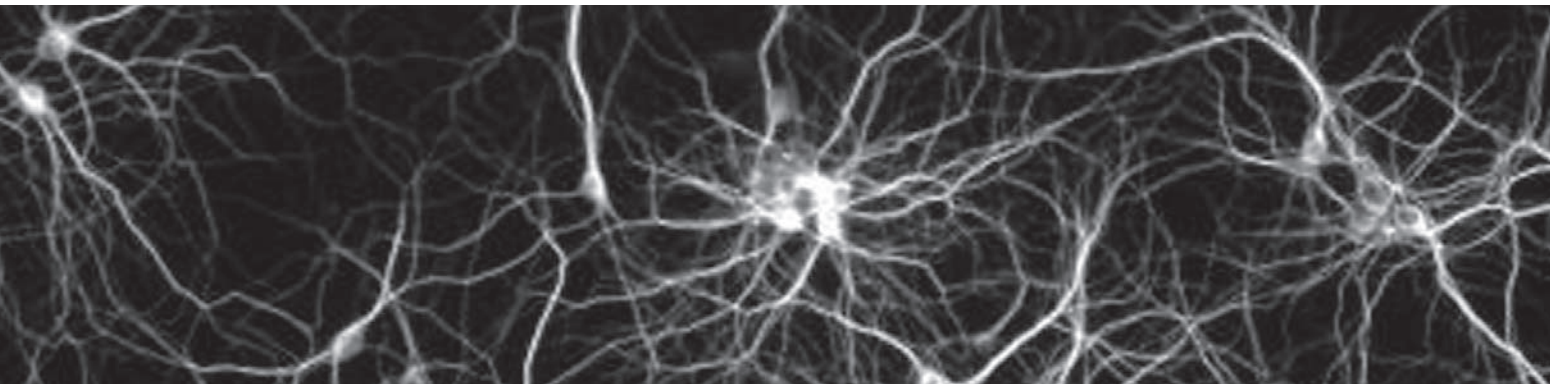

Neuroborreliosis: diagnostic problem in distinguishing from multiple sclerosis

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ABSTRACT - **Objectives:** To present the importance of additional diagnostic procedures in differential diagnosis of multiple sclerosis and neuroborreliosis, exemplified by a case of our patient. Neurological manifestation of Lyme disease varies and sometimes can imitate multiple sclerosis, especially in the early disseminated or late phase when there are no data on clinical infection. **Case report:** We present a patient with neuroborreliosis, initially considered as multiple sclerosis. Positive serology for *Borrelia burgdorferi* is an indicator of a past infection. However, the presence of specific IgG and IgM antibodies in the CSF confirms the diagnosis. In our case, magnetic resonance imaging (MRI) of the brain showed normal findings, whereas during spinal cord MRI, edema and hyperintense lesions of the thoracic spinal cord were found. Visually evoked potentials revealed prolonged latencies of the P wave on the left side. CSF analysis showed proteinorrhachia and distinct pleocytosis, with positive serology for specific antibodies to *Borrelia burgdorferi*. **Conclusion:** The clinical symptoms, MRI and CSF findings in combination with good response to antibiotic therapy confirmed the diagnosis of neuroborreliosis.

Key words: neuroborreliosis, Lyme borreliosis, encephalomyelitis, multiple sclerosis

INTRODUCTION

Neurological manifestation of Lyme disease is very diverse and can resemble multiple sclerosis (MS) (1). Acute Lyme disease is caused by a spirochete called *Borrelia burgdorferi* (Bb). Clinical features of Lyme disease (LD) can be divided into three phases: early localized LD (phase I), early disseminated LD (phase II) and late LD (phase III). In the early phase of LD, more common manifestations include redness of the skin at the site of the tick bite (*Ixodes*

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ricinus), which appears 5-10 days to a few weeks later, spreading around the bite (erythema migrans). This can be followed by more general symptoms like headache, lymphadenopathy, conjunctivitis, fever and myalgia. In rare cases, manifestations in the early phase include lymphocytoma benignum cutis, also called *Borrelia* lymphocytoma. Spreading of spirochete through the blood or lymph system causes the second phase. Symptoms depend on the affected organs and more common ones are multiple erythema migrans, neuroborreliosis and arthritis. Neuroborreliosis includes central (CNS) or/and peripheral nervous system (PNS) symptoms that occur after several weeks to months after the tick bite and include meningitis, polyradiculitis, encephalitis and neuritis. If LD is not treated properly, it evolves to the late phase, commonly presenting with arthritis, but in some cases also in the form of acrodermatitis chronica atrophicans or chronic meningoencephalitis. This chronic neurologic disease presents a differential diagnostic problem on distinguishing it from MS, particularly if there are no data on clinical infection. Magnetic resonance imaging (MRI) can show disseminated lesions within the CNS white matter (2). Positive serologic findings in Bb are only an indicator of a past infection and may not be relevant to the exclusion of other causes of the CNS infection (3,4). The intrathecal synthesis of specific antibodies against Bb in the cerebrospinal fluid (CSF) is a more reliable indicator to which extent the CNS is involved (5).

However, positive specific antibodies against Bb in CSF may be present in patients with MS (3,6,7). Therefore, the diagnosis of neuroborreliosis is based on the identification of typical acute symptoms/signs, migrating erythema and antibodies against Bb in high concentrations in the serum and CSF, as well as on the isolation of spirochetes (8-10).

CASE REPORT

We present a case of a female patient who, at the age of 42, experienced acute vision impairment on her left eye, accompanied by pain on any eyeball movement. Neurologic findings showed increased tendon reflexes of her right hand, highly exhaustive cutaneous abdominal reflexes and absence of the musculus triceps surae reflex on both sides. Fundus findings and radiologic analysis of the optic canal and sella turcica were normal. The report of visually evoked potentials showed slightly streamlined latency P wave to the left (128 ms) and the ophthalmologist diagnosed left optic neuritis.

Three years later, at the age of 45, the patient suffered paresthesias of both legs, followed by difficulties in walking. Disturbing sensation expanded to the chest level, with retention of urine. Physical findings showed red, rounded efflorescence of the left shoulder and chest. Neurologic examination revealed horizontal nystagmus, ataxia with left intention tremor, increased tendon reflexes of the left hand, absence of cutaneous abdominal reflexes and extinct left plantar reflex. It also revealed subjective hypoesthesia below the Th3-Th4 dermatomes. MRI of the brain was normal. CSF analysis showed distinct proteinorrhachia (0.85 g/L; normal range 0.15-0.45 g/L) and pleocytosis ($127x10^6$/L; normal range 0-$4x10^6$/L), with predominant monocytes and lymphocytes. Also, an increased local synthesis of IgG was found, with dysfunction of the blood-brain barrier, including a disproportionate increase of IgG quotient. Serology for neurotrophic viruses including tick-borne encephalitis, herpes simplex virus type 1 and 2, rubella, measles, mumps and varicella zoster virus in CSF was negative. As we recorded the red efflorescence on the left shoulder and chest, indicative of migrating erythema, as well as inflammatory findings of CSF, we tried empirical therapy with intravenous ceftriaxone, 2 g b.i.d. for three weeks and oral methylprednisolone every other day in a dose of 32 mg for two weeks. On the fifth day of therapy, the CSF findings showed decreased lymphocytic pleocytosis ($50x10^6$/L) and blood-brain barrier dysfunction, with a proportional increase of the IgG quotient. After eighteen days of treatment, the CSF findings revealed mild proteinorrhachia (0.48 g/L) and dysfunction of the blood-brain barrier with a proportional increase of IgG.

After two years, the patient was readmitted for disease deterioration. Neurologic examination revealed mild spastic paraparesis with hyperesthesia of the band type in the central part of the chest. Basic laboratory tests were normal. A year later, the patient was re-hospitalized due to mild worsening of the disease. On admission, she was subfebrile and complained of a feeling of chest tightness, or, as she put it "armor-like sensation". Neurologic examination revealed mild ataxia, paraparesis with sensation disturbance below the level of Th4, static and intentional hand tremor, and the "yes-no" motion of the head, dysdiadochokinesia to the left, positive Babinski's reflex on the left, and the need of urgent urination. Ultrasound of the abdomen showed diffuse damage to the liver and pancreas. Serum testing revealed the presence of IgG titers to Bb at 1:5120 and IgM titers at 1:320 (ELISA method), positive IgG (310.2 AU/mL; positive >15) and

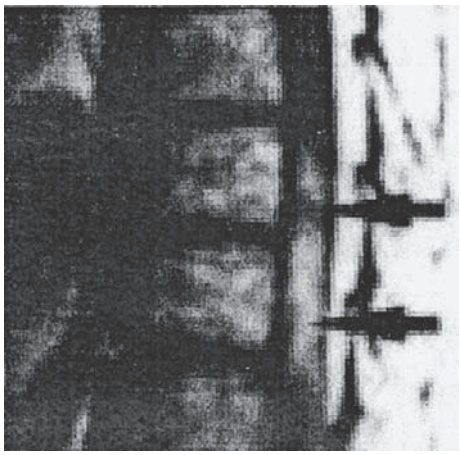

Fig. 1. *Magnetic resonance image of the spinal cord (T1, gadolinium) showing contrast enhanced lesion in the thoracic segment of the spinal cord.*

IgM (67.2 AU/mL; positive >22) with CLIA method. Specific IgG antibodies (74.4 AU/mL; positive >5.5) and IgM (22.1 AU/mL; positive >3.5) were positive in the CSF (CLIA method). Serologic analysis of neurotrophic viruses (tick-borne encephalitis, herpes simplex virus type 1 and 2, rubella, measles, mumps and varicella zoster virus) in CSF was negative. The patient was treated with ceftriaxone, receiving a dose of 2 g on a daily basis, intravenously, for a period of three weeks. Repeated antibiotic therapy resulted in remarkable recovery of the neurologic deficit, with only thoracic dysesthesias persisting. At this point, MRI of the spinal cord was performed and showed edema and hyperintense lesions of the spinal cord thoracic segment (Fig. 1), while repeated brain MRI findings were normal. Even though our patient was initially treated as a case of MS, the development of clinical symptoms, the CSF and MRI findings, along with a good response to the antibiotic therapy administered confirmed that it was a case of neuroborreliosis, even though there was no information on tick bite.

DISCUSSION

Neuroborreliosis can sometimes clinically mimic MS (11,12). There may be various neurologic deficits such as spastic paraparesis, hemiparesis, crossmyelitis, cerebellar ataxia, cranial or/and peripheral nerve damage, encephalitis, making it difficult to distinguish these two diseases (13). In the case of neuroborreliosis, MRI shows periventricular white matter damage, just like MS (1). As with other types of meningitis, MRI enhanced with contrast shows meningeal adhesions, which are not typical for MS (2,14,15). It is difficult to diagnose neuroborreliosis using laboratory analysis. Serologic tests for the detection of antibodies to Bb can be useful, but they could be positive in other CNS diseases like MS (16).When it comes to MS and neuroborreliosis, lymphocytic pleocytosis, intrathecal synthesis of IgM and IgG immunoglobulins and IgG oligoclonal bands in isoelectric focusing on polyacrylamide gel are present in the CSF. For neuroborreliosis, intrathecal synthesis of specific antibodies against Bb is characteristic, but it can be found in patients with MS (3,4). In patients with neuroborreliosis, IgM values were significantly higher compared to those suffering from MS, and the number of cells was significantly higher in the majority of patients in the acute stage of the disease. In the case of specific IgG, IgM, especially in CNS, without the virus-specific immune response, we can, with great certainty, speak about Lyme disease (5). However, specific antibodies against Bb can be found in patients with MS. Additional diagnostic parameters are significant damage to the blood-brain barrier and positive findings of Bb in CSF culture. During the last few years, a lot of discussion has been conducted about the possible causal relationship between the Bb infection and the appearance of MS. The finding of specific antibodies for spirochetes in the CSF of MS patients confirms this assumption. Findings of the synthesis of specific antibodies are not confirming that the neurologic symptoms are the result of Bb infection (17,18).

CONCLUSION

A large number of patients with neuroborreliosis are still found within the groups of patients erroneously diagnosed with MS. This is due to the similarity of clinical symptoms and MRI findings of CNS (19,20), as well as to the fact that the concentration of specific IgG oligoclonal bands depends on the duration of disease. In the case of intrathecal synthesis of specific IgG and IgM antibodies, especially for *Borrelia burgdorferi*, without the virus-specific immune response, we can with high certainty claim that it is a case of Lyme disease. Additional diagnostic indicators are significant damage to the blood-brain barrier, as well as the presence of *Borrelia burgdorferi* in the CSF culture (21).

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Neuroborelioza: dijagnostički problemi razlikovanja od multiple skleroze

SAŽETAK – **Ciljevi:** Prikazom slučaja ukazati na sličnost kliničke slike i rezultata neuroradiološke obrade u neuroboreliozi i multiploj sklerozi te istaknuti važnost dopunskih pretraga u postavljanju završne dijagnoze. Neurološka prezentacija lajmske bolesti je raznolika i katkad može oponašati multiplu sklerozu, osobito u ranoj diseminiranoj fazi i kasnoj fazi bolesti ako ne postoji podatak o kliničkoj infekciji. **Prikaz slučaja:** Prikazujemo slučaj bolesnice s neuroboreliozom, od početka shvaćenog kao multipla skleroza. Pozitivna serologija na bakteriju *Borrelia burgdorferi* je indikator infekcije u prošlosti. Ipak, prisutnost specifičnih IgG i IgM protutijela u središnjem živčanom sustavu može potvrditi dijagnozu neuroborelioze. U našem slučaju MR mozga je bio uredan, dok je MR leđne moždine pokazao edem i hiperintenzivno oštećenje grudnog odsječka. U vidnim evociranim potencijalima evidentiran je produžen P val lijevo. Analiza cerebrospinalnog likvora (CSL) pokazala je zamjetnu proteinorahiju, izrazitu pleocitozu, pozitivan nalaz specifičnih protutijela te negativnu serologiju na neurotropne viruse. **Zaključak:** Razvoj kliničke slike, nalaz MR i CSL u kombinaciji s dobrim odgovorom na antibiotsku terapiju potvrdili su dijagnozu neuroborelioze.

Ključne riječi: neuroborelioza, lajmska borelioza, encefalomijelitis, multipla skleroza