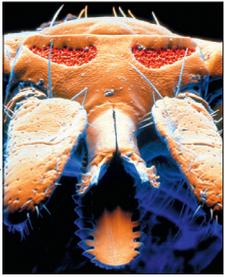




A case of meningoencephalitis by the relapsing fever spirochaete *Borrelia miyamotoi* in Europe

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Ixodes ricinus

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See Online for appendix

On April 1 2012, a 70-year-old patient came to our clinic reporting slow cognitive processing, memory deficits, and a disturbed gait, all of which had gradually developed over several months and progressed during the last few weeks before the patient's initial visit. He did not report fever, and he had not been outside the country for several years. He had recently been treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), polychemotherapy, and rituximab (last dose on Aug 2, 2011) for a stage 4 diffuse large B cell lymphoma. His medical history also included *Pneumocystis jirovecii* pneumonia, unexplained chronic diarrhoea, a splenectomy, extensive tick exposure, and two tick bites in the summer and fall before onset of symptoms. On neurological examination there was a distinct bradyphrenia, and on cognitive assessment, the patient scored 26 of 30 points on the mini mental state examination. Vital signs were normal and body temperature was 36.4°C. Cranial MRI showed no abnormalities, but two lumbar punctures showed cerebrospinal fluid pleocytosis with raised protein values. The cause of this chronic meningitis was not identified by wide-ranging microbiological, pathological, and haematological diagnostic testing (appendix). A C6-immunofluorescence assay for *Borrelia burgdorferi* in serum, but not in cerebrospinal fluid, was weakly positive (index 1.8). However, a *B burgdorferi* IgG and IgM immunoblot were non-conclusive and negative, respectively. A *B burgdorferi* sl qPCR in cerebrospinal fluid was negative. Nonetheless, because of the absence of an alternative diagnosis and the progression of symptoms, on April 17, 2012, the patient was treated for a possible Lyme neuroborreliosis with once daily 2000 mg ceftriaxone intravenously for 2 weeks. During several weeks the patient fully recovered. At his last visit to the outpatient clinic in May, 2013, the patient did not have residual symptoms.

Supported by the recent evidence of the presence of *B miyamotoi* in *Ixodes ricinus* ticks across Europe,^{1,2} the relation in time of the patient's symptoms with the tick bites, and his immunocompromised status, we retrospectively considered *B miyamotoi* as the causative agent. We identified motile spirochaetes in stored pre-treatment cerebrospinal fluid by dark-field microscopy (appendix). Additionally, a 16S rDNA pan-relapsing fever *Borrelia* quantitative (q)PCR and a qPCR targeting the *B miyamotoi* flagellin gene was positive in two separate pre-treatment cerebrospinal fluid samples and one pre-treatment blood sample (appendix). Notably, 2.2% of 352 *I ricinus* nymphal ticks from the vicinity of the patient's recreational house in the dunes of Zandvoort, the

Netherlands, proved to be positive for *B miyamotoi* by qPCR (appendix). Amplification and sequencing of the *glpQ* and *p66* genes confirmed *B miyamotoi* as the causative agent and showed 100% identical sequences in ticks and the patient's clinical samples (appendix). We were unable to culture the spirochaetes in modified Barbour-Stoenner-Kelly medium from stored blood and cerebrospinal fluid samples. Finally, ELISA and Western blot did not show anti-GlpQ antibodies in blood and CSF.

Relapsing fever is caused by various *Borrelia* species, which are predominantly transmitted by soft ticks. However, relapsing fever *Borrelia* species have also been identified in hard ticks, including *B miyamotoi* in *Ixodes* ticks.³ *B miyamotoi* infection has been associated with systemic complaints, including malaise and fever, in case series.^{4,5} Recently, in the USA, *B miyamotoi* was shown to be able to cause meningoencephalitis in an immunocompromised patient.⁶ Physicians worldwide managing immunocompromised patients from *Ixodes* tick-endemic areas with a meningoencephalitis should consider *B miyamotoi* as a potential causative agent and should be aware that regular diagnostic tests for *B burgdorferi* will most probably overlook this diagnosis. Whether *B miyamotoi* is also able to cause neurological symptoms in non-immunocompromised patients requires further investigation.

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