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Case Report

Peripheral neuropathy due to neuroborreliosis: Insensitivity for CXCL13 as early diagnostic marker

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ABSTRACT

The case of a 69-year-old woman with peripheral neuropathy caused by Lyme neuroborreliosis (LNB) in an endemic region in Eastern Austria is reported. The patient had noticed transient numbness of her left leg. On initial examination, she had patchy sensory disturbances of the left lower leg, but ancillary examinations of nerve conduction and cerebrospinal fluid (CSF), including the B-cell chemokine CXCL13, were normal. A re-tap performed 54 days later, following clinical progression with foot drop, widespread lower leg paresthesia, and pain, revealed an increased cell count, autochthonous IgM production, synthesis of *Borrelia*-specific IgM, and elevated CXCL13. Neurophysiological examinations disclosed an incomplete conduction block, mixed axonal and demyelinating sensorimotor neuropathy, and subacute neurogenic damage of muscles innervated by the peroneal nerve. This case study presents rare evidence of very early diagnostic findings in peripheral neuropathy caused by LNB. These are characterized by insensitivity of CXCL13 in CSF to aid earlier diagnosis and the development of an intrathecal immune response against *Borrelia* at a later stage. These findings reinforce the need for a re-tap to confirm the diagnosis and facilitate appropriate treatment in this rare manifestation of LNB.

Introduction

Lyme borreliosis is a multi-organ disease primarily transmitted by ticks. The condition is endemic in different parts of Europe and North America, and is caused by the spirochetes *Borrelia burgdorferi* sensu stricto, *Borrelia garinii*, and *Borrelia afzelii*. Nervous system manifestations termed 'Lyme neuroborreliosis' (LNB) are seen in 10–15% of all *Borrelia* infections in adults. The most common manifestations are meningoradiculitis and cranial neuritis (Summer and Rupprecht, 2019). Rarer neurological complications include brain and spinal cord involvement, cerebral vasculitis, and peripheral neuropathies (Moser et al., 2019). The intrathecal antibody response against *Borrelia* is negative in 10–30% when symptom duration is less than 6 weeks (Blanc et al., 2007; Ljostad et al., 2007). This underscores the need for an additional diagnostic biomarker. A recent meta-analysis revealed an overall sensitivity and specificity of CXCL13 in cerebrospinal fluid (CSF) of 89% and 96%, respectively (Rupprecht et al., 2018).

The case of female patient with isolated peripheral neuropathy caused by LNB, in which CXCL13 in CSF did not aid clinical suspicion and earlier diagnosis, is reported here.

Case report

A 69-year-old woman living in Eastern Austria, a region endemic for borreliosis, had noticed patchy areas of tingling and numbness distal to her left knee for the last 4 weeks. Examination of the skin was unremarkable and she could not recall a tick bite or erythema. On neurological examination, sensory symptoms were intermittent and did not follow a dermatomal distribution. Nerve conduction studies of the upper and lower extremities were unremarkable. She did not recall a trauma to her leg and did not report meningeal or radicular symptoms. Her medical history included hypertension and hypercholesterinemia, and cerebral or brain stem infarction was ruled out on brain/cervical spine magnetic resonance imaging (MRI). CSF did not reveal any

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abnormalities except for oligoclonal bands (OCB). CXCL13 in CSF was below the detection limit. Serum *Borrelia* IgG antibodies were elevated. Treatment with pregabalin was started, which only relieved her sensory symptoms slightly.

At the follow-up examination 14 days later, she reported a further increase in sensory symptoms and new-onset burning pain in the left leg during the night, which partly improved with physical activity. Considering restless legs syndrome, treatment with rotigotine was initiated, which was stopped after 5 days due to unresponsiveness.

She presented to the Emergency Room on day 33 after pain progressed and a left-sided foot drop had occurred, at that time grade 4 according to the Medical Research Council (MRC) grading. Nerve conduction studies revealed an incomplete nerve conduction block of the peroneal nerve at the head of the fibula level. An orthopaedic examination was unremarkable. She was readmitted on day 50 after the foot drop progressed to plegia. Needle electromyography (EMG) of the clinically affected muscles showed fibrillation potentials and reduced recruitment, consistent with a subacute neurogenic process. The neurophysiological findings were consistent with a postganglionic asymmetric mixed axonal and demyelinating sensorimotor neuropathy. Based on the clinical course and neurophysiological findings, a diagnosis of mononeuropathy multiplex was made. The patient was started on oral prednisolone on empirical grounds, but this was terminated after pain was only minimally lessened and motor deficits were unaltered.

A re-tap on day 54 revealed a lymphomononuclear pleocytosis of 13 cells/μl (normal range, <5/μl). Autochthonous synthesis of total immunoglobulin M (IgM, 6.5%) and *Borrelia*-specific IgM antibodies in CSF (antibody index (AI) 41.6 (<0.3)), and for *Borrelia*-specific IgG (AI 27.1) was found. This time, CXCL13 in CSF was 44 pg/ml (cut-off <30 pg/ml, according to Euroimmun, Lübeck, Germany), which further supported the diagnosis of isolated peripheral LNB neuropathy. Normal values were found for complete blood count, routine blood chemistry, vitamin B12 and folate levels, creatine kinase, erythrocyte sedimentation rate, and C-reactive protein. Ancillary investigations for anti-ganglioside and vasculitis-associated antibodies were negative. Other infectious agents were excluded in an extensive search with serology and PCR.

The subsequent 14-day course of intravenous ceftriaxone led to a rapid improvement of the pain. The recovery of motor deficits has been incomplete so far; the MRC grade was 3–4 at the outpatient clinic visit on day 99. The graphical course of clinical findings, ancillary investigations, and treatments is shown in Figure 1.

Discussion

The features of acute peripheral LNB neuropathy include axonal or demyelinating disease with a distal asymmetric distribution of motor and/or sensory symptoms and pain (Kaminsky et al., 2020). Acute peripheral LNB may manifest as mononeuritis or with a multiplex distribution (Lazaro and Butt, 2019; Osman et al., 2020). Nerve biopsy can disclose axonal injury accompanied by patchy perineural and perivascular infiltrates, vessel wall infiltration without necrosis, and no deposition of spirochetes, immunoglobulins, or complement (Lazaro and Butt, 2019). In contrast, chronic sensory axonal neuropathy is a late manifestation of European LNB, which is frequently associated with acrodermatitis chronica atrophicans (ACA). Typically observed months to years after the tick bite, ACA starts with a diffuse reddish or purplish discoloration of the skin of the involved limb, which evolves to marked skin atrophy (Halperin, 2019). Our patient did not recall any erythema, which is identified in up to 60% of patients with LNB in the course of the disease (Ogrinc et al., 2016).

While some patients with peripheral neuropathy show evidence of meningeal involvement, CSF examination is often unremarkable when LNB is restricted to the peripheral nervous system (PNS). The patient presented here had pure PNS symptoms over the entire course; she had an unremarkable CSF examination 4 weeks after symptom onset, but inflammatory changes and *Borrelia*-specific antibody responses in the CSF after a total of 11 weeks. It can therefore be assumed that in peripheral LNB neuropathy, the development of a *Borrelia*-specific immune response in the CSF is a time-dependent process. The extent of the pleocytosis and blood–brain barrier disruption was relatively limited; this is usually higher in adult LNB. In a German study, the median cell count was 171 × 10^6/l (interquartile range (IQR) 57–369 × 10^6/l) and the albumin quotient 17.2 × 10^3 (IQR 9.2 × 10^3 to 28.7 × 10^3) (Djukic et al., 2012).

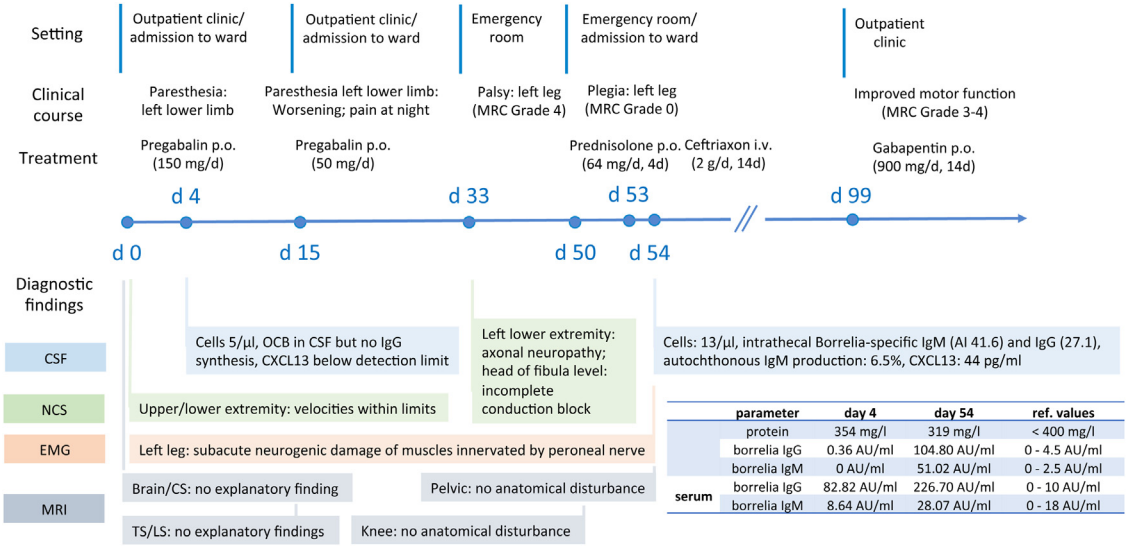

Figure 1. Course of clinical findings, ancillary investigations, and treatments in a patient with peripheral neuropathy caused by Lyme neuroborreliosis.
Abbreviations: AI, antibody index; CS, cervical spine; CSF, cerebrospinal fluid; d, day; LS, lumbar spine; EMG, electromyography; MRC, Medical Research Council; MRI, magnetic resonance imaging; NCS, nerve conduction study; OCB, oligoclonal bands; TS, thoracic spine.

The CSF findings and CXCL13 level in the case reported here may have been related to a less intensive intrathecal immune response in peripheral LNB neuropathy, but may also have been a consequence of the prior treatment with steroids. Steroids altered neither sensory symptoms nor motor symptoms, and their use may even be associated with worse outcomes (Garcia-Monco and Benach, 1995). There were CSF-specific OCB already in the first spinal tap, which is a frequent observation in LNB (Berek et al., 2020). Since no intrathecal Ig synthesis was present at that time point according to the quantitative analysis (Reiber diagram), this observation is likely more related to previous exposure to *Borrelia*. According to the Reiber scheme, intrathecal IgM and IgG production is seen in 90–100% and 60% of early LNB, respectively (Rauer et al., 2020). CSF CXCL13 has been studied as a diagnostic biomarker and shows high sensitivity in a time frame when antibody indexes for *Borrelia* are still negative. In the patient reported here, with definite LNB, CXCL13 was negative in the first spinal tap and did not aid earlier diagnosis. Admittedly, the diagnostic algorithm of the German Neurological Society does not list PNS LNB in their workflow (Rauer et al., 2020). This algorithm excludes the diagnosis of LNB with a normal cell count and protein level in the CSF. The diagnostic threshold for CXCL13 in LNB is under investigation; a recent meta-analysis identified an optimal cut-off value of 162 pg/ml. However, as in the case reported here, CXCL13 may add little specificity to the demonstration of a pleocytosis or presence of specific IgG production in the CSF (Eckman et al., 2020).

This case of peripheral LNB mononeuropathy revealed the insensitivity of CXCL13 in the CSF to aid in earlier diagnosis. This observation reinforces the need for a higher index of suspicion in endemic areas to initiate a re-tap to confirm the diagnosis and facilitate appropriate treatment for this rare manifestation of LNB.

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Ethical approval

The patient provided signed consent for publication of the case.

Conflict of interest

None.

Author contributions

All authors made a substantial contribution to the manuscript and approved the final version.

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