

Powassan Virus Encephalitis: A Tertiary Center Experience

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Background. Powassan virus (POWV) is an emerging arthropod-borne flavivirus, transmitted by *Ixodes* spp. ticks, which has been associated with neuroinvasive disease and poor outcomes.

Methods. A retrospective study was conducted at Mayo Clinic from 2013 to 2022. We included clinical and epidemiologic data of probable and confirmed neuroinvasive POWV cases.

Results. Sixteen patients with neuroinvasive POWV were identified; their median age was 63.2 years, and 62.5% were male. Six patients presented with rhombencephalitis, 4 with isolated meningitis, 3 with meningoencephalitis, 2 with meningoencephalomyelitis, and 1 with opsoclonus myoclonus syndrome. A median time of 18 days was observed between symptom onset and diagnosis. Cerebrospinal fluid analysis showed lymphocytic pleocytosis with elevated protein and normal glucose in the majority of patients. Death occurred within 90 days in 3 patients (18.8%), and residual neurologic deficits were seen in 8 survivors (72.7%).

Conclusions. To our knowledge, this is the largest case series of patients with neuroinvasive POWV infection. We highlight the importance of a high clinical suspicion among patients who live in or travel to high-risk areas during the spring to fall months. Our data show high morbidity and mortality rates among patients with neuroinvasive disease.

Keywords. tick-borne diseases; Powassan virus; arbovirus.

Powassan virus (POWV) is an RNA tick-borne flavivirus, identified in 1958 in Ontario, Canada [1]. Between 2012 and 2021, the Centers for Disease Control and Prevention reported 202 cases in the United States, among which 189 patients had neuroinvasive disease and 24 cases resulted in death [2]. While most cases occur in the upper Northeast and Midwest regions, the true incidence of POWV infections is unknown owing to limited awareness of this tick-borne pathogen (TBP), low clinical suspicion in cases of mild or nonneuroinvasive disease, and lack of routinely accessible diagnostics.

There are 2 genetically distinct lineages, POWV and deer tick virus, which are serologically indistinguishable [3–5]. We do not differentiate between the 2 lineages in this article and refer to either as “POWV.” The tick species most commonly associated with POWV transmission is *Ixodes scapularis* [6]. POWV is transmitted within 15 minutes of tick attachment [7], in contrast to *Borrelia burgdorferi*, which requires 36–72 hours [8, 9]. The prevalence of POWV in ticks ranges from 1% to 3% in *I. scapularis*, which is less common than other TBPs [10].

POWV diagnoses have been increasing in recent years, with approximately 1 documented case per year from 1958 to 2005, up to 20–40 cases per year between 2016 and 2019 [11]. Given the rise in cases, it is important for clinicians to be familiar with the presentation, diagnosis, and course of POWV infection. Here we describe the clinical features of 16 patients with POWV infection at our institution.

METHODS

This is a retrospective, institutional review board–approved, study of patients evaluated at Mayo Clinic from 2013 to 2022. We collected clinical and epidemiology information from laboratory confirmed POWV cases. The majority of patients (n = 12) were identified using POWV diagnostic results from the Minnesota and Wisconsin departments of health. Four patients were identified through both serologic and molecular testing for POWV at Mayo Clinic following implementation of these tests between February and May 2022. Two patients had metagenomic next-generation sequencing performed through the University of California, San Francisco. We used the Centers for Disease Control and Prevention case definition for arboviral diseases [12] (Supplementary Table 1). It is important to highlight that in the state of Wisconsin, POWV seroreactivity has been reported even in patients without neuroinvasive disease [13].

RESULTS

Patient Cohort

We identified 16 cases; 15 patients met diagnostic criteria for confirmed POWV neuroinvasive disease and 1 for probable

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neuroinvasive disease (Table 1). Ten patients were male, and their median age was 63.2 years. Four patients were immunosuppressed; 2 were taking ibrutinib for chronic lymphocytic leukemia (patients 1 and 5), 1 was receiving chemotherapy for lung adenocarcinoma (patient 11), and 1 was taking methotrexate for rheumatoid arthritis (patient 13). All patients lived in either Minnesota or Wisconsin according to their zip codes (Figure 1). Seven patients lived in a rural setting, and 10 were routinely active outdoors. Seven patients reported a history of tick bite.

Clinical Presentation

Patients presented for clinical evaluation between May and November (Figure 2), with a median of 4 days after experiencing symptoms. The most common symptom at presentation was fever, in 15 patients (Table 2).

Neurologic presentation was variable but followed certain phenotypes. Six patients presented with rhombencephalitis, 4 with isolated meningitis, 3 with meningoencephalitis, 2 with meningoencephalomyelitis and 1 with opsoclonus myoclonus syndrome (OMS) 7 days after developing a meningitic syndrome (Table 3). Patients presenting with rhombencephalitis had evidence of ataxia, nystagmus, dysarthria, ptosis, cranial nerve palsies, or paresis. Patients with ataxia often had profound truncal ataxia, although appendicular ataxia was also noted. Dysarthria ranged from mild to anarthria. Five patients had cranial nerve palsies on examination. Sixth nerve palsies were most common, but bilateral seventh nerve palsies, third and fourth nerve palsies and bilateral optic perineuritis were also observed. Patients 5 and 16 presented with meningoencephalomyelitis. Patient 16 developed flaccid right upper-extremity monoparesis with electromyographic and nerve conduction study findings consistent with a subacute disorder of anterior horn cells. Patient 5 presented with rapidly progressive quadriplegia and was noted to have subtle ventral cervical cord enhancement, along with T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities in the cerebellum (Figure 3).

Three patients (4, 5, and 16) experienced seizures, including 1 patient with persistent encephalopathy and frequent focal subclinical seizures. Although all 3 patients responded to initiation of antiseizure medications, 2 ultimately died of their infections

Laboratory Results

A summary of laboratory results is shown in Table 2. The most common abnormalities noted on the cell blood count was thrombocytopenia in 43.8% of cases, followed by lymphopenia. Fifteen of 15 patients underwent a lumbar puncture at presentation (Tables 1 and 2). The majority had mildly elevated protein in cerebrospinal fluid (CSF), with a median of 79 mg/dL. None had hypoglycorrhachia. Ten patients had lymphocytic pleocytosis, with median nucleated, lymphocyte and neutrophil

cell counts of 121/ μ L, 58/ μ L, and 11.72/ μ L, respectively. Five patients presented with a neutrophilic/mixed pleocytosis, with an average time of symptom onset to CSF analysis of 4 days, compared with 5.4 days in patients with a predominant lymphocytic pleocytosis. Two of the 5 patients with neutrophilic/mixed pleocytosis (patients 1 and 16) had repeated lumbar punctures 2 and 8 days later, both with conversion to a predominantly lymphocytic profile.

Diagnostic Evaluation

Fifteen patients met diagnostic criteria for confirmed POWV neuroinvasive disease, and 1 met the criterion for probable neuroinvasive disease, owing to concomitant Lyme disease. A median time of 18 days was observed between symptom onset and diagnosis, and a median of 12 days between admission and diagnosis.

Thirteen patients underwent POWV immunoglobulin M (IgM) testing of serum samples, performed at either a public health laboratory ($n = 12$) or Mayo Clinic ($n = 4$); 12 (92.3%) had positive results. Six patients underwent CSF POWV IgM evaluation, and 5 tested positive. Plaque reduction neutralization tests (PRNTs) were performed in serum samples from 13 patients, with positive results in 12. Semiquantitative PRNT titers ranged from 1:32 to 1:2560, with higher titers suggesting more recent infection. One patient underwent CSF POWV nucleic acid amplification testing (NAAT), with positive results for deer tick virus lineage 2. Results of CSF metagenomic next-generation sequencing were positive for POWV in 1 of 2 patients tested (Table 1).

Patients were evaluated for other causes of meningoencephalitis. A meningoencephalitis NAAT panel was performed in 12 patients, with negative results in all. Fifteen of the 16 patients were also evaluated for infection with *B. burgdorferi* in serum, and 7 were assessed for neuroborreliosis using an antibody index assay (AIA) in CSF and serum. Among these patients, patient 5 had an equivocal Lyme AIA result (value of 1.4) with negative CSF polymerase chain reaction and negative serological results in serum; this patient was not considered to have confirmed neuroborreliosis. Patient 11 had a positive Lyme AIA result with a value of 1.8 (values ≥ 1.5 are considered indicative of intrathecal pathogen-specific antibody synthesis [14]), with positive results for anti-*B. burgdorferi* IgM in serum. Patients were tested for other endemic mosquito-borne viruses and TBPs, all with negative results (Supplementary Table 3).

Imaging

Fifteen patients underwent magnetic resonance (MR) imaging during their hospitalization, 11 (73%) with postgadolinium sequences included. Eight patients (53%) had abnormal MR imaging findings related to their infection. Leptomeningeal enhancement was seen in 5 patients. Two patients with rhombencephalitis (patient 1 and 12) and 1 with meningoencephalomyelitis (patient 5) had

Table 1. Clinical and Laboratory Presentation of Patients With Diagnosed Powassan Virus

Characteristic	Patient															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sex	M	F	F	M	M	F	M	M	M	M	M	F	F	M	M	F
Time of symptom onset, mo/y	11/2021	7/2022	6/2022	5/2022	11/2021	6/2022	8/2022	8/2019	11/2019	7/2019	7/2020	8/2013	8/2021	7/2018	10/2021	10/2016
Age, y	75	74	34	0.14	68	50	76	76	49	58	74	33	71	78	44	56
IS (cause)	Yes (CLL)	No	No	No	Yes (CLL)	No	No	No	No	No	Yes (lung cancer)	No	Yes (RA)	No	No	No
Neurologic phenotype	RE	RE	Meningitis	ME	MEM	Meningitis	Meningitis	ME	RE	RE	RE	RE	Meningitis	ME	OMS	MEM
MR imaging findings	Abn	Ni	NA	Ni	Abn	Ni	Ni	Ni	Abn	Abn	Abn	Abn	Ni	Ni	Ni	Abn
Platelet count (cells x10 ⁹ /L)	142	187	186	416	159	143	147	121	198	117	97	168	409	117	239	165
CSF findings																
TNCs (cells/ μ L)	6	121	257	480	274	40	55	85	193	66	5	585	43	NA	860	153
Neutrophils (cells/ μ L)	3 (50)	17 (14)	8 (3)	230 (48)	0	16.4 (41)	32 (58)	17.85 (21)	15.44 (8)	5.3 (8)	0.45 (9)	6 (1)	0.86 (2)	NA	NA	53.5 (35)
Lymphocytes (%)	2 (33)	87 (72)	242 (94)	62 (13)	236 (86)	16.4 (41)	9 (16)	43 (51)	176 (91)	57 (87)	3 (50)	579 (99)	39 (91)	NA	705.2 (82)	58 (38)
Diagnostic test	mNGS CSF	Serum IgM and PCR	Serum IgM	Serum IgM	CSF IgM	Serum IgM	Serum IgM	Serum IgM	Serum IgM	Serum IgM, CSF IgM	Serum IgM, CSF IgM	CSF IgM	Serum IgM	Serum IgM	Serum IgM	CSF IgM
PRNT result	NA	NA	1:640	1:640	NA	1:640	1:2560	1:640	1:40	1:160	<1:10	1:32	1:1280	1:640	1:640	NA
Death within 90 d ^a	Yes (at 35 d)	No	No	No	Yes (at 80 d)	No	No	No	No	No	No	No	No	No	No	Yes (at 62 d)
Length of hospitalization, d	30	8	3	6	76	1	7	38	16	5	21	17	12	16	11	28
Modified Rankin score (last follow-up)	6 (NA)	3 (LTF)	1 (2 y)	0 (1 y)	6 (NA)	0 (LTF)	1 (2 mo)	3 (3.5 y)	0 (2 mo)	1 (4 y)	4 (8 mo)	2 (9 y)	2 (1 y)	0 (5 y)	0 (3 mo)	6 (NA)

Abbreviations: Abn, abnormal; CLL, chronic lymphocytic leukemia; CSF, cerebrospinal fluid; F, female; IgM, immunoglobulin M; IS, immunosuppression; LTF, lost to follow-up; M, male; ME, meningoencephalitis; MEM, meningoencephalomyelitis; mNGS, metagenomic next-generation sequencing; MR, magnetic resonance; NA, not available; Ni, normal; OMS, opsoclonus myoclonus syndrome; PCR, polymerase chain reaction; PRNT, plaque reduction neutralization test; RA, rheumatoid arthritis; RE, rhombencephalitis; TNCs, total nucleated cells.

^aDeath within 90 days from symptom onset.

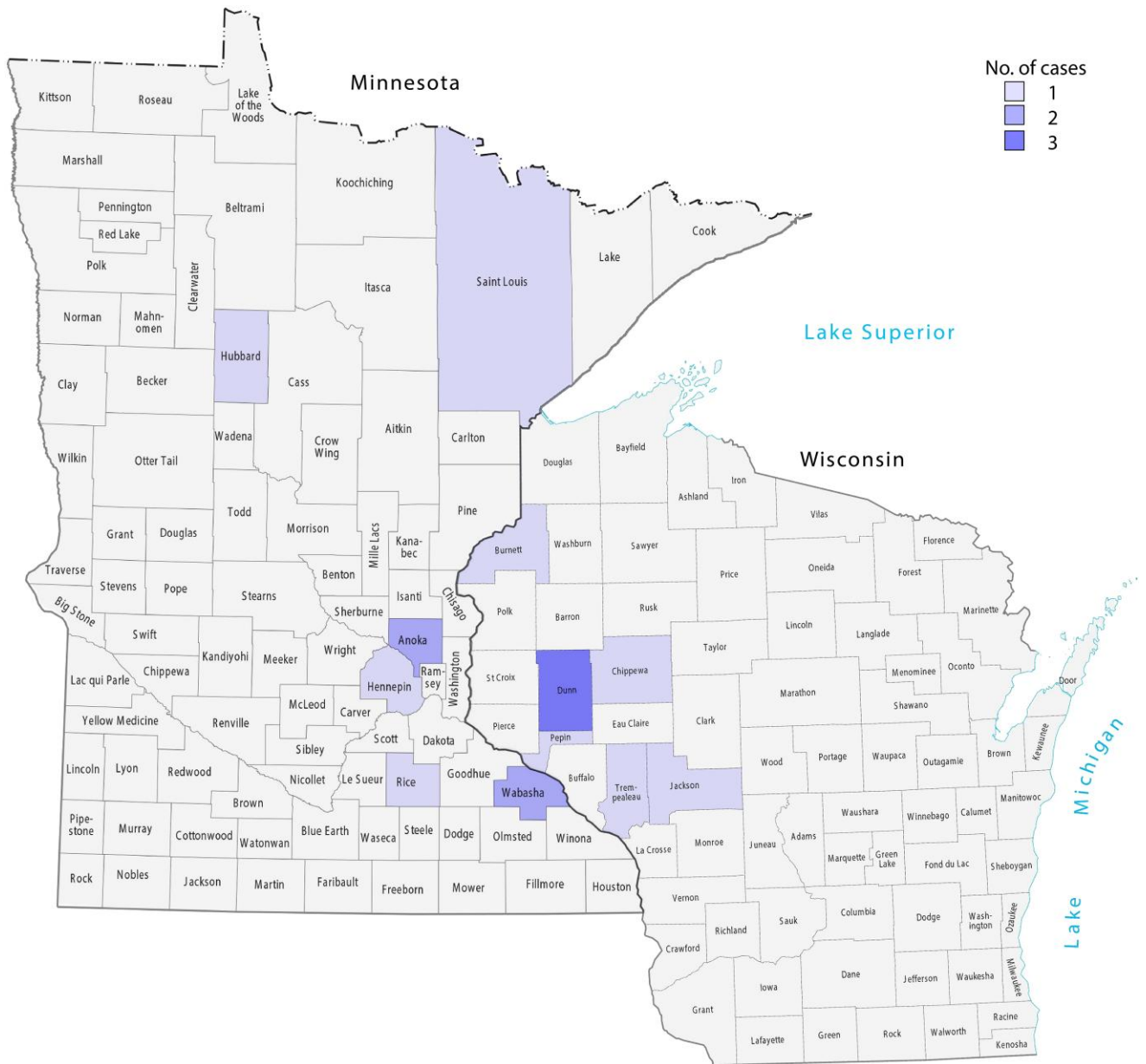


Figure 1. Geographic location of patients diagnosed with Powassan virus (only 1 patient reported recent travel, to Wyoming 1 month before hospitalization).

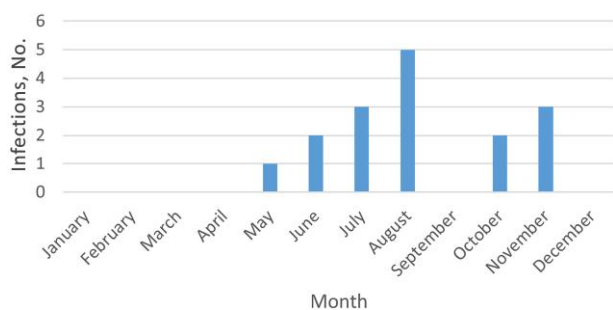


Figure 2. Number of Powassan infections stratified by month of presentation.

cerebellar T2/FLAIR hyperintensities, with patient 12 also having T2/FLAIR brainstem hyperintensities in the midbrain and pons, with subsequent development of postencephalitic parkinsonism (Figure 3). T2/FLAIR basal ganglia hyperintensities were seen in 2 patients (patients 2 and 16), with patient 16 going on to have postencephalitic parkinsonism. One patient with meningoencephalomyelitis (patient 5) had evidence of subtle ventral cervical cord enhancement. Seven patients had normal brain imaging findings.

One patient with meningoencephalomyelitis (patient 5) and 1 with rhombencephalitis (patient 11) underwent fluorodeoxyglucose positron emission tomography imaging as part of their

Table 2. Patient Characteristics and Presentation

Characteristic	Patients, No. (%) ^a (n = 16)
Age, median (IQR) y	63.2 (48.2–74.6)
Age range	1.6 mo to 78 y
Male sex	10 (62.5)
Immunosuppression	4 (25)
Symptoms at presentation	
Fever	15 (93.8)
Rash	4 (25)
Headache	8 (50)
Altered mental status	9 (56.3)
Neurologic phenotype	
Rhombencephalitis	6 (37.5)
Meningoencephalitis	3 (18.8)
Meningitis	4 (25)
Meningoencephalomyelitis	2 (12.5)
OMS	1 (6.3)
Laboratory results at admission, median (IQR)	
Hemoglobin, g/dL	12.4 (12.2–13.7)
WBC count, ×10 ⁹ cells/L	10.9 (7.6–12.3)
Absolute neutrophil count, ×10 ⁹ cell/L	8.0 (5.8–9.7)
Absolute lymphocyte count, ×10 ⁹ cells/L	1.27 (0.9–1.8)
Platelets, ×10 ⁹ cells/L	162 (136.8–189.8) ^b
Creatinine, mg/dL	1.09 (0.8–1.4)
ALT, mg/dL	24.5 (18.8–35.8)
AST, mg/dL	30 (23.0–41.3)
Total bilirubin, mg/dL	0.6 (0.4–0.7)
CSF results, median (IQR) (n = 15)	
Protein, mg/dL	79 (70.5–100.5) ^c
Glucose, mg/dL	58 (52–67)
Glucose/serum ratio	0.6 (0.5–0.6)
Nucleated cells, cells/μL	121 (49–265.5) ^c
Neutrophils, cells/μL	11.72 (3.6–17.6)
Lymphocytes, cells/μL	58 (27.8–205.8)
Monocytes, cells/μL	10.73 (3.08–25.33)
MR imaging results (n = 15)	
Normal	7 (46.7)
Cerebellitis	3 (20)
Leptomeningeal enhancement	5 (33.3)
Basal ganglia involvement	2 (13.3)
POWV diagnosis, no. positive/no. tested)	
Serum IgM positivity	10/13
CSF IgM positivity	5/6
CSF POWV PCR	1/1
Serum POWV PCR	1/1
CSF POWV mNGS	1/2
Seizures	3 (18.8)
ICU admission	6 (37.5)
Deaths (at 90 d)	3 (18.8)
Neurologic sequelae (n = 11)	8 (72.7)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSF, cerebrospinal fluid; ICU, intensive care unit; IgM, immunoglobulin M; IQR, interquartile range; mNGS, metagenomic next-generation sequencing; MR, magnetic resonance; OMS, opsoclonus myoclonus syndrome; PCR, polymerase chain reaction; POWV, Powassan virus; WBC, white blood cell.

^aData represent no. (%) of patients unless otherwise specified.

^bResults in 7 patients with thrombocytopenia.

^cProtein elevated in 100% of patients/>400 cells/μL in 3 patients.

diagnostic workup, and both were noted to have basal ganglia and cerebellar hypermetabolism (Figure 4). Neither of these patients had basal ganglia T2/FLAIR hyperintensities, and only 1 had cerebellar T2/FLAIR hyperintensities on MR images. One of the patients with postencephalitic parkinsonism (patient 12) underwent dopamine transporter single-photon emission computed tomography 2 years after infection, which demonstrated marked diminution of tracer uptake in the putamen and caudate bilaterally [15] (Figure 5).

Electroencephalography

Eight patients underwent electroencephalography (EEG), 7 for persistent encephalopathy and 1 after a witnessed self-limited episode of generalized shaking. Six patients had EEG evidence of generalized slowing, 2 of whom also had generalized triphasic waveforms, and 2 had electrographic seizures, 1 with diffuse midline and frontal rhythmic delta activity associated with head jerking (patient 5) and the other with focal left temporal onset associated with persistent encephalopathy (patient 16).

Treatment

Initially, 13 patients received antibiotics for possible bacterial meningitis. Nine patients received immunotherapy in the form of steroids or intravenous immunoglobulin. Eight patients received steroids, 7 during the period of diagnostic uncertainty and 1 for presumed parainfectious OMS. Four patients received intravenous immunoglobulin: patient 1 for his known hypogammaglobulinemia, patient 5 as empiric therapy during the period of diagnostic uncertainty, and patients 8 and 15 specifically for treatment of POWV infection.

Outcomes

Six patients needed intensive care unit level of care, with a median stay of 9 days. Six patients required mechanical intubation (range, 4–14 days), with 1 proceeding to tracheostomy. Seven patients required temporary tube feeding supplementation, with 4 requiring percutaneous endoscopic gastrostomy tube placement. Patient 1 developed obstructive hydrocephalus secondary to cerebellar edema and fourth ventricle effacement, requiring an extraventricular drain for 7 days. Two patients died within 90 days after diagnosis of complications attributable to POWV, and 1 patient died after developing Richter transformation and being transferred to hospice (Supplementary Table 2).

Thirteen of 16 patients (81.3%) survived after 90 days of diagnosis. In 1 patient with meningitis, cerebral venous thrombosis without infarct developed 6 weeks after symptom onset, requiring rehospitalization. Of the 13 patients who survived their infection, 2 were discharged to a rehabilitation facility, 2 to a skilled nursing facility, 1 to a transitional care unit, and 8 to home.

Table 3. Neurologic Summary and Sequelae

Patient	Neurologic Presentation	MR Imaging Findings	EEG Findings	Neurologic Phenotype	Neurologic Sequelae
1	Encephalopathy, anarthria, quadriparesis, vertical gaze restriction	Cerebellitis with obstructive hydrocephalus	Generalized periodic discharges with triphasic wave morphology and diffuse slowing (3–5-Hz range)	Rhombencephalitis	Persistent encephalopathy and anarthria (expired)
2	Left-sided weakness, dysarthria, tremor, truncal ataxia	Symmetric T2 hyperintensities in bilateral thalami	Normal	Rhombencephalitis	Lost to follow-up
3	Headache, fever, nausea, altered mental status	Not performed	Not performed	Meningitis	Cognitive impairment (short-term recall, word finding and concentration) and headaches
4	Seizures	Normal ^a	Normal	Meningoencephalitis	None
5	Rapidly progressive quadriparesis, encephalopathy, multiple cranial neuropathies (left 3rd and 4th, bilateral 6th, and bilateral optic perineuritis)	Cerebellitis and ventral cervical cord enhancement	Generalized periodic discharges, rhythmic delta activity with sharp features, and generalized slowing (5–7-Hz range, 2–3 Hz posteriorly)	Meningoencephalomyelitis	Quadriplegia and facial dyskinesias (expired)
6	Headache, fever, neck pain	Normal	Not performed	Meningitis	Lost to follow-up
7	Headache, fever, falls	Normal	Not performed	Meningitis	Cognitive impairment (slowed processing speed)
8	Encephalopathy, multifocal myoclonus	Normal ^b	Moderate diffuse slowing (4–6-Hz range)	Meningoencephalitis	Cognitive impairment and gait disturbance
9	Left 6th nerve palsy, dysarthria, upper-extremity dysmetria	Cerebellar and occipital lobe leptomeningeal enhancement	Not performed	Rhombencephalitis	Gait disturbance
10	Headaches, dysarthria, appendicular and truncal ataxia	Leptomeningeal enhancement at cerebellar folia and cerebral hemispheres	Not performed	Rhombencephalitis	Gait disturbance
11	Truncal > appendicular ataxia, encephalopathy, anarthria	Diffuse sulcal hyperintensities on postgadolinium FLAIR sequence	Not performed	Rhombencephalitis	Persistent ataxia, dysarthria and deconditioning at last follow-up (8 mo)
12	Headache, encephalopathy, ataxia and left 6th nerve palsy	Midbrain, pons, and cerebellar FLAIR hyperintensities ^a	Moderate diffuse slowing (4–5-Hz range)	Rhombencephalitis	Postviral levodopa-responsive parkinsonism at last follow-up (9 y)
13	Headache, fever, meningismus, encephalopathy	Normal ^a	Not performed	Meningitis	Headaches and gait disturbance
14	Fever, headache, encephalopathy	Normal ^a	Moderate diffuse slowing (4–6 Hz) with intermittent triphasic waveforms	Meningoencephalitis	None
15	Fever, headache, meningismus, truncal ataxia, tremulousness, opsoclonus	Normal	Not performed	OMS	None
16	Encephalopathy, truncal ataxia, quadriparesis, dysarthria, left 6th nerve palsy	Leptomeningeal enhancement and left basal ganglia FLAIR hyperintensities	Left temporal seizures	Meningoencephalomyelitis	Parkinsonism and poliomyelitis (expired)

Abbreviations: EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; MR, magnetic resonance; OMS, opsoclonus myoclonus syndrome.

^aNo postgadolinium sequences MR imaging obtained.

^bMotion degraded, limited study.

Neurologic Sequela

Of the survivors, 2 were lost to follow-up. Eight patients (72.7%) had evidence of neurologic sequela, defined as neurologic symptoms believed to be a downstream consequence of

their infection beyond the infectious period. Patient 12 had partially levodopa-responsive, postviral parkinsonism, which was present at 9-year follow-up [15]. Four patients had persistent gait disturbances, 2 had new headaches, 3 had subjective

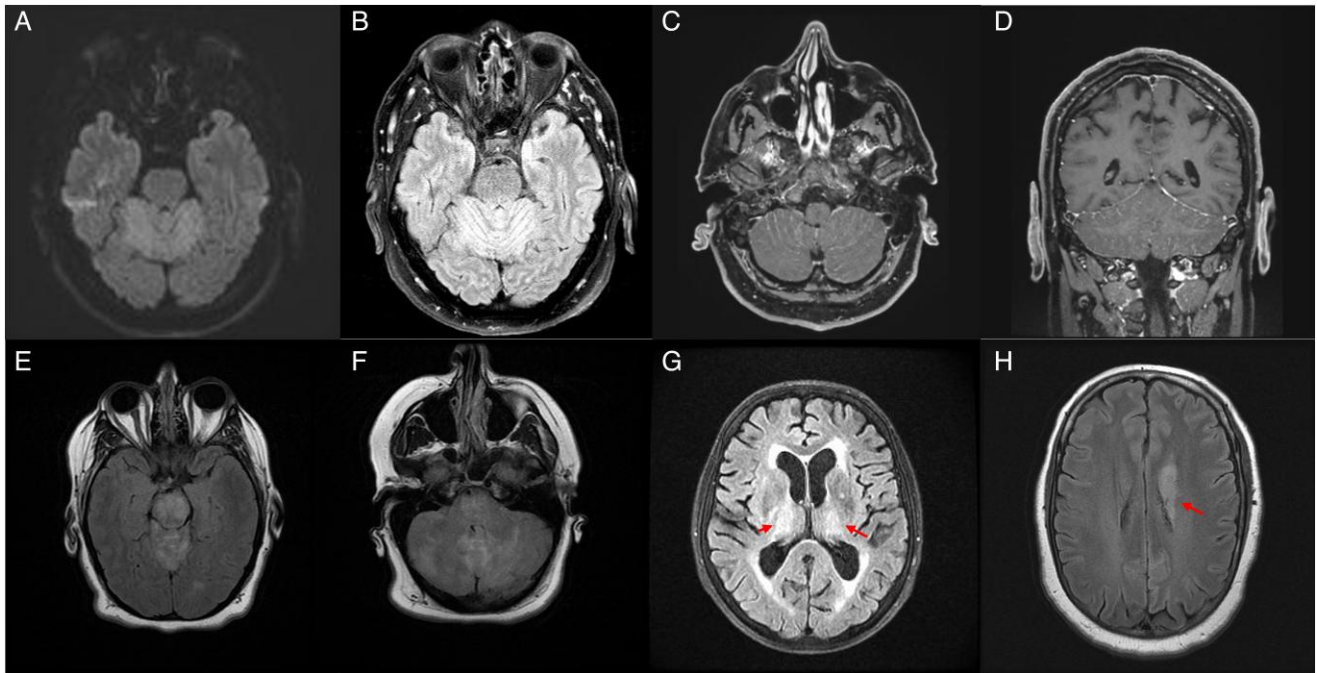


Figure 3. Magnetic resonance imaging findings. *A–D*, Cerebellitis in patient 5 demonstrated by cerebellar diffusion restriction (*A*), T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities (*B*), and leptomenigeal enhancement (*C, D*). *E, F*, Extension of T2/FLAIR hyperintensities involving the midbrain (*E*) and pons (*F*) in addition to the cerebellum in patient 12. *G*, Bilateral thalamic T2/FLAIR hyperintensities in patient 2 (two red arrows). *H*, Left caudate T2/FLAIR hyperintensities in patient 16 (red arrow).

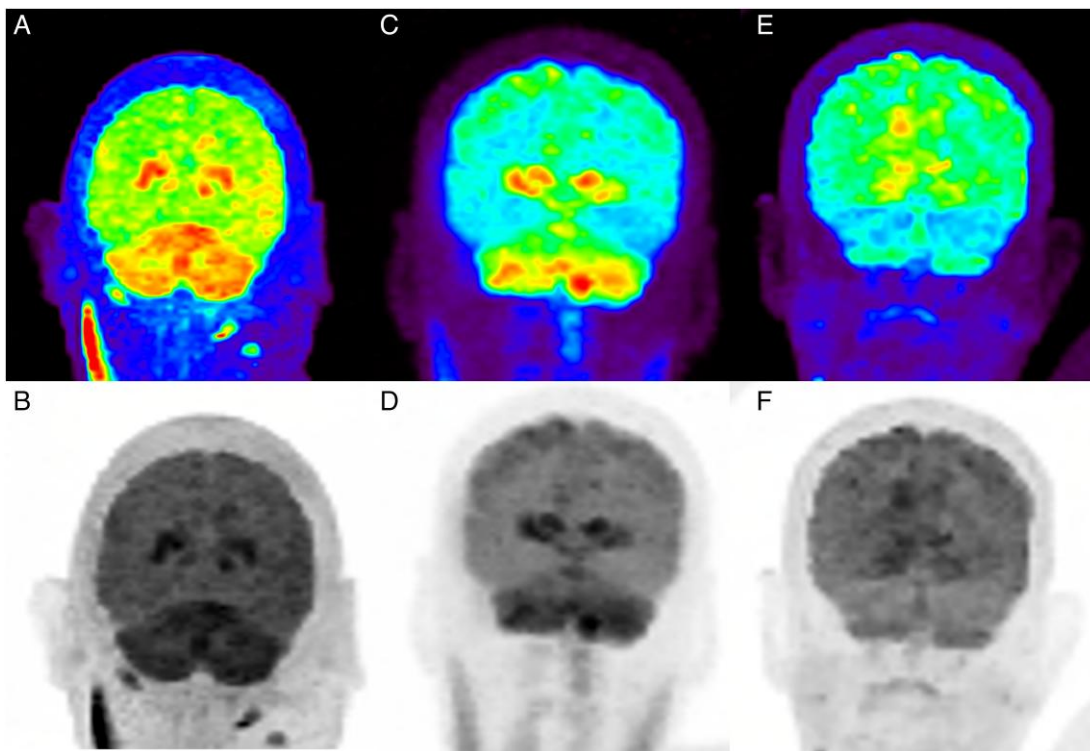


Figure 4. *A–D*, Fluorodeoxyglucose positron emission tomography (FDG-PET) scans from patients 5 (*A, B*) and 11 (*C, D*), showing hypermetabolism in the basal ganglia and cerebellum. *E, F*, Partial resolution of hypermetabolism noted in patient 11 on repeated FDG-PET 7 months later.

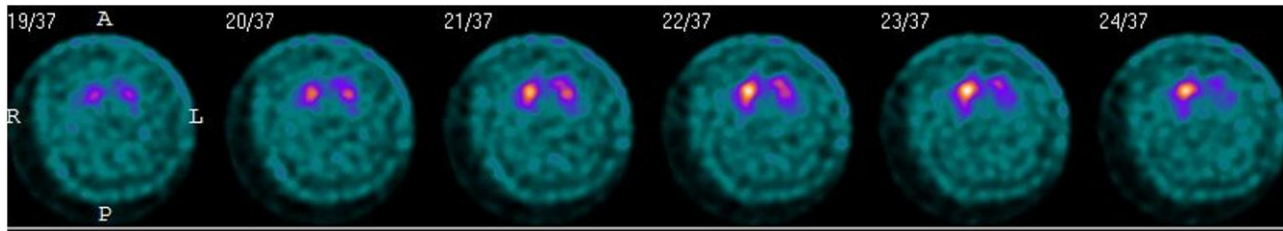


Figure 5. Dopamine transporter single-photon emission computed tomographic scan of patient 12, showing marked diminution of tracer uptake in the putamen and caudate bilaterally.

cognitive impairment (described as poor memory, mental slowing, or decreased concentration), and 1 had persistent ataxia and dysarthria (Table 3). In patients who survived their infection, modified Rankin scores ranged from 0–4 (median, 1) at last follow-up, indicating that most patients had at least some degree of disability after infection.

DISCUSSION

POWV is an emerging infectious disease with an increasing incidence due to multiple factors, including expansion of the geographic range of ticks such as *I. scapularis*, wider availability of diagnostic methods and heightened clinical awareness. We report a case series of 16 patients, 15 confirmed and 1 with probable Powassan disease from 2013–2022 at a tertiary care center in the Midwest United States. The most commonly found laboratory abnormality was thrombocytopenia, even in the absence of other TBP coinfections, which has been reported in the literature [16, 17]. We found a 90-day mortality rate of 18.8% among patients with diagnosed POWV infection, consistent with previous reports in the literature (10%–15%) [18].

All patients were from Minnesota and Wisconsin, with many clustered in counties bordering major waterways, including the Mississippi and Chippewa rivers. These areas are likely to be at higher risk for human transmission, given their proximity to human population centers, attractiveness for recreational activities, and decreased habitat fragmentation, which may lead to higher densities of ticks and reservoir hosts [19]. Patients presented between May and November, which is longer than the classic presentation between May and September in the northern hemisphere and highlights the importance of having a high clinical suspicion even during the early winter, as reported elsewhere [20]. This wider temporal distribution may be due to the effects of climate change, leading to longer seasonal activity and increased tick populations [21]. In addition, higher temperatures result in people spending longer time outdoors [22].

In our cohort, the majority of the patients presented with encephalitis-related syndromes (fever and altered mental status), such as rhombencephalitis, meningoencephalitis, and isolated meningitis, similar to prior reports [23]. Two patients

presented with prominent weakness that could be localized to the ventral spinal cord. One of them presented with rapidly progressive quadriplegia with subtle ventral cervical cord enhancement, and the other with flaccid monoparesis and poliomyelitis demonstrated by electromyography. Other flaviviruses are known to cause a poliomyelitislike flaccid paralysis, and this clinical phenotype has rarely been reported with POWV [24]. Involvement of motor neurons within the ventral horn of the spinal cord has been described in mouse models [25].

One patient presented with OMS, a presumed immune-mediated disorder characterized by chaotic uncontrolled movements of the eyes and involuntary jerklike movements of the body. OMS can be paraneoplastic but has also been described in the setting of infection, including neuroinvasive disease with other flaviviruses [26, 27]. Our patient developed OMS 1 week after presenting with a meningitic syndrome. Given a potential immune-mediated mechanism, immunotherapy may be indicated in cases of OMS, despite the lack of evidence supporting its use in flavivirus meningoencephalitis.

Nearly half of the patients in our cohort had normal head imaging. MR imaging abnormalities, when present, commonly showed evidence of cerebellitis and/or leptomeningeal enhancement. Less commonly observed in our cohort was basal ganglia involvement (12.5%), compared to other case series where basal ganglia involvement was reported to occur in 38%–54% of cases [17, 28]. Interestingly, in 2 patients who underwent fluorodeoxyglucose positron emission tomography as part of a cancer workup, basal ganglia and cerebellum hypermetabolism was found incidentally, possibly suggesting basal ganglia dysfunction that was not evident at MR imaging. One of these patients died of their illness, while the other had persistent ataxia and dysarthria at 8-month follow-up. Neurologic sequelae were observed in 72.7% of our cohort, compared with 50% in previous reports. Notable sequelae included cognitive impairment, headaches, gait disturbance, and parkinsonism, which is similar to previous reports [13].

We also evaluated the incidence of coinfections in patients with POWV. Among the 16 individuals, 1 patient was suspected to have a coinfection with *B. burgdorferi*; however, it is unclear whether neuroborreliosis would explain his neurologic

symptoms. and patients that have had Lyme infection years earlier may have a persistently elevated Lyme AIA results. Another patient was positive for anti–West Nile virus IgM in serum, but confirmatory PRNT titers were <1:10, suggesting that West Nile virus IgM positivity was likely secondary to cross-reactivity [29–31].

We observed that the median time between admission and POWV diagnosis was 12 days, while the time between symptom onset and diagnosis was 18 days. Although there are currently no targeted antiviral treatments, prompt diagnosis of POWV infections is essential to deescalate antibacterial treatment, provide accurate prognostic information, and document the epidemiology of this emerging TBP. There is also a need for more widely available diagnostic testing options, outside of public health laboratories. We were able to appraise how improved accessibility to POWV testing affected the diagnosis at our institution. Four of the 16 cases presented in this case series were diagnosed within 4 months of offering POWV-specific diagnostics in our laboratory, compared with diagnosis of 12 cases between 2018 and 2021.

Alongside test availability, clinicians need to be cognizant of appropriate test use relative to the timing of patient presentation and the limitations associated with currently available diagnostic assays. Importantly, immune response to POWV may not be detectable until 5–7 days after infection, as it has been reported in other tick-borne encephalitis during the initial viremic phase [32, 33], making POWV NAAT preferable during this acute stage of disease, similar to preferences in other arboviral and tick-borne diseases [34], although some reports suggest that specific antibody levels start to increase within 1–2 days [23]. However, a negative NAAT result does not rule out infection as POWV viral loads are transient and low, leading to the potential for clinically false-negative results. As a result, for patients with suspected POWV infection, testing with both NAAT and an anti-POWV IgM assay is recommended. For immunocompromised patients who are unable to mount a strong immune response, serologic results may be false-negative for prolonged periods of time, as seen in one of our patients with chronic lymphocytic leukemia.

Owing to the small sample size, we cannot draw definitive conclusions in terms of risk for mortality and neurologic sequelae. The median age of the 3 patients who died was higher than that of survivors, but this difference was not significant. On the other hand, 2 of the 3 patients who died were immunocompromised owing to chronic lymphocytic leukemia. These 3 patients had abnormal MR imaging findings, consistent with cerebellitis in 2 and left basal involvement in 1. All 3 had abnormal EEG findings, ranging from nonspecific slowing to seizures. Given these cases, we suggest that being immunosuppressed, male, having seizures and cerebellitis on imaging may be associated with a higher mortality risk [17, 28].

Our study has several limitations. First, our sample size was small, which may limit the generalizability of our findings.

Second, our study was retrospective, and we could not control for all potential confounding factors. Finally, we were not able to assess the impact of treatment on mortality risk, owing to the limited availability of effective treatments for POWV infections.

In summary, we recommend that POWV infection should be considered in patients who present with acute meningoencephalitis or rhombencephalitis and who live in or travel to endemic areas regardless of tick exposure history. For these patients, we recommend performing lumbar puncture and MR imaging with and without gadolinium contrast. If done early, CSF analysis can demonstrate neutrophilic and lymphocytic mixed pleocytosis, although the most common findings include high protein levels and mild lymphocytic pleocytosis. Normal MR imaging findings do not preclude the diagnosis. Although seizures are relatively rare, subclinical seizures can occur, and EEG should be considered in patients with persistent encephalopathy. Our study provides important insights into the clinical presentation as well as the neurologic profiling of these patients both clinically and by imaging. Our findings underscore the need for increased awareness, surveillance, testing capabilities and prevention of POWV infections, particularly among older patients and those with underlying comorbid conditions.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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