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Powassan virus encephalitis

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Introduction

Powassan virus is a tick-borne flavivirus that is endemic to the United States, causes severe encephalitis, and is diagnosed with increasing frequency. Since its discovery in 1958, approximately 270 cases have been reported in the United States and Canada; however multiple lines of epidemiological evidence suggest that it may be more prevalent than is currently appreciated. Here, we will briefly summarize the virology, ecology, and epidemiology of Powassan virus and review clinical features of infection, with a focus on brain imaging, diagnostic testing, and neuropathology.

Powassan virus belongs to the *Flaviviridae* family, and is a small enveloped virus with an approximately 10.8 kb positive-sense RNA genome that encodes a single open reading frame[1]. It is a member of the flavivirus genus, which is primarily comprised of arthropod-borne viruses, and it is closely related to tick-borne encephalitis virus (TBEV). TBEV is a relatively well-studied cause of encephalitis in Europe and Asia, and several of its features are worth considering as they may parallel Powassan virus. First, TBEV causes a substantial burden of disease, with more than 10,000 cases per year despite the availability of a vaccine[2]. Many TBEV infections are asymptomatic[3], and its seroprevalence ranges from 2–5% or higher in high-risk populations[4–6]. Finally, within TBEV, there are three viral subtypes that differ by about 5% at the amino acid level, have different (but overlapping)

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geographic distributions, and cause different frequencies of neuroinvasive disease and fatality[7].

Compared to TBEV, relatively less is known about Powassan virus. It was discovered in 1958 in Ontario, Canada[8], and only about 25 cases were reported over the subsequent 40 years[9]. In part, this may have been due to under-recognition and limited testing. However, infection may truly have been infrequent because the canonical Powassan virus lineage I is transmitted by tick species rarely encountered by humans, *Ixodes cookei* and *Ixodes marxi*. In 1996, a second lineage of Powassan virus was discovered and termed deer tick virus (DTV), as it is transmitted by the common vector of human disease, *Ixodes scapularis*[10]. Unlike other Ixodes-borne infections, Powassan virus can be transmitted within a very short period of tick attachment[11,12]. To date, more than 240 cases have been reported. The two Powassan virus lineages differ by around 15% at the nucleotide level and 5% at the amino acid level[13] and thus can be distinguished by molecular testing such as polymerase chain reaction (PCR) and sequencing. All recent human infections for which molecular characterization was performed have been due to lineage II / DTV[14–21]. However, because most Powassan virus infections are diagnosed by serology, and lineages I and II are serologically indistinguishable, they are clinically diagnosed together as “Powassan virus encephalitis.”

Ecology

Powassan virus is maintained in an enzootic cycle that is comprised of small mammal reservoir hosts and tick vectors. Ticks can become infected by feeding on a viremic host or co-feeding with an infected tick, even on a non-viremic host. The virus persists through later stages of the tick life-cycle, e.g. an infected larval tick will remain infected as a nymph and adult (through transstadial transmission), and ticks can pass the virus on to progeny (through transovarial transmission)[22]. Large mammals, including humans, become infected as incidental, dead-end hosts. In addition to being transmitted by different vectors, Powassan virus lineages I and II are maintained by different small mammal reservoir species in different geographic regions. Lineage I has been detected primarily in woodchucks and squirrels in regions of Canada and the U.S. surrounding the Great Lakes. By contrast, Powassan virus lineage II / DTV is found in the northeast and north central U.S. Shrews have recently been implicated as a primary reservoir[23], and there is little evidence that it is maintained in white-footed mice, which are the primary reservoir for other *Ixodes scapularis*-borne pathogens.

Powassan virus has a prevalence of around 1–3% in *Ixodes scapularis* ticks in endemic regions of the northeast and north central U.S. and has higher prevalence in adult ticks[24–29]. By comparison to other tick-borne pathogens, a study of *Ixodes scapularis* from New York found a prevalence of 3.4% for Powassan virus, 3.2% for *Babesia microti*, 18% for *Anaplasma phagocytophilum*, and 55% for *Borrelia burgdorferi*[29]. Experimental work has demonstrated that other tick species, *Amblyomma americanum* and *Dermacentor variabilis*, are competent vectors for Powassan virus[30]. However, relatively little is known about how frequently these vectors carry Powassan virus in the wild[31], and to what extent Powassan virus is present in parts of the U.S. with lower prevalence of *Ixodes scapularis*. Interestingly,

Powassan virus is also found in *Ixodes* ticks and humans in Far Eastern Russia, and is proposed to have been introduced from Canada through fur trade in the twentieth century[32].

Multiple wild mammals have high seroprevalence for Powassan virus. A study in Ontario identified positive sera in 50% of coyotes, 47% of skunks, 26% of foxes, and 10% of raccoons[33], although another study identified only one positive elk from 217 total cervid samples[34]. In the U.S., Powassan virus seroprevalence increased in white-tailed deer between 1979 and 2009, reaching over 80% in Connecticut in 2005, 2006, and 2009[35]. In nearby Vermont and Maine, 11% and 13% of deer were seropositive, respectively, in 2010[35]. In New York, serologic evidence of Powassan virus infection was detected in woodchucks (4/6), an opossum (1/6), and birds (4/727)[28]. The relatively widespread seropositivity in mammals, combined with the prevalence in ticks and the expansion of the tick vector itself[36], suggest increasing risk of human exposure to Powassan virus, similar to what has been observed with other *Ixodes*-borne infections.

Epidemiology

The high prevalence of Powassan virus in ticks and wild mammals raises the question of whether human infection may be more common than is currently appreciated. Powassan virus neuroinvasive disease was formally added to the list of notifiable diseases in the U.S. in 2001, and non-neuroinvasive infection was added in 2004, while Canada has no national reporting requirements. Diagnosis of Powassan virus infection has increased from around 1 case/year between 1958–2005, to 7.7 cases/year from 2006–2015[13], to 21–43 cases/year from 2016–2019[37,38]. However, the true incidence of Powassan virus infections in North America is unknown, and likely well above the number of reported cases. Because there is limited to no testing in patients without neuroinvasive symptoms, very little is known about subclinical or mild infection.

The few recent human seroprevalence studies that have been conducted to date have yielded a range of results[13]. Positive serology was detected in 9/95 (9.5%) of patients with suspected tick exposure and 2/50 (4%, p=0.33) of patients without suspected tick exposure in Wisconsin in 2015[39]. Similarly, seroprevalence was significantly higher in samples submitted for Lyme disease testing in Wisconsin (10/106, 9.4%) than in samples from patients in the northeastern United States without tick exposure or symptoms of tickborne disease (2/100, 2%, p=0.034)[40]. A seroprevalence study identified Powassan virus neutralizing antibodies in 1% of individuals in a general population in Sussex County, New Jersey, where a cluster of recent encephalitis cases was described[41]. Only a single equivocal result was detected among 230 serum samples from individuals bitten by *Ixodes scapularis* or *I. cookei* ticks in Maine from 20092013[42]. Among samples from 52 patients with confirmed Lyme disease in New York between 2011–2015, only one was positive for IgM, and this sample was negative by confirmatory testing for neutralizing antibodies[43]. Given the variability in reported seroprevalence rates, it would be of value to conduct larger studies across the broader geographic area from which Powassan virus has been reported.

With the important caveat that most available information is from patients with neuroinvasive disease, epidemiological information can be derived from approximately 270 cases described in case reports and case series (Table 1) and reported by the CDC National

Arbovirus Surveillance System (ArboNET)[44]. The geographic distribution of Powassan virus cases in North America centers around the Great Lakes region and east coast (Figure 1). The first case was identified in Ontario in 1958[8], and the majority of subsequent cases from Canada have been from Ontario (approximately 8) and Quebec (approximately 5). Single cases have also been reported from Newfoundland and New Brunswick[45,46]. The first case in the U.S. was identified in New Jersey in 1970[47], and an additional 10 cases were described in New York in the 1970s[48–50]. Subsequently, Powassan virus was not reported until 1994 in Massachusetts[44], 1999 in Vermont[51], and 2000 in Maine[51,52] coinciding with the recognition of DTV (lineage II). The first cases reported in the Midwest include Michigan in 2002, Wisconsin in 2003, and Minnesota in 2008[51,53,44]. Altogether in the U.S., more than 250 cases have been reported from 16 states. The greatest number of cases of have been reported from New York (n=50), Wisconsin (n=46), Minnesota (n=45), and Massachusetts (n=44). Fewer cases have been reported from Maine (n=16), New Jersey (n=14), Connecticut (n=13), and Pennsylvania (n=10), with a handful from Rhode Island (n=5), New Hampshire (n=5), and North Dakota (n=2), and one case each in Indiana, Michigan, North Carolina, Ohio, Vermont, and Virginia.

Detailed clinical descriptions are available for 86 cases (Table 1), and general information from annual or aggregated summaries is available for another 147 cases[38,54–56]. Of these 233 cases, the majority were males (n=167; 72%) and over age 60 (n=135, 58%), with 59 (25%) cases ages 18–59, and 39 (17%) cases under age 18. Illness onset most often occurred from April to June (n=104, 45%), followed by July to September (n=71, 30%) and October to December (n=51, 22%), with only rare cases in January to March (n=3, 1%). The vast majority of reported cases were from hospitalized patients (n=217, 93%) and patients with neuroinvasive disease (n=218, 94%), likely reflecting a bias in testing. The overall number of deaths was 28 (12%), including deaths from sequelae of hospitalization for Powassan virus disease.

Tick identification and skin pathology

Patients may present at the time of, or soon after, a known tick bite, and ticks may be submitted for laboratory identification[57]. *I. scapularis* females are characterized by: a red abdomen; a black, ovoid scutum covering up to half of the dorsum; black capitulum and legs; narrow and elongated, straight club-like palps; no eye spots or festoons; and an inverted U-shaped anal groove (Figure 2A). *I. scapularis* nymphs appear increasingly black during feeding, with an unchanged black ovoid scutum. The length of feeding can be estimated by the scutal index, the ratio of tick body length to scutum width[58], although the relevance to POWV disease is negligible due to the short time required to transmit infection[11,12].

Skin at the site of a tick bite can appear normal to markedly erythematous while the tick is attached, and papular and nodular rashes may develop once removed[59]. Acute lesions may show histological evidence of tick mouthparts attached to the epidermis, with an intradermal cavity containing red blood cells and a predominantly neutrophilic inflammatory infiltrate, which transitions to eosinophilic over time. Chronic lesions contain a dense inflammatory infiltrate of lymphocytes and eosinophils in a wedge shape, with overlying acanthotic and pseudoepitheliomatous epidermis, and associated with granulomata. While the features of

Powassan virus infection in skin have not been well described, mouse models do provide some insight into the distribution of virus and inflammatory response[60,61].

Clinical Evaluation

Powassan virus has an incubation period of approximately two weeks, though this can range up to a month or longer[31]. Patients may initially experience nonspecific symptoms such as fever and fatigue. Mild disease is occasionally identified (Box 1). However, neuroinvasive disease occurs in about 95% of recognized cases[37,38] and patients often develop confusion and focal neurological deficits requiring hospitalization[19,62]. Powassan virus has also rarely been described to cause chororetinitis[63] (which is also seen in West Nile virus), ophthalmoplegia[64], and spinal cord (anterior horn) involvement leading to flaccid weakness[45].

Although thrombocytopenia has occasionally been reported[62,65], there are no peripheral laboratory abnormalities classically associated with Powassan virus. Cerebrospinal fluid (CSF) analysis generally demonstrates low-to-moderate elevation in protein, normal glucose, and pleocytosis in the range of hundreds of white blood cells (WBC)/microliter, which can be either lymphocyte or polymorphonuclear predominant[62]. It is worth considering that, like other tick-borne pathogens, Powassan virus may occur in co-infection[66], so compatible clinical findings or laboratory abnormalities should prompt testing for Lyme disease, *Borrelia miyamotoi*, anaplasmosis, or babesiosis. Finally, although primarily associated with tick exposure, Powassan virus can be transmitted by blood transfusion[67] and is worth considering in the differential diagnosis for patients who receive transfusion in endemic areas.

Imaging

Results of neuroradiological studies from head CT or brain MRI have been reported for approximately 60 cases of Powassan virus encephalitis, and the wide range of findings is consistent with a similarly wide spectrum of clinical symptoms. Approximately 25% of published cases reported no acute abnormalities or nonspecific findings, including in two fatal cases[9,68]. The most common abnormalities reported were T2/FLAIR hyperintensities (suggestive of edema and inflammation) in basal ganglia (50%), cerebellum (40%), thalamus (30%), brainstem (30%), cerebral cortex (30%), and temporal lobes (10%). Occasional diffusion restriction, suggesting cytotoxic edema, and non-specific white matter hyperintensities have also been noted. Leptomeningeal contrast enhancement was present in 15% of cases, and parenchymal enhancement was rare. Cerebellar involvement has previously been suggested to be a poor prognostic factor for POWV disease[62], which is supported here by cerebellar abnormalities in approximately 70% of fatal cases compared to less than 20% of non-fatal cases ($p = 0.0004$). Overall, imaging findings range from mild to diffuse meningoencephalitis/rhombencephalitis and do not have distinguishing features compared to other viruses infecting the central nervous system.

Diagnostic Approach

The nonspecific nature of the symptoms, laboratory, and imaging findings associated with Powassan virus makes it incumbent upon physicians to consider it as a potential cause of

encephalitis and pursue dedicated diagnostic testing. Diagnostic criteria have been outlined by the Centers for Disease Control and Prevention (CDC) for Powassan virus and other arboviruses[68] (Figure 3). Diagnosis can be made by direct detection, and although Powassan virus is rarely recovered in culture, molecular tests frequently detect its RNA, and this may be particularly useful in immunocompromised patients who do not mount sufficient antibody responses[14,16]. Several studies have demonstrated the use of sequencing-based assays to detect Powassan virus RNA in CSF and brain tissue[14–18]. It can also be identified by PCR[20,21], and a multiplex PCR for Powassan virus and other *Ixodes*-borne infections has been used in nonclinical applications[69]. While these reports suggest that molecular diagnostics are generally higher-yield for Powassan virus than other arboviral infections such as WNV, they are rarely available outside of a research setting. Direct detection in brain tissue samples can also be useful, as discussed in the subsequent section.

However, serology is the most common method used to diagnose Powassan virus infection. The diagnosis can be made by observing a four-fold rise in antibody titers between acute and convalescent sera (including seroconversion), or by detecting both virus-specific IgM and neutralizing antibodies in serum or CSF. Confirmation of neutralizing antibodies via a plaque reduction neutralization test (PRNT) is necessary due to the high overall antibody cross-reactivity between flaviviruses. According to CDC guidelines, neuroinvasive disease can also be diagnosed by detecting Powassan virus IgM in CSF and not detecting IgM to other endemic viruses, though in practice a positive IgM from CSF is generally followed up with confirmation by PRNT.

Neuropathology

Information regarding the neuropathology of Powassan virus encephalitis has been derived from both biopsy and autopsy reports. Surgical brain biopsies may be collected for diagnostic purposes after less invasive testing options have been exhausted, or in conjunction with procedures to relieve intracranial pressure, while autopsies are performed to establish or confirm a suspected cause of death and to document the extent of the disease process. Neuropathological findings have been published for 10 cases of Powassan virus encephalitis including 2 non-fatal cases. Four cerebellar biopsies showed mild to severe T-cell predominant lymphocytic inflammation involving leptomeninges and cerebellar cortex, microgliosis with occasional microglial nodules, Purkinje cell loss with Bergmann gliosis, and thickened dura[14,16,19,21]. A thalamic biopsy showed hemorrhagic infarction with lymphoplasmacytic infiltrate[70]. These histological features, including the lack of significant neutrophilic or granulomatous inflammation, are characteristic of arboviral encephalitis, but require correlation with other laboratory and clinical findings to rule out other infectious and non-infectious causes of encephalitis.

Seven autopsies have been reported, with gross brain findings ranging from unremarkable[8], to mild diffuse swelling of cerebral hemispheres[9], to marked edema resulting in herniation and Duret hemorrhages[14,19,21]. The degree of involvement of different brain regions varied between cases, but included cerebellum, thalamus, basal ganglia, cerebral cortex, deep white matter, hippocampus, midbrain, medulla, pons, and spinal cord. Histological findings at autopsy included leptomeningeal, perivascular, and parenchymal inflammation

consistent with meningoencephalitis (Figure 2B–C)[8,9,19,21,68]. Mild to severe T lymphocyte-predominant inflammatory infiltrates were present in the meninges and Virchow-Robin spaces (Figure 2D). Focal to dense perivascular T-cell predominant inflammation was observed surrounding parenchymal blood vessels without true vasculitis. Parenchymal inflammation (greater in grey matter than white matter) consisted of diffuse microgliosis with focal to dense microglial nodules, neuronophagia, and focal areas of tissue necrosis without true infarction. Severe loss of neurons was present including cerebellar Purkinje cell and spinal cord anterior horn cells. These histological findings likely reflect viral infection and death of neurons with associated host inflammatory responses. General autopsy findings have not suggested infection outside of the central nervous system, except in one patient who presented with orchitis and was found to have chronic inflammation and positive Powassan virus immunohistochemistry (IHC) in testicle sections[14,16].

In contrast to many other causes of CNS viral infections, including herpesviruses, polyomaviruses, and rabies virus, no viral inclusions have been seen in biopsy or autopsy sections for any of the reported cases of Powassan virus, which is typical for arboviral encephalitis. Powassan virus immunohistochemistry (IHC), available at reference laboratories including the CDC Infectious Diseases Pathology Branch, has identified viral antigen in neurons and macrophages, likely representing the primary cellular targets in the CNS and subsequent clearance of infected cells[14,16,19,21,68]. Overall, the gross and histopathological findings of Powassan virus infection are consistent with other causes of viral meningoencephalitis, thus definitive diagnosis requires detection of viral antigen by IHC or viral RNA by *in situ* hybridization (Figure 2E–F) or molecular studies.

Therapeutic Options and Clinical Outcomes

Treatment for Powassan virus is largely supportive, and no antiviral therapies have been tested to date. Because much of the disease is believed to be due to neuro-inflammation, some patients have been treated with steroids, sometimes with apparent benefit[19,66] and other times without[16,71]. Given the small number of cases and the difficulty in assessing confounders such as age and comorbidity, there is too little data to support or refute the use of steroids. Similarly, intravenous immunoglobulin (IVIG) has been used in some cases[66], based on reports of success in WNV[72], but its effectiveness is unclear[62]. The overall mortality for Powassan virus is around 10%, as discussed above and in prior reviews[73]. Many patients have substantial long-term morbidity, including persistent neurological symptoms in approximately a third of patients who survive[31].

Discussion

Given the substantial morbidity and mortality associated with known cases of Powassan virus encephalitis, as well as the likelihood that exposure and infection are more common than appreciated, there is substantial need to better understand the pathogenesis of this emerging virus and develop preventative and therapeutic strategies.

In vitro and animal studies of Powassan virus and the closely related TBEV suggest several salient features of pathogenesis. First, tick saliva enhances transmission and neuroinvasion[74,75], likely by stimulation of an inflammatory response and recruitment

of target cells. Thus, interventions targeting tick saliva represent an intriguing strategy to prevent this and other tick-borne infections[36]. Following transmission, dendritic cells and macrophages are thought to be among the first cells infected, allowing transport to lymph nodes, virus replication, and viremia[76]. Mechanisms of neuroinvasion are poorly understood, though a recent study suggests possible crossing of the blood-brain barrier through vascular endothelial cells[77]. Neuropathogenesis occurs through direct infection of neurons, and astrocytes restrict replication[78]. Interestingly, while laboratory mice (BALB/c and C57BL/6) experience lethal infection with Powassan virus, the white-footed mouse *Peromyscus leucopus* is refractory to intraperitoneal infection and experiences only mild brain inflammation after intracranial infection[79]. This suggests the presence of one or more restriction factors[10,79], which RNAseq analysis suggests may be an interferon stimulated gene[80]. As an interesting parallel, TRIM79alpha was shown to restrict TBEV by degrading the NS5 polymerase[81]. Improved understanding of Powassan virus pathogenesis and host-virus interactions is needed to guide intervention strategies.

Currently, no antiviral medications are available to treat Powassan virus, though preclinical studies have identified several possibilities[82,83]. Vaccination is another compelling avenue of future research, especially given the successful implementation of vaccines against TBEV. Unfortunately, TBEV vaccines themselves do not provide cross-protection against POWV, as they do for other tick-borne flaviviruses[84]. Recently, a lipid nanoparticle mRNA vaccine targeting the Powassan virus premembrane and envelope genes was shown to protect mice[85]. As further research into pathogenesis, treatment and prevention continues, minimizing the effects of Powassan virus infection will rely on ecological approaches to decrease tick population, as well as individual practices for tick avoidance and removal[36].

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Box 1.

Case Title: 67-year old woman with systemic illness

Case Presentation:

A 67-year-old woman presented to an outpatient clinic with a subacute systemic illness. She initially had a week of fever, headache, and profound fatigue. Following resolution of her fevers, she felt tremulous with dysregulated temperature, had difficulty concentrating, and noted decreased quality in handwriting; these symptoms were gradually improving. She had a persistently poor appetite and mild nausea without vomiting. Her gastrointestinal symptoms worsened with doxycycline. Over the last 2 days, she developed a pruritic rash on the extensor surface of her hands, elbows, and knees. Notable exposures include ticks, mosquitoes, and her baby grandchild. On physical exam, she had an erythematous papular rash most notable on her knees and extensor surfaces of her hands. Neurologic exam was unremarkable, including cranial nerves, motor strength, sensation, fine motor coordination, balance, and gait.

Clinical Questions:

What are potential causes of this patient's improving systemic illness? What additional testing could be ordered to confirm the diagnosis?

Discussion:

Recommended tests included Lyme test with Western blot, *Anaplasma/Ehrlichia* PCR, Powassan virus antibody, West Nile virus antibody, and CMV IgM and IgG. This patient's serum Powassan virus IgM was positive with PRNT of 1:20 indicating recent infection.

Learning Point:

Powassan virus may present with mild symptoms and minimal neurological involvement.

Box 2.

Case Title: 58-year-old immunocompromised man with subacute neurological symptoms

Case Presentation:

A 58-year-old man with a history of hypertension, hyperlipidemia, hypothyroidism, non-alcoholic fatty liver disease, remote Hodgkin's lymphoma treated with bone marrow transplant and rituximab, and hypogammaglobulinemia requiring IVIG infusions every 6 weeks, presented with 1 to 2 days of gradual onset vertical diplopia, ataxia, dysarthria, and short-term memory loss. He reported a subjective fever. On exam, although alert and oriented, he had profoundly impaired short-term memory and an odd affect with mildly elevated mood and inappropriate laughter at times. MRI showed mild T2/FLAIR hyperintensity in the cerebellar vermis, pons, midbrain, and medial temporal lobes (left greater than right), with no significant contrast enhancement or diffusion restriction (Figure 4). A lumbar puncture was performed at day 6 after symptom onset, with an opening pressure of 22 cm H2O, and cerebrospinal fluid analysis was notable for protein=84.7 mg/dL (normal 10–44 mg/dL), glucose=56 mg/dL (normal 40–70 mg/dL), and cell counts with 1 RBC/μL and 92 WBCs/μL (89% lymphocytes, 11% monocytes, 0% neutrophils). Testing for specific pathogens was negative, including Powassan virus IgM from CSF.

Clinical Questions:

What are potential causes of this patient's illness? What additional testing could be ordered to confirm the diagnosis? What treatment should the patient receive?

Discussion:

The patient was empirically treated with acyclovir, which was stopped when testing for herpes simplex virus was negative. All targeted viral studies were negative. The patient was treated empirically with 1g methylprednisolone daily for 3 days and received scheduled intravenous immunoglobulin during admission. His symptoms improved during his hospital stay, with better speech, and regained ability to walk. He was discharged to a subacute care facility on hospital day 7 (approximately 13 days after symptom onset) with mild residual ataxia and had no residual side effects at one year follow up. Metagenomic next-generation sequencing performed on CSF was positive for Powassan virus.

Learning Point:

Powassan virus serology may be negative in patients with immunodeficiency, and molecular testing should be considered. In all patients with suspicion for Powassan virus infection and negative initial serology, convalescent serology testing should be pursued.

Key Points:

- Powassan virus is an *Ixodes*-borne flavivirus that can cause severe encephalitis.
- Prevalence studies in ticks, and seroprevalence studies in wild mammals and humans suggest that human exposure to Powassan virus is more common than currently appreciated, and non-neuroinvasive disease is likely under-recognized.
- Diagnosis is typically established by serological testing of blood or cerebrospinal fluid, but can also be confirmed by RT-PCR or sequencing from cerebrospinal fluid or immunohistochemistry, *in situ* hybridization, or molecular testing of brain tissue.

Synopsis:

Powassan virus is an increasingly-recognized cause of severe encephalitis that is transmitted by *Ixodes* ticks. Given the nonspecific clinical, laboratory, and imaging features of Powassan virus disease, providers should consider it in patients with compatible exposures and request appropriate testing.

Clinics Care Points:

- Testing for Powassan virus infection should be considered in *Ixodes*-endemic regions in patients presenting in the spring, summer, and fall. A high index of suspicion is needed, as symptoms and clinical evaluation can be nonspecific.
- Diagnosis of Powassan virus infection is generally made by serology testing of blood or cerebrospinal fluid. In immunocompromised patients who may not mount sufficient antibody response, molecular testing can be helpful.
- Treatment for Powassan virus is supportive. There is too little evidence to support or refute the use of high-dose steroids or intravenous immunoglobulin.

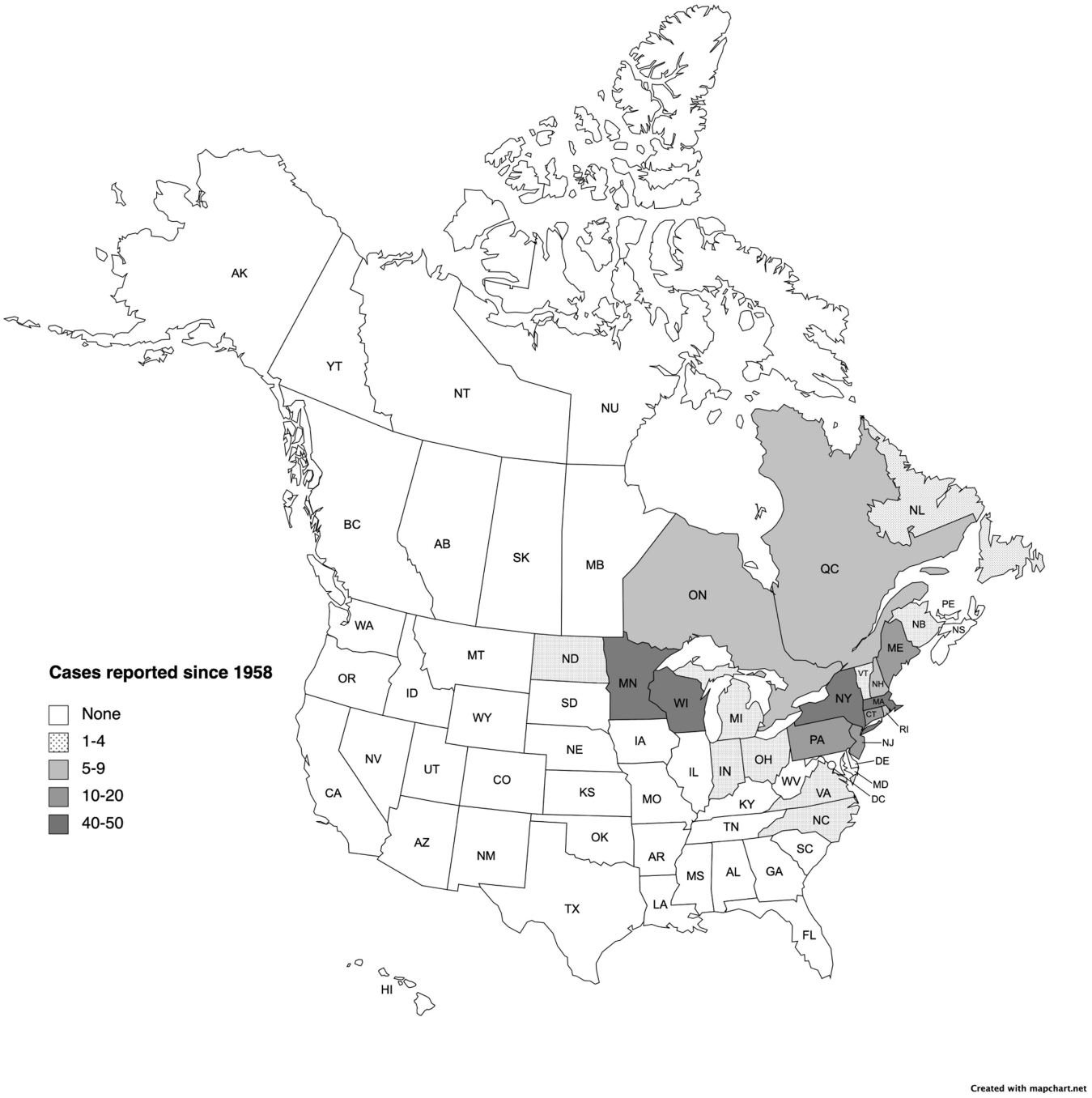

Figure 1:

Geographic distribution of 273 human Powassan virus infections reported between 1958–2021. (*Created with* mapchart.net)

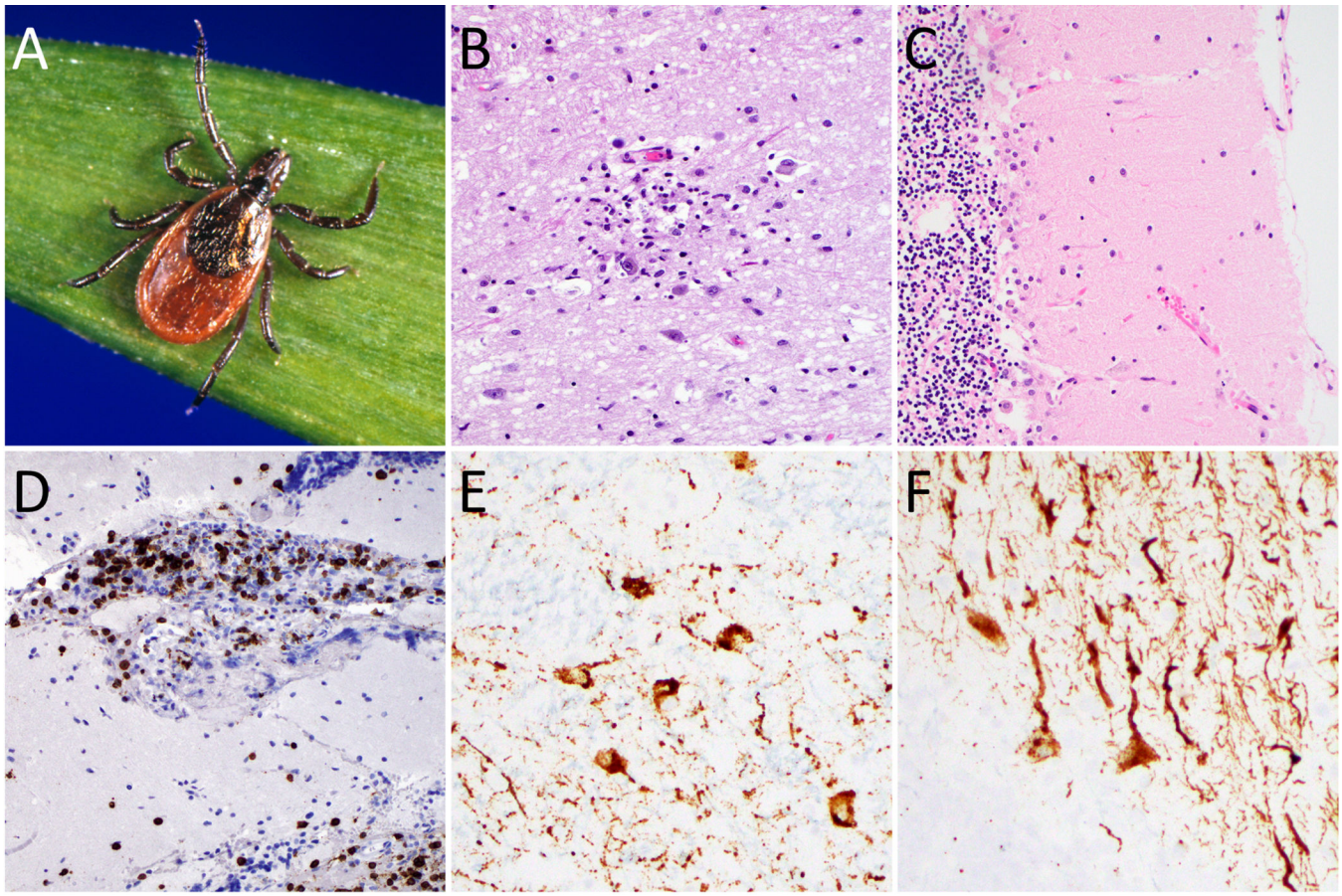

Figure 2: Powassan virus neuropathological features.

Female *Ixodes scapularis* (deer tick, black-legged tick) can be grossly identified by characteristic U-shaped anal groove (A). Sections from fatal Powassan encephalitis cases show a microglial nodule with neuronophagia in the thalamus (B), marked Purkinje cell loss and Bergmann gliosis in the cerebellum (C), and CD3-positive T cell infiltrate in the leptomeninges (D). Powassan virus RNA *in situ* hybridization highlights infected neurons in the thalamus (E) and cerebellum (F). (*Image A courtesy of Michael L. Levin, PhD via the CDC Public Health Image Library*)

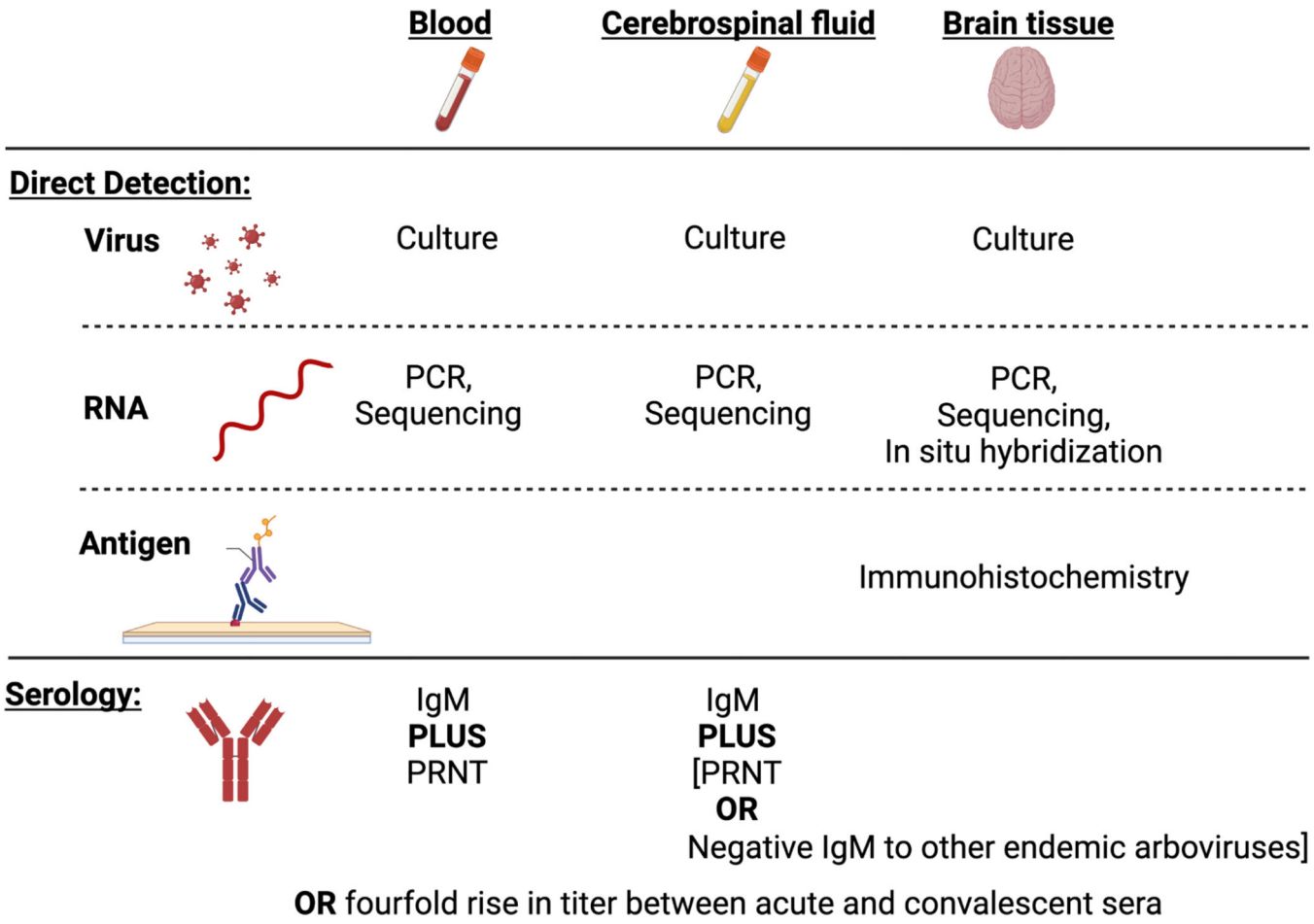

Figure 3: Diagnostic Approaches for Powassan virus.

Testing modalities are listed for each specimen type (blood, cerebrospinal fluid, and brain tissue) and target (virus, RNA, antigen, antibody). Abbreviations: PCR, polymerase chain reaction; PRNT, plaque reduction neutralization test. (*Created with* BioRender.com)

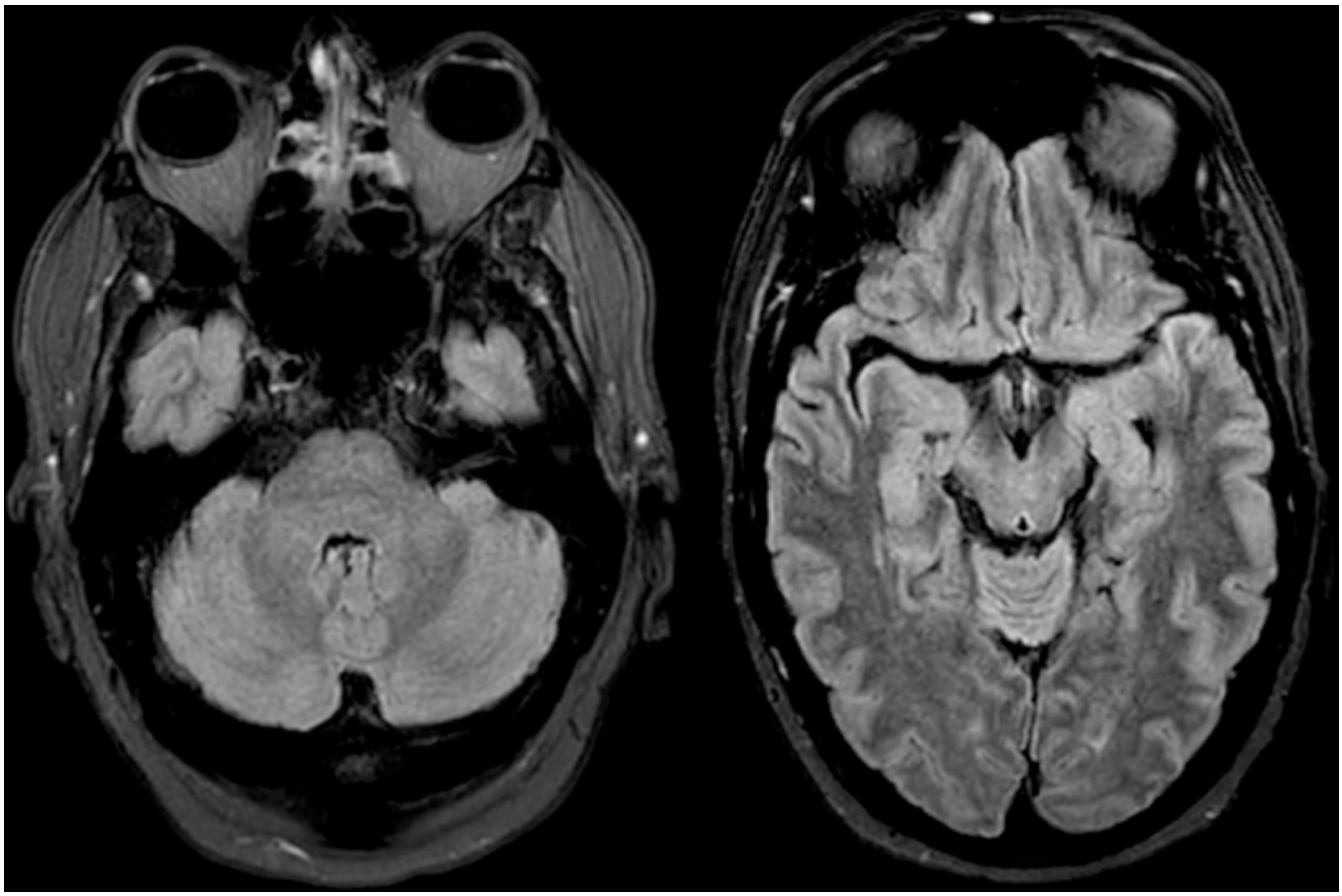

Figure 4: Brain MRI -

MRI from patient in Box 2 at four days from initial symptom onset shows mild T2/FLAIR hyperintensity in the cerebellar vermis, pons, midbrain, and medial temporal lobes. No significant contrast enhancement or diffusion restriction was identified.

Table 1.

Published cases of Powassan virus infection

Case number	Age/Sex	Year/Location	Fatal (Y/N)	Immunocompromised (Y/N)	PMID(s)
1	5 M	1958 Canada (Ontario)	Y	N	13652010
2	57 F	1970 New Jersey	N	N	4684890
3	7 M	1971 New York	N	N	222159; 4856896
4	5 F	1972 New York	N	N	4856896
5	12 M	1972 New York	N	N	222159; 4856896
6	14m M	1972 New York	N	N	222159; 4856896
7	8 M	1972 Canada (Quebec)	N	N	4829843
8	6–15 M	1974 New York	N	N	222159; 1059007
9	3 M	1975 Canada (Quebec)	N	N	N/A: Can Dis Wkly Rep 1976;2:85–7.
10	6–15 M	1975 New York	N	N	222159; 267829
11	6–15 M	1975 New York	N	N	222159; 267829
12	82 M	1975 New York	Y	N	222159; 267829
13	15 F	1976 Canada (Ontario)	N	N	N/A: Can Dis Wkly Rep 1976;2:202–3
14	13m F	1977 Canada (Ontario)	N	N	223757
15	0–5 F	1977 New York	N	N	222159
16	8 M	1978 New York (Canada, Nova Scotia)	N	N	6297420
17	19 F	1979 Canada (Ontario)	N	N	N/A: Can Dis Wkly Rep 1979;5:129–30.
18	7 M	1979 Canada (Ontario)	N	N	6254625
19	9 F	1980 Canada (Quebec)		N	N/A: Can Dis Wkly Rep 1982; 8:185–91.
20	62 M	1987 Canada (Ontario)	N	N	2547526
21	76 M	1988 Canada (New Brunswick)	N	N	21233909
22	49 F	1994 Massachusetts	N	N	7643850
23	4m ?	1994–1995 Canada	N	N	9502462
24	64 M	1997 Canada (Ontario)	Y	N	10906899
25	66 M	1999 Vermont	N	N	18959500; 11693145
26	25 M	2000 Maine	N	N	18959500; 11693145
27	53 F	2000 Maine	N	N	18959500; 12771287; 11693145

Case number	Age/Sex	Year/Location	Fatal (Y/N)	Immunocompromised (Y/N)	PMID(s)
28	70 M	2001 Maine	N	N	18959500; 11693145
29	60 F	2002 Michigan	N	N	18959500
30	69 M	2003 Wisconsin	N	N	20443328; 18959500
31	74 F	2004 Maine	N	N	18959500
32	91 F	2004 New York	N	N	24274334; 18959500
33	83 M	2005 New York	N	N	24274334; 18959500
34	49 M	2006 Wisconsin	N	N	20443328
35	47 F	2007 Wisconsin	N	N	20443328
36	81 ?	2007 New York	Y	?	24274334
37	81 ?	2007 New York	N	?	24274334
38	77 ?	2007 New York	Y	?	24274334
39	62 M	2007 New York	Y	Y	24274334; 19439744
40	5 ?	2007 New York	N	?	24274334
41	70 ?	2007 New York	Y	?	24274334
42	61 M	2008 Canada (Quebec)	N	N	20929710
43	9 F	2008 New York	N	N	24274334; 20736878
44	22 M	2009 New York	N	N	23969017
45	73 ?	2009 New York	N	?	24274334
46	76 ?	2009 New York	N	?	24274334
47	4 ?	2009 New York	N	?	24274334
48	77 M	2010 New York	Y	N	24274334; 23166187
49	67 F	2011 Minnesota	Y	Y	23017222
50	69 M	2011 Minnesota North Dakota	N	N	23111001
51	61 M	2011 Minnesota	N	Y	23111001
52	60 M	2011 Minnesota North Dakota	N	N	23111001
53	18 M	2011 Minnesota	N	N	23111001
54	43 M	? Minnesota	N	N	22040725
55	32/34 M	2012 New York	N	N	24274334; 23969017
56	44 M	2013 New Hampshire	N	N	26668338

Case number	Age/Sex	Year/Location	Fatal (Y/N)	Immunocompromised (Y/N)	PMID(s)
57	35 F	2013 Wisconsin	N	N	29431163
58	49 M	2014 Massachusetts	Y	N	26668338
59	52 M	2014 Massachusetts	N	N	26668338
60	65 F	2014 Massachusetts	N	N	26668338
61	67M	2014 Massachusetts	N	N	26668338
62	21 M	2014 Massachusetts	N	N	26668338
63	74 M	2015 Massachusetts	N	Y	26668338
64	82 M	2015 Massachusetts	Y	N	26668338
65	81 F	2016 Rhode Island	N	N	29942757
66	61 M	2016 Massachusetts	N	Y	29020227
67	63 M	2016 Massachusetts	Y	Y	33094116; 29554185
68	5m M	2016 Connecticut	N	N	33111953, 28426641
69	72 F	? Maine	Y	N	28903511
70	55 M	2017 Massachusetts	N	N	31538917
71	56 M	2017 New York	N	N	32007325
72	8 F	2017 Wisconsin	N	N	32060042
73	51 M	2017 New Jersey	N	Y	34283672
74	70 M	? Pennsylvania	N	Y	30104234
75	68 F	? Canada (Quebec Ontario)	N	N	30559280
76	79 M	2018 Massachusetts	Y	N	33094116
77	30 F	2018 Indiana	N	Y	32539111
78	62 M	? Canada (Newfoundland Ontario)	N	N	31158072
79	88 M	2018 Wisconsin	Y	N	33020816
80	87 M	? New York	N	N	31712240
81	75 F	2019 Massachusetts	Y	N	33094116
82	2m M	2019 Connecticut	N	N	33111953
83	42 M	2019 Wisconsin	N	N	33227515
84	76 M	? Wisconsin	N	N	33758161
85	62 M	? Connecticut	N	Y	34430178

Case number	Age/Sex	Year/Location	Fatal (Y/N)	Immunocompromised (Y/N)	PMID(s)
86	82 F	? New York	Y	Y	34596868