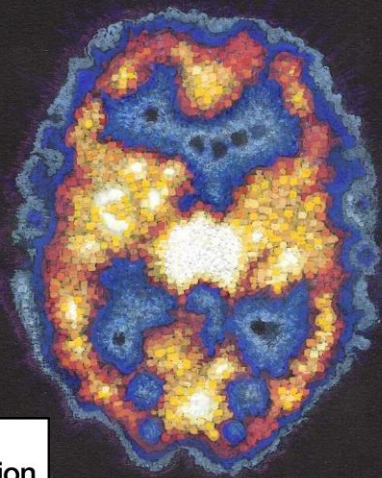
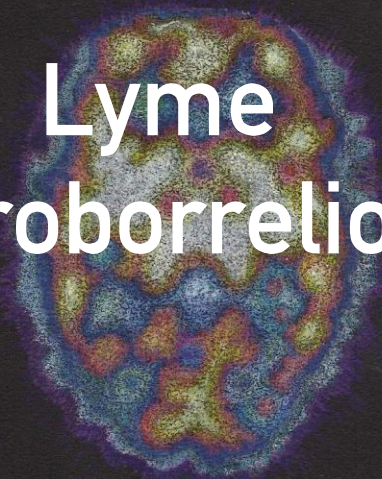


Lyme Neuroborreliosis



What is Lyme Neuroborreliosis?

Lyme disease is caused by some species of bacteria in the genus *Borrelia*, which belongs to the group of spiral-shaped bacteria called spirochaetes. Those which cause syphilis also belong to this group. In nearly all known cases, Lyme disease bacteria are transmitted to humans by the bite of an infected tick.

Lyme disease has been called 'The New Great Imitator' since, like syphilis, it may affect many parts of the body, including the skin, nervous system, heart, joints and eyes. Lyme neuroborreliosis (LNB) occurs when the disease affects the nervous system. If not diagnosed and treated early there can be a more severe illness with worse outcome.

In Europe *Borrelia garinii* is the main species causing LNB. Less frequently *Borrelia afzelii* may lead to an atypical picture (dizziness, non-specific symptoms). *Borrelia burgdorferi sensu stricto* causes LNB in the USA but rarely in Europe. In rare cases, *Borrelia valaisiana* has been identified as the likely cause of LNB.

How does LNB develop?

Most guidelines refer to LNB going through stages:

- **Early LNB:** less than 6 months from onset.
- **Late LNB:** more than 6 months.

However, the evidence suggests that these stages may not be clear cut. Neurological symptoms can appear early, before a rash develops, or later on if the disease persists.

LNB may involve the central nervous system (**CNS**) and peripheral nervous system (**PNS**). CNS symptoms involve the brain and spinal cord and PNS symptoms involve the motor and sensory nerves, including the facial nerve if there is a facial palsy.

Lyme bacteria may evade the immune system and spread within the body. They can cross the blood brain barrier into the CNS and persist in the brain, an immune privileged site. LNB may become latent and be reactivated by stress or other illness. Co-infection with other tick-borne diseases may complicate the picture, causing atypical symptoms and a more severe illness.

What are the symptoms of LNB?

In the first days and weeks, early symptoms of Lyme disease may resemble 'flu' with fatigue, headache, neck pain, muscle/joint pains and fever. In LNB only 40-50% of people remember a tick bite and 20-30% recall a slowly expanding 'bull's eye' rash called erythema migrans (EM) appearing on the skin.

Individuals vary
Acute or gradual onset
Rash not always first sign

In Europe, symptoms which affect the nervous system are thought to develop in 15-25% of people days to months after infection.

The following early, typical symptoms and signs are referred to as 'Bannwarth's syndrome':

- **Radiculitis** – inflammation of motor and/or sensory spinal nerve roots. Motor symptoms may cause weakness eg foot-drop or paralysis. Common sensory symptoms include nerve root pain which may be severe with paraesthesiae such as tingling, itching or reduced sensation/numbness, often in a dermatomal distribution.
- **Cranial neuritis** – inflammation of the cranial nerves which emerge directly from the brain. Most commonly the facial nerve (VII) causing facial palsy with weakness or paralysis on one or both sides of the face. Involvement of other cranial nerves may cause double vision (diplopia), drooping eyelid (ptosis), numbness, pain and tingling of the face, hearing loss, dizziness and tinnitus.
- **Meningitis** – inflammation of the membranes which surround the brain and spinal cord. Symptoms may include headache, neck stiffness and sensitivity to light (photophobia). The onset of this may be gradual (sub-acute) and unlike other forms of meningitis, neck stiffness can be minimal or absent. Headache may be severe. LNB causes an 'aseptic' meningitis; less commonly, chronic meningitis.

Any one patient will have from one to many of the above symptoms.

What other symptoms occur in LNB?

Any part of the nervous system may become affected giving a wide range of symptoms and signs:

- Cognitive: memory problems, slowed thinking and information processing, word finding difficulty, word/letter reversals, difficulty with numbers, episodes of disorientation, confusion, difficulty concentrating and maintaining/dividing attention.

"I got into the car to drive and couldn't remember what to do."

- Fatigue – profound/debilitating.
- Headache - may be severe and prolonged.
- Pain – neuropathic pain, experienced as tingling, pricking, crawling sensations, itching, coldness, burning, shooting pains and 'electric shock' sensations, which can be intermittent and worse at night.
- Dizziness, hearing loss and tinnitus.
- Sensitivity to light and sound, altered sense of taste/smell. Visual disturbances.
- Seizures and movement disorders.
- Tremor, muscle weakness, unsteady gait (ataxia).
- Mood disturbance: anxiety/panic attacks, depression, mood swings - episodes of rage/irritability; suicidal thoughts/behaviour.
- Disturbed sleep and nightmares.
- Gastrointestinal motility problems eg diarrhoea or constipation.
- Urinary problems eg retention or incontinence.

Many areas of life may be adversely affected including relationships, education, work and recreation. Activities such as driving, using the telephone and holding a conversation may become difficult which may lead to increased isolation.

"I couldn't cope with the phone or even leaving the house."

Is it different in children and older people?

Facial palsy with headache and fever has been shown to predict early LNB in children during peak Lyme disease season (May-Oct). Aseptic meningitis can occur which has slower onset than viral or meningococcal meningitis. Compared to adults, painful radiculitis is less common.

In a significant proportion of children, neurological examination may be normal. Weight loss and gastrointestinal symptoms may occur.

"My 8 year old had very aggressive episodes of hitting and biting - quite out of character."

In children, anxiety, emotional disorders and difficulties with attention and learning may develop if LNB is undetected or untreated. This may affect social and educational development. It may be mistaken for ADHD and other behavioural and developmental disorders. Small children may only have non-specific symptoms such as loss of appetite, fatigue, headache and behavioural problems.

Children can be affected indirectly if a parent or family member has Lyme disease.

Older adults may develop painful radiculitis as the main symptom. They may be more vulnerable to LNB as a result of immune suppression caused by other medical conditions, drug treatments or age.

LNB is a treatable cause of acute confusional states and dementia.

Course of the disease

Individuals vary in the type and severity of symptoms they develop, and the onset may be acute or gradual. The illness may follow a relapsing course.

It may progress to cause peripheral neuropathy and when this affects a number of unrelated nerves, is called mononeuritis multiplex.

There may be evidence of acrodermatitis chronicum atrophicans (ACA) skin changes in the affected limb.

Encephalopathy refers to mild/moderate cognitive problems occurring in the absence of CNS inflammation.

"I didn't know where my legs were unless I looked at them."

Central nervous system complications are said to be rare and include

- **encephalitis** (inflammation of the brain)
- **myelitis** (inflammation of the spinal cord)
- **vasculitis** (inflammation of cerebral blood vessels).

If lower parts of the brain (brain-stem) and spinal cord are affected this may cause problems with the **autonomic nervous system** which controls bodily functions such as blood pressure and heart rate. This can lead to difficulty in standing (orthostatic intolerance).

Tilt-table testing may help diagnose this and various treatments are available. One type of autonomic problem seen with LNB is postural orthostatic tachycardia syndrome (POTS), where the pulse rate rises by over 30 beats/min on standing.

How is LNB diagnosed?

- Whilst taking account of test results, the diagnosis of LNB is ultimately a clinical one. Alternative diagnoses may need to be excluded (see below).
- Physical and neurological examination may show weakness/paralysis, cranial nerve deficits, reduced sensation, mild meningeal irritation, abnormal reflexes, reduced vibration sense in the limbs, unsteady gait, poor coordination, cognitive problems, clouded consciousness and confusion.
- If there is any degree of confusion, memory problems or altered consciousness level, it is important to listen to others who can give an account of the illness and the patient's usual self.

What tests help in diagnosis?

Routine blood tests – inflammatory markers may be normal. Full blood count and liver function tests may be normal if there are no co-infections.

Serology - The ELISA and immunoblot (western blot) are indirect tests on blood serum and other bodily fluids. They are used to confirm the presence of antibodies to *Borrelia*. Serology has its limitations and a negative result does not exclude a diagnosis of LNB.

Gold Standard tests have limitations:

- Culture is difficult. *Borrelia* are fastidious and slow-growing
- Polymerase Chain Reaction (PCR) and microscopy are insensitive due to the low numbers of *Borrelia* present in blood and CSF

Nerve conduction studies - may be abnormal.

MRI brain scan - May be normal or show areas of high signal in the white matter, indicating patches of inflammation similar to multiple sclerosis.

SPECT scan - may show areas of reduced blood flow in late LNB.

Lumbar puncture (LP) - in early LNB may show signs of inflammation:

- ↑ white blood cells (lymphocytic pleocytosis);
- ↑ protein, +/- oligoclonal IgG bands;
- ↑ or normal opening pressure.

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

Cerebro-spinal fluid (CSF) testing - *Borrelia* are present in low numbers in LNB.

- Direct tests such as PCR are insensitive.
- Culture of the organism is difficult.
- Indirect tests: IgG and IgM ELISA and immunoblot may confirm the presence of *Borrelia*-specific antibodies in the CSF. Negative tests do not exclude a diagnosis of LNB. CSF can be positive before the blood serology becomes positive (esp. in children).

Antibody Index - This compares paired samples of serum/CSF to see whether antibodies in the spinal fluid are produced within the CNS (intrathecal antibody production). A positive antibody index is proof of LNB but sensitivity may be only 55-80%.

Cognitive Neuropsychological Assessment - This provides an objective measure of memory problems, word-finding difficulty, visuo-spatial problems etc.

What conditions can LNB be mistaken for?

LNB may resemble a wide range of conditions including but not limited to multiple sclerosis, Bell's Palsy, stroke, polio-like syndrome, Parkinson's disease, dementia, delirium, motor neurone disease, Guillain-Barré syndrome, transverse myelitis, sarcoidosis, ME/CFS, fibromyalgia. Other infections that can involve the nervous system, such as syphilis and HIV may need to be excluded.

LNB may present as a psychiatric disorder eg depression, bipolar disorder, anxiety disorder, panic disorder, OCD, manic psychosis, schizophrenia-like psychosis, organic psychosis, hypochondriacal, somatoform, conversion and dissociative disorders.

Pointers towards a non-psychiatric diagnosis include:

- Symptoms and signs of physical illness
- Atypical or unusual psychiatric symptoms
- New onset, especially > 40 years of age
- Absence of psychological factors
- No personal/family history of psychiatric illness
- Poor response/sensitivity to side-effects of medication

Chronic illness, pain and disability may have a profound negative impact on quality of life and in some cases lead to depression, anxiety, loss of confidence, feelings of worthlessness and possibly suicidal thoughts/behaviour.

What is the Treatment?

Most people with LNB respond to treatment with antibiotics which should be given promptly to avoid late stage LNB and prevent late complications.

If there is reasonable suspicion of LNB, treatment should not be delayed in waiting for antibodies to develop.

- Research in Europe has mainly studied early LNB. The treatment of late LNB is uncertain as there have been no good quality European trials. It is unclear whether 'standard' treatment for early uncomplicated illness will treat more complex disease.
- There are no good quality comparisons of different treatment length. *Borrelia* divide much more slowly than most bacteria, so some clinicians favour a longer course of treatment.
- It is also unclear whether long-term or re-treatment is helpful. Two UK studies suggest this may be so.
- It is unknown whether continuing symptoms after 'standard treatment' are due to persistent infection, immune activation or tissue damage. It may be prudent to treat patients on a pragmatic basis pending further research.

Treatment is antibiotics with

- good CSF penetration
- good tissue penetration

The most effective agent, dose and duration are currently unknown.

- Oral doxycycline, intravenous (IV) ceftriaxone and IV penicillin G which cross the blood brain barrier are used to treat LNB. The usual dose of doxycycline is 100mg twice daily. One study showed 200mg of doxycycline twice daily was needed to reach a high enough level quickly in the CSF.
- In the UK, doxycycline is usually not advised for children under the age of 12 years or pregnant women. European and American guidelines allow doxycycline treatment in children over the age of 8 years.

Data is lacking on treatment of LNB in children with oral amoxicillin or cefuroxime. Children with CNS disease or meningitis may need treatment with IV antibiotics.

While recognising the uncertainties and need for further research, European guidelines make recommendations for diagnosis and treatment (see European Federation of Neurological Societies Guidelines 2010).

There may be marked improvement of symptoms within days of treatment, though recovery may take several months. Residual symptoms may occur in 12 - 50%, especially if there was delay in treatment or CNS involvement. As with any serious illness, rest and sleep are important in recovery.

Treatment failure and relapse may occur, but it is uncertain how often this happens. UK studies have reported successful repeat treatment.

Can any other Treatments help?

Neuropathic pain may be hard to treat and tends not to respond to ordinary painkillers.

Antidepressants (eg amitriptyline, duloxetine), anti-epileptic medications (eg gabapentin, pregabalin,) and opioid painkillers (eg tramadol) provide varying degrees of relief, but side-effects can occur. Doses may need to be gradually tapered.

Specialist pain clinics may help where pain is severe or disabling.

It is important to treat any resulting psychiatric problems such as depression. Any suicide risk needs to be carefully assessed and managed, including urgent referral to mental health services if necessary.

Useful NICE Guidelines

CG96 Neuropathic pain in non-specialist settings

CG91 Depression in adults with a chronic physical health problem

CG103 Delirium: diagnosis, prevention and management

Summary

When Lyme disease infects the nervous system it is referred to as Lyme neuroborreliosis (LNB).

Lyme neuroborreliosis

- can be difficult to diagnose unless it presents with typical symptoms and clinicians actively consider this diagnosis;
- can affect any part of the nervous system, including the brain, if left untreated;
- 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;
- needs antibiotics with good tissue and CSF penetration;
- has a set of European guidelines which acknowledge the limited evidence on which to base treatment recommendations.

Further help

www.samaritans.org

www.carersUK.org Carers and close relatives may benefit from meeting with a carers' officer who is usually linked to the GP practice. Carer support and if necessary counselling may be beneficial.

www.gov.uk provides information on benefits and financial help for those with a disability and for carers, which is important as financial hardship can add to the burden of illness. Disability rights, work, transport and provision of specialist equipment is also covered.

Further Information

All our leaflets are available free of charge from our website where you can find out more about Lyme disease, including links to many other resources, a glossary and our patient help email line. References for any information given in this leaflet can be supplied on request.

www.LymeDiseaseAction.org.uk

Leaflets are also available from:
Lyme Disease Action,
PO Box 235, Penryn, TR10 8WZ, UK



Including a donation/SAE will help us in our work for people affected by Lyme disease.

Cover image: SPECT scan before (top in background) and after treatment.

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