

Encephalitis Caused by Jamestown Canyon Virus in a Liver Transplant Patient, North Carolina, USA, 2017

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We describe the first documented case of Jamestown Canyon virus (JCV) in North Carolina, which occurred in a liver transplant patient who presented acutely with headache, aphasia, and confusion. This is also the first report of recovery from JCV encephalitis following treatment with intravenous immune globulin.

Keywords. arboviruses; encephalitis; immunocompromised host; emerging infectious diseases; vector-borne diseases.

A man in his 50s with a history of liver transplantation for alcoholic hepatitis 3 years prior presented at the end of October with 4 days of headache, congestion, and malaise and a few hours of confusion, slurring of words, and stuttering. His immunosuppressive regimen was cyclosporine and prednisone 5 mg daily, and he had been treated for rejection 3 months earlier with oral steroids. He lived in Western North Carolina and was an avid woodturner, spinning wood blocks at high speed to shave them into objects. He reported wearing a HEPA filter mask when working with woods known to be toxic. He had recently returned from a woodturners' conference in a mountainous region of North Carolina and had traveled to New Jersey 1 month before onset of symptoms. He could not recall any recent tick or mosquito bites.

On presentation, his temperature was 38.3°C, heart rate was 85 beats per minute, blood pressure was 167/77, and oxygen saturation was 95% on room air. He was alert and oriented

to person, but not place, or time. Initial neurologic exam revealed word finding difficulties and clonus bilaterally, but intact strength, sensation, and cranial nerve function. Laboratory studies were at his baseline (Table 1). Magnetic resonance imaging (MRI) of his brain was normal. He was empirically started on cefepime and admitted to the hospital.

During the first 24 hours of hospitalization, his fever resolved, but he became nonverbal and tremulous with bradykinesia, generalized stiffness, and upper extremity cogwheel rigidity. Intravenous vancomycin, acyclovir, and doxycycline were added to his antimicrobial regimen. Cerebrospinal fluid (CSF) testing on hospital day 2 showed an elevated protein level (78 mg/dL; upper limit of normal 45 mg/dL) and mild lymphocytic pleocytosis with 6 nucleated cells (78% lymphocytes) (Table 1). Blood and CSF cultures and herpes simplex virus CSF polymerase chain reaction (PCR) were negative, so acyclovir and vancomycin were stopped on hospital day 3.

Despite empiric treatment for bacterial meningitis and tick-borne encephalitis, the patient's mental status did not improve, and fever recurred on hospital day 7. Repeat MRI of the brain was again normal. Given high suspicion for arboviral encephalitis, in particular West Nile virus, he was given 0.5 g/kg (35 g) of intravenous immunoglobulin (IVIG) daily for 4 days (Figure 1). Over the following 3 days, his mental status rapidly improved. Neurologic deficits improved more gradually and did not completely return to baseline. Therefore, on hospital day 16, he received a second course of IVIG (0.5 g/kg/d—35 g daily for 4 days), with further recovery of neurologic function. The patient was discharged home on hospital day 21 with physical and speech therapy for mild residual mobility and speech issues.

An extensive evaluation for infectious and autoimmune causes of his illness was unrevealing (Table 1). A thorough literature review was undertaken to identify potentially relevant exposures from the patient's woodturning hobby. Although exposure to some solvents used for wood processing has been associated with central nervous system effects [1], we found no case reports of focal neurologic deficits associated with woodworking or turning. Additionally, CSF collected on HD 6 (~10 days after symptom onset) was sent to the University of California–San Francisco (UCSF) for metagenomic sequencing, but no pathogen was detected.

Approximately 2 months after symptom onset, Jamestown Canyon virus and Powassan virus testing performed by the Centers for Disease Control and Prevention (CDC) resulted. Acute phase CSF testing for JCV IgM was positive. Acute CSF JCV plaque reduction neutralization titer (PRNT) was positive at 2 (positive is ≥ 2), and early convalescent serum JCV PRNT was 320 (positive is considered ≥ 10) (Figure 1). As the

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Table 1. Laboratory Test Results From Evaluation of Liver Transplant Patient With Encephalitis

Timing of Sample Collection	Sample	Pertinent Negative/Normal Lab Results
Admission	Serum/blood	CBC with differential; CMP; blood cultures; salicylate, acetaminophen, ethanol, and ammonia levels; cyclosporine level
	Urine	Toxicology screen; urinalysis
HD2	Serum	Ehrlichia and RMSF antibody testing; RPR
	CSF	VDRL; CMV, enterovirus, HSV1/2, and VZV PCR; VZV IgM/IgG; cryptococcal antigen; toxoplasma PCR; bacterial culture; arboviral antibody panel ^a ; PRNT—LAC and POW/TBE <2 (positive: ≥2)
HD3	Serum	Arboviral antibody panel ^a
HD4	Nasopharyngeal swab	Multiplex respiratory viral panel (RSV, influenza A/B, metapneumovirus, parainfluenza 1–4, rhinovirus, coronavirus, adenovirus)
	Serum	Lyme antibody testing; cryptococcal antigen; hepatitis C antibody; HIV fourth-generation antigen/antibody test; hepatitis B surface antigen and total core antibody
HD6	CSF	HHV6, EBV, HSV1/2, and VZV PCR; bacterial culture; fungal serologies (<i>Histoplasma</i> , <i>Blastomyces</i> , <i>Coccidioides</i>); metagenomic sequencing (UCSF); autoimmune encephalopathy antibody panel
HD9	Serum/blood	Autoimmune encephalopathy antibody panel; lead level; copper level
	Urine	Heavy metals screen
HD14	Serum	PRNT—LAC = 10, POW/TBE < 10 (positive: ≥10)
3 mo postillness	Serum	PRNT—LAC = 10 (positive: ≥10)

Abbreviations: CBC, complete blood count; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; CSF, cerebrospinal fluid; EEE, eastern equine encephalitis; HD, hospital day; HHV, human herpesvirus; HSV, herpes simplex virus; IVIG, intravenous immune globulin; LAC, La Crosse virus; PCR, polymerase chain reaction; POW/TBE, Powassan virus; PRNT, plaque reduction neutralization test; RMSF, Rocky Mountain spotted fever; RPR, rapid plasma reagin; RSV, respiratory syncytial virus; SLE, St. Louis encephalitis; UCSF, University of California–San Francisco; VDRL, venereal disease research laboratory test; VZV, varicella zoster virus; WEE, Western equine encephalitis; WNV, West Nile virus.

^aArboviral antibody panel includes EEE virus IgG, LAC IgM and IgG, SLE virus IgG, WEE virus IgG, WNV IgM and IgG.

initial serum sample was collected after the first IVIG dose, serum obtained 3 months after IVIG treatment was also tested, and the PRNT remained positive at 320, confirming the diagnosis. Human IgG has a half-life of ~30–40 days, and clinical efficacy wanes about 3–4 weeks after therapy [2, 3]; therefore, the 3-month interval should have been more than sufficient to allow for clearance of IVIG. The patient’s deficits completely resolved with rehabilitation therapies ~4 months after illness.

JCV is an orthobunyavirus of the California Encephalitis serogroup that is transmitted by several species of mosquitoes, including *Aedes* and *Culex* spp. [4]. Animal and human

neutralizing antibody studies suggest that JCV exists throughout North America, with the majority of cases occurring in the Midwest and Northeast United States. Human seroprevalence estimates in the United States are as high as 15%–30% [5, 6]. First detected as a cause of encephalitis in 1997, JCV became a CDC-reportable infection in 2004. Although confirmed human cases are rare, it is an emerging pathogen, with 75, 41, and 25 cases reported in 2017, 2018, and 2019 respectively [7–9]. The discrepancy between serological survey data and reported cases is likely due to underdiagnosis and under-reporting, particularly of less severe cases, at least in part because of the lack of

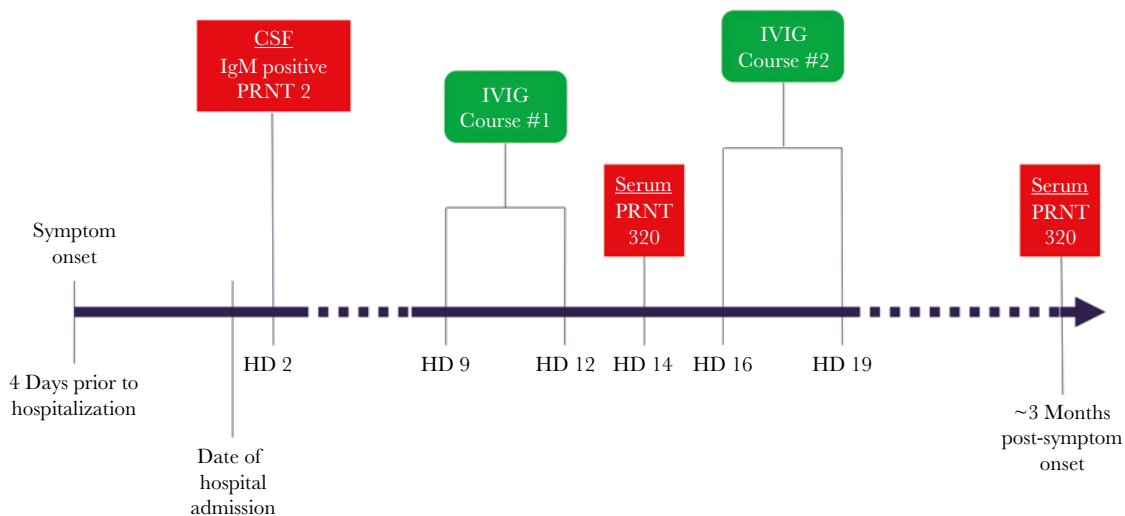


Figure 1. Timeline of JCV-specific testing and treatment over disease course. Abbreviations: CSF, cerebrospinal fluid; HD, hospital day; IVIG, intravenous immune globulin; JCV, Jamestown Canyon virus; PRNT, plaque reduction neutralization test.

commercially available diagnostic tests. To our knowledge, this is the only documented case of JCV infection in North Carolina, first reported by the CDC [9, 10]. Two cases have been reported in neighboring Tennessee, but none have been documented in Virginia or South Carolina.

This patient's immunosuppressive medications may have played a role in increasing his risk for development of neuroinvasive disease from JCV. Calcineurin inhibitors depress the function of both effector and regulatory T cells and affect regulatory B lymphocyte function, all of which are important in responding to acute viral infections [11]. Glucocorticoids have more of an anti-inflammatory effect; they blunt cytokine responses and pro-inflammatory cascades but also impair the migration and function of monocytes, macrophages, and circulating CD4 T cells [12]. In West Nile virus infection, a related RNA virus that causes neuroinvasive disease in humans, immune suppression does not seem to increase the risk of severe illness, although it has been associated with an increased risk of death [13, 14].

The clinical presentation of JCV infection ranges from asymptomatic to nonspecific febrile illness, meningitis, or encephalitis with a strong male predominance [4, 5]. JCV is associated with high rates of neuroinvasive disease, usually normal CSF parameters, and low fatality rates [5, 15]. However, although rare, JCV has also been found to be associated with chronic infection, viral compartmentalization, and possibly evolution that resulted in a fatal infection [16]. Fever and altered mental status, as seen in this patient, commonly occur. Arboviruses circulate in the blood and CSF transiently early in illness, and often at low levels, which likely explains why JCV was not detected by CSF metagenomic sequencing in the case of our patient [5, 17]. Therefore, diagnosis is primarily made using serology with confirmation by plaque reduction neutralization testing given antibody cross-reactivity among California serogroup arboviruses [4, 18].

As there are no specific antiviral therapies available for JCV, treatment is usually supportive, with most patients making a gradual, full recovery. Although IVIG has been used to treat other viral encephalitides, such as West Nile virus, to our knowledge, this is the first report of its use and association with a clinical response for JCV [19]. There is 1 case report of JCV encephalitis in a solid organ transplant recipient who was treated with ribavirin and had a similarly prolonged course but also ultimately achieved complete recovery [20].

In conclusion, Jamestown Canyon virus is an emerging arboviral infection in the United States that can cause severe neuroinvasive disease in individuals who have undergone solid organ transplantation and are on immunosuppressive medications such as calcineurin inhibitors and glucocorticoids. Therefore, JCV and other arboviral diseases should be considered as potential causes of encephalitis in immunocompromised patients.

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Patient consent. The patient whose case is described in this article provided verbal and written consent for its publication. This report was also reviewed by the University of North Carolina Institutional Review Board (IRB; 20-3240), and it was determined that it does not constitute human subjects research and therefore did not require IRB approval.

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