

# Acute Fever of Unknown Origin: A Presentation of West Nile Encephalitis

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## ABSTRACT

**Introduction:** West Nile virus is an asymptomatic infection in most cases, but it can present with a rare complication of deadly neuroinvasive disease.

**Case Presentation:** A 81-year-old White man presented with altered mental status and fever of unknown origin. After extensive workup, he was diagnosed with West Nile encephalitis based on positive serology, lumbar puncture, and clinical presentation.

**Discussion:** West Nile virus is a mosquito-borne RNA arbovirus that, in rare cases, can lead to encephalitis, which is a challenging diagnosis. There is no current treatment; however, a 5-day course of intravenous immunoglobulin seemed to show acute clinical improvement in both mentation and magnetic resonance imaging of the head and no long-term effects.

**Conclusion:** We report this case to increase awareness among clinicians to include West Nile virus in the differential diagnosis of encephalitis with fever of unknown origin, particularly in endemic areas.

asymptomatic infection to West Nile fever and encephalitis. Neuroinvasive West Nile virus is a severe complication and a major cause of morbidity and mortality.<sup>3</sup> Currently, there is no specific therapy, and treatment is based on supportive care. Anti-West Nile virus intravenous immunoglobulin (IVIG) has shown promise only in murine models in studies where the disease is endemic.<sup>2</sup>

In this paper, we describe a case of neuroinvasive West Nile virus in Wisconsin, with clinical symptoms of encephalitis and positive West Nile virus serology and cerebrospinal fluid (CSF) immunoglobulins. In our literature review, we found 239 reported cases of West Nile virus in Wisconsin; less than 1% were neuroinvasive.<sup>4</sup>

The goal of this paper is to discuss the prevalence of West Nile virus in Wisconsin, the upper midwestern United States, and Ontario, Canada, and describe a neuroinvasive case to increase awareness of West Nile virus among clinicians. This case also highlights the importance of considering this diagnosis in patients with unexplained altered mental status. Our patient was started on IVIG with a transient response to treatment.

## INTRODUCTION

West Nile virus (WNV) is a mosquito-borne RNA arbovirus belonging to the *Flaviviridae* family. The *Flaviviridae* genus also includes other pathogens, such as dengue, yellow fever, and Japanese encephalitis viruses. It was first isolated in 1937 from the blood of a woman with febrile disease who lived in the West Nile of Uganda.<sup>1</sup>

West Nile virus is the most common widespread mosquito-borne virus in Africa, the Middle East, and Southern Asia and recently has spread to North America.<sup>2</sup> It ranges in severity from

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## CASE PRESENTATION

An 81-year-old White man presented to the emergency department with low-grade fever and altered mental status with a maximum temperature of 102.9°F. He was falling asleep during the interview, which his wife noted was unusual. However, he was alert and oriented to person, place, and time, with normal muscle strength bilaterally. His past medical history included benign prostatic hypertrophy, type 2 diabetes mellitus, gastroesophageal reflux disease (GERD), hearing loss of aging bilateral,

hyperlipidemia, coronary artery disease, polymyalgia rheumatica, obstructive sleep apnea, depression, and lumbar spinal stenosis. He was taking rosuvastatin for his hyperlipidemia, pantoprazole for GERD, metformin and sitagliptin for type 2 diabetes, and citalopram for depression. Further review of his history revealed nausea, vomiting, myalgias, excessive sleepiness, recent travel to northern Michigan 4 weeks prior to admission, and unintentional 3-pound weight loss 6 months prior with 1-month diarrhea.

At the time of admission, his initial vitals demonstrated a blood pressure of 154/54 mmHg, temperature of 103 °F, and heart rate of 97 beats per minute. Initial investigation revealed negative blood cultures and a normal white blood cell (WBC) count of 5.8 10e3/uL. Computed tomography (CT) head showed progressive brain matter loss with ex vacuo ventriculomegaly from previous imaging. He was started on ceftriaxone and vancomycin given concern for sepsis or meningitis. Workup for fever of unknown origin and altered mental status included lumbar puncture, magnetic resonance imaging (MRI) brain, and Lyme and West Nile virus serum antibodies. Given concern for his month-long history of diarrhea, 24-hour urine 5-hydroxyindoleacetic acid was decreased at 8 mg per day, ruling out possible carcinoid tumor. Infectious disease and neurology were consulted for ongoing fever and mental status changes. The patient also developed a maculopapular rash on his right thigh, which then migrated to his inner thigh. The rash was not itchy or painful and disappeared within 24 hours with topical triamcinolone cream.

At this point, metabolic causes were unlikely due to normal basic metabolic panel, thyroid-stimulating hormone, hepatic function panel, urinalysis, and urine drug screen. Lumbar puncture revealed an elevated CSF WBC of 63/uL, elevated CSF polyeosinophilic neutrophils at 66%, decreased CSF lymphocytes at 23%, decreased CSF monocytes at 10%, elevated CSF protein of 51 mg/dL, elevated CSF glucose of 96 mg/dL, negative CSF aerobic bacterial culture with gram stain, negative CSF fungal culture, negative CSF cryptococcal antigen. Biofire meningitis/encephalitis panel, which includes nucleic acid amplification test (NAAT) for *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, group B streptococcus, *Streptococcus pneumoniae*, cytomegalovirus, enterovirus, human parechovirus, human herpesvirus 6, herpes simplex virus 1 and 2, varicella-zoster virus, and *Cryptococcus neoformans* were negative. Lyme and West Nile virus CSF antibodies were added and pending.

Infectious disease was consulted and recommended *Clostridioides difficile* stool NAAT for diarrhea and weight loss, which came back negative, while Lyme and West Nile antibodies were still pending. Neurology also was consulted and was concerned for toxic metabolic encephalopathy due to a comprehensive metabolic panel revealing decreased serum sodium of 135 mmol/L, decreased serum potassium of 2.9 mmol/L, decreased serum bicarbonate of 19 mmol/L, decreased calcium of 8.1 mg/dL, and elevated glucose of 190 mg/dL. Folate, niacin,

**Table.** Pertinent Labs and Cerebrospinal Fluid Values Throughout Patient's Hospital Course

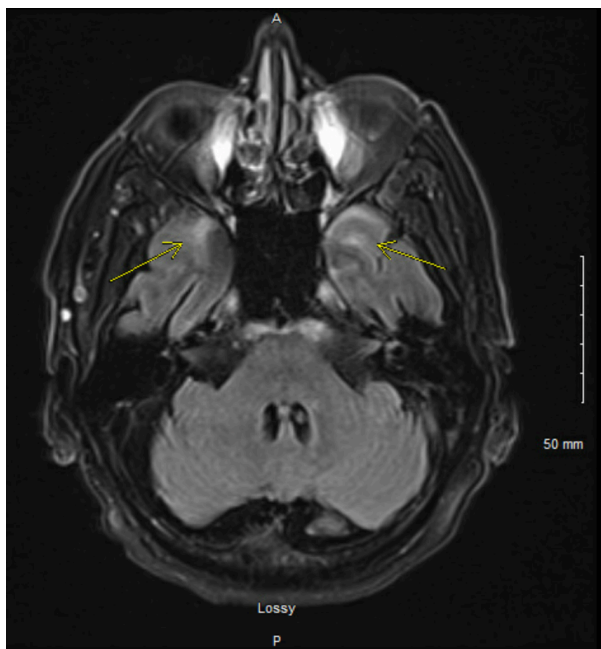
Test Result	Value	Reference Range
WBC	5.8 10e3/uL	3.9-11.2 10e3/uL
Initial CSF		
WBC	63/uL	0 – 5/uL
Polysegmented neutrophils	66%	0% – 7%
Lymphocytes	23%	28% – 96%
Monocytes/macrophages	10%	16% – 56%
Protein	51 mg/dL	15 – 45 mg/dL
Glucose	96 mg/dL	40 – 70 mg/dL
WNV Ab IgG	2.10 index value	≤ 1.29 index value
WNV Ab IgM	1.19 index value	≤ 0.89 index value
Repeat CSF		
WBC	14/uL	0-5/uL
Polysegmented neutrophils	2%	0 – 7%
Lymphocytes	91%	28% – 96%
Monocytes/macrophages	7%	16% – 56%
Protein	77 mg/dL	15 – 45 mg/dL
Glucose	82 mg/dL	40 – 70 mg/dL
WNV Ab IgG	3.41 index value	≤ 1.29 index value
WNV Ab IgM	5.13 index value	≤ 0.89 index value
Comprehensive metabolic panel		
Sodium	135 mmol/L	136 – 145 mmol/L
Potassium	2.9 mmol/L	3.4 – 5.1 mmol/L
Bicarbonate	19 mmol/L	22 – 29 mmol/L
Calcium	8.1 mg/dL	8.6 – 10.2 mg/dL
Glucose	190 mg/dL	65 – 99 mg/dL
WNV Ab serum		
IgG	0.83 index value	≤ 1.29 index value
IgM	4.21 index value	≤ 0.89 index value
Striational Ab	1:245,760	≤ 1:60
Acetylcholine Receptor Ab	0.35 nmol/L	≤ 0.02 nmol/L

Abbreviations: WBC, white blood cell count; CSF, cerebrospinal fluid; WNV, West Nile virus; Ab, antibodies.

rapid plasma reagin, serum *Helicobacter pylori* IgG antinuclear antibody, antineutrophil cytoplasmic antibodies, erythrocyte sedimentation rate, and c-reactive protein were recommended, and all were within normal limits. DPPX (dipeptidyl-peptidase-like protein 6) receptor antibody-associated encephalitis and serum La Crosse encephalitis IgM antibodies were added and also were negative. Continuous electroencephalogram was started for potential subclinical seizures and revealed continuous mild generalized slowing of the background consistent with mild diffuse cerebral dysfunction and encephalopathy with an absence of epileptiform discharges or seizures.

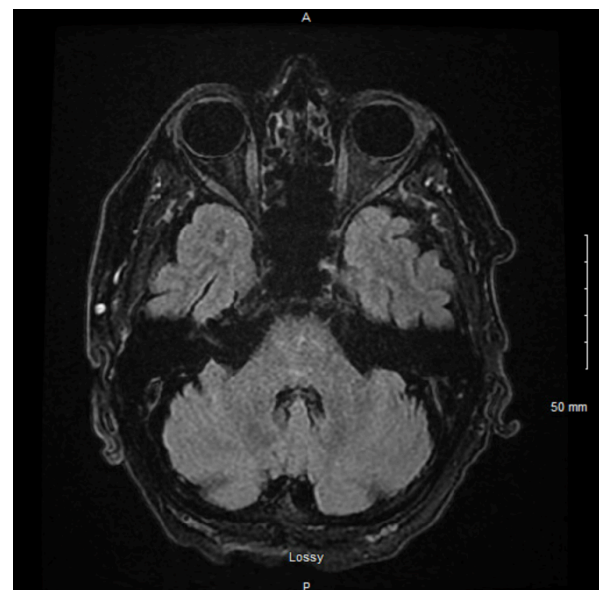
With supportive care, the patient's fever resolved on day 7 and ceftriaxone and vancomycin were discontinued; however, his mental status did not improve. West Nile virus CSF antibodies were still pending, and a repeat lumbar puncture was warranted. Results demonstrated an elevated CSF WBC of 14/uL, decreased CSF monocytes at 7%, elevated CSF protein of 77 mg/dL, elevated CSF glucose of 82 mg/dL, elevated CSF albumin of 49 mg/dL, negative Biofire meningitis/encephalitis panel, and negative

**Figure 1.** Initial Magnetic Resonance Imaging of Patient's Brain



Indeterminate signal alteration approximating sulci overlying the anterior temporal lobes. Differential includes artifact, sequela of recent oxygen therapy, and other nonspecific leptomeningeal process (eg, mild meningitis, neoplasm, infectious encephalitis).

**Figure 2.** Post Intravenous Immunoglobulin Magnetic Resonance Imaging of Patient's Brain



Previously demonstrated indeterminate signal alteration overlying the anterior temporal lobes is no longer demonstrated.

CSF aerobic/anaerobic bacterial culture with gram stain (Table). Geriatrics was consulted for underlying dementia, current altered mental status, and atypical encephalitis and recommended a CSF paraneoplastic autoantibody evaluation for an underlying contribution of autoimmune encephalopathy from malignancy.

On day 14 of admission, West Nile virus CSF IgG was elevated at 3.41 (reference range:  $\leq 1.29$  index value). Results from the first lumbar puncture revealed undetectable serum Lyme IgG and IgM, serum West Nile virus IgG was decreased at 0.83 (reference range:  $\leq 1.29$  index value), and serum West Nile virus IgM antibodies were elevated at 4.21 (reference range:  $\leq 0.89$  index value).

On day 18 of admission, supportive care was not helping, and his encephalopathy and confusion were progressing. Neurology recommended a 5-day treatment of 1g/kg IVIG, which is half the normal dose, due to the high risk of thrombotic events and high rate of death related to West Nile virus encephalitis. An improvement in the patient's encephalopathy, orientation, and confusion was noted initially following his 5-day course of IVIG; however, it began reverting to his previous baseline prior to IVIG therapy. Brain MRI pre-IVIG treatment revealed signal alteration approximating sulci overlying the anterior temporal lobes (Figure 1). This can be seen in leptomeningeal processes such as mild meningitis, but it is important to note this also may be due to artifact in the initial imaging. Brain MRI post-IVIG therapy demonstrated

the disappearance of previous signal alteration, despite initially declining from his best mentation state following IVIG treatment (Figure 2). Striational antibodies were elevated at 1:245,760 (reference range:  $< 1:60$ ), and acetylcholine receptor antibodies also were elevated at 0.35 nmol/L (reference range:  $\leq 0.02$  nmol/L).

The patient remained delirious during his hospital stay, and his family decided to pursue hospice care without any further workup for malignancy.

## DISCUSSION

West Nile virus invaded North America in 1999. Since then, there have been approximately 7 million infections, 22,999 neuroinvasive cases, and 2163 deaths in the United States. West Nile virus outbreaks in Wisconsin have varied by species, place, and time and have been affected by geographical, climatic, and environmental factors. A map of confirmed and probable West Nile virus cases in Wisconsin counties is shown in Figure 3 for reference.<sup>4</sup> West Nile virus was detected in 71 of 72 Wisconsin counties, resulting in 239 human and 1397 wildlife cases in a 15-year period. Due to decreased precipitation and increasing mean temperature, the transmission of mosquito-borne diseases will increase in cooler locations, especially in Wisconsin.<sup>3</sup> The best predictors of increased West Nile virus cases in most mosquito species were average temperature and proximity to urban areas.

Following transmission, the early phase includes viral replication in dermal dendritic cells and keratinocytes. This is followed by the visceral organ dissemination phase, including viral rep-

lication in draining lymph nodes, viremia, and spread to the visceral organs. Finally, it can spread to the central nervous system and replicate, which primarily induces injury, inflammation, and cytotoxic response. This results in a loss of neurons within the spinal cord and brainstem grey matter.<sup>5</sup>

The West Nile virus incubation period is 2 to 15 days. Most cases—approximately 80% of humans infected with West Nile virus—are asymptomatic, and around 20% develop West Nile fever. Symptomatic infections typically are mild and include myalgia, malaise, and a self-limiting fever.<sup>6</sup> Up to 50% of patients present with a maculopapular rash on the trunk; our patient presented with a migratory rash on his right hip and inner thigh.<sup>7</sup> Neuroinvasive West Nile virus is a rare and sometimes deadly complication of West Nile virus infection that occurs in less than 1% of infected people.<sup>8</sup> These patients initially present with features of encephalitis or meningitis that progress rapidly. Neurological symptoms, such as changes in mental status, severe muscle weakness, seizures, or flaccid paralysis also can be seen.<sup>9</sup> Our patient lacked severe muscle weakness, seizures, or flaccid paralysis; however, he had drastic impairment in mentation and orientation throughout his hospital course.

Treatment is primarily supportive care.<sup>10</sup> Several agents, such as interferon, ribavirin, and IVIG, have been tried with no clear efficacy.<sup>10-12</sup> There is no vaccine currently available for prevention.<sup>12</sup> The role of IVIG is undetermined and needs to be further elucidated. One study of 12 patients with neuroinvasive West Nile virus revealed some effectiveness in neurological response following IVIG treatment.<sup>13</sup> Conversely, a prospective randomized control trial of 62 hospitalized patients found a lack of efficacy of high-titered immunoglobulin in neuroinvasive West Nile virus.<sup>14,15</sup> Further investigation and research of this treatment modality are critical, especially due to the high morbidity and mortality rates of neuroinvasive West Nile virus disease. Our patient received a 5-day course of IVIG, where we observed improvement in his encephalopathy and mentation acutely. This was short-lived, and his delirium and poor mentation were still present at the end of his hospital course.

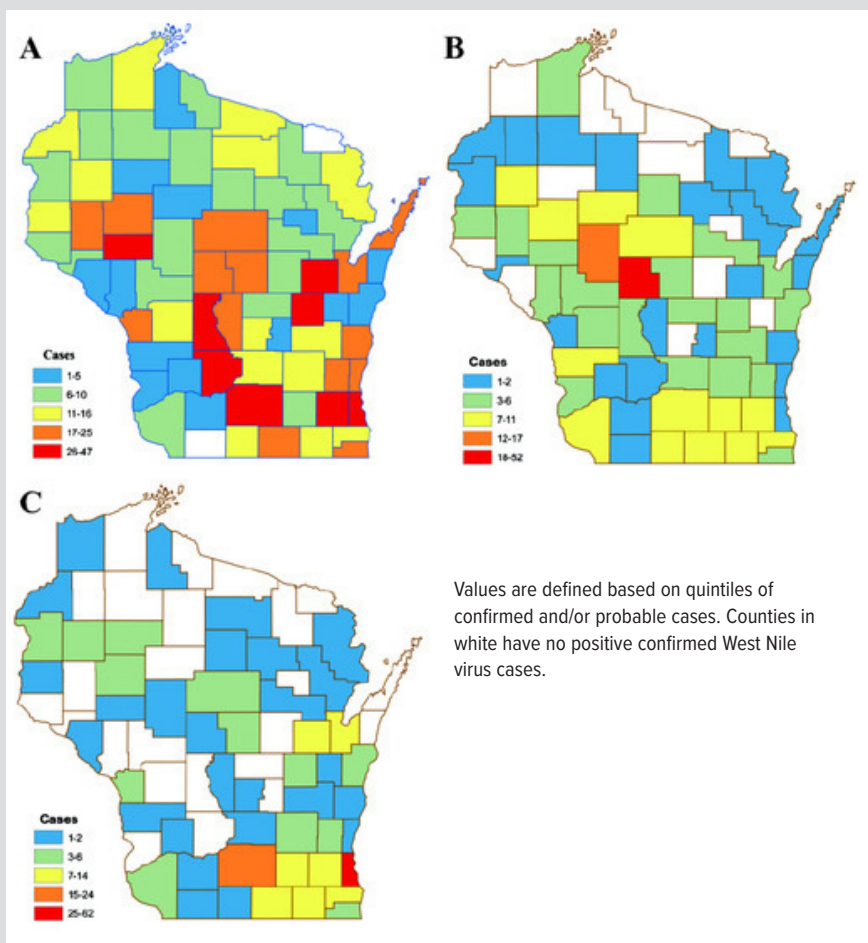
Typically, the prognosis for neuroinvasive cases of West Nile virus is poor, with a mortality rate of 10%.<sup>2</sup> The syndrome has

a wide range of neurological deficits that may last for years or even become permanent.<sup>9</sup> In Wisconsin over a 15-year period, there were 239 confirmed human cases of West Nile virus, which resulted in 17 deaths (7.1%).<sup>4</sup> The highest population at risk for neuroinvasive disease is the geriatric population.

## CONCLUSION

We present this case of West Nile virus encephalitis to increase awareness among practicing clinicians to consider this as a diagnosis in patients who present with altered mental status and fever with an unknown source. Illinois has detailed statewide epidemiology of high annual West Nile virus activity and mosquito control programs to monitor disease-related trends, neither of which are available in Wisconsin.<sup>3</sup> Since 2007, Wisconsin has relied on passive reporting of West Nile virus cases. Passive surveillance in combination with a large variability of disease incidence annually and many asymptomatic cases has led to a high degree of underestimation of West Nile virus prevalence in Wisconsin.<sup>4</sup>

**Figure 3.** Wisconsin Choropleth Map of Total Confirmed Positive and Probable West Nile Virus Cases by County for All Avian (A), Equine (B), and Human (C) species, 2001–2016.<sup>4</sup>



Values are defined based on quintiles of confirmed and/or probable cases. Counties in white have no positive confirmed West Nile virus cases.

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