Encephalomyelitis Resulting from Chronic West Nile Virus Infection: A Case Report

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Abstract

West Nile virus (WNV) is a mosquito-borne RNA flavivirus and human neuropathogen. The overall mortality rate for WNV disease is < 0.1% for all patients infected with WNV. Most WNV-related morbidity and mortality results from neurologic and respiratory involvement. For patients with WNV encephalitis, the mortality rate ranges from 12% to 15% and can range from 10-30% for patients with West Nile neuroinvasive disease. Mortality rates can reach up to 50% for patients presenting with acute flaccid paralysis and respiratory failure.

We report a fatal case of meningoencephalomyelitis due to chronic WNV infection in a 21-year-old male who presented with muscle weakness progressing to ascending paralysis and respiratory distress requiring mechanical ventilatory support. He was diagnosed with acute motor axonal neuropathy, a GBS variant, and had a prolonged hospital course until he died 8 months after the onset of symptoms. Microscopic examination of the central nervous system samples collected during autopsy revealed meningoencephalomyelitis. Subsequent serologic testing revealed antibodies to WNV, and immunohistochemistry detected presumed WNV antigens in neurons in multiple foci in the cerebrum, cerebellum, brainstem and spinal cord, later confirmed by an in situ hybridization technique. Myelitis and motor neuron degeneration in the spinal cord with subsequent atrophy in skeletal muscle were also observed.

Our case exemplifies chronic WNV infection causing meningoencephalomyelitis due to chronic WNV infection in a 21-year-old male who presented with muscle weakness progressing to ascending paralysis and respiratory distress requiring mechanical ventilatory support. He was diagnosed with acute motor axonal neuropathy, a GBS variant, and had a prolonged hospital course until he died 8 months after the onset of symptoms. Microscopic examination of the central nervous system samples collected during autopsy revealed meningoencephalomyelitis. Subsequent serologic testing revealed antibodies to WNV, and immunohistochemistry detected presumed WNV antigens in neurons in multiple foci in the cerebrum, cerebellum, brainstem and spinal cord, later confirmed by an in situ hybridization technique. Myelitis and motor neuron degeneration in the spinal cord with subsequent atrophy in skeletal muscle were also observed.

Our case exemplifies chronic WNV infection causing meningoencephalomyelitis that manifested clinically as acute motor axonal peripheral neuropathy. WNV-associated encephalomyelitis as well as peripheral neuropathy should be considered in patients presenting with muscle weakness and paralysis, especially when occurring in known endemic regions.

Keywords

West Nile virus, Human neuropathogen, Guillain–Barre syndrome, Central nervous system, Paralysis

Case Report

A 21-year-old Hispanic male presented to a hospital in east Texas with a three-month history of progressive ascending muscle weakness requiring intubation, tracheostomy and PEG tube placement in 2013. The weakness...
Pathologic Findings

During the autopsy, aseptically collected lung tissue was sent for culture, sural nerve was dissected, and skeletal muscle sections were obtained for further examination. Blood samples were also collected for serologic testing for WNV. Serological enzyme immunoassay for West Nile IgG and IgM antibodies was performed on post-mortem blood by the Texas Department of State Health Services (DHS). Sections from CNS were formalin fixed and paraffin-embedded. Routine hematoxylin–eosin and myelin (Luxol fast blue) staining was done as well as additional special staining of slow myosin and fast myosin for muscle fiber typing, myelin and toluidine blue staining of nerve sections and immunohistochemical staining (IHC) with anti-WNV antibodies of CNS sections. IHC for WNV was performed using polyclonal immune serum (gift of Dr. Robert Tesh, University of Texas Medical Branch) and titrated using sections of infected mouse brain (gift of Dr. Tian Wang, University of Texas Medical Branch). Immunostaining employed the standard avidin–biotin peroxidase technique (Vectastain, Vector Labs). Due to concerns about the specificity of the West Nile virus (WNV) antibody used for immunohistochemistry, the findings were later confirmed by an in situ hybridization technique. In this procedure, RNA in situ hybridization was performed using RNAscope 2.5 (Advanced Cell Diagnostics) using the manufacturer’s instructions. Tissue sections were deparaaffinized by xylene followed by 100% ethanol. Slides were then boiled in RNAscope Target Retrieval reagents and incubated with RNAscope Protease plus. Endogenous peroxidase activity was quenched using hydrogen peroxide. The probe targeting WNV was created by Advanced Cell Diagnostics (catalog #475091). Positive control tissue (mouse brain acutely infected with WNV) and negative control tissue (human spinal cord from confirmed non-infected) were stained simultaneously, similar to the IHC procedure. Sections were counterstained with Gill’s hematoxylin.

Autopsy findings relevant to this presentation include a thick yellow exudate found in the tracheostomy, diffuse consolidations of both lungs, which had increased weights (right lung: 810 gm, left lung: 612 gm) and multiple hemorrhages on the pleural surfaces. Bacterial culture from lung tissue grew Pseudomonas aeruginosa, revealing that the immediate cause of death was bronchopneumonia caused by this microorganism. Gross examination of the brain and spinal cord did not reveal any abnormalities. Microscopic examination of the central nervous system samples collected during autopsy revealed meningoencephalomyelitis, see figure 1. Myelitis and motor neuron degeneration in the spinal cord (Figure 2) with subsequent atrophy in skeletal muscle were also observed. Subsequent serologic testing revealed antibodies to WNV, and immunohistochemistry detected presumed WNV antigens in neurons in multiple foci in the cerebrum, cerebellum, brainstem and spinal cord (Figure 3). More recently, we were able to confirm the IHC findings using RNAscope in situ hybridization to demonstrate WNV RNA in the same CNS
regions (Figure 4). From these findings, we can deduce that the patient’s muscle weakness and atrophy were secondary to myelitis and motor neuron degeneration as part of diffuse involvement of the CNS.

**Discussion**

WNV is a mosquito-borne, single-stranded RNA flavivirus and human neuropathogen [1-7]. Approximately 80% of patients with WNV infection are asymptomatic and approximately 20% of patients present with a clinical illness manifested by a flu-like syndrome and maculopapular rash, termed West Nile fever (WNV) [1, 6-8]. West Nile neuroinvasive disease (WNND) occurs in up to 1% of patients infected with WNV, and is more frequently seen in patients of age 55 and above or patients who are immunosuppressed [9]. WNND has been reported to manifest in several ways, including West Nile encephalitis, West Nile meningitis, and acute flaccid paralysis, which can appear as a poliomyelitis-like syndrome or Guillain-Barré-like syndrome [1-4, 7-9]. These can present separately or with a considerable amount of overlap. West Nile meningoencephalitis or encephalomyelitis are terms that have also been used to describe patients with WNND [1-4, 7-9]. The overall mortality rate for patients with WNV disease in general is less than 0.1%, whereas the mortality rate for WNND can range between 10-30% [10]. Mortality rates range between 12-15% in patients presenting with West Nile encephalitis. However, mortality can reach up to 50% in patients presenting with acute flaccid paralysis and respiratory failure [9]. Acute WNV infection is usually cleared by an effective immune response after several days of viremia [4]. Several animal studies, however, suggest that long-term persistence of WNV occurs [1, 4, 10-12]. Persistence of WNV infection in humans has been detected in urine [12]. Since the original presentation of this patient was somewhat atypical for WNV polio-like disease, West Nile testing was not performed at the time of admission. Because he was confined to hospital or a rehabilitation center from the time of admission until his death, it is unlikely that he was infected during this period. Patients who survive WNND go on to exhibit a significant amount of morbidity due to sequelae from the disease [4, 6, 7, 9-12]. Chronic neurologic sequelae (which can persist for months to years) include fatigue, memory problems, cognitive impairment, muscle weakness, and impairment of daily activities as well as movement disorders (tremor, myoclonus) [4, 6, 7, 9-11]. However, rates of the chronic neurologic sequelae vary considerably between studies [7, 9-11].

Our case illustrates chronic WNV infection causing meningoencephalomyelitis that manifested clinically as acute motor axonal neuropathy. Autopsy demonstrated the presence of presumed WNV antigens in the cerebrum, cerebellum, brainstem, and spinal cord as well as evidence of motor neuron involvement. Note that the diagnostic IHC on brain tissue employed polyclonal antisera, which has been suggested to possibly cross-react with other flaviviruses (not tested). Therefore infections by other flaviviruses, in particular both Zika virus and St. Louis encephalitis viruses that are both known to have infected humans in Texas, may not be
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References


completely excluded by this technique. Epidemiologically, WNV activity occurs regularly in Texas, and there were no outbreaks of either Zika or St Louis encephalitis viruses in 2013 when this case occurred. The newer RNAscope in situ hybridization technique provided an independent confirmatory test for WNV. RNAscope includes multiple probes of 20-25 base pairs in length. Two probes must bind to the same RNA strand, adjacent to each other, for signal to be produced. Because two probes are unlikely to hybridize to non-target RNA, non-target binding is rare. One study found that RNAscope could differentiate between viruses with as much as 85% overall sequence identity [13]. Although reports of cross reactivity of this probe with other closely related flaviviruses are not available, a study using the same technology but targeting Zika virus reported no cross reactivity with WNV and dengue virus [14].

Although most cases of WNND are seen in patients with age > 50 and who are immunosuppressed [15], our patient was in his early 20’s and did not have any history of immunosuppression. We postulate that the patient’s symptoms of neuropathy (weakness and paralysis) and corresponding atrophy in skeletal muscle were secondary to myelitis and motor neuron degeneration in the spinal cord and brainstem due to chronic WNV infection. WNND should be considered in all patients presenting with not otherwise explained muscle weakness and paralysis in endemic areas.