



## Review Article

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# West Nile Virus Nervous System Manifestations

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## Review

West Nile Virus (WNV) is a member of the Flaviviridae, a family of single-stranded RNA viruses transmitted by the *Culex* mosquitoes and is characterized by the presence of neuro invasive strains causing disease and death in humans, birds and horses. While long identified in Africa, and other parts of the world, WNV was first diagnosed in North America in 1999, causing a surge in the number of WNV-related neuro invasive cases in 2002-2003, and again in 2012.

West Nile virus is spread between birds by mosquitoes. It is maintained in the wild bird population. Humans and horses become infected after being bitten by mosquitoes harboring the virus that have fed on infected birds. The virus enters the horse's bloodstream and spreads to the spinal cord and brain causing inflammation. Clinical signs of disease usually present within three to fifteen days of exposure [1-3].

## History and Epidemiology

West Nile virus was first isolated in Uganda in 1937, it has since become endemic in some parts of Africa where the prevalence of WNV antibody among children may be up to 8% [3-5]. WNV disease first appeared in North America in the summer of 1999, when an unusual number of deaths of exotic birds and crows in the New York City (NYC) Metropolitan Area was reported.

## Transmission

Transmission of WNV to humans occurs mostly following a bite from an infected mosquito, which acquires the virus after feeding on amplifying hosts, namely birds. WNV is primarily transmitted by *Culex* mosquitoes. However, the virus has been isolated from more than 60 species of mosquitoes, as well as from ticks [6]. Person-to-person transmission of WNV only occurs as a result of transfusion of blood products and organ transplantation, as well as following intrauterine, percutaneous (occupational) or breastfeeding exposure [7]. WNV may be transmitted from mother to child by

intrauterine transmission causing chorioretinitis, microcephaly and intracranial calcifications [8].

## Clinical Features

Several clinical features may support the diagnosis of CNS infection with WNV. Symptoms of fever (in 70–100% of patients), headache (50–100%) and altered mental status (50–100%) are common. Vomiting (30–75%), diarrhea (15–35%) and rash (5–50%) are seen in a significant percentage of patients [9-11]. Meningoencephalitis may occur in 30–50% and is often of a lower-motor-neuron pattern with flaccid paralysis without sensory abnormalities [12]. Bilateral facial nerve palsy may occur during the second or third week of the illness. Movement disorders such as dyskinesias are common in patients with WNV meningoencephalitis and may include postural or kinetic tremor in up to 90% of the patients, parkinsonism including cogwheel rigidity, bradykinesia and postural instability, and myoclonus may also occur [12].

Acute flaccid paralysis may occur in isolation, or in association with meningitis or meningoencephalitis in up to 50% of cases [13]. In West Nile Virus infection, motor weakness results from a poliomyelitis-like process presenting as pure motor deficit, unlike Guillain-Barré syndrome that presents with motor as well as sensory symptoms. Guillain-Barré-like syndrome affecting peripheral nerves, radiculopathy and demyelinating peripheral neuropathy have also been reported, however true Guillain-Barré syndrome is rare. Respiratory failure requiring endotracheal intubation, is seen in 38% of affected patients in a recent series. Bowel and bladder dysfunction occur in a third of patients [12].

## Laboratory Findings

Complete blood counts may initially show minor abnormalities, however, there may be absolute or relative lymphopenia [14]. Up to one third of the patients develop significant hyponatremia, secondary to syndrome of inappropriate antidiuretic hormone

secretion (SIADH). This may be noted during the acute illness or in the recovery period [15]. Cerebrospinal fluid pleocytosis is noted with an initial neutrophilic predominance, followed by lymphocytic predominance in the second week. Proteins are usually moderately to severely elevated (up to 300 mg/dL), and CSF glucose is usually normal [16,17]. An acute WNV infection is diagnosed by detecting the virus itself by a positive real-time polymerase chain reaction (RT-PCR), which has a sensitivity of 55% in the CSF and 10% in the serum. This test detects IgM antibodies in the CSF by enzyme-linked immunosorbent assay (ELISA) method; demonstrating more than a fourfold increase in the titer of the specific neutralizing antibody [15]. IgM ELISA in the serum has a sensitivity of 95% and a specificity of 90% when done within 8 days of the symptom onset.

### Radiological Findings

In a recent series reporting 39 consecutive cases of WNV including both meningitis and meningoencephalitis, MRI was unremarkable in all except one patient [18]. In two more recent case series [19,20], around 70% of patients with WNV CNS disease had abnormal MRI findings. Patients with normal MRI or only DW-image abnormalities had the best prognosis, whereas those with T2 and FLAIR abnormalities had the worst outcomes.

### Prognosis of West Nile Virus Disease

The overall case-fatality rate for WNV infection is 2–7%, based on US cases by the CDC report from 2002–2005. Mortality is mostly reported in patients with neuroinvasive disease with meningitis or meningoencephalitis in whom the death rate may reach 9%. In patients with WNV encephalitis, the overall mortality is approximately 12–15%, although it could be as high as 35% in elderly patients [21]. Most patients with WNV meningitis without focal neurological deficits make a complete recovery. Long-term outcomes of WNV-related severe neurological deficits may persist for months or even years [12]. Younger age at infection may be a predictor of recovery. A recent study indicated that patients with normal MRI, or with abnormalities detected only on DW images, had better outcomes than those with abnormalities on FLAIR and T2-weighted images [19].

Patients with acute flaccid paralysis often have significant residual weakness. In a prospective study of 32 patients with WNV-associated paralysis, 25 showed varying degrees of improvement at 4 months after the onset of symptoms, and the remaining 7 patients showed no improvement [22,23].

### Therapeutics

Current management of WNV disease is mainly supportive, including pain control for headaches, antiemetic therapy and rehydration for associated nausea and vomiting. Monitoring and treatment of increased intracranial pressure or controlling seizures if they occur. Preventative measures include wearing protective clothing, applying insect repellents such as 10% to 50% N,N-diethyl-3-methylbenzamide, and avoiding activities in areas and times when mosquitoes are most active area advisable.

There are numerous case series reporting on the use of various products such as standard and hyperimmune polyclonal immune globulin, monoclonal immune globulin, interferon, ribavirin, and corticosteroids in patients with WNV disease. Several of these products have been studied in controlled clinical trials for infections due to WNV or closely related flaviviruses (i.e., St. Louis encephalitis and Japanese encephalitis viruses). According to these studies, none have shown benefit. However, the studies often had small sample sizes and the results from some of the clinical trials have not been published [24]. Physicians have chosen to treat cases of WNV with concomitant immunosuppression.

Winston et al. [25] published a case series where they reported the use of polyclonal intravenous immune globulin (IGIV) to treat four patients with WNV disease transmitted through organ transplantation. All received 500 mg/kg per day IGIV but for variable numbers of days. In addition to IGIV, two patients received interferon-alpha2b, one patient received interferon- $\alpha$ 2b and WNV IgG-positive plasma, and one patient received ribavirin. Two patients died and two survived; one of the survivors received a second liver transplant at 27 days after the first procedure. In the authors review of the literature of transplant recipients with donor-derived WNV infection, three (43%) of seven patients with encephalitis treated with IGIV alone or IGIV with WNV-IgG containing plasma improved, and all four patients with asymptomatic WNV infection treated with IGIV or plasma survived. However, five (71%) of seven transplant recipients with encephalitis and receiving only supportive care also improved.

Kumar et al. [26] conducted A controlled study in India in 2005–2007 randomizing children with Japanese encephalitis to receive ribavirin (10 mg/kg per day for 7 days) or placebo. Japanese encephalitis virus is a flavivirus that is closely related to WNV. There was no difference between the two groups in mortality. There were also no statistically significant differences in secondary outcome measures.

Ribavirin appears to have limited clinical efficacy despite demonstrated efficacy against WNV *in vitro* [27, 28]. Inhibitors of nucleoside triphosphatase (NTPase)/helicase activities of Flaviviridae have not shown promising results against WNV *in vitro* [29]. The efficacy of IFN treatment in humans is still unclear, as it has only been studied in a non-blinded, non-placebo-controlled clinical trial. A vaccine has been developed for veterinary use in horses, no vaccines are yet approved for use in humans.

### Conclusion

WNV was first isolated more than eighty years ago. It became a worrisome flavivirus as it has invaded North America and became the most frequent cause of epidemic meningoencephalitis in humans in North America. Although less than 1% of infected individuals develop neuroinvasive disease as meningitis, meningoencephalitis or acute flaccid paralysis, mortality is high in this group of patients. No specific therapy has yet been shown to be effective for treatment of WNV encephalitis. Antiviral therapy,

immunomodulatory therapies and vaccines, are currently areas of research.

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## Conflict of Interest

No Conflict of interest.

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