

# Infection with *B. burgdorferi* s.l., and the CNS demyelinating disease

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This paper is dedicated to the 70<sup>th</sup> birthday of Prof. Traubner

## Abstract

The work describes three cases of patients at various ages, diagnosed for CNS demyelinating disease. The presence of specific antibodies to *B. burgdorferi* sensu lato, and findings of *B. burgdorferi* s.l. DNA, identified in one case as the genospecies *B. garinii* in the liquor, indicated previous experience with the infection. Presumably, persistence of borrelia in the organism could act as one of the autoimmune process triggers, resulting in the demyelinating disease.

## INTRODUCTION

Lyme borreliosis (LB) is a multisystem disease, showing clinical symptoms which, at later stages, may be suggestive of various other disorders. Late-stage Lyme borreliosis may become manifest several months or years after the infection, and attack joints (Lyme arthritis), the skin (acrodermatitis chronica atrophicans), or the nervous system. In Europe, damage to the nervous system appears relatively more frequently – 40% to 60% in untreated patients (Bojar 1996). Isolated lesions of the facial nerve as a separate symptom appear in 7% of Lyme disease patients, or as much as 25% in endemic regions (Halperin *et al.* 1992). The disease presents a very variegated clinical picture, afflicting periph-

eral as well as central nervous systems. Nearly all neurological syndromes, ranging from meningoencephalitis, neuritis of cranial nerves or even polyradiculoneuritis, psychical changes in the form of depressions, chronic fatigue syndrome to panic attacks, etc., were referred to be borreliosis connected. Radiculitis, imitating vertebro-disco-genically preconditioned radiculopathy may also appear (Pachner 1989).

Certain authors in the U.S. use the persistent infection designation, i.e. the Post-Lyme Disease Syndrome. Such manifestations may be triggered by prior *B. burgdorferi* infections, with active symptoms of the infection absent at the time

of their demonstration. They appear also in treated patients who are in remission. The clinical image of disseminated damage to the central nervous system (CNS), appearing as sclerosis multiplex (SM), relatively frequently occurs in neurological practice, while the disorder is, in fact, linked to Lyme borreliosis, usually designated as the SM-like syndrome (Reik 1991; Halperin *et al.* 1991). Cerebral MRI of these patients shows multiple hyper-intense foci typical for demyelination, although neither sclerosis multiplex nor borreliosis nor any other inflammatory demyelination (e.g. herpesvirus infections or morbilli) are characterized by such foci. It follows from this that a pathognomonic clinical picture for borreliosis is nonexistent; therefore the disease is very difficultly diagnosed and may, in some case, result in misdiagnosis.

Late-stage LB pathogenesis is primarily expressed in autoimmune processes with CNS affections, also appearing in demyelinating CNS disorders. Their etiology is multifactorial, preconditioned genetically as well as environmentally (Staines 2008; Pohl 2009). Some studies point upon the risks of occurrence of such diseases in connection with specific infections, e.g. with the Epstein-Barr virus (Ascherio & Munger 2010) or with prolonged-persistence microorganisms, which directly or indirectly activate autoimmune processes in the central nervous system. Experimental works have indicated that at least some demyelination processes are macrophage mediated, and the persistence of pathogens is considered an important factor indicative of demyelination (Jayasri 2010). Schmutzhard (2002) pointed out that *Borrelia burgdorferi* infection could also be in a causal relationship with sclerosis multiplex, and the progressive SM form may clinically resemble a case of progressive encephalomyelitis caused by borrelia (Hartmann & Pfadenhauer 2003).

Three patient cases, diagnosed as CNS demyelinating disease, whose laboratory results indicate an association with Lyme borreliosis are described below.

## CASE REPORT 1

Patient B.D. (28), treated for psoriasis and hypertension, was admitted for feelings of stiffened lips, tongue, palate, teeth, nose and dextral parts of the forehead since mid-May 2007. Stiffening started to recede approximately two weeks from the first symptoms. The anamnesis showed tick bite, without subsequent erythema.

Cerebral MRI showed a small noninvasive focus in the dextral cerebellar peduncle + changes in the adjacent n. trigeminus l. dx. part along with sporadic minute nonspecific foci bilaterally in the white cerebral matter, and a venal temporo-parietal angioma sinistrally and also in the frontal dextral position. No substantial topical neurological findings were found. After admittance, vascular etiology of the condition was also considered but, due to the patient age, inflammatory etiology or potential occurrence of the demyelinating disease could

not be excluded. A second cerebral MRI showed moderate regression of the cerebellar focus, without gadolinium enhancement.

The liquor showed moderate pleocytosis, hyperproteinorachia and hyper- $\gamma$ -globulinaemia.

Antibodies to *B. burgdorferi* s.l. – serum enzyme-linked immunosorbent assay (ELISA) Immunoglobulin G (IgG) positive (semi-quantitative evaluation R 1,3), Immunoglobulin M (IgM) negat., Western blot (WB) IgG – positive outer surface protein (OspC+, OspA+, p41+++ and 6 nonspecific lines), liquor immunofluorescence (IF) IGAM 1:2. Presence of *B. burgdorferi* s.l. in the liquor was proven by the polymerase chain reaction (PCR) (Amplisens kit for 16S rRNA detection). Ultrasonography (USG) of the cerebrum was carried out to exclude vascular genesis, USG extra-, and intracranially without stenotic changes, cerebral computed tomography (CT) and trans-oesophageal echocardiography, all of which were within the norm. After a comprehensive reevaluation of the anamnesis, objective findings and test results, the condition was concluded as a CNS demyelinating disease case.

## CASE REPORT 2

Patient O.I. (46) without tick bite anamnesis. In May 2007 she experienced a non-rotational vertigo attack lasting 2 days, then receding spontaneously. She had not consulted a physician. She had difficulties over the last half-year, first expressed as fatigue and heavy-leg feelings dextrally, stumbling but not falling during a walk. Gradually, dextral coxalgia evolved with radiation into the thigh and anterior through the knee to the big toe. Frequent urination was observed, without incontinence. Cerebral CT was normal, MRI of the lumbo-sacral spine, taken in 2008, showed minimal L4 retrolisthesis, L3/4 and L4/5 discs protrusion with sinistral neuroforaminal stenosis and instability in the segment. Injection of the dextral hip joint in orthopedic treatment had only temporary effects, without improvement of overall conditions. Objective findings showed quadrihyperreflexion, slight atrophy m. triceps surae dextrally, weakened dorsal flexion of the big toe dextrally, dead planta sinistrally, sigmoid spinal scoliosis Th-L. Potential vertebrogenic etiology of the complaints was assumed, but the patient's central symptomatology pointed upon possible pyramidal tract lesions. Cerebral MRI showed numerous demyelinating foci in the CNS meeting the Barkhof criteria for SM, correlated with the liquor test showing increased  $\gamma$ -globulin levels and the presence of intrathecal oligoclonally structured IgG synthesis. Antibodies to *B. burgdorferi* s.l. – serum IF IgG 1:256, IgM negative, WB IgG – positive antigen (p30+, Vls+, p41+++), liquor IF IGAM 1:2. PCR in liquor proved the presence of *B. burgdorferi* s.l. (kit Amplisens for detection 16S rRNA). Transcranial magnetic stimulation supported the assumed presence of lesions in the central motor tract. Evaluation of the clinical picture, of

the anamnesis and of the ancillary tests resulted in the diagnostic conclusion of Type SM CNS demyelinating disease.

### CASE REPORT 3

Patient G.M. (55), treated 5 years earlier for L.B. with antibiotics. In that year he had also surgery for L4/5 and L5/S1 discs hernia. Hospitalized in the years 2006 and 2007 with SM diagnosis for disorders of articulation, of the fine coordination of hands, tingling in the thighs. Repeated cerebral MRI in T2 found hyperintensity foci highly parietally to the left, and further bilateral foci parietally. The liquor showed increased  $\gamma$ -globulins, without the presence of oligoclonal structure. Based on clinical tests, the patient condition was concluded as Type SM demyelinating disease, secondary progressive form. The patient was again hospitalized in 2009 for worsening of the condition. The liquor showed slight proteinocytological dissociation and hyper- $\gamma$ -globulinaemia without damage to the blood-liquor barrier. Antibodies to *B. burgdorferi* s.l. – serum ELISA IgG positive, (semiquantitative evaluation R 2,5), IgM negative, WB IgG – positive (Vls++, p17++, p18++ and 5 nonspecific lines), liquor IF IgG 1:4, IgM negative, liquor was positively PCR tested for *B. burgdorferi* s.l. using the Amplisens 16S rRNA detection kit, after isolation of deoxyribonucleic acid (DNA) using the commercial DNA easy-tissue (Qiagen) kit, nested PCR confirmed the presence of *B. garinii*.

Considering the vascular etiology possibility the following tests were carried out: USG cerebral circulation extra-, and intracranially, without substantial stenotic changes; cerebral CT and trans-oesophageal echocardiography were both within norm. The condition was concluded as CNS demyelinating disease of unclear etiology.

### DISCUSSION

The clinical course and laboratory tests of these patients pointed toward the demyelinating CNS disease diagnosis. Laboratory tests for specific *B. burgdorferi* s.l. antibodies showed their presence in the serum, but intrathecal production of these antibodies, typical of chronic borreliosis, was not confirmed. On the other hand, PCR tests showed the presence of *B. burgdorferi* s.l. DNA, and in the case of one patient, also of the genospecies *B. garinii* in the liquor. In itself, PCR examination manifests low sensitivity, the tests are not standardized, and borrelia are present in low concentrations in the biological material (Moravcová *et al.* 2009). The importance of finding borrelia or *B. burgdorferi* s.l. DNA in the liquor is not always clear. Although this finding is linked to clinically diagnosed neuroborreliosis in the majority of patients, it appears as a surprise in some cases (Strle *et al.* 2006) in which the clinical symptoms characteristic for Lyme borreliosis were not

found; this was previously observed more often in connection with the isolation of *B. afzelii* than in *B. garinii* findings, which was nearly always linked to the typical clinical symptoms of Lyme borreliosis.

Cerebral MRI has, in all three patients, shown multiple hyperintensity foci, typical for demyelination. Lyme borreliosis frequently proceeds in a masked way, subclinically or with only moderate clinical symptoms (Plícha *et al.* 2008); this is shown also by the occurrence of antibodies to Borrelia in the healthy population (Bazovská *et al.* 2010). *B. burgdorferi* DNA may, after an infection, be retained for months or even years in the organism (Honegr *et al.* 2001, Plícha *et al.* 2008, Strle *et al.* 2006). Patient G.M. had been treated for L.B. in the year 2004, and it remains unclear whether or not the persistence of *B. garinii* DNA could have resulted in such response of the organism that supported the occurrence of the demyelinating disease, while the anamneses of the remaining two patients show no previous L.B. experience, notwithstanding the positive ELISA IgG as well as positive PCR in the lab tests.

Slovakia is an area with endemic occurrence of Lyme borreliosis, and tick examinations showed that the genospecies *B. garinii* (Smatanova *et al.* 2007), which is prevailingly linked to neurological damage, appears most frequently. The later-stage pathogenesis of Lyme borreliosis as well as of different CNS diseases entails autoimmune processes.

This work was aimed at the provision of information relating to three case histories of patients where, considering their anamnesis, age, clinical picture and laboratory test results, an unequivocal diagnosis could not be easily reached, and the respective conditions were concluded as CNS demyelinating disease. Presumably, all three patients had been infected with L.B., resulting in persistence of borrelia in the organism, which could have been one of the triggers of the autoimmune process leading to the CNS demyelinating disease.

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