

Borrelia miyamotoi Meningoencephalitis in an Immunocompetent Patient

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Borrelia miyamotoi is an underdiagnosed cause of tick-borne illness in endemic regions and, in rare cases, causes neurological disease in immunocompetent patients. Here, we present a case of serologically confirmed *Borrelia miyamotoi* meningoencephalitis in an otherwise healthy patient who rapidly improved following initiation of antibiotic therapy.

Keywords. *Borrelia*; meningoencephalitis; *miyamotoi*.

Diagnosis of culture-negative meningoencephalitis remains a challenge; a causative organism is not identified in 30%–60% of cases [1, 2]. Tick-borne zoonoses, including those caused by spirochetes in the *Borrelia* genus, are an important cause of potentially treatable meningoencephalitis in endemic regions [3]. Although *B. burgdorferi* remains the most common spirochetal cause of tick-transmitted central nervous system (CNS) infection, the relapsing fever spirochetes, including *B. miyamotoi*, have been reported to cause meningoencephalitis and should be considered in the appropriate epidemiologic setting. We report a case of meningoencephalitis due to *B. miyamotoi* in an immunocompetent host living in the Northeastern United States.

CASE

A 73-year-old male Connecticut resident was referred to our hospital in the summer of 2021 for a 16-day history of confusion and intermittent headaches (Figure 1A). His medical history included only hypertension. He did not take any medications. He was an avid gardener and had noted tick bites in the past, but none in the weeks before presentation. He had not traveled outside of the Northeastern United States in several years. His symptoms began abruptly with right-sided facial droop and associated numbness, confusion, and word-finding

difficulties (Figure 1A, day 0). At that time, he underwent evaluation at another hospital where a noncontrast magnetic resonance imaging (MRI) scan of the brain showed no evidence for acute ischemia or intracranial hemorrhage, and electroencephalography showed no seizure activity. His symptoms, which had improved, were attributed to a transient ischemic attack, and he was discharged to home with instructions to take aspirin for stroke prevention.

Over the next 2 weeks, he continued to feel numbness in his right face and developed worsening confusion, intermittent headaches, and excessive fatigue; he was afebrile throughout this time (Figure 1A). Twelve days before admission (day 3 since symptom onset), he was evaluated in the emergency department of the other hospital and underwent a workup that included urinalysis, blood electrolyte measurement, and cardiac monitoring. These tests revealed no evidence for urinary tract infection or cardiac arrhythmia. Focal neurological deficits were not identified. Four days before admission (day 11 since symptom onset) he returned to the emergency department again and underwent workup including complete blood count and serum testing for antibodies to *Borrelia burgdorferi*, the causative agent of Lyme disease, with modified 2-tier testing (MTTT; ZEUS Scientific [4]). The initial enzyme immunoassay (EIA) and the reflex immunoglobulin G/M (IgG/IgM) EIA were positive (Figure 1A). Fifteen days after symptom onset, he was referred to our hospital for further treatment.

The patient was disoriented on admission but without meningismus, and his neurological exam was without any focal deficits. He was afebrile. An MRI of the brain with contrast showed no evidence for acute ischemia, intracranial hemorrhage, or demyelination. Blood tests revealed a normal peripheral blood leukocyte count and normal liver function tests. Serum polymerase chain reaction (PCR) testing for *Anaplasma phagocytophilum* and blood smear for *Babesia microti* were negative. Serum testing for HIV (fourth-generation

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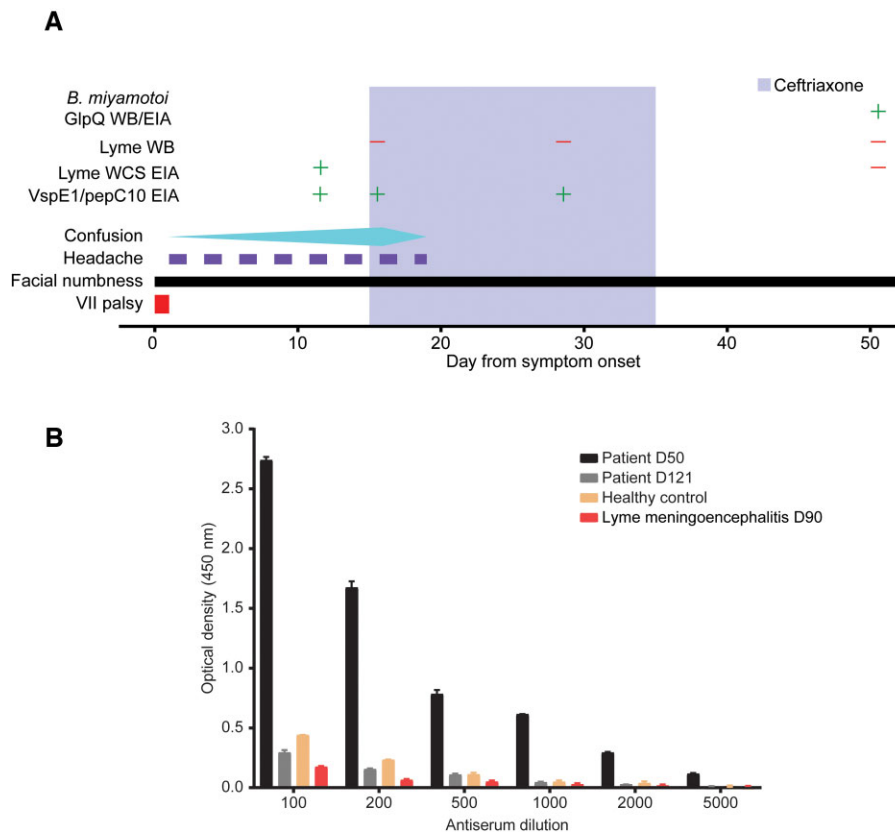


Figure 1. Case timeline and serum antibody testing. A, Clinical course of a 73-year-old man with *Borrelia miyamotoi* encephalitis. The timeline below begins with the onset of symptoms, through hospital admission, antibiotic treatment, and recovery. Facial numbness was the only symptom that persisted at the 6-month follow-up visit (not shown). Test results for *Borrelia burgdorferi* EIAs and WB are shown. The antigen used in the *B. burgdorferi* EIA was *B. burgdorferi* WCS. B, EIA testing for antibodies against recombinant GlpQ in serum from the patient at day 50 (black bars) and day 90 (gray bars) after symptom onset is compared with an age-matched healthy control (orange bars) and an age-matched patient control who had recent *B. burgdorferi* meningoenephalitis. Abbreviations: EIA, enzyme-linked immunoassay; WB, Western blot; WCS, whole-cell sonicate.

antibody/antigen test) and *Treponema pallidum*-specific antibodies was negative. Other blood laboratory test results are shown in Table 1.

A lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis demonstrated 50 white blood cells/ μ L (92% lymphocytes), 199.7 mg/dL protein, and a CSF/serum glucose ratio of 0.47. CSF PCR for varicella zoster virus (VZV), herpes simplex virus (HSV), cytomegalovirus (CMV), and *B. burgdorferi* were all negative, as were CSF antibody (EIA) tests for *B. burgdorferi*, Powassan virus, West Nile virus, and Jamestown Canyon virus. Other CSF laboratory tests results are shown in Table 2. On day 15, *B. burgdorferi* serum antibody testing was repeated with standard 2-tiered testing (STTT). The screening EIA was positive, but the reflex Western blot (WB) was negative for both IgM and IgG antibodies (Figure 1A).

The patient was empirically treated with intravenous ceftriaxone for treatment of presumed Lyme meningoenephalitis, and his mental status rapidly improved. He was discharged to home on day 19 to complete 3 weeks of

ceftriaxone. He was seen again on day 28, at which point *B. burgdorferi* serum antibody was again negative by WB (Figure 1A), prompting consideration of alternative causative pathogens, including *Borrelia miyamotoi*. Stored serum and CSF from the initial hospitalization were not available for testing; therefore, blood was obtained at follow-up on day 50 for further testing. Serum from day 50 was tested in a research laboratory for GlpQ antibodies using recombinant GlpQ EIA (Figure 1C) and GlpQ WB, as previously described (Supplementary Figure 1) [5]. GlpQ is an immunogenic protein that is produced by *B. miyamotoi* and other relapsing fever *Borrelia* species, but not *B. burgdorferi* [6]. Serum from day 50 was positive for GlpQ antibodies and repeat serological testing on day 121, demonstrated decreasing GlpQ antibody titers, consistent with *B. miyamotoi* convalescence (Figure 1C). *B. burgdorferi* antibodies were again negative by EIA and WB on day 50 and day 112. The patient noted a nearly full neurological recovery on day 28, with only residual intermittent right facial numbness. Upon

Table 1. Laboratory Blood Data

Variable	Reference Range, Adults	15 Days Before Presentation, Other Hospital Emergency Room	12 Days Before Presentation, Other Hospital Emergency Room	4 Days Before Presentation, Other Hospital Emergency Room	On Admission, This Hospital
Hemoglobin, g/dL	12.0–18.0	15.6	15.6	15.9	15.8
Hematocrit, %	37.0–52.0	45.5	45.6	45.0	45.7
WBC, ×1000/μL	4.0–10.0	7.9	7.6	7.5	5.1
Platelets, ×1000/μL	140–440	165	173	193	188
AST, U/L	10–35				24
ALT, U/L	9–59				16
Alkaline phosphatase, U/L	9–122				54
Creatinine, mg/dL	0.40–1.30	1.0	0.9	0.9	0.94
Blood microbiological tests					
Cryptococcal, Ag	Negative				Negative
<i>T. pallidum</i> , Ab	Nonreactive				Nonreactive
HIV, Ab/Ag	Negative				Negative
<i>A. phagocytophilum</i> , PCR	Not detected				Not detected
<i>B. burgdorferi</i> , Ab	Negative			IgG/IgM positive (EIA)	IgG/IgM positive (EIA), Western blot negative
Babesia smear	Negative				Negative

Abbreviations: Ab, antibody; Ag, antigen; ALT, alanine transaminase; AST, aspartate aminotransferase; EIA, enzyme immunoassay; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; WBC, white blood cell count.

Table 2. Cerebrospinal Fluid Data

Variable	Reference Range, Adults	On Admission, This Hospital
Hematology, tube 1		
RBC, cells/μL		199
WBC, cells/μL	<6	50
Granulocytes, %		1
Lymphocytes, %		92
Monocytes, %		7
Hematology, tube 4		
RBC, cells/μL		13
WBC, cells/μL	<6	73
Granulocytes, %		0
Lymphocytes, %		95
Monocytes, %		5
Glucose, mg/dL	40–70	59
Protein, mg/dL	15.0–45.0	199.7
Albumin, mg/dL	10.0–30.0	144.8
CSF microbiological tests		
CSF culture gram stain		2+ WBCs, no organisms seen, no growth
VZV, PCR	Not detected	Not detected
HSV, PCR	Not detected	Not detected
CMV, PCR	Not detected	Not detected
<i>B. burgdorferi</i> , PCR	Not detected	Not detected
<i>B. burgdorferi</i> , Ab, IgG, and IgM ^a	Negative	Negative
West Nile virus, Ab, IgG, and IgM ^a	Negative	Negative
Powassan virus, Ab, IgM ^{a, b}	Negative	Negative
Jamestown Canyon virus, Ab, IgM ^{a, b}	Negative	Negative

Abbreviations: Ab, antibody; Ag, antigen; CMV, cytomegalovirus; CSF, cerebrospinal fluid; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; RBC, red blood cell; VZV, varicella zoster virus; WBC, white blood cell.

^a*B. burgdorferi*, West Nile virus, Powassan virus, and Jamestown Canyon virus antibody testing was all done via enzyme immunoassay.

^bCenters for Disease Control and Prevention assay.

Table 3. Previously Reported Cases of *B. miyamotoi* CNS Diseases

Case	1	2	3	4	5	6	7
Citation	Gugliotta et al., 2013	Hovius et al., 2013	Boden et al., 2016	Henningsson et al., 2019	Henningsson et al., 2019	Mukerji et al., 2020	Gandhi et al., 2022 (this case)
Location	New Jersey, USA	Netherlands	Germany	Sweden	Sweden	Massachusetts, USA	Connecticut, USA
Demographics	80F	70M	74F	53F	66F	63M	73M
predisposing illness	Non-Hodgkin's lymphoma	Non-Hodgkin's lymphoma	Non-Hodgkin's lymphoma	None	Rheumatoid arthritis	Primary membranous nephropathy	None
Immunosuppression	R-CHOP; maintenance rituximab	R-CHOP; splenectomy	R-CHOP; maintenance rituximab	None	Methotrexate, rituximab	R-CHOP	None
Clinical symptoms and signs	Confusion	Cognitive slowing	Headache	Headache	Headache	Headache	Headache
	Hearing loss	Memory deficits	Neck stiffness	Neck stiffness	Fatigue	Photophobia, sonophobia	Confusion
	Ataxia	Ataxia	Dizziness, vomiting	Fever	Fever	Word-finding difficulties	Fatigue
	Weight loss				Hearing loss	Neck stiffness	Facial droop
					Weight loss	Facial droop	Uveitis, vitritis
				Uveitis, iritis, vitritis			
Duration from onset of illness to hospitalization	4 mo	2.5 mo	5 d	1 wk	9 mo	3 mo	16 d
Treatment	IV ceftriaxone initiated (2 g dose: Jarisch-Herxheimer reaction) switched to IV penicillin G (24 MU/d for 30 d)	IV ceftriaxone (2 g 1x/d for 2 wk)	IV ceftriaxone (2 g 1x/d for 3 wk)	IV ampicillin; oral doxycycline (200 mg 2x/d for 14 d)	Oral doxycycline (200 mg 2x/d for 14 d)	IV ceftriaxone, ampicillin, vancomycin initiated; IV ceftriaxone 4 wk—switch to doxycycline due to facial rash development	IV ceftriaxone (2 g 1x/d for 3 wk)
Outcome	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery	Persistent facial numbness; otherwise full recovery
CSF findings							
Leukocytes, cells/ μ L (normal <5 cells/ μ L)	65	388	70	321	331	146	50
	70% lymphocytes, 23% PMN, 6% monocyte	60% mononuclear	61% lymphocyte, 32% PMN, 7% monocyte	86% mononuclear	82% mononuclear	25% lymphocyte, 50% PMN, 25% monocyte	92% lymphocytes, 1% PMN, 7% monocytes
Protein level, mg/dL	>300	NA	171	NA	NA	358	200
Glucose, mmol/L	1.8	1.6	2.41	NA	NA	2.1	3.3
CSF microscopy	Spirochetes visible with Giemsa stain	Spirochetes visible with dark-field microscopy	Spirochetes visible after acridin orange staining	NA	NA	NA	NA
<i>B. burgdorferi</i> testing							
Serum	ELISA IgM, IgA, IgG: negative	C6-IFA weak positive; WB IgG: inconclusive; WB IgM: negative	CLIA: negative	CLIA: negative; ELISA IgM/IgG: negative	CLIA: negative; ELISA IgM/IgG: negative	ELISA: negative	ELISA: IgM/IgG positive; WB: negative
CSF	ELISA IgM, IgA, IgG: negative	C6-IFA: negative	CLIA: negative	CLIA IgM positive	CLIA IgM positive	ELISA: negative	ELISA IgM/IgG: negative; PCR negative
<i>B. miyamotoi</i> diagnosis							
Serum	NA	PCR (<i>flagellin</i>)	PCR negative	PCR+ (<i>flagellin</i>); GIpQ IgG+, IgM+	PCR+ (<i>flagellin</i>); GIpQ IgG-, IgM+	GIpQ IgG+, IgM-	GIpQ IgG+
CSF	PCR+ (<i>flagellin</i> and <i>glpQ</i>)	PCR+ (<i>flagellin</i> , <i>glpQ</i> , and <i>p66</i>)	PCR+ (panbacterial 16S rRNA)	PCR+ (<i>flagellin</i> , <i>glpQ</i> , and <i>p66</i>)	PCR+ (<i>flagellin</i> , <i>glpQ</i> , and <i>p66</i>)	PCR+ (<i>glpQ</i>)	NA

Normal CSF protein range: 15–45 mg/dL. Normal CSF glucose range: 2.2–4.2 mmol/L.

Abbreviations: CLIA, chemiluminescent immunoassay (LIAISON); CSF, cerebrospinal fluid; ELISA, enzyme-linked immunoassay; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; IV, intravenous; PCR, polymerase chain reaction; PMN, polymorphonuclear leukocytes; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; WB, Western blot.

follow-up 6 months later, he reported a persistent and intermittent right facial numbness and tingling.

DISCUSSION

Borrelia miyamotoi, a spirochete of the relapsing fever family, is a recently discovered cause of febrile illness and meningoencephalitis in endemic regions [7]. Like Lyme disease, *B. miyamotoi* is transmitted by *Ixodes* ticks and is endemic in New England. A recent study found a seroprevalence of 2.8% for *B. miyamotoi* in this region, compared with 11% for *B. burgdorferi* [8]. Although *B. miyamotoi* was first identified in ticks in 1995, its clinical significance was not established until 2011, when 46 of 302 Russian patients from Yekaterinburg City who presented with nonspecific febrile illness and suspicion for tick-borne disease were confirmed to have *B. miyamotoi* disease (BMD) by PCR of serum [9]. Cases have since been reported in Europe, Japan, and North America. Lyme disease and other *Ixodes* tick-borne diseases have markedly increased in number and expanded geographically, and it is likely that human *B. miyamotoi* infection will eventually be found wherever Lyme disease is endemic. Because *B. miyamotoi* is endemic in New England and can cause relapsing fever and meningoencephalitis, it is important that clinicians recognize the spectrum of *B. miyamotoi* disease and challenges in diagnosis.

Our patient, who resided in an area endemic for both *B. burgdorferi* and *B. miyamotoi*, presented with facial palsy and disorientation and CSF parameters consistent with neuroborreliosis. His symptoms of encephalopathy improved rapidly with anti-*Borrelia* antibiotic treatment, and subsequent serologic testing failed to confirm a diagnosis of Lyme disease but was consistent with a diagnosis of *B. miyamotoi* infection. All previously reported cases of *B. miyamotoi* meningoencephalitis due to *B. miyamotoi* were confirmed with PCR testing on serum and/or CSF, whereas confirmation of the diagnosis in our case was accomplished only with serologic testing in addition to consistent epidemiological and clinical features. Anti-*B. miyamotoi* antibody decreased markedly from 2 to 4 months after diagnosis, consistent with recent acquisition of *B. miyamotoi* infection.

There have been 6 previously reported cases of *B. miyamotoi* CNS disease, with features as listed in Table 3. While confusion, meningoencephalitis, and facial nerve palsy have been reported in immunocompromised patients with *B. miyamotoi* disease, meningismus was the sole neurological symptom in the only other confirmed case of *B. miyamotoi* CNS disease in an immunocompetent patient [10]. *B. miyamotoi* meningoencephalitis cases are characterized by a long duration of illness, with a range of 1 week to 9 months of symptoms before diagnosis [10–14]. All reported cases to date have occurred in adults over age 50, and most (5 of 6) occurred in individuals receiving B-cell-depleting treatment with rituximab. Our case therefore highlights the

need to include *B. miyamotoi* disease in the differential diagnosis for any patient who presents with acute onset, progressive encephalopathy with culture-negative CSF in *B. miyamotoi*-endemic regions, not just those who are immunocompromised.

B. miyamotoi disease remains a challenging diagnosis, as there are no FDA-approved tests for the diagnosis of *B. miyamotoi* and availability of testing is limited. Serology can help support or confirm the diagnosis; however, there are several important caveats to serological-based testing. Serologic responses may not be evident during the acute phase of illness, and thus rising antibody titers may be required to establish a diagnosis [15, 16]. The majority of patients with reported *B. miyamotoi* CNS disease have been treated with B-cell-depleting immunotherapies (eg, rituximab) that impair antibody production and thus may interfere with serodiagnosis. Studies in Lyme disease demonstrate that the serological response to *B. burgdorferi* may be delayed by the use of antimicrobials [17]; whether this is also a feature of *B. miyamotoi* infection is unknown. Glp, the main immunogenic antigen targeted in *B. miyamotoi* serological testing to date, is also present in other relapsing fever spirochetes, which will impact interpretation of this test in geographical settings where *B. miyamotoi* and other relapsing fever spirochetes coexist [18]. New *B. miyamotoi* immunoreactive antigens have been developed and can improve antibody assay sensitivity and specificity [19]. Newer diagnostic testing approaches using metagenomic next-generation sequencing may provide a useful alternative to serodiagnosis and aid in the detection of several tick-borne zoonoses, including those caused by *Borrelia* [20, 21].

While our patient developed anti-GlpQ antibodies, he also tested positive for Lyme disease by EIA on the MTTT, raising the question of whether he was coinfecting with *B. burgdorferi*. However, repeated negative Lyme antibody testing by Western blot up to 16 weeks after symptom onset showed that the patient did not seroconvert and therefore experienced a single infection with *B. miyamotoi*. A positive serological result on *B. burgdorferi* EIA can be explained by the presence C6 peptide sequence within the VlsE antigen utilized in the EIA. This protein sequence has been shown to cross-react to *B. miyamotoi*, most likely due to homology with *B. miyamotoi* variable large proteins [22–24]. Our case highlights the importance of considering *B. miyamotoi* in clinically suspicious cases of meningoencephalitis, including when *B. burgdorferi* EIA results are positive but the WB is negative. This case also emphasizes the limitation of relying on EIA alone—as in the MTTT—to distinguish between BMD and Lyme disease.

CONCLUSIONS

B. miyamotoi can cause meningoencephalitis in immunocompetent patients. *B. miyamotoi* should be suspected in cases with clinical symptoms consistent with acute or subacute meningoencephalitis in endemic regions.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. S.G. and S.F.F. provided clinical care to the patient and wrote the manuscript with input from all authors. S.N. and M.M. carried out experiments. J.Y. and A.W. provided assistance with research studies and literature review. P.J.K. and S.F.F. conceived the study and were in charge of overall direction and planning.

Patient consent. The patient's written consent was obtained. The design of the work has been approved by the Yale University Institutional Review Board Human Investigations Committee (HIV approval # 1502015318).

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