“Double Trouble”: Severe Meningoencephalitis Due to Borrelia burgdorferi and Powassan Virus Co-Infection Successfully Treated with Intravenous Immunoglobulin

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Patient: Male, 76-year-old
Final Diagnosis: Powassan virus encephalitis
Symptoms: Confusion • fever • respiratory distress
Medication: Immunoglobulin • ceftriaxone
Clinical Procedure: —
Specialty: Infectious Diseases • General and Internal Medicine • Neurology

Objective: Rare co-existence of disease or pathology
Background: Powassan virus (POWV) is an emerging tick-borne flavivirus transmitted to humans by ticks. While infection is asymptomatic in some people, others develop life-threatening encephalitis with high mortality rates. Co-infection between POWV and Borrelia burgdorferi is rare despite the fact that both pathogens can be transmitted through the same tick vector, Ixodes scapularis. It is unclear if co-infection leads to more severe clinical presentation and worse outcome.

Case Report: A 76-year-old Wisconsin man was admitted for meningoencephalitis complicated by hypoxemic and hypercapnic respiratory failure requiring endotracheal intubation. The patient had no known tick bites but lived in a heavily wooded area. Extensive work-up for infectious, autoimmune, and paraneoplastic causes was positive for Borrelia burgdorferi and Powassan virus infection (POWV). Following treatment with ceftriaxone for neuroborreliosis and supportive care for POWV infection, the patient failed to improve. Intravenous immunoglobulins (IVIG) were started empirically, and the patient attained gradual neurological improvement and was successfully extubated.

Conclusions: Treatment for POWV infection is supportive, and at this time there are no approved targeted antivirals for this disease. At this time, it remains unclear if co-infection with 2 pathogens leads to a more severe clinical presentation and higher mortality. In the absence of contraindications, IVIG might be beneficial to patients with POWV infection who are not improving with supportive care.

Keywords: Encephalitis, Tick-Borne • Immunoglobulins, Intravenous • Lyme Disease • Powassan virus, co-infection

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/929952
Background

Powassan virus (POWV) is an emerging tick-borne flavivirus named after the city of Powassan in the Canadian province of Ontario where it was first described in a 5-year-old boy who tragically died from severe encephalitis [1]. Unlike other flaviviruses, which are transmitted to humans by mosquitoes, the vectors for POWV and the eastern hemisphere’s tick-borne encephalitis (TBE) virus are ticks. Since its discovery, 2 serologically indistinguishable yet distinct genotypes have been described: POWV lineage I (prototype POWV) transmitted by *Ixodes* *cookei*, and POWV lineage II (or deer tick virus) transmitted by the black-legged tick known as *Ixodes scapularis* (*I. scapularis*) [2,3].

In the United States the disease is most prevalent in the Northeast and the upper Midwest, and this geographical distribution mirrors those of *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia burgdorferi*, and *Borrelia mayoni*, as all of these pathogens are transmitted to humans by the same vector. The transmission of 2 other pathogens (*Borrelia mayonii* and *Ehrlichia muris euclairensis*) by *I. scapularis* seems to be restricted to the states of Wisconsin and Minnesota. In the Midwestern US, the true prevalence of ticks co-infected with POWV and *B. burgdorferi* is not known, with wide variation of estimates (between 0.08% and 29%), depending on the tick sampling technique and the region [4-6].

Neurologic manifestations of Lyme disease (LD) and POWV infection are protean. Encephalitis is a common presentation of POWV infection, while aseptic meningitis is the most common clinical manifestation of Lyme neuroborreliosis (LNB) [7,8]. While there is a well-established treatment protocol for LNB, the care of patients with POWV infection is primarily supportive. Some case reports have described successful outcomes with immunosuppressive therapy in patients with severe POWV encephalitis, yet no rigorous study has been performed due to the rarity of the disease.

Here, we report a patient who developed severe meningoencephalitis due to LD and POWV co-infection. Treatment for LD with intravenous ceftriaxone failed to yield neurologic improvement. He was subsequently given intravenous immunoglobulins (IVIG) for POWV encephalitis, which did result in gradual neurologic recovery.

Case Report

A 76-year-old Wisconsin man was brought in by his daughter for abrupt onset of fever and confusion with onset 1 day prior. The patient had been born and raised in Wisconsin and lived in a heavily wooded area. He had no domestic or international travel within the last year. He was a nonsmoker, drank socially, denied illicit drug use, and had no pets. He had reported no known tick bites. His medical history was significant for well-controlled hypertension, hyperlipidemia, depression, type II non-insulin-dependent diabetes mellitus, and remote history of prostate cancer. His home medication regimen included Atorvastatin, Lisinopril/Hydrochlorothiazide, Clonidine, Sertraline, and Terazosin. The surgical history was relevant for prostatectomy approximately 10 years prior.

The patient presented to the emergency department with normal vital signs aside from a fever of 38.8°C. A physical exam revealed a well-developed man in no distress, who was somnolent but arousable, and able to protect his airway. He had positive meningeal signs and notable asterixis. Results of a limited neurologic exam were consistent with encephalopathy with inattention, absence of spontaneous speech, and inability to follow commands. He moved all 4 extremities spontaneously, his muscle stretch reflexes were normal and symmetric, and both Babinski and Hoffman signs were absent bilaterally. His sensory and cranial nerve exams were unremarkable as assessed within the limitations of his encephalopathy. Results of heart, lung, and abdominal exams were normal. A skin exam revealed no rash.

Complete blood cell count was significant for mild thrombocytopenia of 134×10^3/L. Liver and renal function were normal, and electrolytes were significant for hypokalemia of 3 mmol/L. EKG demonstrated normal sinus rhythm. Computed tomography of the head was negative for intracranial hemorrhage, acute ischemic infarct, encephalomalacia, or any mass lesion. Cerebrospinal fluid (CSF) was clear and contained 68 total nucleated cells with 55% lymphocytes. CSF protein level was elevated at 81 mg/dl (normal level 15-45 mg/dl), and CSF glucose was normal. Gram stain was negative for bacteria, and CSF cultures remained without growth. Since the patient presented in the summer and lived in an LD-endemic area, he was started empirically on ceftriaxone. Acyclovir was also started empirically for herpes simplex virus (HSV) coverage.

The following day the patient’s condition further deteriorated. His fever recurred with worsening encephalopathy, obtundation, and myoclonus. He developed hypoxemic and hypercapnic respiratory failure requiring intubation and mechanical ventilation. A repeat lung exam remained normal, and a chest X-ray was negative for pulmonary infiltrates, pleural effusion, or pulmonary vascular congestion. A comprehensive work-up for infectious, autoimmune, and paraneoplastic causes of encephalopathy was performed (Table 1). Electroencephalography (EEG) demonstrated diffuse slowing of background, but neither epileptiform discharges nor electrographic seizures were captured. Magnetic resonance imaging (MRI) of the brain with and without contrast was interpreted as normal (Figures 1, 2). Cyproheptadine was empirically given due to suspicion for...
Table 1. Summary of negative diagnostic tests that were done in our patient to rule out autoimmune, infectious, and paraneoplastic etiologies of encephalitis. Positive tests included: *B. burgdorferi* serum IgM and IgG, *B. burgdorferi* PCR in CSF (Mayo Medical Laboratories), and CSF IgM and plaque reduction neutralization test (PRNT) against POWV (CDC, Arboviral Disease Branch, Fort Collins, CO, USA).

<table>
<thead>
<tr>
<th>Tests done on serum</th>
<th>Tests done on CSF</th>
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<tbody>
<tr>
<td><em>A. phagocytophilum</em> Ab and PCR</td>
<td>HSV-1 PCR</td>
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<tr>
<td><em>E. chaffeensis</em> Ab and PCR</td>
<td>HSV-2 PCR</td>
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<tr>
<td><em>B. dermatitidis</em> Ab</td>
<td>VZV PCR</td>
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<tr>
<td><em>M. pneumoniae</em> Ab</td>
<td>EBV PCR</td>
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<tr>
<td><em>C. neoformans</em> Ag</td>
<td>CMV PCR</td>
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<tr>
<td>QuantiFERON TB GOLD RPR</td>
<td>Enterovirus PCR</td>
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<tr>
<td>West nile virus PCR</td>
<td><em>Human parechovirus</em> PCR</td>
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<tr>
<td>CMV Ab</td>
<td>Adenovirus PCR</td>
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<tr>
<td>EBV Ab</td>
<td><em>Cryptococcus neoformans/gattii</em> PCR</td>
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<tr>
<td>HIV Ab</td>
<td>St. Louis Encephalitis IgM and IgG Ab</td>
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<tr>
<td>HBV Ab</td>
<td>Calif (LaCrosse) Encephalitis Virus IgM and IgG</td>
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<td>HCV Ab</td>
<td>West Equine Encephalitis Virus IgM and IgG Ab</td>
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<tr>
<td>ANA</td>
<td>Anti-ANNA-1 (anti-Hu) Ab</td>
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<tr>
<td>RF</td>
<td>Anti-ANNA-2 (anti-Ri) Ab</td>
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<tr>
<td>SSA Ab</td>
<td>Anti-ANNA 3 Ab</td>
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<tr>
<td>SSB Ab</td>
<td>AGNA (Sox 1) Ab</td>
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<td></td>
<td>Amphiphysin Ab IgG</td>
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<td></td>
<td>Anti-PCI-1 Ab (anti-Yo) Ab</td>
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<td>Anti-PCI-Tr Ab</td>
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<td>Anti-PCI-2 Ab</td>
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<td>Antibodies to Ta Ab</td>
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<td>GAD-65 Ab</td>
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<td>Anti-VGKC Ab</td>
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<td>NMO Ab</td>
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<td>AQP-4 Ab</td>
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Ag – antigen; AGNA – anti-glial/neuronal antibody; Ab – antibody; ANA – anti-nuclear antibody; ANNA – anti-neuronal nuclear antibody; AQP-4 – aquaporin-4; CMV – cytomegalovirus; EBV – Ebstein Barr virus; HBV – hepatitis B virus; HCV – hepatitis C virus; GAD – glutamic acid decarboxylase; HIV – human immunodeficiency virus; HSV – herpes simplex virus; NMO – neuromyelitis optica; CMV – polymerase chain reaction; RPR – rapid plasma regain; RF – Rheumatoid factor; SSA – anti-Sjogren’s syndrome A; SSB – anti-Sjogren’s syndrome B; VZV – Varicella zoster virus; VGKC – voltage gated potassium channel; PCA – Purkinje cell cytoplasmic antibody.

serotonin syndrome, but this failed to improve his neurologic status. The patient was continued on supportive care, and intravenous ceftriaxone was continued following initial CSF lab tests returning positive for both POWV and LD. He was maintained on Ceftriaxone IV for another week, yet remained obtunded and failed multiple attempts at weaning from mechanical ventilation. Intravenous immunoglobulin (IVIG) was started on day 8 of his hospitalization at a dose of 1g daily for 5 days. Following the third dose of IVIG, the patient’s mental status gradually started to improve. He was more awake, cooperative, and intermittently following commands. After completion of the IVIG course, the patient further improved, and was subsequently extubated. He remained in the hospital for total of 36 days, and was discharged to a skilled nursing facility to continue physical rehabilitation. Two months following his critical illness, the patient continued to depend on a walker, and continued to exhibit intermittent memory impairment.

**Discussion**

Encephalitis is a neurological emergency defined as inflammation of the brain parenchyma, and manifested by personality changes or altered mental status in combination with 2 or more of the following: fever, focal neurological deficit, seizures, CSF pleocytosis, EEG abnormalities, or imaging suggestive of encephalitis [10]. If the meninges are affected by a pathological process, then a patient will experience the classic hallmarks of meningitis, including fever, headache, and nuchal rigidity. Due to the close proximity of brain parenchyma to the subarachnoid space and CSF, both processes can occur concurrently, presenting as meningoencephalitis [10,11].

In an immunocompetent host, such as our patient, encephalitis is most commonly caused by neurotropic viruses. Inflammatory/autoimmune diseases and paraneoplastic phenomena are other...
causes of encephalitis [10-12]. Community-acquired meningitis, on the other hand, is most commonly due to encapsulated bacterial pathogens such as Streptococcus pneumoniae and Haemophilus influenzae. Despite thorough investigation, the etiology of encephalitis remains elusive in up to 62% of patients [10]. Our patient presented with a constellation of symptoms and signs consistent with meningoencephalitis. He was diagnosed with meningitis due to early disseminated LD, and encephalitis due to POWV. While LD can present as encephalitis, it remains exceedingly rare, typically occurring in Europe as either the chronic form or as encephalomyelitis [12]. One of the reasons might be higher neurotropism of Borrelia garinii and Borrelia afzelii (rather than B. burgdorferi sensu stricto), which are the most common pathogens causing LNB in Europe [12]. POWV has not been described as a cause of meningitis, unlike Eastern Hemisphere flavivirus, TBE virus which can cause meningitis, encephalitis, myelitis, and spinal paralysis [13]. Furthermore, TBE virus usually presents with headache and encephalopathy while fever is rare, unlike in POWV infection. Rather than meningoencephalitis due to a single pathogen, our patient had 2 distinct entities developing concurrently. An extensive work-up for meningoencephalitis in our patient, as illustrated in Table 1, was diagnostic for both POWV and LD.

While some neurotropic viruses cause disease predominantly in children (eg, La Crosse virus), others more commonly cause severe encephalitis in the elderly (eg, West Nile virus) [12]. Similar to HSV type I (the most common cause of viral encephalitis across all age groups), POWV and LD also have no age predilection [11,12].

As with any neuro-infection, the diagnosis of POWV and LNB rests on appropriate epidemiological data, clinical manifestations, and the detection of a pathogen or specific antibodies in blood and/or CSF. Our patients extensive work up returned positive only for B. burgdorferi serum IgM and IgG, B. burgdorferi PCR in CSF (Mayo Medical Laboratories), and CSF IgM and plaque reduction neutralization test (PRNT) against POWV (CDC, Arboviral Disease Branch, Fort Collins, CO, USA). EEG and neuroimaging are additional tools that might help in diagnosing these challenging entities. Our patient was from an area endemic for LD and POWV, and he spent significant amounts of time outdoors, which placed him at high risk for acquiring these infections. Although he did not notice any tick bites, it should be noted that many patients do not recall being bitten. The majority of I. scapularis ticks that transmit infections to humans are nymphs, which are very small and rarely noticed. While it takes at least 24-36 hours for B. burgdorferi to be transmitted from the tick to humans, POWV can be transmitted in as little as 15 minutes [7,9].

Lymphocytic pleocytosis is the most common CSF finding in patients with meningitis due to LNB and POWV encephalitis. CSF protein level may be slightly elevated, while CSF glucose...
levels are expected to be normal. CSF Gram stain and cultures are negative, which, when taken together with other findings, help exclude bacterial meningitis. Imaging and EEG findings in POWV are nonspecific. EEG shows diffuse and severe slowing in up to 80% of patients, while around one-third of patients have epileptiform waveforms [9]. MRI imaging findings in POWV encephalitis are either nonspecific or normal, as was documented in our patient.

MRI is the best imaging modality to detect brain changes in encephalitis [10]. MRI is abnormal in more than 90% of patients with HSV encephalitis, while in cases of autoimmune or para-neoplastic encephalitis, it may be normal or with very subtle changes [10,11]. Due to the small number of cases, our understanding of specific MRI changes in cases of POWV encephalitis is limited. In addition, most cases have nonspecific findings which cannot be used to differentiate POWV encephalitis from other etiologies. In one review, only 12 of 102 patients with TBE had MRI abnormalities, and the thalami were most commonly affected in this group of patients [7,14]. Hemorrhagic involvement of bilateral thalami has been described as well [15]. One retrospective case series suggested that patients with POWV encephalitis with brainstem involvement on MRI have a worse prognosis [9]. In cases with POWV rhombencephalitis, the MRI might be normal and the absence of MRI changes might suggest a favorable prognosis [16].

While I. scapularis co-infection with 2 or more pathogens has been reported, the exact prevalence of co-infection with B. burgdorferi and POWV is not clear. One study from Minnesota reported that among 1240 ticks that were collected, only one was co-infected with B. burgdorferi and POWV, and was therefore the rarest combination of co-infection [4]. Meanwhile, a study from New York reported that up to 29% of ticks were co-infected with these 2 pathogens. A unique combination of co-infection was recently reported in a case of a patient who had POWV encephalitis, Lyme carditis, and severe babesiosis [17]. Due to changes in seasonal tick activity compounded by climate change contributing to the expansion of the vector I. scapularis, we may expect to see a significant increase in these infections and co-infections in years to come [18].

LNB should be treated with 4 weeks of ceftriaxone [19]. In some cases of LNB, steroids have been used successfully, although there is a lack of consensus about their efficacy [20]. Conversely, there is no proven effective therapy for POWV encephalitis, and the care is supportive [21]. The fact that in some cases patients favorably responded to immunosuppressive therapy [6,7,9,16] poses an intriguing question about whether, in addition to direct viral pathological effects, the patient’s immune system might play a significant role in the pathogenesis of POWV infection [16]. Hence, use of immunosuppressive therapy in the form of steroids or IVIG has been attempted in some cases of POWV encephalitis. In a retrospective study, none of the patients treated with IV steroids died [9]. In the only case reported to date (excluding ours), the use of IVIG for POWV encephalitis resulted in an excellent outcome [7]. Our patient is only the second reported case of POWV encephalitis that had improvement with IVIG despite having the severe form of the disease.

There has been no trial testing either steroids or IVIG for the treatment of patients with POWV encephalitis. One double-blind, placebo-controlled trial of patients with Japanese encephalitis did not show a clear benefit of IVIG; however, it was not powered for a clinical end-point [22]. Another trial that tested safety and tolerability of IVIG in patients with West Nile encephalitis also failed to demonstrate any statistically significant benefit [23]. Consequently, the use of immunosuppressive therapy remains experimental until more rigorous studies are conducted. In cases of severe POWV encephalitis, and in the absence of contraindications, we recommend the use of either steroids or IVIG.

Patients with POWV encephalitis have a protracted hospital course, and the majority of patients need prolonged physical rehabilitation following the acute illness. As many as 50% of POWV encephalitis survivors remain with some form of neuropsychological impairment, and the prevalence of behavioral, emotional, and cognitive deficits remains high up to 3 years following onset of the illness [10,24].

Conclusions

We describe a patient who developed severe meningoencephalitis secondary to co-infection with B. burgdorferi and POWV. When the patient failed to improve with intravenous ceftriaxone and supportive care, IVIG was administered empirically for a clinical end-point [22]. Another trial that tested safety and tolerability of IVIG in patients with Japanese encephalitis also failed to demonstrate any statistically significant benefit [23]. Consequently, the use of immunosuppressive therapy remains experimental until more rigorous studies are conducted. In cases of severe POWV encephalitis, and in the absence of contraindications, we recommend the use of either steroids or IVIG.

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Conclusions

We describe a patient who developed severe meningoencephalitis secondary to co-infection with B. burgdorferi and POWV. When the patient failed to improve with intravenous ceftriaxone and supportive care, IVIG was administered empirically, which resulted in significant neurological recovery. POWV is associated with significant morbidity and mortality, and further studies are needed to assess the role of immunosuppressive therapy for treatment of patients with POWV encephalitis with or without B. burgdorferi co-infection.
References: