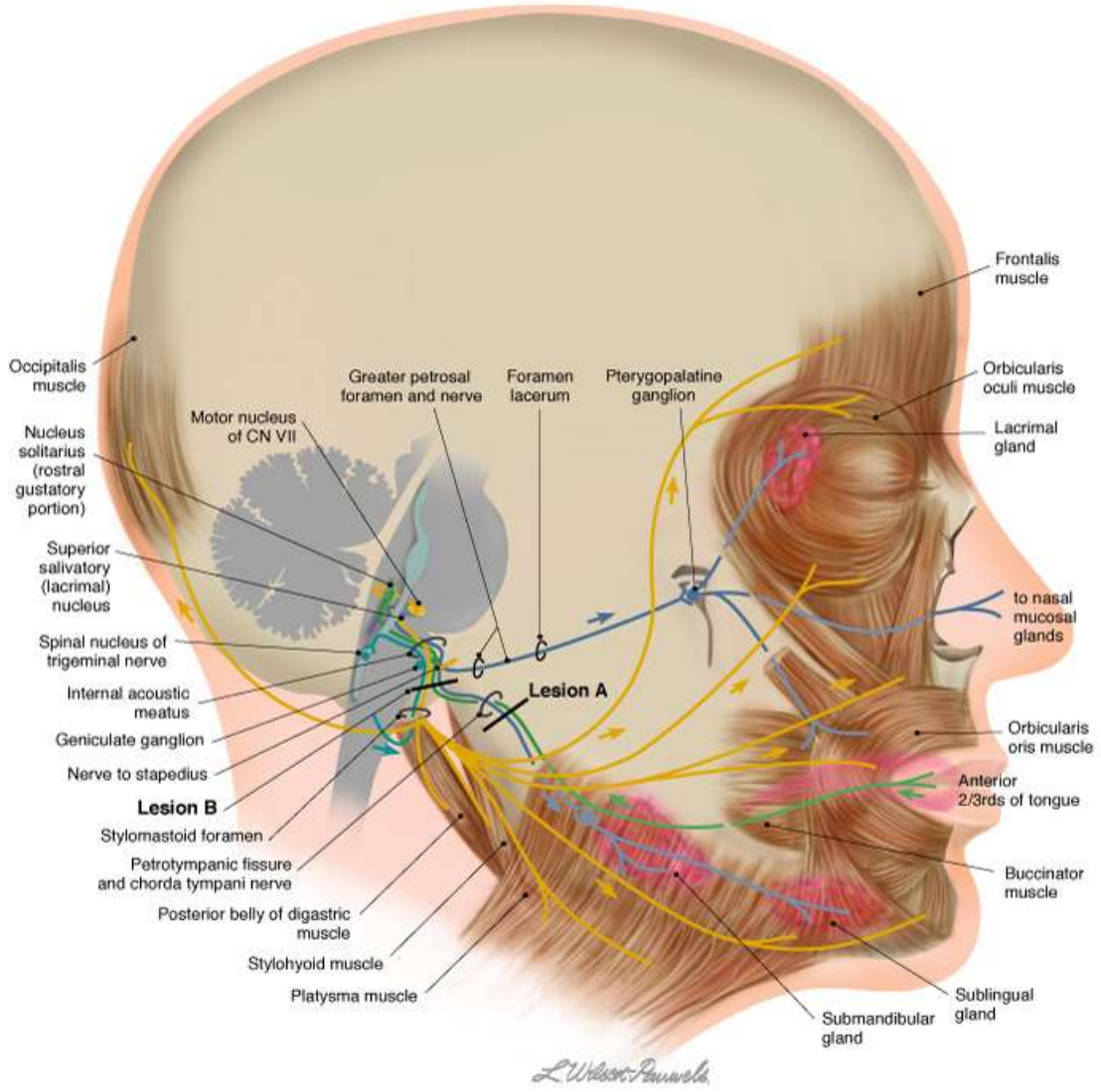


Figure VII–1 Overview of facial nerve components (parotid gland removed).

From "Cranial Nerves in Health and Disease" 2002, © Wilson-Pauwels, Akesson, Stewart, Spacey, B C Decker Inc.

www.neuroanatomy.ca/index.html

Lyme neuroborreliosis: Facial Palsy

- 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

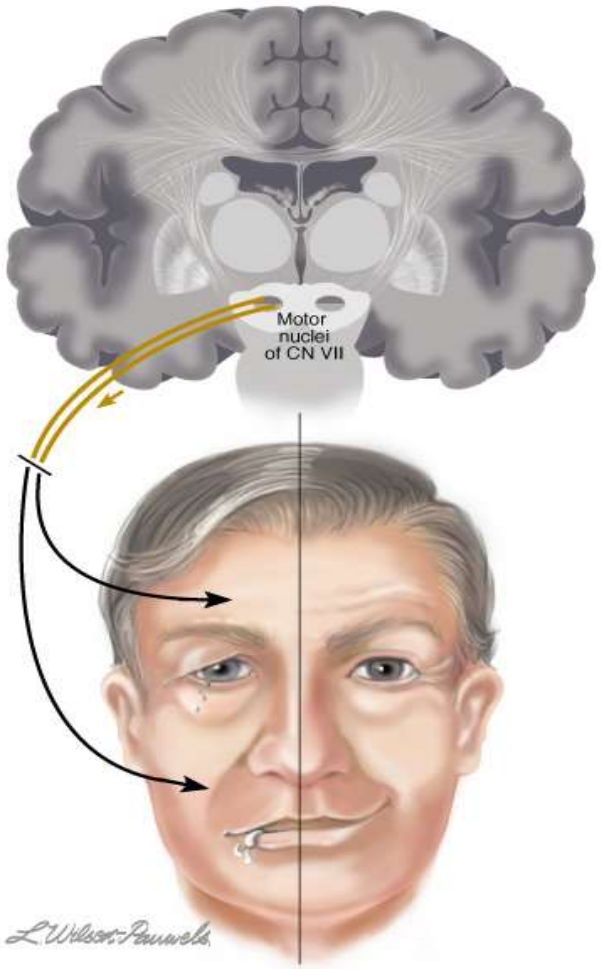


Figure VII–14 Lower motor neuron lesion in Bell's palsy with facial asymmetry—ipsilateral paralysis of upper and lower quadrants.

From "Cranial Nerves in Health and Disease" 2002,
© Wilson-Pauwels, Akesson, Stewart, Spacey, B C Decker Inc.

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

Definite LNB* All 3 criteria	Possible LNB** 2 Criteria
Neurological symptoms suggestive of LNB without other obvious reasons	
Cerebrospinal fluid pleocytosis	
Intrathecal Bb antibody production	

*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.

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

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

Fallon B *et al.* Clin Infect Dis 1997; 25 Suppl 1, S57–63. http://www.ncbi.nlm.nih.gov/pubmed/9233666

Donta ST *et al.* Clinical Nuclear Medicine 2012; 37(9), 219–222.

Lyme neuroborreliosis: Serology tests

- 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

Clinical condition	IgG % positive	IgM % positive	IgG & IgM % positive
Erythema migrans n=45	80	55.6	88.9
*Neuroborreliosis n=57	93	57.9	96.5

* Case definition includes positive serology.

Specificity of IgM = 96.6 % and IgG = 98%

Lyme neuroborreliosis: CSF testing 1

- 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.

Fallon B *et al.* Clin Infect Dis 1997; 25 Suppl 1, S57–63. http://www.ncbi.nlm.nih.gov/pubmed/9233666
Strle F *et al.* Clin Infect Dis 2006; 43(6):704–10.
Strle F,& Stanek G. Current problems in dermatology 2009; 37: 51–110.

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

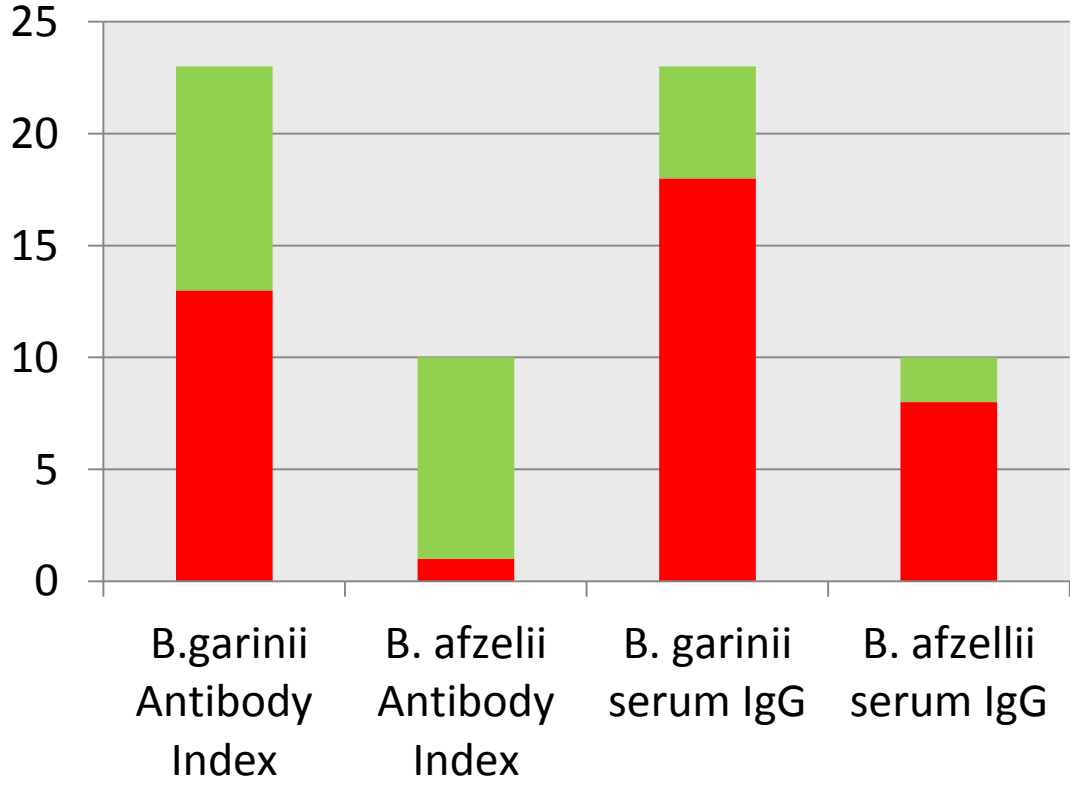
(Strle F *et al.* Clin Infect Dis 2006; 43(6):704–10)

- n = 485> CSF culture (prospective trial: Slovenia 1995 -2004)
- 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*

- *B. garinii:* typical LNB

- Majority of *B. afzelii* did not fulfil typical LNB criteria



Lyme neuroborreliosis: CSF testing 2

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**

Fallon B *et al.* Clin Infect Dis 1997; 25 Suppl 1, S57–63. http://www.ncbi.nlm.nih.gov/pubmed/9233666

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

Lyme neuroborreliosis: Principles of treatment 1

- 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

- Doxycycline 200mg bd →Higher levels in CSF: Dotevall L *et al.* Antimicrobial agents and chemotherapy 1989; 33(7): 1078–80.

Lyme neuroborreliosis: Principles of treatment 2

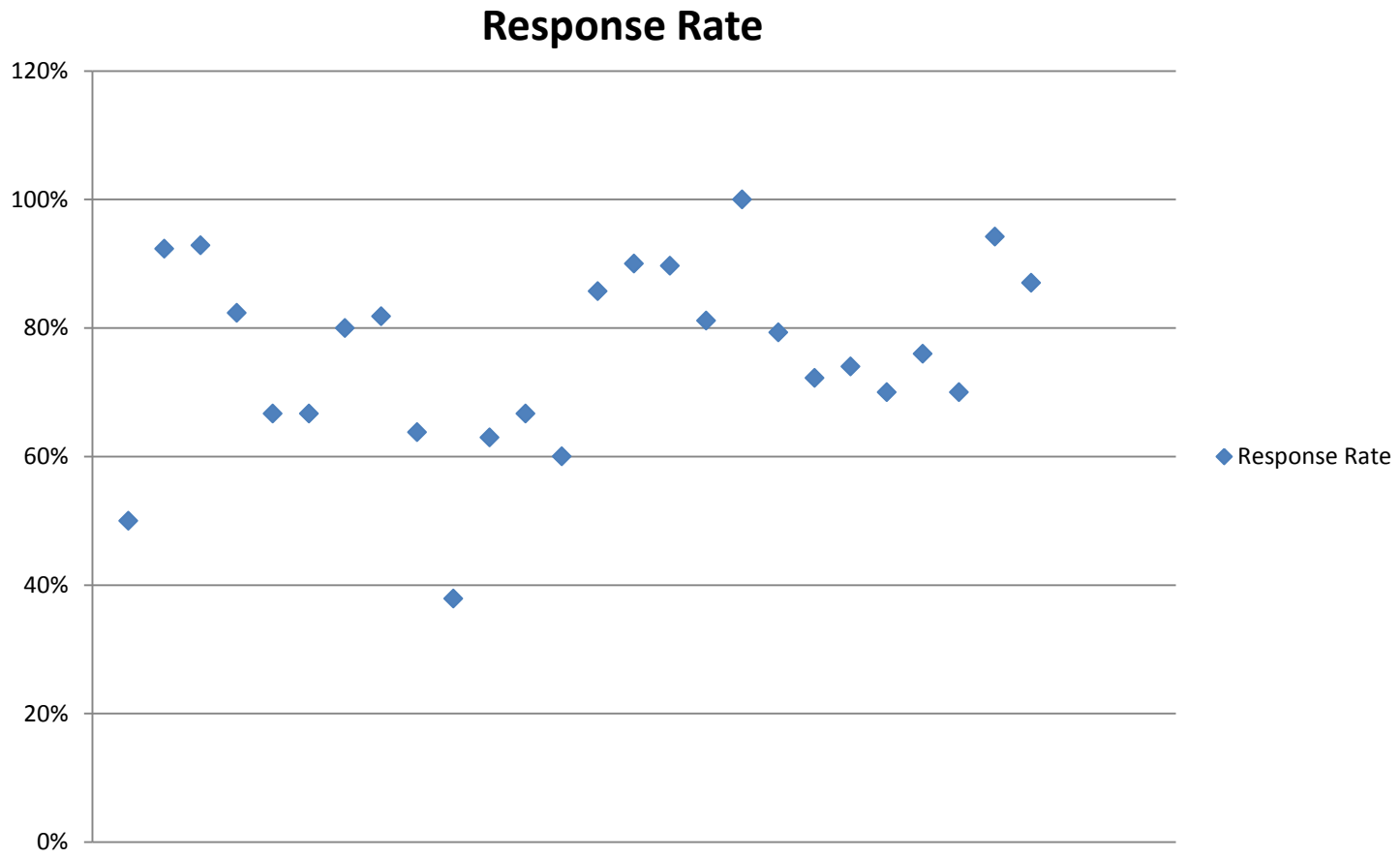
- Research in Europe has mainly studied early LNB
- Guidelines for late LNB extrapolate from early LNB and a small number of US trials of variable quality
- 2 UK studies suggest re-treatment and longer treatment may be beneficial[1,2] (1.Dillon R *et al.* Clinical medicine 2010; 10, no. 5 : 454-7. 2. White B *et al* QJM: 2012; 1–6.)
- Treatment of Late LNB is uncertain
- Polarisation of Expert opinion: (Easy vs. Hard)

EFNS Recommendations 2010

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

	Adults	Children
Early LNB - PNS (meninges, cranial nerves, nerve roots, peripheral nerves	Oral doxycycline 200mg, IV ceftriaxone 2g, IV Penicillin, IV Cefotaxime 14 days Level B	Oral doxycycline*, IV ceftriaxone 14 days *EFNS: not < 8years *BNF: not < 12 years
Early LNB – CNS (encephalitis, myelitis, vasculitis)	IV ceftriaxone 2g 14 days GPP	IV ceftriaxone 2g 14 days GPP
Late LNB – PNS (peripheral neuropathy + ACA)	Oral doxycycline 200mg, IV ceftriaxone 2g 21 days GPP	
Late LNB – CNS (encephalitis, myelitis, vasculitis)	IV ceftriaxone 2g 21 days GPP	IV ceftriaxone 14 days GPP

EFNS Guidelines: Treatment Outcomes



Lyme borreliosis:
Studies of late stage treatment A

- Fallon B A *et al.* A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology 2008*; *70*(13): 992–1003

- Krupp LB *et al*. Study and treatment of post Lyme disease (STOP-LD): A randomized double masked clinical trial. *Neurology 2003*; *60*(12): 1923–1930

- Donta ST. Macrolide therapy of chronic Lyme Disease. *Medical science monitor : International medical journal of experimental and clinical research 2003*; *9*(11): PI136–42

Lyme borreliosis:
Studies of late stage treatment B

- Klempner MS *et al*. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *New England Journal of Medicine 2001*; *345*(2): 85–92

Lyme neuroborreliosis: what remains?

- 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)

The Journey

- 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