Delayed Diagnosis of Lyme Neuroborreliosis Presenting With Abducens Neuropathy Without Intrathecal Synthesis of Borrelia Antibodies

Daiva Radzišauskienė1, Arvydas Ambrozaitis1, Eglė Marciuškienė2
1Department of Infectious, Chest Diseases, Dermatovenerology and Allergology, Vilnius University, 2UAB “Endemik diagnostika” Laboratory, Lithuania

Key Words: abducens neuropathy; chemokines; Lyme disease; Lyme neuroborreliosis; mononeuropathy multiplex; serological diagnosis.

Summary. Lyme borreliosis is the most common tick-born infection in Europe. Global climate change expanding the range of tick vectors and an increase in the incidence suggest that this disease will remain an important health issue in the forthcoming decades. Lyme borreliosis is a multisystem organ disorder affecting the nervous system in 10% to 15% of cases. Lyme neuroborreliosis can present with any disorder of the central and peripheral nervous systems. The neuro-ophthalmological manifestations are a rare feature of the disease. The intrathecal synthesis of Borrelia burgdorferi antibodies is of diagnostic importance, but in rare cases, immunoglobulins against the Borrelia burgdorferi antigen may not be detected. We report a case of possible Lyme neuroborreliosis presenting with sixth cranial nerve neuropathy at the onset of the disease further developing into typical meningo- radiculitis and multiple mononeuropathy. Surprisingly, Borrelia burgdorferi antibodies were not detected in the cerebrospinal fluid.

Introduction

Lyme borreliosis (LB) is the most common tick-born infection in Europe. Global climate change expanding the range of tick vectors and an increase in the incidence suggest that LB will remain an important health issue in the forthcoming decades (1). It is possible to make only approximate estimates of the LB incidence in Europe because few countries report LB as a compulsorily notifiable disease (1, 2). Epidemiological studies indicate that the mean annual number of LB-notified cases in Europe is higher than 65 400 (1). It is apparent that LB shows a gradient of increasing incidence from the West to the East with the highest incidence in Central and Northern Europe (e.g., more than 100 cases per 100 000 population) and the lowest in the Southern Europe (e.g., fewer than 1 case per 100 000 population) (1, 2). In Lithuania, this disease is mandatory notifiable. The incidence of LB during 2008–2011 ranged from 34 per 100 000 to 107 per 100 000 with the highest incidence being in 2009 (3). The disease is caused by spirochetes of the Borrelia burgdorferi (Bb) group. Lyme disease is a multisystem organ disorder affecting the nervous system in 10% to 15% of cases (4). Nervous system disorders present as aseptic meningitis, recurrent meningoencephalitis or meningoencephalomyelitis, meningoaradiculitis (described by Bannwarth), which is the most common presentation of Lyme neuroborreliosis (LNB), and cranial and spinal neuropathies, where the seventh cranial nerve is most often involved (5, 6).

Although the clinical course of LNB has been well described, sometimes the presentation of the disease along with the lack of agreement on a precise clinical definition of this illness and the lack of standardization of serological assays with a high rate of false-positive results lead physicians to confusion, and a late diagnosis is common. Confusion exists regarding the interpretation of positive or negative results of the serological tests for antibodies to Lyme disease. The intrathecal synthesis of Bb antibodies is of diagnostic importance, but in rare cases, immunoglobulins against the Bb antigen may not be detected (7). According to the data of previous studies, LNB can present with any disorder of the central and peripheral nervous systems (5, 8). Although neuro-ophthalmological manifestations have been reported, this remains a rare feature of Lyme disease (9, 10), and the diagnosis can be delayed in some cases. An early diagnosis and prompt establishment of an adequate antibiotic treatment is needed to achieve a rapid resolution of symptoms and theoretically to avoid spreading and persistence of the infection (6, 8). In this report, we describe a case of possible Lyme neuroborreliosis presenting with abducens mononeuropathy at the very onset of
the disease further developing into typical meningoradiculitis and multiple mononeuropathy. Surprisingly, the Bb antibodies were not found in the cerebrospinal fluid (CSF).

**Case Report**

A 43-year-old previously healthy man developed diplopia on January 18, 2008. He was consulted by ophthalmologists, and left abducens neuropathy was diagnosed. He was treated with the vitamins of group B. Diplopia persisted despite the treatment. Because of an unclear reason of diplopia, the patient was admitted to Alytus County S. Kudirkas Hospital on February 15. The results of blood, liver, and renal function tests and the blood glucose value were within the reference ranges; the results of serological tests for human immunodeficiency virus and syphilis were negative. Cerebral magnetic resonance tomography (MRT) showed no pathological findings. All possible metabolic disorders were excluded. The treatment with prednisone at a dosage of 60 mg a day orally for 7 days, followed by dose tapering by 5 mg every second day, was administered. On the fourth day of hospitalization, the patient developed severe back pain radiating to the abdomen, which was more intense during the night, and the patient had no relief on treatment with any available analgesics. Abdominal ultrasound revealed no pathological changes. An MRT scan of the chest and the lumbar spine excluded a compressive lesion. The serological Bb antibody testing was performed, and specific IgG positivity was determined; however, no IgM antibodies were detected. The patient was discharged from the hospital on February 25 without any improvement. A consultation of an infectious disease specialist was recommended. Back pain disappeared spontaneously within 7 days, but diplopia persisted. On March 3, the patient developed severe back pain again, and 3 days later, right peripheral facial palsy was documented. The patient was consulted by an infectious disease physician in Alytus. The serological testing for Bb antibodies was performed by the immunoblot analysis (Western blotting), which showed the presence of specific IgG antibodies with proteins p31 and VlsE (weak antigen–antibody reaction), but specific IgM antibodies were not detected. The EUROLINE-WB test was applied for the analysis (Germany). The test kit contained test strips with electrophoretically separated antigen extracts of *Borrelia afzelii* (p83, p39, p31, p30, OspC [p25], p21, p19, p17). Each test strip contained a membrane chip coated with a recombinant VlsE antigen. The reaction is considered positive if serum antibodies bind with at least one of these specific antigens. This reaction can be strong, weak, or negative. The sensitivity of this test in case of LNB is 94%. Lyme neuroborreliosis was diagnosed, and the treatment with oral cefuroxime was initiated. Despite the treatment, the condition of the patient worsened within 7 days, and on March 13, he was admitted to the Republican University Hospital of Infectious Diseases and Tuberculosis in Vilnius. He had diplopia, which was more intense when moving the eye to the left side, severe back pain worsening at night, pain in the right side of the occiput and the neck, and numbness in the region of the right ulnar nerve. The patient’s medical history included numerous tick bites in summer and autumn. No erythema migrans was noticed. His mother and wife had erythema migrans after tick bites in autumn, and both of them were treated with doxycycline. On examination, the patient had malaise and fatigue, but no confusion. The signs of neuropathy of the left abducens and the right facial nerve were observed (Fig. 1). The examination of the patient revealed hypoesthesia in the regions of Th10–Th12 dermatomes, the right ulnar nerve, and the right greater occipital nerve. During the examination by the otorhinolaryngologist, hypokinesis of the left vocal fold was documented. A lumbar puncture (LP) was performed on March 13. The examination of the CSF showed lymphocytic pleocytosis (160 cells/mm³), an elevated protein level up to 1.7 g/L, and a glucose level within the reference range. The CSF culture was negative for bacteria. A complete blood count revealed no changes except leukopenia (3.2×10⁹/L), which disappeared within 8 days. The treatment with ceftriaxone at a dosage of 2.0 g per day intravenously was started, despite the absence of specific IgM and IgG antibodies against Bb in the CSF. Later on, the serum and the CSF were repeatedly tested in 2 other laboratories of Lithuania.
Lyme Neuroborreliosis Presenting With Abducens Neuropathy

No Bb antibodies in the CSF were found, and only specific IgG antibodies in the serum were detected. The diagnosis of possible Lyme neuroborreliosis was established and confirmed by positive serological testing results, typical clinical presentation, and pleocytosis in the CSF. The patient showed an improvement on the fourth day of the treatment with ceftriaxone. He was able to close his right eyelid, and occipital pain was less severe. The neuropathies of the greater occipital, ulnar, and facial nerves disappeared on the seventh day of the therapy (Fig. 2). The patient had been complaining of severe back pain with numbness and burning, which worsened at night. There were sleep disturbances because of pain. He became nervous, expressed his thoughts of suicide, lost confidence in doctors, and had no appetite. The LP and the consultation of the otolaryngologist were repeated on the 17th day of the treatment with ceftriaxone. No hypokinesis of the vocal fold was found. The CSF showed lymphocytic pleocytosis (144 leukocytes/mm³), with the elevated protein level (2.3 g/L) and the glucose level within the reference range (Table). After 17 days of therapy with ceftriaxone, the treatment was switched to oral doxycycline at a dosage of 200 mg daily and continued for 11 days. His back pain disappeared on 25th day of the antibiotic therapy. The patient was discharged from the hospital on 27th day of the therapy. The patient had no complaints. A physical examination revealed no strabismus, no movement disorders of the eyes, and no hypoesthesia. Testing of the CSF revealed only 4 lymphocytes per mm³ with an elevated protein level of 1.0 g/L, but a normal glucose level. All the results of blood tests were within the reference ranges. Bb antibodies were not detected in the CSF. All the laboratories used the ELISA qualitative test for the detection of Bb antibodies in the CSF. Bb-specific IgG antibodies were detected in the blood by ELISA. The antibody lev-

<table>
<thead>
<tr>
<th>Date</th>
<th>CSF Analysis</th>
<th>Serum Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lymphocyte, count/mm³</td>
<td>Protein, g/L</td>
</tr>
<tr>
<td>March 3 (before hospitalization)</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>March 13 (on admission)</td>
<td>160</td>
<td>1.7</td>
</tr>
<tr>
<td>March 30 (17th day after hospitalization)</td>
<td>144</td>
<td>2.3</td>
</tr>
<tr>
<td>19 May (40th day after discharge)</td>
<td>4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Bb, *Borrelia burgdorferi*; CSF, cerebrospinal fluid.

*Analysis was done in the laboratory of UAB “Endemik diagnostika” (reference range for Bb IgG, 0–9 U/mL).
†Analysis was done in the Virology Laboratory of Vilnius University.
‡Analysis was done in the Lithuanian National Reference Laboratory of Center for Communicable Diseases and AIDS.

(Table). No Bb antibodies in the CSF were found, and only specific IgG antibodies in the serum were detected. The diagnosis of possible Lyme neuroborreliosis was established and confirmed by positive serological testing results, typical clinical presentation, and pleocytosis in the CSF. The patient showed an improvement on the fourth day of the treatment with ceftriaxone. He was able to close his right eyelid, and occipital pain was less severe. The neuropathies of the greater occipital, ulnar, and facial nerves disappeared on the seventh day of the therapy (Fig. 2). The patient had been complaining of severe back pain with numbness and burning, which worsened at night. There were sleep disturbances because of pain. He became nervous, expressed his thoughts of suicide, lost confidence in doctors, and had no appetite. The LP and the consultation of the otolaryngologist were repeated on the 17th day of the treatment with ceftriaxone. No hypokinesis of the vocal fold was found. The CSF showed lymphocytic pleocytosis (144 leukocytes/mm³), with the elevated protein level (2.3 g/L) and the glucose level within the reference range (Table). After 17 days of therapy with ceftriaxone, the treatment was switched to oral doxycycline at a dosage of 200 mg daily and continued for 11 days. His back pain disappeared on 25th day of the antibiotic therapy. The patient was discharged from the hospital on 27th day of the therapy with the complaints of diplopia and hypoesthesia in the Th10–Th12 dermatomes. On the follow-up examination on the 40th day after discharge, the patient had no complaints. A physical examination revealed no strabismus, no movement disorders of the eyes, and no hypoesthesia. Testing of the CSF revealed only 4 lymphocytes per mm³ with an elevated protein level of 1.0 g/L, but a normal glucose level. All the results of blood tests were within the reference ranges. Bb antibodies were not detected in the CSF. All the laboratories used the ELISA qualitative test for the detection of Bb antibodies in the CSF. Bb-specific IgG antibodies were detected in the blood by ELISA. The antibody lev-

![Neuropathies of the Ulnar Nerve and the Greater Occipital Nerve](image)

![Neuropathy of the Facial Nerve](image)

![Hypoesthesia in Th10–Th12](image)

![Back Pain](image)

![Diplopia](image)

*Fig. 2. Duration of symptoms and signs in the patient with Lyme neuroborreliosis*
els persisted without any decline (10.81 U/mL) (Table). In the subsequent 4 years, the patient was feeling quite well; no recurrence of any LNB symptoms was reported, and no new diseases were diagnosed. In April 2012, Bb-specific IgG antibodies were detected in the blood by ELISA (18.0 U/mL).

Discussion

According to the European Federation Neurologist Society (EFNS) guidelines on the diagnosis and management of European LNB, definite neuroborreliosis can be diagnosed if all 3 following criteria are fulfilled: neurological symptoms suggestive of LNB, pleocytosis, and intrathecal Bb-specific antibody production. Possible neuroborreliosis is diagnosed if 2 of the 3 criteria are fulfilled (2, 6). American diagnostic criteria do not require a positive Bb antibody index in the CSF (6). In this report, we described a case of possible Lyme neuroborreliosis. We strongly believe in the correct diagnosis of LNB.

The patient presented with typical symptoms, such as painful meningoradiculitis and facial palsy; besides, he responded well to the treatment with an-dorferi is erythema migrans, but it develops at the site of the tick bite only in 40% to 60% of patients with confirmed LB (8). Another common leading syndrome is the Bannwarth syndrome, which involves radicular neuritic pain, particularly during the night, and lymphocytic pleocytosis (2, 5, 6, 8). In about 60% of patients with this syndrome, cranial neuropathies with the facial nerve most commonly involved are documented (2, 5, 6). In rare cases, LNB starts out with paresis of other cranial nerves. Ophthalmoplegia and retrobulbar neuritis have been reported as rare features of neuroborreliosis in some studies (10). In our patient, the presentation of cranial neuropathy at the very onset of the illness was not typical. The disease manifested with neuropathy of the sixth cranial nerve, and no erythema migrans was found. The patient had only a single complaint of diplopia for 1 month. Isolated cranial mononeuropathy (except for the facial nerve) makes the clinical diagnosis difficult. Sixth cranial nerve mononeuropathy is not a specific symptom of LNB and may occur in many other diseases. Abducens neuropathy can develop in autoimmune and metabolic diseases, viral or bacterial infections, and tumors. Autoimmune and metabolic diseases were excluded in this case since cerebral and spinal MRT showed no pathological abnormalities. The CSF examination was not performed. This was the main reason of the late diagnosis of LNB.

Lymphocytic pleocytosis is very typical of LNB, although the blood cell count may be within the reference range in very early stages of peripheral neurogenic disor-ders (4). We suggest performing a lumbar puncture to test the CSF for Lyme disease in the presence of any cranial mononeuropathy or mononeuropathy multiplex, when other diseases are excluded.

Our patient developed Bannwarth syndrome within 1 month. The analgesic medications were ineffective. The pain disappeared only after the treatment with antibiotics. This is a classical syndrome of LNB. Despite this, the clinical picture is often misinterpreted, and patients go through numerous investigations (5), as in this case. Family physicians and other physicians should be aware of the typical clinical symptoms of LNB in endemic regions.

During LNB, spirochete Bb invades the CSF. The host immune system reacts to the spirochetes with local inflammation, leading to an intrathecal accumulation of leukocytes. The percentage of B cells in the CSF of LNB patients reaches up to 80%, which is higher than in other CNS infections (11). B cells show a substantial migration only to very few chemokines: CC19, CCL21, CXCL12, and CXCL13. The results of the studies demonstrate that monocyte cells produce CXCL13 in response to the incubation with Bb through the interaction of the TLR2 receptor of the innate immune system with the outer surface proteins of spirochetes (11–13). CXCL13 is a major regulator of B cell recruitment in acute LNB. Studies show that CD27+ B cells appear to be the main migrating B cell population in neuroinflammation (11). These cells can produce 5- to 100-fold greater levels of immunoglobulins than CD27− cells. Some studies indicate that the successful resolution of LNB is associated with a strong T helper (Th) type 1 immune response in the CSF early in the infection, followed by a Th type 2 response, capable of suppressing the Th1 inflammation (14). The activation of B cells is driven by cytokines from Th2 cells. Chemokines have a crucial role for the Th1/Th2 balance. One study has shown the absence of both IL-17 and Bb antibodies in the CSF in children with possible LNB with pleocyto-sis (14). In this case, no Bb antibodies were found in the CSF, and only a very low level of IgG antibodies was found in the blood serum. The results of Western blot were positive only for 2 Borrelia antigens. The antibody-antigen reaction was weak. These findings may suggest a poor immune system response to the infection. It is difficult to say which part of intrathecal production of Bb antibodies was altered in our patient. Some reports have suggested that in immunosuppressed patients, the results of tests for Borrelia antibodies may be negative (15). However, our patient was immunocompetent. The previous prednisone therapy could have been one of the possible reasons of the lack of intrathecal Bb antibodies in our case, although some patients, treated with prednisone, have been reported to have Bb antibodies in the CSF. Further studies on the role of...
prednisone and other immunosuppressive medications in the Th1/Th2 balance, chemokine/cytokine level, and the percentage of CD27+ B cells in the CSF of LNB patients are needed. The intrathecal synthesis of Bb antibodies is of great importance for diagnosing LNB. The antibody index has a very high specificity (97%), but only a moderate sensitivity ranging from 40% to 89% (8, 16, 17). Some investigators suggest that Bb antibodies in the CSF may be absent in some patients initially, but specific intrathecal IgG production should be detectable 6–8 weeks after the onset of symptoms (2, 6). On the other hand, there are some reports of LNB without the intrathecal synthesis of Bb antibodies after a period of 6 weeks (7, 11, 15, 17). The problem lies in the confirmation of the diagnosis without intrathecal synthesis of Bb antibodies. Other laboratory tests are needed in rare cases of LNB without Bb antibodies in the CSF to prove the diagnosis. Although PCR performed in the CSF samples has a low sensitivity, it may be useful in very early LNB with a negative antibody index or in patients with immunodeficiency (6). Despite the limitations such as a low sensitivity and slow growth, the detection of Bb in CSF cultures by may be useful for the confirmation of uncertain cases (2). Recent studies have suggested a CXCL13 chemokine test (6, 11–13) and detection of antibodies to the C6–peptide (12) in the CSF for the diagnosis of LNB in seronegative patients and for the control of therapy. All these methods are still not used in Lithuania. We hope that they will be available in future because Lithuania is endemic for Lyme disease, the morbidity is increasing, and as our report demonstrated, there can be occasional cases of LNB without specific antibodies in the CSF. Some researchers suggest that a clinical response to treatment may be the best option to confirm the diagnosis in such cases (7).

We suggest a specific antibiotic therapy if LNB is suspected despite the absence of Bb antibodies in the CSF. According to the EFNS, adult patients with definite or possible early LNB (symptoms lasting <6 months) with symptoms confined to the meninges, cranial nerves, nerve roots, or peripheral nerves should be offered a single 14-day course of antibiotic treatment. Oral doxycycline (200 mg daily) and intravenous ceftriaxone (2 g daily) are equally effective (6). Although this was a case of early LNB, we decided to treat the patient for 28 days because the diagnosis was delayed; the patient was wrongly treated with prednisone and had a relapse of back pain. Longer courses are recommended for relapses or more serious and/or chronic forms (1). The choice of the best antibiotic, the mode of administration, and the duration of treatment are still debated issues (4). Over-treatment is an urgent problem. The duration of treatment cannot be longer than 21–30 days (4, 6). Antibiotic therapy has to be discontinued despite the presentation of certain symptoms.

The limitation of this case report is the absence of testing for Epstein–Barr virus (EBV), cytomegalovirus (CMV), and Mycoplasma pneumoniae DNR by PCR in the CSF. These are rare causes of aseptic meningitis in adults (18, 19). The primary EBV or CMV infection causes infectious mononucleosis, a disease characterized by fever, tonsil and lymph node swelling, atypical lymphocytosis, and liver function abnormalities. Neurological complications can be caused by a direct viral invasion or by indirect immune mechanisms. If a direct pathogen invasion occurs, a patient usually presents with meningeal signs and symptoms of the CNS dysfunction in combination with the symptoms of infectious mononucleosis (19) or infection with Mycoplasma pneumoniae. If indirect immune mechanisms occur, patients present with postinfectious polynuropathy with elevated protein levels in the CFS, but a normal or very slightly elevated level of leukocytes (20). Moreover, postinfectious demyelinating encephalitis can occur in very rare cases after these acute infections in adults. Patients have a good response to antiviral (19) or antibiotic treatment for Mycoplasma pneumonia in cases of a direct invasion of the pathogen into the CSF. The treatment with prednisone, immunoglobulin, and plasmapheresis should be effective in cases of postinfectious neurological complications of EBV or CMV infections, Mycoplasma pneumoniae, and other infections (20). Our patient had no symptoms of infectious mononucleosis and infection with Mycoplasma pneumoniae, no meningeal signs, and no signs of the CNS involvement. Lymphocytosis and atypical mononuclear cells were not observed in the blood. MRT did not show any demyelinating abnormalities. The clinical presentation and findings in the CSF were not characteristic of postinfectious polynuropathy. This patient had asymptomatic meningitis, which is very typical of LNB. The disease had been progressing until the treatment with ceftriaxone was started. Moreover, a good response to the specific treatment of LNB was the main reason why the CSF was not tested for the infections with CMV, EBV, and Mycoplasma pneumoniae.

In summary, infection with Borrelia should be considered in the differential diagnosis of any isolated or multiple mononeuropathy, and CSF examination should be done. The absence of specific immunoglobulins in the CSF does not exclude the LNB diagnosis. A specific antibiotic therapy should be started immediately when there is clear evidence of a clinical picture of the characteristic symptoms and signs of LNB.

**Statement of Conflict of Interest**
The authors state no conflict of interest.

---

*Medicina (Kaunas) 2013;49(2)*
References


Received 10 February 2011, accepted 15 February 2013