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Diagnostic Workup and Treatment of Lyme Disease

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Diagnostic Workup and Treatment of Lyme Disease

Fig. 1: Miniaturized immunoblots for infection diagnostics in microplate format

Laboratory diagnostics of tick-borne infections are based on direct and indirect detection methods. Direct methods include blood smears, pathogen culture, or PCR-based tests, while indirect detection is usually based on measuring specific antibodies against the particular pathogen in the patient serum, plasma, or CSF. For cases where obtaining suitable sample material is difficult or the pathogen quantity in the sample is too low, antibody detection is often the most important laboratory diagnostic method. For detecting antibodies with suspected Borrelia infection, there are various serological test systems available such as ELISA, ChLIA, immunoblots, and EUROMicroblots (miniaturized immunoblots in microplate format).

Lyme disease is a vector-borne disease that is transmitted by tick bites. The infectious disease is caused by the bacterium *Borrelia burgdorferi* or related species in this group of spirochetes and has a range of presentations—often with characteristic cutaneous manifestations, joint symptoms, or neurological complications (neuroborreliosis). The laboratory diagnosis is based on serological tests, e.g., an enzyme-linked immunosorbent assay (ELISA) or immunoblot. The clinical presentation and progression of the disease must be evaluated as part of the diagnostic workup and other causes must be considered or ruled out by differential diagnostic evaluation. Because it is a bacterial infection, the disease can be very well treated, particularly in the early stage, with specific antibiotics.

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Introduction

Lyme disease is an infectious disease caused by the spirochete *Borrelia burgdorferi* sensu lato. Lyme disease is transmitted by vectors—in this case ticks—to humans and occurs predominantly in the summer months in Germany. The risk of infection depends on the prevailing weather conditions with acute disease occurring more commonly between July and August. This does not apply to manifestations with a longer latent period such as Lyme arthritis or late Lyme neuroborreliosis.

In Germany, it can be assumed that 12.7% to 16.5% of all ticks can transmit Borrelia. Not every tick bite necessarily leads to neuroborreliosis or Lyme disease. Only about one in 100 patients develop Lyme disease after a bite from a tick that is confirmed as infected.

The classic skin rash, erythema migrans, frequently develops with Borrelia infection after a tick bite *(Fig. 2)*.

Erythema migrans is a local skin rash that is characteristically clear in the middle and migrates as the disease progresses, that is, its size and shape change. However, erythema migrans can also completely fail to materialize or may be diagnostically overlooked. The course of multisystemic Lyme disease is often divided into three stages. This division is based on a transition from an initially rather local manifestation to systemic symptoms.

While all Borrelia can trigger erythema migrans, *B. garinii* and *B. bavariensis* in particular are associated with neurological manifestations.

Manifestations and symptoms of neuroborreliosis

Typical neurological symptoms of Lyme disease that define neuroborreliosis are inflammation of the meninges and nerve roots (meningopolyradiculitis) or cranial nerve deficits. Patients affected with meningopolyradiculitis typically develop headaches, pronounced back pain, which can be attributed to inflammation of the nerve roots (with increasing pain symptoms at night), and paralysis of the extremities. These symptoms can also be observed singly, which makes clinical diagnosis difficult.

Cranial nerve deficits—most commonly affecting the facial nerve—are frequently associated with facial palsy (unilateral or bilateral) that is occasionally mistaken for a stroke in the differential diagnosis.

More rarely, the central nervous system is involved in neuroborreliosis. This encephalomyelitis is caused by an inflammatory response (generally in the spinal cord) and leads to sensory problems and spastic pareses of the legs as well as bladder and rectum dysfunction. In rare cases, Lyme disease can also lead to inflammation of the blood vessels, which in turn leads to local thromboses and circulatory disorders. This Borrelia-associated vasculitis is associated with a high risk of stroke for affected patients.

Due to the highly variable symptoms, there is often considerable uncertainty about which symptoms can be attributed to neuroborreliosis and which neurological deficits are non-specific and/or have a different origin. This includes, for example,

fatigue, concentration problems, and also impaired memory performance. These symptoms occur very frequently in the population and there are no indications that these symptoms are caused by Lyme disease in every case. Even the assumption that chronic polyneuropathy is often triggered by Lyme disease is not confirmed in studies. Borrelia appear to cause polyneuropathy rather rarely (<1%).

Diagnostic workup

The diagnosis of neuroborreliosis requires:

1. Clinical symptoms that are compatible with neuroborreliosis.
2. A positive serological finding, that is, evidence of antibodies against Borrelia.
3. Findings indicating inflammatory changes in the cerebrospinal fluid.

All three of these criteria must be fulfilled for a reliable diagnosis of neuroborreliosis, because even healthy persons can have antibodies against Borrelia. In Germany about 5.8% of women and 13.0% of men have antibodies against Borrelia.

Serology

With clinically suspected neuroborreliosis, a serological examination should immediately be initiated. The antibody diagnostics involves testing for IgG and IgM antibodies against Borrelia in the blood and CSF (see below) of the patient. These antibodies are directed toward antigens that are expressed on the cell surface of the Borrelia bacteria. Important targets for immunoglobulins are, e.g., OspC (outer surface protein C) and VLsE (variable major protein-like sequence, expressed). These proteins are expressed recombinantly and used for test diagnostics using ELISA and immunoblots. The serological antibody determination is performed in two steps with screening carried out first. This uses an ELISA or comparable methods. In the second step, the confirmatory test (Western blot or line blot) is carried out. Newer procedures use miniaturized line blots arranged in 96-well microplates as the confirmatory test so that screening and confirmatory tests can be performed using an ELISA reader *(Fig. 1)*.

A staged test procedure is generally recommended, as a matter of principle, that is, a confirmatory test should only be carried out for a pathological screening test. Just as important as careful performance of the antibody test is correct interpretation of the antibody findings. In this context the following criteria must be noted:

1. About 5.8% of all women and 13.0% of all men have specific antibody titers against Borrelia with no symptoms and no clinical significance.
2. As soon as a confirmatory test has been carried out, it also becomes critical for the overall interpretation of the findings. If the confirmatory test is negative, the overall finding is negative, while if it is positive, the overall finding is also considered positive.
3. Antibodies are detected in most cases of neuroborreliosis. Seronegative Borrelia infections only occur in the initial stage with erythema migrans (and also only rarely in this constellation). Conversely, with suspected neuroborreliosis or Lyme disease should neither IgG nor IgM antibodies be detected, the patient does not have neuroborreliosis.
4. Some patients have an isolated increase in IgM antibodies against Borrelia. It is then assumed that this is an early stage of the infection. This assumption is, however, generally wrong. Detecting isolated weak IgM levels often occurs as part of oligoclonal stimulation (Epstein-Barr virus infection, cytomegalovirus infection) or as a cross-reaction to other spirochete infections (*T. pallidum*; also IgG).

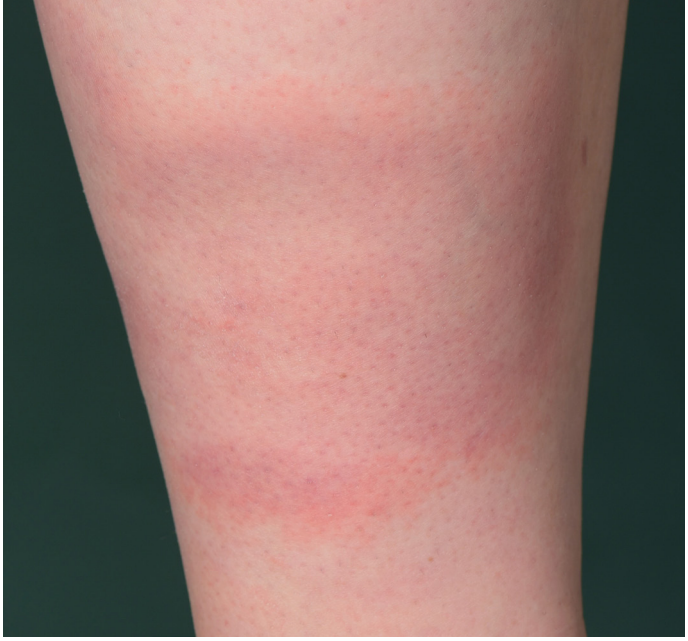

Fig. 2: Typical skin change: erythema migrans
Copyright: Priv.-Doz. Dr. med. Dr. rer. nat. Jan Ehrchen, Clinic for Skin Diseases, Münster University Medical Center

Testing the CSF

For suspected neuroborreliosis, it is also generally recommended to test the cerebrospinal fluid. This is done to detect inflammation in the CSF, rule out other possible causes of the neurological symptoms, and investigate specific antibody formation in the central nervous system using the "antibody index" (see below).

Neuroborreliosis is associated with a significantly elevated cell count in the CSF that is not uncommonly as high as between 100 and 300 cells/µL (normally <5 cells/µL). Intrathecal antibody synthesis in the form of oligoclonal bands can also be demonstrated (in the CSF). This is not specific for neuroborreliosis and is also present with other infectious and autoimmune diseases of the central nervous system. To confirm a Borrelia infection in the nervous system, direct culture of the bacteria in a petri dish could be considered in principle—this procedure is, however, difficult and laborious. PCR from a CSF sample is also possible in principle but the overall low number of bacteria (even with a florid infection) means that the result is often a false negative. Therefore, an indirect but highly sensitive and specific detection method is usually used that requires a CSF and a serum sample: the specific antibody index.

The specific antibody index

The Borrelia-specific antibody index (AI) can show if there is specific (!) intrathecal production of antibodies against Borrelia.

The AI is generally already calculated by the microbiological laboratories and noted on the findings. The essential prerequisite for calculating the AI is sending paired serum and CSF samples to the laboratory.

The antibody index is calculated as follows:

$$\frac{IgG\ AB\ in\ CSF : IgG\ AB\ in\ serum}{Total\ IgG\ in\ CSF\left(\frac{x}{x}\right) : total\ IgG\ in\ serum\left(\frac{x}{x}\right)}$$

If the value is ≥1.5, neuroborreliosis should be considered. This threshold is generally exceeded with neuroborreliosis (with the exception of a very short disease duration). An increased antibody index can also be demonstrated under some circumstances years after resolved neuroborreliosis.

In unclear cases, the CSF should be tested for the chemokine CXCL13. The chemokine CXCL13 is formed by monocytes, macrophages, and dendritic cells and has a chemotactic effect on B cells and T helper cells. In early neuroborreliosis the interaction of *Borrelia burgdorferi* with monocytes leads to increased secretion of CXCL13 and thus to elevated CXCL13 concentrations in the CSF.

However, CXCL13 is not specific and is also found with other diseases such as multiple sclerosis.

Diagnostic criteria for neuroborreliosis

Based on the clinical symptoms (see table), the serology, and the results of the CSF examination, diagnosis of neuroborreliosis is classified as possible, probable, or definite.

Treatment

Patients with a definite or probable diagnosis of neuroborreliosis should be treated with the appropriate antibiotics. There are various active ingredients available with ceftriaxone (intravenous) or doxycycline being very commonly used.

Antibiotic treatment should be administered over a period of 14 to a maximum of 21 days. The period can be adjusted to the clinical symptoms. For the common manifestation of neuroborreliosis, generally a 14-day antibiotic treatment period is sufficient. There is no scientific evidence that Borrelia persist beyond a longer antibiotic treatment. There is thus also no indication to continue antibiotic treatment beyond this period. One study showed that longer antibiotic treatment did not lead to an improvement in the neurological symptoms but the rate of antibiotic-associated adverse effects increased. (Under drug treatment there is generally a decrease in the CXCL13 in the CSF, meaning that CXCL13 can also be used as a therapeutic marker.)

Prognosis and treatment monitoring

In more than 90% of cases, the clinical deficits that occur as part of neuroborreliosis rapidly regress under antibiotic treatment.

In contrast, CSF changes (such as the increase in the cell count and the antibody index) may persist for a long time. This situation should not mislead clinicians to assume chronic neuroborreliosis.

There is no scientific basis to suggest that Borrelia can lead to a chronic infection of the nervous system after antibiotic treatment. Non-specific symptoms such as fatigue or cognitive impairment after neuroborreliosis are by and large rare and should not be considered an expression of persistent "chronic neuroborreliosis". Several randomized placebo-controlled studies showed no indication of an effect of prolonged antibiotic therapy on these symptoms.

Prevention

The most effective preventive measure is to wear clothing with long sleeves and pant legs that covers the body when outdoors in nature. The skin should be carefully checked if there is suspected tick contact. If a tick bite is confirmed, the parasite must be removed as soon as possible, for example, using special forceps. The body of the tick must not be crushed during removal to prevent potential transmission of Borrelia from an infected tick.

	Definite	Probable	Possible
typical clinical symptoms	✓	✓	✓
IgG or IgM antibodies in the serum	✓	✓	✓
inflammatory CSF syndrome (lymphocytic pleocytosis, intrathecal Ig synthesis)	✓	✓	✗ (not present / not performed)
positive AI or culture or PCR in the CSF	✓	✗	✗

Table: Diagnostic criteria for neuroborreliosis

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https://www.euroimmun.de/en/products/infection-diagnostics/id/tick-borne-infections/

Deutsche Gesellschaft für Neurologie e.V. (German Society for Neurology)
https://dgn.org/leitlinien/ll-030-071-2018-neuroborreliose