Case Report

Neuroborreliosis (Lyme Disease) or Multiple Sclerosis? Two cases with overlapping features

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Abstract

Background. The etiology of multiple sclerosis is heterogeneous and resulting from a complex genetic and environmental interaction, so that infectious agents have been considered. Borrelia infections of the central nervous system (neuroborreliosis) can cause an intrathecal inflammatory response with accompanying cerebral and spinal imaging findings.

Cases. Two children with acute or subacute initial neurological presentation, subsequent relapsing course and magnetic resonance imaging features suggestive of multiple sclerosis are presented. A history of tick bite or dramatic response to antibiotic treatment supported neuroborreliosis in the beginning, but the requirement of disease-modifying treatment later in the course supported multiple sclerosis.

Results. These cases, which have features supportive of both multiple sclerosis and neuroborreliosis, caused clinical dilemma and the children were treated for both disorders. Borrelia species-specific IgG index testing before any treatment could have prevented the difficulty in differential diagnosis.

Conclusions. Clinical, imaging and cerebrospinal fluid findings of multiple sclerosis and acute or chronic progressive borrelia encephalomyelitis may overlap and testing for Borrelia-specific intrathecal antibody synthesis should not be omitted in endemic areas.

Keywords: Multiple sclerosis, Lyme, Neuroborreliosis, demyelinating, inflammation

Background

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). Onset of the disease is most commonly seen in the second or third decade of life, however the disease begins before 16 years of age in 1.2–6% of cases [1]. The estimated incidence of pediatric MS in a recent German study was 0.64 per 100 000 person-years [2]. The pathogenesis of MS is still unclear, but is heterogeneous, comprising of a complex genetic (HLA system) interaction with the environment, particularly with infectious agents such as Epstein-Barr virus. Foreign antigens may activate immune events by several mechanisms, including molecular mimicry, inflammatory mediators stimulating myelin-specific T-cells, or infection unmasking or altering self epitopes which are then targeted by the immune system [3].

The similarity between neuroborreliosis (Lyme disease) and MS suggested *Borrelia burgdorferi* (*B. burgdorferi*) as a possible microorganism in the etiology of CNS inflammatory diseases [4–6]. Sequence homology is described between myelin basic protein and flagellin of the spirochete [7], and cross-reactive polyclonal and monoclonal antibodies, which recognize flagellar antigenic determinants as well as epitopes on neural cells, were detected [8–10]. Such cross-reactivity triggered by *B. burgdorferi* could contribute to a chronic, relapsing-remitting, immune-mediated neurological disorder similar to MS.

The possible overlap between MS and Lyme disease has been investigated in several studies, with inconclusive results. An analysis using the enzyme-linked immunosorbent assay (ELISA) showed twice as many patients with MS tested positive for *B. burgdorferi* compared to non-MS neurological controls [11].

In a study performed in Norway, 7% of patients with MS had antibodies to *B. burgdorferi* [12]. Conversely, cases with serologically confirmed neuroborreliosis may have antibodies against CNS proteins at a rate of 85% [13]. *B. burgdorferi*'s surface lipoproteins are known to exert proinflammatory effects and surface glycolipids may elicit cross-reactive antibodies; for instance, molecular similarities have been shown between outer surface protein A (OspA) and human neural tissue. Other antigens proposed to induce autoimmunity in *B. burgdorferi* infection are neural proteins released due to damage and chronic exposure to persistent *B. burgdorferi* microorganisms at different developmental stages [14].

While white matter is attacked by immune-mediated damage in neuroborreliosis, the microorganism can also infect the nervous system directly during the early or late stages of the disease. Manifestations consist of meningitis, meningoradiculitis, polyneuritis, or cranial neuritis, especially facial nerve palsy. Late neuroborreliosis is characterized by chronic meningitis, meningoradiculitis, mono- or polyneuritis, encephalopathy, or chronic progressive encephalomyelitis resembling MS.

The encephalopathy may result either from the release of toxic metabolic products (neurotoxin produced by *B. burgdorferi*, Bbtox1), the spirochetes crossing the blood-brain barrier, or lymphocytic migration and inflammation, especially invasion of brain endothelium causing vascular and intrathecal inflammation.

Pathological changes in chronic neuroborreliosis are described as lymphocytic infiltrates, diffuse and nodular microglial activation, astrocytosis, spongiform changes, diffuse demyelination of the cerebral white matter, multifocal inflammatory changes in the perivascular areas and cranial nerve nuclei and roots [15–17].

We present two cases which illustrate the overlap between pediatric MS and Lyme neuroborreliosis by their subacute and relapsing neurological symptoms, imaging findings and response to treatment.

Case 1

A 14-year-old girl with normal developmental and family history presented with walking difficulty. She had suffered from arthritis at the age of 12 years, which affected her left knee and right metacarpophalangeal joints. Although antistreptolysin O titer was <200 IU, she was treated with benzathine penicillin and underwent tonsillectomy one year later. However, arthralgias persisted in her upper limbs. At the age of 13 years, gait disturbance appeared with imbalance, she suffered frequent falls, and her performance at school declined. The ataxia quickly progressed and, within a month, left her unable to walk. Her past history was negative for tick bite. She had a family history of autoimmune thyroiditis and her mother had psoriasis.

The patient was hospitalized in the Department of Pediatrics and Medical Genetics, Medical University, Plovdiv**.** Physical and neurological examination revealed mild thoracic scoliosis, pes cavus, cerebellar ataxia, paresthesia and hypoesthesia of the lower limbs and diminished ankle reflexes.

The first suspected diagnosis was Friedreich ataxia. Two weeks later new neurological signs appeared as right hemiparesis, extensor plantar responses, and absent abdominal skin reflexes.

Blood count and serum biochemistry were normal. Cerebrospinal fluid (CSF) analysis showed normal protein and glucose levels, no cells, high IgM (10.6mg/l, normal range: 0.0-0.3) high IgG (50.03 mg/l, normal: 0-30) normal IgA. Oligoclonal bands were not detected.

Visual evoked potentials (VEP) showed prolonged P100 latency and somatosensory evoked potentials showed prolonged latency of P25 bilaterally. Brainstem auditory evoked potentials and peripheral nerve conduction velocity were normal. Magnetic resonance imaging (MRI) of the brain and spinal cord showed multiple hyperintense lesions on T2 and FLAIR images, especially in corpus callosum, subcortical and periventricular areas, medulla oblongata and cervical and thoracic spinal cord (Fig.1 A, B and C).

The diagnosis of MS was considered based on the clinical course, MRI and VEP results. Steroid treatment (500 mg/day methylprednisolone for five days) was given followed by tapering over a further 15 days. Ataxia and hemiparesis improved, although Romberg sign and absence of abdominal reflexes persisted. ELISA test for *B. burgdorferi* was received as positive IgM in both serum and CSF, and positive IgG in serum. The diagnosis was revised as chronic progressive borrelia encephalomyelitis. Treatment with Ceftriaxone 1.0 g i.v. twice a day was administered for 20 days. Full recovery was achieved, with the absence of abdominal reflexes as the only remaining sign.

Two months after recovery (about six months after the first attack) there was a relapse with ataxia, sensory disturbances (paresthesia in lower limbs and left hand) and quadripyramidal signs. Repeated MRI showed no new lesions, but contrast enhancement was demonstrated in some of the spinal cord lesions (Fig.2 A, B and C). VEP showed further prolongation of P100 latency. CSF protein was 0.2 g/l. CSF total IgM (2.76mg/l) and IgG (42mg/l) were lower than the first sample, and IgM and IgG against *B. burgdorferi* were negative.

The diagnosis was revised again as probable MS, and pulse therapy with methylprednisolone was given again. Motor activity recovered, but discrete distal spasticity, absence of abdominal reflexes, and Romberg sign persisted. Treatment with amantadine was administered for 3 months. Nine months later there was no limitation of motor activity, but sensory disturbances, partial urinary retention and mild left hemiparesis were found. New MRI of brain and spinal cord did not reveal new lesions, but enlargement of previous lesions.

At the age of 15 years, the patient had another relapse with ataxia and quadripyramidal signs. New demyelinating lesions in periventricular areas were demonstrated on MRI, so that

the McDonald criteria (2010) for MS were fulfilled [18]. Methylprednisolone treatment resulted in a gradual improvement over the next three months.

The next relapse occurred at the age of 16 years and after recovery the patient was started on treatment with Beta-interferon 1a, 30 mg, once a week. She had no other relapses in the following eight years (26 years old at the present time).

Case 2

This 12-year-old boy developed left hemiparesis together with choreoathetoic movements in his left hand. The symptoms rapidly progressed over one week.

He had a history of a tick bite followed by rash, fever and stiff neck at the age of five. At that time, serum IgM titers against *B. burgdorferi* were elevated and the patient was given antibiotics for just a few days. When he was 11 years old and a few months before the onset of the neurological disorder, he experienced pain and swelling of the right knee. Serum testing for *B. burgdorferi* by ELISA revealed high titers of IgM, which were confirmed by Western blot. He was given IV cefuroxime for two weeks.

At the onset of neurological signs, brain and spinal cord MRI revealed disseminated demyelinating lesions (Fig.3 A and B). CSF protein was normal; no cells, but oligoclonal bands were detected. Serology and PCR for *B. burgdorferi* in CSF were negative. VEP were normal. He was given methylprednisolone 0.5 g/day for seven days with no effect. As the hemiparesis was still progressing, intravenous immunoglobulin (IVG) treatment was introduced and resulted in slow clinical improvement.

Six months later he had no disability, but follow-up brain MRI revealed new and gadolinium enhancing lesions. The diagnosis of MS was considered and discussed with his parents, who were opposed to immunomodulatory treatment at that point.

One year after the first neurological episode, the patient developed right sided hemiparesis together with involuntary movements. Serum ELISA and Western blot tests for neuroborreliosis were positive: both IgM and IgG titers were elevated. Serology for *B. burgdorferi* in CSF was negative, but CSF total IgG index was 0.89. Brain and spinal cord MRI revealed new and gadolinium enhancing lesions. Antibiotic treatment for six weeks did not affect the progression of hemiparesis, neither did methylprednisolone. IVG therapy resulted in improvement and a few weeks later the patient had no neurological disability. The third neurological episode manifested with pyramidal signs (lack of abdominal reflexes, Babinski sign on the left) six months later. MRI revealed new lesions. VEP showed bilaterally prolonged P100 latency. Serum tests for *B. burgdorferi* (ELISA, lymphocyte transformation test) were negative. The diagnosis and treatment of MS were discussed with his parents and glatiramer acetate was started.

Four weeks later the patient developed ataxia and slurred speech. Methylprednisolone therapy resulted in recovery. The patient remained neurologically stable on glatiramer acetate for three years' follow-up.

Discussion

These cases present with subacute progressive neurological signs which evolved into a relapsing-remitting course, raising the issue of differential diagnosis between MS and neuroborreliosis and to the hypothesis of a relationship between these disorders, such as *B. burgdorferi* infection playing a role in the development of MS. These cases have features that both favor and dispute the diagnoses of neuroborreliosis and MS or other non-MS relapsing demyelinating syndrome [19].

The initial presentation of case 1, with the progressive onset and response to antibiotics suggests neuroborreliosis; the relapse associated with negative *B. burgdorferi* serology, however, supports MS, despite the absence of oligoclonal bands and the fact that

there was not sure space distribution in the first two relapses, but sure time distribution, using MRI 0.5 Tesla. The patient's next relapse at the age of 15, ending with gradual improvement over three months, is atypical for MS, while the long-term remission under interferon-beta-1 favors this diagnosis.

Case 2 initially presented with neuroborreliosis, with a history of tick bite and neurological involvement at the age of 11 years. However, the development of clinically silent new lesions on MRI is consistent with MS, while the lack of response to steroids is atypical for this diagnosis. Further relapses responding to methylprednisolone and the stability of the patient under glatiramer acetate support MS.

The diagnosis of Lyme neuroborreliosis requires demonstration of intrathecal *B. burgdorferi*–specific antibody production (specific antibody index AI>1.5) according to European guidelines [20]. The specific antibody index was not calculated in case 1**.** The relapse of case 2 one year after the initial neurologic episode suggests reinfection because the CSF returned to normal between the two episodes, as described in rare cases in the literature. However, there was no clinical response to antibiotic therapy. Although the possibility of recurrent neuroborreliosis is very small, a few cases of neuroborreliosis occurring more than once in the same subject have been published in children from Germany [21, 22].

Cases have been reported in the literature with chronic borrelial encephalomyelitis and a relapsing course, where the initial diagnosis was incorrect. Immunosuppressive treatment resulted in partial improvement, but significant recovery was achieved after antibiotic treatment, supporting the diagnosis of neuroborreliosis [23]. Severe neuroborreliosis may improve after the addition of steroids to antibiotics [24]. The relapse seen in our case 1 could have been due to insufficient antibiotic treatment: a 20-day course of ceftriaxone may have been insufficient to treat late neuroborreliosis. Response to treatment is usually slow and may be incomplete. However, re-treatment is not recommended unless relapse is shown by reliable objective measures.

Our case's negative serology excluded the possibility of reactivation of *B. burgdorferi*: all her relapses occurring within two years, the absence of any new clinical or MRI activity during the subsequent long follow-up argue against the possibility of neuroborreliosis.

On the other hand, positive *B. burgdorferi* serology in an MS patient with no suggestive features of the infection is unlikely to indicate neurological Lyme disease.

In a study of 283 consecutive MS patients, 19 had a borderline or positive *B. burgdorferi* serology. Repeat testing in eight of them did not confirm the diagnosis, and CSF examined in 10 of them showed intrathecal production of anti- *B. burgdorferi* antibodies in five patients. However, antibiotic treatment did not prevent subsequent neurological relapses [25].

Brain white matter abnormalities in neuroborreliosis can mimic those of MS. Unlike MS, resolution of MRI lesions may take many years. Another aspect helpful in the differentiation of these two entities may be normal tissue integrity in neuroborreliosis as assessed by advanced imaging techniques, brain magnetization transfer and diffusion tensor MR imaging, while in MS the normal-appearing white and gray matter show tissue damage which is not apparent on routine MR imaging [26].

By analysing literature data and data based on our own experience, we can recommend possible differential-diagnostic criteria between neuroborrelial encephalomyelitis and MS (see Table 1).

In conclusion, the considerable overlap of clinical, imaging and CSF findings between MS and chronic progressive borrelia encephalomyelitis emphasizes the importance of measuring specific intrathecal antibody synthesis, the reliable marker of neuroborreliosis, in relapsing demyelinating syndromes, especially in aquaporine-4 and myelin oligodendrocyte glycoprotein antibodies negative cases in *B. burgdorferi* endemic areas. Serology, especially

ELISA tests, can be positive in patients with MS or control subjects. Patients manifesting encephalomyelitis and positive serology for *B. burgdorferi* should receive a 20-day course of ceftriaxone and follow-up for alternative diagnoses is mandatory.

Table 1. Differential diagnosis of neuroborreliosis and multiple sclerosis

Criteria	Multiple Sclerosis	Borrelia progressive encephalomyelitis
Course	Relapsing–remitting, rarely chronic progressive	Chronic progressive, rarely chronic-recurrent
Symptoms typical for early borreliosis	No	Erythema migrans, arthritis, Aseptic meningitis, bilateral facial paralysis, radiculoneuritis
History of tick bite	No	Very often
Ophthalmology symptoms	Optic neuritis (decreased vision, diplopia	Paresis of oculomotor nerves, keratitis, orbital myositis, rare optic neuritis
Brain MRI, especially FLAIR	Periventricular lesions with peripheral contrast enhancement. Occult brain tissue damage	Larger subcortical, rarely periventricular lesions. No occult brain tissue damage
MRI lesions in cervical cord	Frequent	Rare
MRI resolution after antibiotic treatment	No	Yes (delayed)
Cerebrospinal Fluid	Cells under 15/mm^3 Normal or slightly increased protein,↑↑ IgG, ↑IgM	Pleocytosis (plasma cells), Increased protein ↑↑IgM, ↑IgG, ↑IgA
Serology for *B. burgdorferri*	± (low titer) – based on disturbed blood-brain barrier	IgM, IgG, IgA – intrathecal synthesis
Antibodies against myelin basic protein	+	±
Visual Evoked Potentials	Abnormal	Rarely abnormal

Fig. 1 (A) Sagittal T2 weighted image showed T2 hyperintense lesions in the body and genu of the corpus callosum, brainstem and cervical cord.

Fig. 1 (B) Periventricular T2 hyperintense lesions.

Fig. 1 (C) Sagittal T2-weighted imaging showed ovoid hyperintense lesions with different size at level: craniovertebral junction, C1-2, C2-3, C5-6-7, TH1-2, TH 3-4-5.

Fig. 2 (A) Eight months later.

Fig. 2 (B) Six months later.

Fig. 2 (C) Six months later.

Fig. 3 (A) and (B) Case 2. Axial and sagittal views of cranial MRI demonstrate ovoid white matter and spinal lesions.

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Author contributions

All the authors have made substantial contributions to the conception and design of this article, or been involved in the acquisition of data, or analysis and interpretation of data. The authors have been involved in drafting the manuscript or revising it critically for important intellectual content and have given final approval of the version to be published.

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