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Case Report

Suspected Neuro-invasive Powassan Virus Infection in a Pediatric Patient

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Abstract:

Powassan virus lineage II (POWV), also known as deer tick virus, is an emerging tick-borne pathogen, transmitted by *Ixodes scapularis*, the natural vector for the organisms that causes Lyme disease, babesiosis, and anaplasmosis. POWV is the only tick-borne flavivirus in North America known to cause disease in humans. We present a suspected pediatric case of POWV infection in northern Wisconsin.

Key Words: Powassan virus, encephalitis, arbovirus, tick-borne disease, pediatric

Case Report:

In August 2017, a previously healthy 8-year-old Caucasian female presented to a clinic in Wisconsin with a one-day history of headache, photophobia, fever to 101 ˚F, lethargy, poor oral intake, diffuse abdominal pain, and vomiting. Three days prior, the patient was camping and had exposure to lake water, wooded areas, mosquitoes, and other insects. No tick bite was noted. The patient, reportedly, lived next door to an uncle who was recently diagnosed with Rocky Mountain Spotted Fever (RMSF). The patient had no history of travel outside of Wisconsin within the past 30 days. On arrival to the clinic, her physical exam was notable for stiff neck, but was otherwise non-focal. Laboratory studies at that time included a negative rapid Group A Streptococcus antigen test, negative urinalysis, complete blood cell count with leukocytosis (white blood cells (WBC) of 26.3 x 10^3 /L (ref 4.5-13.5 x 10^3/L, elevated C-reactive protein (2.8 mg/dL; ref <1.0 mg/dL) and mild hyponatremia (133 mEq/L; ref 133-144). Given persistent vomiting, an abdominal ultrasound to evaluate for appendicitis was completed and was normal. Due to her symptom severity and neck stiffness, the patient was transferred to Marshfield Medical Center in Marshfield, Wisconsin for further management.

On arrival to our facility, the patient's diffuse headache persisted, and she admitted to jaw pain but specifically denied neck pain. She complained of abdominal pain, which she attributed to hunger along with dysuria and nocturnal enuresis. She was afebrile with vital signs within normal limits. CT scan without contrast of the brain was completed and was normal. Reverse transcriptase polymerase chain reaction (RT-PCR) in whole blood was negative for *Anaplasma phagocytophilum*, *Babesia microti*, and *Ehrlichia chaffeensis*. Two-tier Lyme serology was negative. Lumbar puncture was performed and showed red blood cells (RBC) at 1 cells/ µL (ref 0 cells/µL) and elevated WBCs at 88 cells/ µL (ref 0-5 cells/µL) with 0% blasts, 23% neutrophils, 66% lymphocytes, and 11% monocytes. Total protein was 35 mg/dL (ref 15-45 mg/dL) and glucose was 66 mg/dL (ref 40-70 mg/dL). Ceftriaxone was started (50 mg/kg every

12 hours) for possible Lyme meningitis and doxycycline was started (2mg/kg every 12 hours) empirically for treatment of possible RMSF. Cerebrospinal fluid (CSF) was sent for culture as well as Lyme, Herpes Simplex Virus (HSV)-1, HSV-2, and Varicella Zoster Virus (VZV) PCR. An arbovirus IgM capture enzyme-linked immunosorbent assay (MAC-ELISA) panel was ordered on serum and CSF through the Wisconsin Division of Public Health.

On the second day of hospitalization, Lyme, HSV-1, HSV-2, and VZV CSF PCR returned negative and CSF cultures had no growth. Ceftriaxone was discontinued. Throat culture showed light growth of Group A Streptococcus and the patient was started on amoxicillin which was continued for a total of 10 days. Despite treatment, the patient's symptoms persisted with fever to a maximum temperature of 102.2˚F, headache, and nausea. On the fifth night of hospitalization, the patient was playing a board game and developed periods of confusion with inability to understand rows, columns and letters. On examination, a tremor was noted in bilateral hands particularly with finger to nose testing. The tremor was noticeably worse on the left side. She also experienced urinary urgency and progressive ataxia with inability to ambulate without assistance. As the night progressed, she developed expressive aphasia. Neurology was consulted and recommended MRI of the brain and repeat CSF studies.

MRI of the brain with and without contrast was normal. Repeat lumbar puncture showed RBCs at 1 cell/ µL (ref 0 cell/µL) and WBC at 39 cell/ µL (ref 0-5 cells/µL) with 84% lymphocytes, 11% monocytes, 0% blasts, and 5% neutrophils. Total protein was 58 mg/dL (15-45 mg/dL) and glucose was 54 mg/dL (ref 40-70 mg/dL). Given concern for worsening meningoencephalitis, she was started on methylprednisolone 250 mg IV (8.4mg/kg) daily. On hospital day 8 the patient began to show improvement and her neurologic exam returned to baseline. Steroids were decreased on day 9 of hospitalization to half the dose of methylprednisolone without worsening of neurologic symptoms and were subsequently

discontinued. The patient was discharged on hospital day 10 with amoxicillin for Group A Streptococcus pharyngitis and doxycycline for concerns of RMSF.

After discharge RMSF IgM returned negative. Arbovirus MAC-ELISA IgM and PRNT results are shown in the **Table**. The arbovirus MAC-ELISA IgM panel in serum (collected on day four of illness) was positive for POWV and Jamestown Canyon virus (JCV). Serum IgM for West Nile virus (WNV), St. Louis encephalitis virus (SLEV), eastern equine encephalitis virus (EEEV), and La Crosse virus (LACV) were negative. Serum plaque reduction neutralization tests ($PRNT_{90}$) were positive for POWV (titer 1:40), JCV (titer1:640), and LACV (1:20), providing evidence of infections with POWV and JCV. CSF IgM from the initial lumbar puncture was positive for POWV and JCV, and negative for LACV, WNV, SLEV, and EEEV. $PRNT_{90}$ for JCV and LACV were completed on the initial (day four) CSF sample and were negative (titer <1:2); insufficient quantity of CSF was available to run POWV PRNT in the initial CSF specimen. CSF IgM from the second lumbar puncture (collected on day 8 of illness) was positive for JCV, POWV, equivocal for LACV, and negative for WNV, SLEV, and EEEV. $PRNT_{90}$ for POWV was completed on the day eight CSF specimen and was positive (titer 1:4); insufficient quantity of CSF was available to run JCV and LAC PRNT in the day eight specimen. A convalescent serum was requested but was unable to be obtained as the patient was lost to follow up and no residual specimen was available to complete metagenomic sequencing. While serum antibody testing suggested recent infections with both POWV and JCV, neutralizing antibodies on PRNT against POWV, but not JCV, were detected in CSF. The patient's meningoencephalitis was, therefore, thought to be most likely due to POWV.

Discussion

To date roughly 100 cases of neuro-invasive POWV disease have been reported in the United States with a steady increase in reported cases since 2006[1]. Historically, testing has

been limited to patients with neuro-invasive disease and, thus, both the breadth of disease and the incidence of infection are likely much larger than what has been reported. The sero-prevalance of POWV in North America ranges from 0.5-4% in asymptomatic patients with seroprevalence as high as 9.5% in patients presenting for Lyme disease testing in an endemic region in the Midwest[2]. Up to 16% of *I.scapularis* ticks in some regions carry the virus, which can be transmitted in as little as 15 minutes after attachment[3]. The rapid expansion of the *I.scapularis* territory combined with increased awareness and testing capabilities likely explain the increasing incidence[1].

POWV is detected with an IgM MAC-ELISA or an IgM immunofluorescence antibody (IFA) assay. Cases are confirmed by $PRNT_{90}$, detection of virus-specific nucleic acids (PCR), isolation in culture, or a >4-fold increase in antibody titers from paired acute and convalescent sera or CSF[4]. It is important to note that while PCR testing of CSF for tick-borne diseases and arboviruses can confirm a diagnosis; a negative result cannot exclude a diagnosis. As with most serologic assays, POWV IgM assays show considerable cross-reactivity with other viruses and IgM may not be present in the first few days of infection. Thus, both false positive and negative results are common and serologic assays must be interpreted with caution. PRNT in acute and convalescent samples and/or direct detection of nucleic acids via PCR or metagenomic sequencing are necessary to confirm the diagnosis[4, 5]. In this case, serum tests detected antibiotics against both JCV and POWV. Since illnesses caused by POWV and JCV are both rare and these two viruses are transmitted by different vectors, concurrent infection is unlikely and the presence of JCV serum IgM most likely indicates prior JCV infection with persistent elevated IgM. Persistence of detectable IgM from prior infection with JCV infection may occur, as it has been documented to occur after infection with other arboviruses. In comparison, patient CSF specimens were also IgM positive for POWV and JCV with equivocal results for LACV. However, subsequent CSF $PRNT_{90}$ was negative for JCV and LAC and positive for

POWV indicating that neuro-invasive infection was most likely secondary to POWV. It is important to note that IgM ELISAs and PRNTS were completed on different CSF specimens that were taken 4 days apart. Thus, though unlikely, concurrent neuro-invasive infection with Jamestown Canyon virus cannot be completely excluded as the patient may not have seroconverted when the PRNT was completed.

The POWV case fatality rate in adults is 10-15% with 50% of patients experiencing neurologic sequelae[1]. Though up to 17% of POWV cases occur in children, only two prior pediatric case reports have been described[6, 7]. Thus, optimal management of POWV encephalitis and clinical outcomes for children are poorly understood. Prior pediatric case studies have reported using methylprednisolone or anticonvulsant therapy. In adult patients with severe disease intravenous immunoglobulin (IVIG), ribavirin/interferon, and steroids have been utilized with success. Care for encephalitis, including for other arboviral diseases such as WNV, is largely supportive. Steroids and IVIG for treatment of pediatric encephalitis have not been shown to be efficacious, though studies have been severely limited by sample size. Given the severe worsening in clinical symptoms in this patient, methylprednisolone was given and resulted in significant improvement.

There was concern for RMSF in this patient, though testing was ultimately negative. RMSF, caused by *Rickettsia rickettsii*, is primarily transmitted by *Dermacentor variabilis*. RMSF is an uncommon pathogen in Wisconsin, with most cases being acquired from travel. However, the incidence of regionally acquired RMSF has been increasing and Wisconsin reported its first death from regionally acquired RMSF in July of 2018.Thus, given the high fatality rate of RMSF and deteriorating status of the patient, we feel it was appropriate to initiate treatment in this patient while awaiting test results.

In conclusion, POWV is an emerging tick-borne pathogen capable of causing neuro-invasive disease. Clinicians in Lyme endemic regions should maintain a high degree of suspicion for POWV given the high mortality and long-term morbidity. If POWV is suspected, POWV testing should be specifically requested as many state arbovirus antibody panels do not routinely include this pathogen. It remains to be determined if viral detection changes clinical management. The optimal management remains to be determined but, similar to other arboviruses, is likely supportive care.

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Table 1: Arbovirus diagnostic test results from serum and cerebral spinal fluid on day 4 and 8 of illness.

	Day 4	Day 8
Serum		
MAC-ELISA IgM[1]		
Powassan virus	positive	--
Jamestown Canyon virus	positive	--
West Nile virus	negative	--
St. Louis encephalitis virus	negative	--
Eastern equine encephalitis virus	negative	--
La Crosse virus	negative	--
$PRNT_{90}$[2]		
Powassan virus	1:40	--
Jamestown Canyon virus	1:640	--
La Crosse virus	1:20	--
Cerebral Spinal Fluid		
MAC-ELISA IgM		
Powassan virus	positive	positive
Jamestown Canyon virus	positive	positive
West Nile virus	negative	negative
St. Louis encephalitis virus	negative	negative
Eastern equine encephalitis virus	negative	negative
La Crosse virus	negative	equivocal
$PRNT_{90}$[2]		
Powassan virus	--	1:4
Jamestown Canyon virus	<1:2	--
La Crosse virus	<1:2	--

[1]IgM capture enzyme-linked immunosorbent assay (MAC-ELISA) was completed at Wisconsin State Laboratory of Hygiene. ELISA measures optical density of patient serum dilution with viral antigen (P) / mean optical density of normal human sera (N). Result is positive if P/N ≥ 3.0.

[2]PRNT was performed at the Centers for Disease Control and Prevention Arboviral Diseases Branch. Serum PRNT result is positive if titer ≥ 10. CSF PRNT result is positive if titer ≥ 2.