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LETTER TO THE EDITOR

Powassan virus infection presenting as acute encephalitis in a patient from the New England area: a case report

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Dear editor,

A 75-year-old woman with past medical history significant for hyperlipidemia, glaucoma, and breast cancer status-post lumpectomy and radiation in the distant past presented with 72 h of declining mental status. Her symptoms were notable for progressively worsening hypersomnia that resulted in her husband needing to wake her after 14 h of sleep on the day of presentation. Additionally, the patient displayed apraxia with inability to dress herself and had an episode of fecal incontinence.

At baseline, the patient was reported to be a high-functioning individual, who was able to accomplish her activities of daily living independently. She resided in Martha's Vineyard with her husband and had traveled to Boston 1 day prior to symptom onset. On presentation, the patient was afebrile and hemodynamically stable. Her physical exam, including an extensive neurological exam, revealed that she was oriented to self, but not to place or time. She also exhibited short-term memory loss evidenced by her inability to recall information provided to her just minutes prior. The rest of the exam was unremarkable.

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Basic laboratory parameters on presentation were non-revealing, apart from a mild hyponatremia with a sodium of 131. Cerebrospinal fluid (CSF) evaluation revealed lymphocytic pleocytosis and normal levels of protein and glucose (Table 1).

Imaging studies at presentation, including chest X-ray, head CT, and brain MRI, did not reveal any significant findings. However, a follow up MRI 1 week later revealed increased T2 signal present within the basal ganglia including the caudate nuclei, globus pallidus, and putamen bilaterally, as well as subcortical T2 hyperintensity in the bilateral posterior parietal lobes and in the cerebellum (Fig. 1).

A wide range of microbiology and immunology investigations were carried out (Table 2), including titers for VZV, babesiosis, tularemia, CSF VDRL, eastern equine encephalitis virus, West Nile virus, enterovirus, and CSF cryptococcal antigen, but all were negative. Serum HSV 1&2 IgG were positive, but both serum IgM and CSF PCR were negative. A tick-borne disease panel was notable for past infection (IgG only) with *Borrelia burgdorferi* and *Anaplasma* spp. EBV antibody titers were positive, but serum EBV PCR was negative. EBV convalescent titers obtained 21 days later showed a change in titers but given that the IgM titer did not change by a fourfold and the PCR was negative, it was unlikely that this represented an acute EBV infection. Finally, an autoimmune encephalitis panel did not reveal any findings.

The patient's presentation, which consisted of subacute onset of confusion, lymphocytic pleocytosis in the CSF, and findings of inflammation in the basal ganglia, parietal lobes, and cerebellum on MRI were suggestive of encephalitis. The differential diagnosis included autoimmune encephalitis, acute disseminated encephalomyelitis (ADEM), viral encephalitis, and tick-borne associated encephalitis. Given that the patient resided in Martha's Vineyard, an island off the coast of Massachusetts, USA, which suffers from a heavy burden of tick-borne infections, such as Lyme disease, West Nile Virus, and Anaplasma encephalitis were evaluated for.

Table 1 Results of CSF analysis

CSF	Tube 1	Tube 3	Reference range
Color	Colorless	Colorless	Coloreless
Character	Clear	Clear	Clear
Xanthochromia	Absent	Absent	Absent
WBC	41	69	0–5 10*3/uL
Differential	6% PMN, 84% LY, 10% MONO	3% PMN, 88% LY, 9% MONO	
RBC	8	3	0–5 cells/CCM
Protein		49	12–60 mg/dL
Glucose		60	40–70 mg/dL

Laboratory testing was negative for common viral causes of encephalitis, autoimmune encephalitis, and acute tick-borne illnesses, including West Nile Virus; notably, patient had remote past infection for Anaplasmosis and Lyme disease.

Specifically, the involvement of the basal ganglia made Powassan virus encephalitis a possible diagnosis, as this finding has been associated with infections by Flaviviridae [1]. Therefore, after 9 days of hospitalization, a CSF sample was submitted to the CDC for antibody titers against Powassan virus.

Based on the initial CSF finding of lymphocytic pleocytosis, the patient was started on an empiric 10-day acyclovir course; her CSF PCR for HSV 1 & 2 resulted as negative. She completed a course of ceftriaxone for empiric coverage of central nervous system bacterial infections and received a 28-day course of doxycycline, in the event that she had Lyme meningitis. She also received a 6-day course of Prednisone 60 mg daily with tapering, which was associated with a slight improvement of her symptoms — she could ambulate to the bathroom, was more conversant, and had a slight improvement in her short-term memory. She subsequently also received a 4-day course of IVIG, without any further improvement of her symptoms.

The patient's neurological function improved slightly, as she was more conversant after corticosteroid administration, but she remained oriented only to self. She was discharged after a total of 33 days of hospitalization. Two weeks post-discharge, the CDC reported that her CSF was positive for Powassan virus IgM antibodies. On follow-up examination 7 weeks post-discharge, her cognitive function remained impaired, which was supported by her scoring 13/30 on a Mini Mental State Exam, but she was otherwise physically doing well. Unfortunately, 4 months later, she continues to be cognitively impaired and her MRI remains unchanged.

Between 2010 and 2019, there have been 181 documented cases of Powassan virus encephalitis in the USA. The vast majority have been identified in four states, namely Minnesota, Wisconsin, Massachusetts, and New York, which when combined, make up 74% of cases. Of these 181 cases, 166 had neuroinvasive disease (91.7%) and 21 (11.6%) resulted in death. Of note, death occurred only in patients with neuroinvasive disease [2].

Rates of Powassan virus infections have been increasing, likely due to the increased awareness for arboviral encephalitides secondary to the West Nile Virus outbreaks, as well as the territorial expansion of one of the vectors of Powassan virus, *Ixodes scapularis* [2, 3]. Indeed, 85% of Powassan virus infections reported by the CDC between 2010 and 2015 included patients with encephalitis or meningitis, while only 15% of patients had non-neuroinvasive disease, suggesting that patients without CNS involvement are less likely to be tested for Powassan virus [3].

The 2 variants of Powassan virus are transmitted by different vectors. Lineage I is transmitted by *Ixodes cookei*, while Lineage II is transmitted by *I. scapularis*, the tick vector for *Borrelia burgdorferi*, *Babesia microti*, and *Anaplasma phagocytophilum* [3]. However, whereas the transmission of other tick-borne diseases requires prolonged tick attachment (48 h for Lyme disease and 24 h for babesiosis),

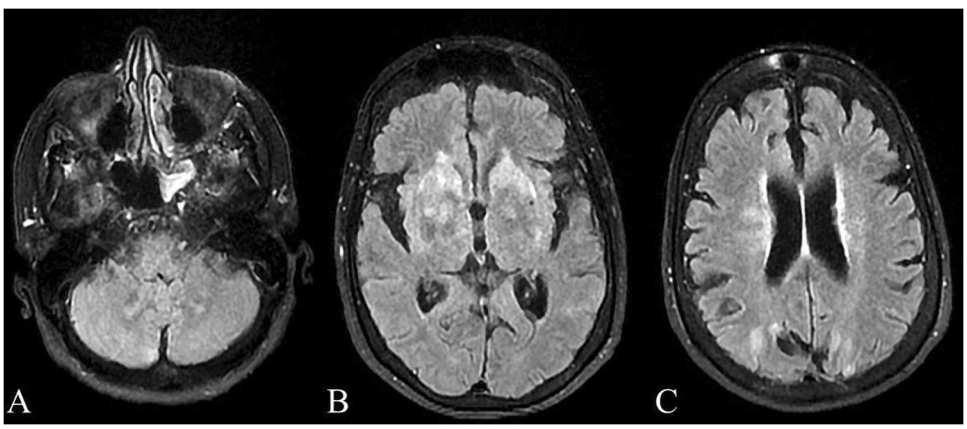

Fig. 1 Findings on MRI, T2 FLAIR sequence, 1 week after presentation. Increased signal can be appreciated bilaterally in the cerebellum (**A**), basal ganglia (**B**), including the caudate nuclei, globus pallidus, and putamen, and posterior parietal lobes (**C**)

Table 2 Microbiology and immunology tests

Test	Admission	Convalescent	Reference range
EBV VCA IgG	340	> 750	< 22.00 U/mL
EBV VCA IgM	82.7	68.7	< 44.00 U/mL
EBV-Na Ab	289	> 600	< 22.00 U/mL
EBV DNA PCR, serum	< 200 copies/ml		< 200 copies/ml
Monospot	Negative		
VZV IgM	< 0.9		< 0.9
VZV IgG	> 4000		> 165 index
HSV 1 IgG	24.70 High		< 0.90 index
HSV 1 IgM	Negative		
HSV1 CSF PCR	Negative		
HSV 2 IgG	7.07 High		< 0.90 index
HSV 2 IgM	Negative		
HSV2 CSF PCR	Negative		
CMV IgM	< 30.00		< 30.00 AU/mL
CMV IgG	< 0.60		< 0.60 U/mL
CMV DNA, real time PCR	< 200 copies/ml		< 200 IU/mL
CMV DNA, QN PCR	< 2.30		< 2.30 log IU/mL
HIV Ag/Ab, 4th generation	Non reactive		
VDRL CSF	Negative		
Cryptococcus antigen, CSF	Negative		
Enterovirus CSF PCR	Negative		
R. rickettsii IgM	Not detected		
R. rickettsii IgG	Not detected		
RSMF IgM	Not detected		
RSMF IgG	Not detected		
E. chaffeensis IgG	< 1:64		< 1:64
E. chaffeensis IgM	< 1:20		< 1:20
E. chaffeensis DNA	Not detected		
A. phagocytophilum IgG	1:64 (High)		< 1:64
A. phagocytophilum IgM	< 1:20		< 1:20
A. phagocytophilium DNA	Not detected		
B. microti DNA	Not detected		
B. miyamotoi DNA	Not detected		
Lyme by PCR, whole Blood	Not detected		
Lyme disease Abs IgG	Positive (7/10 antibodies reactive)		≤ 4/10 reactive against borrelial proteins
Lyme disease Abs IgM	Negative (1/3 antibodies reactive)		≤ 1/3 reactive against borrelial proteins
F. tularencis Ab	< 1:20		< 1:20
M. pneumoniae IgM	59		< 770 U/ml
M. pneumoniae IgG	2.92		< 0.9
S. pneumoniae urinary antigen	Negative		
L. pneumoniae urinary antigen	Negative		
Group A *Streptococcus* antigen, throat swab	Negative		
SARS-CoV-2 RNA	Negative	Negative	
HCV Ab	Negative		
HBsAg	Negative		
HBsAb	Negative		
HBcAb	Negative		
Eastern Equine Encephalitis virus IgG	< 1:16		< 1:16
Eastern Equine Encephalitis virus IgM	< 1:16		< 1:16
West Nile IgG	< 1.3		< 1.3 index

Table 2 (continued)

Test	Admission	Convalescent	Reference range
West Nile IgM	< 0.9		< 0.9 index
Powassan virus IgM, CSF	Positive		
Inflammatory and autoimmune markers			
CRP	< 5		< 10 mg/L
ESR	79	18	0–36 mm/hr
Rheumatoid factor	20.8		< 12 IU/ml
ANA	Negative		
ANCA	Negative		
C3 complement	121		83–193 mg/dL
Complement total (CH50)	37		31–60 U/mL

Powassan virus can be transmitted to a new host within 15 min. What sets it apart is that the virus is located in the salivary glands of the tick prior to the tick bite, allowing it to rapidly infect the new host [4].

Regarding its clinical presentation, after an incubation period of 8 to 34 days, the disease initially manifests with malaise, nausea, and sore throat. Patients who develop neuroinvasive disease go on to manifest high fever, headache, and disorientation 1 to 3 days later. Other findings include cranial nerve palsies, convulsions, obtundation, tremors, twitching, nystagmus, hallucinations, hemiparesis, quadriplegia, and respiratory failure [3, 5].

Imaging findings of Powassan virus neuroinvasive disease are most commonly appreciated using MRI with T2-weighted fluid-attenuated inversion recovery (T2/FLAIR) sequences. Similar to other arboviruses, such as West Nile Virus, Powassan virus has a predilection for the deep foci in the basal ganglia, thalamus and brainstem. In addition, it may affect the cerebellum and cortex [1, 3]. Pathology findings include necrotizing inflammation with a lymphocytic infiltrate primarily in the gray matter, as well as reactive gliosis [3].

The diagnosis of Powassan virus encephalitis is established through the identification of the virus, either directly through PCR in serum or CSF samples during the prodromal phase, or indirectly, either through identification of IgM neutralizing antibodies in the serum or CSF during the acute illness phase or through serum IgG in later phases [2, 3].

Neuroinvasive disease can have devastating long-term complications, including cognitive deficits, memory loss, hearing impairment, aphasia, muscle wasting, dysarthria, apnea, psychosis, and spastic hemiplegia, which develop in about 50% of patients, while approximately 10% of cases result in death. There is no specific treatment for Powassan virus disease; therefore, prevention of the disease through the avoidance of tick bites is of utmost importance [3, 5].

In conclusion, Powassan virus encephalitis is a severe tick-borne infection that can lead to devastating long-term complications or even death. The diagnosis requires a high degree of clinical suspicion and is based on epidemiologic evidence of tick exposure in patients with symptoms and signs of central nervous system infection. In general, the combination of findings of encephalitis, history of recent travel to an endemic region, and T2/FLAIR hyperintensities in the basal ganglia should suggest Powassan virus encephalitis as a probable cause. As treatment remains supportive, prevention of tick bites is critical in limiting occurrence of disease in the population.

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Data availability Available upon request.

Declarations

Ethical approval This work is in accordance with the requirements of the authors' institution regarding research involving human participants, as well as with the 1964 Helsinki Declaration and its later amendments.

Consent to participate The participant as well as her family have consented to the publication of the case report to the journal.

Conflict of interest The authors declare no competing interests.

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