# NEUROLOGICAL COMPLICATIONS OF LYME DISEASE

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## SUMMARY

Neurological signs can occur in every stage during the course of Lyme borreliosis. In this article neurological manifestations, their clinical significance, diagnosis and therapy are discussed in detail.



KEY WORDS

*Lyme borreliosis, neurological manifestations*


## INTRODUCTION

Lyme disease is a tick transmitted, spirochetal illness which generally occurs in stages characterized by different clinical manifestations and preferentially involves the skin, nervous system, joints and heart.

Direct effects of the organism and the host's reaction are determinant in the pathogenesis of the disease. All organ systems may be affected to various degrees, either early or late in the illness. Early infection generally manifests itself as localized erythema migrans (Stage 1), which may be followed by disseminated infection (Stage 2) characterized by multisystem involvement and occurring within weeks or months. Late or persistent infection (Stage 3) usually begins a year or more after onset, and is characterized by sclerotic skin lesions, chronic arthritis and more rare by progressive neurologic abnormalities.

## NEUROLOGIC SYMPTOMS

### Lyme disease

#### Stage 1

Episodes of headache and mild meningism can begin while erythema migrans is still present, more frequently in patients with multiple secondary skin lesions.

The cerebrospinal fluid (CSF) is usually normal, but can show a transitory pleocytosis (1).

**Stage 2**

Weeks to months after onset of illness, usually after EM has faded, nervous system abnormalities may appear and are typically represented by the triad of symptoms meningitis, cranial neuritis and painful radiculitis (2). However, a much broader range of peripheral nervous system (PNS) manifestations including GBS-like syndromes (3), plexopathies (4), entrapment neuropathies (5), multiple mononeuropathies can be observed.

Central Nervous System (CNS) involvement is characterized by impaired memory and emotional lability (6). Acute or subacute myelitis is an infrequent focal CNS impairment sign at stage 2.

## Meningitis

Meningitis is the most common neurologic manifestation of stage 2. It may be the presenting feature of Lyme disease when the skin bite has been neglected. Eighty to ninety % of patients with diffuse acute illness have pleocytosis of the CSF, yet only 25 % have unequivocal meningitic symptoms. Headache affects 50 % of patients with CNS inflammation, less frequent are photophobia, nausea vomiting and low-grade fever.

Symptoms usually begin acutely, persist for one to two months, and then resolve gradually over weeks in untreated patients. CSF pressure may be increased, and cells count typically reveals 100-200 cells/mm$^3$, mainly lymphocytes and less numerous plasma cells. An increase of CSF protein content is also observed, with detection of oligoclonal bands and specific antibodies in 80 % of patients with meningitis. They can persist for years in the absence of clinical signs of activity (2).

## Cranial neuropathies

Bell's palsy is the most common sign. It may be unilateral or bilateral (8). In patients with bilateral Bell's palsy, the two sides become paralyzed within days or weeks of each other. Multiple cranial neuropathies are also observed. They can occur with Bell's palsy or, less commonly, without it. The other most often affected cranical nerves are the third, fourth and sixth. If the fifth cranial nerve is impaired, the symptoms are likely to be sensory, rather than motor. If the eighth cranial nerve is involved the symptoms may be dizziness, otalgia and sensory throat (9).

Optic nerve abnormalities make up approximately 3 % of the cranial neuropathies in stage 2. Optic disc edema is observed more often than optic atrophy (10).

## Lymphocytic meningoradiculitis (Bannwarth's syndrome)

A radicular neuralgia is associated with chronic lymphocytic pleocytosis of the CSF, generally without meningism. The disease is characterized by neurological deficiencies, such as unilateral or bilateral Bell's palsy or disseminated radiculopathies associated with severe pain at times of radiating or of migratory mature (11).

## Parenchymal abnormalities

Cerebral symptoms are occasionally observed during stage 2, and are usually characterized by impaired memory and concentration, depression and emotional lability. More severe CNS symptoms are unusual and can be characterized by focal signs of spinal cord involvement (12). Acute or subacute myelitis usually follows an already established meningoradiculitis. The most common clinical finding is spastic paraparesis at the level of intercostal nerves. Nuclear magnetic resonance (NMR) images are nonspecific. Improvement is slow and often only partial.

## Neurological signs in late Lyme disease

**Stage 3**

Assessment of neurologic abnormalities in persistent Lyme disease may be quite difficult since the manifestations are often subtle, non specific and difficult to quantify (13).

The most common form of chronic CNS involvement is a progressive encefalopathy affecting memory, mood and sleep, sometimes with language disorders (14). Cases of leukoencephalomyelities have been described, sometimes clinically mimicking multiple sclerosis (MS). PNS abnormalities are characterized by prevalent sensory symptoms, at electrophysiologic testing giving evidence of an axonal polineuropathy.

## Encephalopathy

Halperin (6) (1989), Steere (1990) and others have pointed out that many patients with chronic Lyme disease have an antibiotic responsive encephalopathy characterized by deficiencies in memory and concentration. These are often accompanied by profound fatigue, but rarely by either physical abnormalities on neurological examination nor by

CSF inflammation. Similar neurologic abnormalities have been reported in seropositive children whose histories were compatible with Lyme disease.

### Progressive encephalomyelitis

This entity is characterized by sudden focal deficiencies, either permanent or transient. The most common focal abnormalities are hemiparesis, paraparesis, aphasia, and ataxia. Seizures have also been described (15). NMR can show multiple areas of increased T 2-signal intensity in the periventricular regions, mimicking demyelinating lesions.

Several serological studies (16,17) were unable to provide evidence of a relationship between Lyme disease and MS (18). We also detected anti-*Bb* antibodies in cases of MS patients residing in endemic areas; in no case was immunoreactivity detected in CSF, thus confirming that there is no relationship between Lyme disease and MS.

### Polyneuropathy

As many as 50 % of patients with late Lyme disease report tingling paresthesias in the extremities, often intermittent, commonly distal, rarely patchy in distribution. About 25 % of patients with paresthesias have a mild stocking-glove distal sensory loss, but motor weakness and reflex loss are rare. Electrophysiological testing shows diffuse abnormalities suggestive of a patchy, mainly distal axonal neuropathy, possibly due to vasculitis.

Sural nerve biopsy discloses mild loss of myelinated fibers, more evident in the larger ones, a marked thickening of the vessel wall with duplication of the basement membranes and numerous inflammatory infiltrates around small epineurial vessels. Improvement was observed following antibiotic therapy (5).

### Myositis in early disseminated and late Lyme disease

Muscular symptoms are common during stage 2. Over 40 % of patients have myalgias, often migratory in nature, but muscle weakness is usually absent. Rarely, interstitial myositis can be demonstrated on biopsy. Creatinphosphokinase (CK) increased. Typical electromyographic signs of muscular involvement can coexist with those of peripheral nerve involvement. In stage 3 focal nodular myositis can be detected, with evidence of spirochetes in silver stained muscle sections. Here too electrophysiological testing shows, even in such case, coexisting nervous and muscular involvement patterns (19).

## DISEASE MECHANISM

*Bb* is a tick-transmitted spirochete. It can be stained with Giemsa, and can be demonstrated in tissue by silver impregnation techniques. However, *Bb* is difficult to isolate from human biologic material and, even when present, in tissue, the organisms are hard to detect. This suggests that inflammatory and immunological mechanisms are important for the Lyme disease phenotype.

The whole *Bb* as well as its outer surface protein and flagellin, are all chemotactic for polymorphonuclears (PMNS) (20), while LPS has endotoxinlike activity and can stimulate the release of interleukine 1 (IL-1) from macrophages. IL-1 which itself may mediate many of the general features of Lyme disease (21).

Cross reaction of anti *Bb* antibodies with host's antigens, the deposition of immune-complexes in tissue, and the following induction of cellular autoimmunity can be additional pathogenetic factors. In CNS and PNS involvement both mechanisms are probably active. Meningitis almost certainly is caused by borrelial invasion of CSF (22,23). While other CNS abnormalities are perhaps due to vasculitis. Multifocal demielinating lesions revealed by NMR could be explained as an expression of specific T cell lines against *Bb* which cross-react with myelin basic protein (MBP) or galactocerebroside (24,25).

Both the direct effect of the organism and the host's reaction to it may contribute to PNS disease as well. Spinal radiculitis and cranial neuritis may result from direct extension of meningeal inflammation to the nerve roots. Both demyelination and axonal injury occur in the PNS. They probably result from vasculitis, but demyelination could also result from T cell lines cross reactive to peripheral myelin (26).

## TREATMENT

Treatment of early localized disease (erythema migrans) with oral antibiotics does not always prevent development of extracutaneous complications, including nervous system disease. Currently the best choices for treating early disease are doxycycline for adults, with amoxicillin as an alternative, and just amoxicillinolone in children. Treatment should be prescribed for a minimum of ten days. Approximately 15 % of treated patients develop an intensification of symptoms during the first 24 hour of therapy (Jarisch-Herxheimer reaction), but no special supportive treatment is required.

**Treatment of the neurological manifestations in stage 2:**

Parenteral antibiotic therapy is generally necessary. High dose intravenous aqueous penicillin G (20 million units daily for 10 days) are widely used. Alternatively intravenous cefotaxime, ceftriaxone, or chloramphenicol are administered.

In a controlled trial it was shown that intravenous doxycycline is as effective as i.v. penicillin. Systemic symptoms and radicular pain generally improve within days, while motor deficits resolve more slowly, and normalization of CSF parameters can take months.

**Treatment of the neurological manifestations in stage 3:**

Progressive borrelial encephalomyelitis responds to high-dose intravenous penicillin or intravenous doxycycline with resolution of pleocytosis and reduction of CSF protein content, although specific antibodies may persist in the CSF. In a randomized trial Dattwyler (27), compared ceftriaxone to penicillin, with both resulting in the same improvement. Peripheral and central signs of stage 3 take longer to resolve requiring at least six months.

## CONCLUSIONS

The wide range of presentation in neuroborreliosis can make recognition difficult. In a patient with vague, subjective symptoms like headache, musculoskeletal pain or fatigue without any skin or joint involvement the diagnosis can be difficult.

Under such circumstances epidemiologic clues may aid the diagnosis; a history of tick bite, travel or residence in an endemic area or onset in summer in case of stage 2 involvement. Once it is suspected on clinical grounds the diagnosis usually can be confirmed by demonstrating an immune response to *Bb* in serum, CSF or both. The culture or direct visualization of *Bb* from biopsy specimens is difficult.

Anti *Bb* antibodies can be assayed by both indirect immunofluorescence (IFA) and by Elisa (23). The last technique is preferred at present as it is more specific and more sensitive.

Elevated serum levels of specific IgM antibody indicate acute infection, while elevated levels of IgG antibody may indicate either active or past infection. Immunoblot is utilized to confirm the specificity of a positive result on Elisa or IFA. The diagnosis of Lyme disease in a patient with symptoms and signs of involvement of the peripheral and central nervous system can be difficult especially in endemic areas, where about 20 % of healthy subjects have anti-IgG antibodies to *Bb* in IFA or Elisa in the serum (28) and furthermore false positive reactions do occur in patients with rheumatoid arthritis, infectious mononucleosis, syphilis, leptospirosis etc.

Therefore a definite diagnosis of Lyme disease involving the nervous system can be made only if compatible neurologic symptoms are accompanied by at least one of the following parameters:

1) a history of acute or chronic specific skin lesions
2) raised titers of specific antibodies in serum and CSF or in CSF alone
3) a typical involvement of other organ systems
4) seroconversion or a fourfold rise in titers of sequential samples of sera.

One has however to make sure that other etiologic factors were eliminated.

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