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Alyssa Profita

*Medical College of Wisconsin*

Kristin Haglund

*Marquette University, kristin.haglund@marquette.edu*

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# Encephalopathic Presentation of West Nile Virus Neuroinvasive Disease Confounded by Concomitant History of Acute Alcohol Withdrawal

Alyssa Profita

Medical College of Wisconsin, Milwaukee, WI

Kristin Haglund

College of Nursing, Marquette University, Milwaukee, WI

Froedtert & Medical College of Wisconsin, Milwaukee, WI

## Abstract

West Nile neuroinvasive disease (WNND) is a rare and severe manifestation of West Nile virus (WNV) infection that occurs in less than 1% of infected persons. It should be considered in patients who present with fever, neurological symptoms, and a history of recent outdoor activity where mosquitoes were active. This article

highlights a case of a 55-year-old man whose history and symptoms of WNND were confounded with an alternate diagnosis, acute alcohol withdrawal. An overview of WNV infections, and important historical clues and objective findings characteristic of neuroinvasive disease, is discussed to increase readers' knowledge of WNV and awareness of when to consider WNND in the diagnostic differential.

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## Keywords

arbovirus; arbovirus infections; encephalitis; mental status; West Nile fever; West Nile virus

WEST NILE VIRUS (WNV) was first identified in 1937 in Uganda and has spread across the globe ([Montgomery & Murray, 2015](#)). In the United States, WNV spread from a focal area in New York City in 1999 to all of the 48 states, Canada, and south to Argentina ([Nasci, 2013](#)). The virus is classified as an arbovirus that has been found in mosquitoes, birds, ticks, and a variety of mammal species. There are approximately 1,800 cases of WNV infection annually in the United States; most of these infections are mild and self-limiting. Approximately 1% of persons infected with WNV develop neuroinvasive disease ([Centers for Disease Control and Prevention \[CDC\], 2018](#)). West Nile neuroinvasive disease (WNND) is a severe manifestation of infection that occurs primarily in very young children, older adults, persons with immunocompromised conditions such as malignancy, organ transplant, or chronic steroid use, or those with comorbid conditions including diabetes, hypertension, alcohol abuse, and renal disease ([CDC, 2018](#)). Other arboviruses can cause neuroinvasive disease; however, WNV is responsible for 94% of all cases of neuroinvasive disease in the United States ([Krow-Lucal, Lindsey, Lehman, Fischer, & Staples, 2017](#)).

The following case is a report of a 55-year-old man who presented with altered mental status secondary to WNND. However, this diagnosis was not identified initially due to a limited history and because his presentation was consistent with complications of substance use disorder. Important historical clues and objective findings characteristic of neuroinvasive disease are discussed to increase readers' knowledge of WNV and awareness of when to consider WNND in the diagnostic differential.

## Case Report

A 55-year-old Caucasian man presented to the emergency department (ED) via ambulance. He was noted to be hypertensive and febrile and had altered mental status. The patient was presented to the medical team and seen by the nurse practitioner (NP) on the team. On the NP's initial assessment, the patient was alert and oriented to person, place, and time. However, he was agitated throughout the assessment, calling out names and acting aggressive toward the staff. The patient had no focal neurological deficits and strength was intact 5/5 bilaterally in all four extremities. The remainder of his examination was unremarkable. His past medical history included polysubstance abuse, nonischemic cardiomyopathy, hypertension, diabetes Type 2, and Stage III chronic kidney disease (CKD). He was a current every day one-half pack smoker and had daily polysubstance abuse. Of note, the patient reported he had stopped using drugs and drinking "cold turkey" several days before coming to the hospital.

On the basis of his history of alcohol use and short-term period of abstinence, the NP treated him for alcohol withdrawal with benzodiazepines, intravenous fluids, a multivitamin, and thiamine. Wernicke's encephalopathy was considered a top differential for his altered mental status; thus, he was treated with high-dose vitamin B<sub>12</sub>. No restraints or medications other than those for alcohol withdrawal were used to treat the patient's agitation. He was admitted from the ED to a medical-surgical unit in the hospital.

On hospital Day 3, his mentation deteriorated. Because of increased agitation and decreased orientation, he was transferred to the intensive care unit (ICU). Upon arrival to the ICU, a physical examination was performed. The patient was noted to be agitated, trying to get out of bed, and physically aggressive toward the staff. He was disoriented to person, place, and time. He did have asterixis, which is a hand tremor when wrists are extended, and clonus, which is muscular spasm involving repeated contractions. He did not have nystagmus. He had 5/5 strength and equal movement in all extremities. The NP was unable to obtain reflexes due to his agitation. The rest of his examination was unremarkable. The NP attempted to obtain a more thorough history from the patient, but he was unable to provide a cogent history due to his mental status. Of note, the patient had been having intermittent fevers since his presentation in the ED. At this point, the NP reconsidered the diagnoses of alcohol withdrawal or Wernicke's encephalopathy as the patient's condition had deteriorated despite adequate treatment for these two conditions.

Initial differential diagnosis for the patient's encephalopathy was severe alcohol withdrawal, hypertensive emergency, stroke, infection, and seizures. He was sent for a computed tomographic (CT) scan of the head to rule out an ischemic or hemorrhagic stroke. Blood cultures, urine culture, and a chest radiograph were obtained to evaluate for a source of infection. He was also started on broad-spectrum antibiotics, antihypertensives, 24-hr continuous electroencephalogram (cEEG), placed in wrist restraints, and a sitter was placed at the bedside for his safety. While the patient was at his CT scan, the NP on the critical care team called the patient's significant other who stated that the patient had been in a rural setting for a hunting trip prior to his hospitalization. Based on this information, the NP's differential diagnosis for his encephalopathy changed to include tick and mosquito-borne diseases, including WNV. Neurology was consulted because of the patient's deteriorating mental status, and it was recommended to perform a lumbar puncture to evaluate for Lyme disease, WNV infection, viral meningitis, and herpes encephalitis. A lumbar puncture was performed the evening of the patient's admission to the ICU. The CT scan of the head was negative, cEEG did not reveal seizure activity, and the preliminary findings of infectious workup was negative. Given these results, the cEEG and broad-spectrum antibiotics were discontinued. The lumbar puncture was positive for WNV AB IgM, which confirmed this patient's diagnosis of WNND.

Currently, there is no treatment for WNV ([CDC, 2018](#); [Montgomery & Murray, 2015](#)). Multiple treatments have been tested including interferon, ribavirin, and intravenous immunoglobulin; however, none have been shown to be effective ([National Center for Emerging and Zoonotic Infectious Diseases, 2018](#)). It is a self-limiting infection and as such treatment is supportive. The patient's comorbidities were managed (hypertension, diabetes, CKD III), and a sitter was placed at the bedside for safety as the patient was agitated. Psychiatry was consulted and recommended quetiapine every 2 hr for agitation. Over a week's time, the patient's mentation improved and he was ultimately discharged home. No further workup or follow-up was required. No adverse events occurred.

## Discussion

### Epidemiology

West Nile viral infections in humans are most commonly transmitted via mosquitoes ([CDC, 2018](#)). The WNV is maintained in a bird-mosquito-bird cycle in which mosquitoes become infected by feeding on infected birds ([Whitehorn & Yacoub, 2019](#)). West Nile viral infection is not contagious among humans and is not spread via respiratory droplet, contact, fomite, or fecal-oral routes. In rare cases, WNV has been transmitted from person to person through blood transfusions, organ donation, and exposure in a laboratory setting or from mother to infant through pregnancy, delivery, or breastfeeding ([CDC, 2018](#)).

Conditions that promote mosquito infestation include warm climates, rainfall, and stagnant water resources ([Montgomery & Murray, 2015](#)). However, these conditions exist across the United States, albeit with seasonal variation. Since 1996, mild WNV infections have been reported in all of the states in the United States except Alaska; neuroinvasive infections have been reported in all states except Alaska and Hawaii. States along the Eastern seaboard have the lowest incidence of WNV neuroinvasive infections. Central states roughly bordered by the Mississippi River, the Rocky Mountains, and the northern and southern borders of the United States have the highest incidences of WNV neuroinvasive infections ([CDC, 2018](#)). It is important for health care providers to have awareness of WNV infection, for the prevalence may increase as global climate change contributes to increased suitable habitat for the mosquitoes that harbor this virus ([Whitehorn & Yacoub, 2019](#)).

Currently, there are vaccines for horses against WNV. There are no vaccines for humans against WNV, although researchers are actively working to develop one ([National Institute of Allergy and Infectious Diseases, 2015](#)). Therefore, risk reduction is geared toward mosquito control including avoidance of mosquito habitats, staying indoors when mosquitoes are active, draining stagnant water, utilizing mosquito repellants and protective clothing, and utilization of window screens and mosquito netting.

## West Nile Fever

West Nile virus infection is most commonly a self-limiting infection in which the majority of patients are asymptomatic ([Sejvar et al., 2003](#)). Approximately 20% of patients have a mild, systemic febrile illness termed West Nile fever (WNF) ([Sejvar, 2014](#)). West Nile fever occurs more commonly among younger patients. Incubation period is 2-14 days, followed by an abrupt onset of mild and nonspecific symptoms including fever, headache, fatigue, myalgia, nausea and vomiting, lymphadenopathy, and rash (see [Table 1](#); [Sejvar, 2014](#); [Whitehorn & Yacoub, 2019](#)). Rash is more common in WNF than in WNND and is morbilliform, maculopapular, and nonpruritic on the torso and extremities and sparing the palms and soles ([Sejvar, 2014](#)).

Table 1: Symptoms of acute Alcohol withdrawal compared to WNND infection

Body system	Alcohol withdrawal symptoms	WNND
Constitutional	Fever, insomnia, anxiety	Fever, malaise, weight loss
Neurological	Tremors, headache, irritability, disorientation, diaphoresis, dilated pupils, hyperarousal, seizures, paranoia, hallucinations	Tremors, headache, irritability, disorientation, weakness, gait disturbance, dyskinesia, nuchal rigidity, acute flaccid paralysis
Cardiovascular	Palpitations, tachycardia, hypertension	Tachycardia, hypertension
Gastrointestinal	Nausea, vomiting, anorexia	Nausea, vomiting, anorexia
Musculoskeletal	Tremors	Arthralgia, myalgia, acute flaccid paralysis

## Pathogenesis of Signs and Symptoms of Neuroinvasive Disease

Less than 1% of infected persons develop WNND in which the virus invades the intrathecal space causing infection of the structures of the central nervous system (CNS) and neurological symptoms (see [Table 1](#)). After infection via an insect vector, the WNV replicates in the bloodstream for approximately 1 week before the virus becomes detectable in the cerebral spinal fluid (CSF). Presentation of clinical neurological symptoms such as encephalitis, meningitis, or acute flaccid paralysis coincides with viral invasion of the CSF ([Larrieu et al., 2013](#); [Lyons, Schaefer, Cho, & Azar, 2017](#)). In previously published case reports, patients with confirmed WNND presented with fever, headache, weight loss, weakness, and myalgias; irritability and altered mental status were present in some patients or occurred within 12 hr after admission ([Larrieu et al., 2013](#); [Lyons et al., 2017](#); [Sejvar et al., 2003](#)).

Table 2. Symptoms of West Nile virus neuroinvasive disease

CNS structure	Neurological symptoms	Diagnosis
Meninges	Headache, fever, nuchal rigidity, photophobia, phonophobia	West Nile meningitis
Extrapyramidal structures and brainstem	Tremor in upper extremities, myoclonus, dyskinesia, postural instability, gait disturbance	West Nile encephalitis
Lower motor neurons of the spinal cord	Acute and abrupt limb paresis (partial weakness) or paralysis, sensory loss, or numbness usually absent	West Nile poliomyelitis or acute flaccid paralysis
Lower brainstem	Diaphragmatic and intercostal muscle paralysis, neuromuscular respiratory failure	West Nile poliomyelitis

Neurological manifestations of infection vary depending on which CNS structures are affected (see [Table 2](#)).

## Laboratory Testing and Diagnosis

Suspected WNND is defined as an acute infectious illness with clinical evidence of meningitis, encephalitis, or acute focal weakness (Sejvar et al., 2003). For febrile patients with neurological symptoms, it is essential to consider travel history and time spent outdoors. West Nile virus infection should be considered in any person with a febrile or acute neurological illness who has had recent exposure to mosquitoes, especially during the summer months (CDC, 2018). Serum or CSF can be tested to detect WNV-specific IgM antibodies. When WNV invades the CSF, the body mounts a specific humoral immune response that leads to detectable specific antibodies within the blood (Lyons et al., 2017). These IgM antibodies are usually detectable 3-8 days after the onset of illness and can stay elevated for up to 30-90 days after the initial infection. Onset of symptoms within 8 days of a positive test is consistent with an acute WNV infection. If the patient had no symptoms within 8 days of a positive test, it is likely a past infection (CDC, 2018). Positive results obtained with commercially available WNV IgM assays should be confirmed by further testing at a state public health laboratory or CDC. Positive IgG antibodies alone indicate past infection. Polymerase chain reaction (PCR) testing for the WNV is of limited use in immunocompetent persons because viremia is often resolved when symptoms are present, thus negative results do not rule out infection. Polymerase chain reaction testing may be useful in immunocompromised patients because viremia may be prolonged and antibody development may be delayed or absent (Nasci et al., 2013). Viral cultures are less sensitive than PCR and are not recommended. Cases of WNV should be reported to public health authorities.

## Prognosis

Recovery from neuroinvasive disease varies depending on the extent of neurological infection; some patients will experience fatigue, malaise, and weakness for weeks or months and eventually recover completely. Patients who have had WNV encephalitis or poliomyelitis often have residual neurological deficits (CDC, 2018). Complications of neuroinvasive disease include demyelinating neuropathy, parkinsonism symptoms, seizures, chorioretinitis, brachial plexopathy, encephalitis, or meningitis (Larrieu et al., 2013). In the United States., death occurs in approximately 10% of persons with WNND (CDC, 2018).

## Conclusion

This case report described a rare, but serious, presentation of a patient with WNND. Approach to differential diagnosis typically includes considering the most likely causes of patients' presenting symptoms and history. However, to ensure that the differential diagnosis is complete, it is essential to obtain a thorough history. This can be difficult when a patient presents with altered mental status. In these cases, if possible, it is best to contact family and friends who may be able to provide relevant information. Furthermore, if a patient's condition does not improve after treating the working diagnosis, it is important to reconsider the differential diagnosis and additional diagnostic testing. In certain cases, it is important to consider rare diagnoses such as WNND.

This case report was done with the patient's permission.

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