Histopathologically Proven Poliomyelitis with Quadriplegia and Loss of Brainstem Function Due to West Nile Virus Infection


Recent electrophysiological and histopathological reports point to motor neurons in the anterior horn of the spinal cord and the brainstem as targets of severe West Nile virus (WNV) infection. We report histopathological confirmation of this poliomyelitis-like syndrome in a patient with WNV infection in Massachusetts.

We report the clinical and pathological details of one of the first human cases of West Nile virus (WNV) infection (diagnosed in the fall of 2001) identified in Massachusetts. The patient's case is unusual for several reasons. First, his early hospital course was notable for rhabdomyolysis, a feature not previously reported as associated with this illness. Second, although asymmetric flaccid paralysis occurs with WNV [1], this patient developed an areflexic quadriplegia with loss of brainstem reflexes that clinically resembled brain death. Third, examination of the brain and cervical spinal cord at autopsy revealed inflammatory destruction of motor neurons in the brainstem motor nuclei and anterior horns, providing neuropathological confirmation of human WNV infection–related poliomyelitis.

Case report. A 70-year-old man from eastern Massachusetts presented at our hospital in September 2001 with a history of rapid decline in cognitive function over several days accompanied by gait instability. He had a temperature of 39°C and tachycardia. He was disoriented. The only finding of a focal examination was a slight weakness of the right leg. The patient's blood urea nitrogen level was 17 mg/dL, and the creatinine level was 1.2 mg/dL. The alkaline phosphatase level was elevated (426 U/L), and the aspartate aminotransferase level was high (54 U/L). The creatine kinase (CK) level was elevated (3000 IU/L). Urinalysis showed moderate occult blood without red blood cells.

The patient was admitted to the hospital and administered antibiotics empirically to treat his fever, but there was no response to treatment. On day 4 of hospitalization, his creatinine level increased to 2.6 mg/dL and his CK level increased to 8819 IU/L. He became increasingly obtunded and hypotensive. Analysis of urine sediment revealed acute tubular necrosis. Two days later, the patient had 2 generalized tonic-clonic seizures. Analysis of CSF samples revealed a WBC count of 150 cells/mm³, with 87% polymorphonuclear cells; a glucose level of 100 mg/dL; and a protein level of 90 mg/100 mL.

By day 11 of hospitalization, the patient was in a deep coma with minimally reactive pupils but no other cranial nerve responses. There was no response to the oculocephalic (doll’s eyes) maneuver, no corneal reflexes, no response to cold caloric vestibular testing, and no gag reflex. No movement of the patient’s head or limbs occurred either spontaneously or with noxious stimulation. The muscle tone was flaccid, and the deep tendon reflexes were absent.

Electroencephalogram (EEG) findings showed no focal or epileptiform abnormalities and revealed low-voltage (attributed to marked scalp edema) 5–6 Hz waves diffusely mixed with 7–8 Hz and 15–20 Hz waves. The EEG findings were interpreted as indicative of diffuse encephalopathy with preserved cortical rhythms and organization. The findings of a second EEG, performed 4 days later, were unchanged.

Findings of electromyography and nerve conduction studies showed severe losses of the motor and sensory nerve fibers and diffuse denervation. Widespread fibrillation and positive sharp waves were found in the arms and legs. There was absence of the compound muscle action potential from the extensor digitorum brevis and from the left anterolateral calf muscles. All other compound muscle action potentials showed severe reductions. Only 2 thenar motor nerve fibers were found, whereas the normal age-adjusted count would be at least 100 motor units. Repetitive stimulation revealed no evidence of neuromuscular transmission defect. Sensory nerve action potentials were absent in the legs, and amplitudes were severely reduced in the arms. On day 19 of hospitalization, with the consent of

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The patient’s family, life support was withdrawn and the patient died.

CSF and serum samples were forwarded to the State Laboratory of the Massachusetts Department of Public Health (Jamaica Plain, MA). The CSF samples were positive for antibody to WNV by IgM capture EIA, and WNV RNA was detected in the samples by RT-PCR. The serum samples were positive for WNV antibody using an IgM capture EIA and an IgG EIA; these findings were confirmed by WNV-specific plaque reduction neutralization assay. RT-PCR analysis of specimens of the patient’s fixed skeletal muscle failed to detect virus.

The gross appearance of the brain was normal, both externally and in routinely obtained sections. Microscopic examination of sections stained with hematoxylin and eosin and Luxol-fast blue revealed mild-to-moderate inflammatory infiltrate in the cortical leptomeninges, frontal cortex, and hippocampus. There was moderate-to-severe inflammation of the substantia nigra in the midbrain. The portion of the upper cervical spinal cord available for examination showed severe leukocytic inflammation of the anterior horns with striking loss of motor neurons (figure 1). Extensive neuronophagia was seen. The inflammation was revealed in all areas by immunostains directed against leukocyte common antigen. This stain also revealed a sparse leukocytic infiltrate in the ventral roots, but it revealed no infiltrate in the dorsal roots. The dorsal motor nucleus of cranial nerve 10 and the hypoglossal nucleus in the medulla both showed changes similar to those seen in the anterior horns of the spinal cord. One section of skeletal muscle was available for microscopic analysis, and it showed only mild focal inflammation without necrosis. No peripheral-nerve tissue specimens were available for neuropathological examination.

**Discussion.** We report a case of WNV encephalomyelitis with flaccid paralysis, electrophysiological study findings consistent with a poliomyelitis-like syndrome, and histopathological demonstration of motor neuron destruction in anterior horn regions of the spinal cord and in the brainstem motor nuclei, a pattern similar to that of poliomyelitis. In recently reported cases [2], clinical and electrophysiological findings suggested that WNV infection may involve motor neurons in the brainstem and spinal cord, and the first histopathologically proven case of spinal cord anterior horn cell involvement in human WNV infection has just been reported [3]. Our findings provide further confirmation of spinal cord involvement, and, although previous reports have shown perivascular inflammation and microglial nodules in the medulla [4, 5], our findings are the first to demonstrate motor neuron loss that is consistent with poliomyelitis in the brainstem.

Widespread recognition of WNV infection as a potential cause of poliomyelitis is very recent, but it has been known that infection with other flaviviruses [6–8] and the echoviruses and Coxsackie enteroviruses [9, 10] can cause nonpolio virus poliomyelitis. Experimental primate WNV infection [11] and
equine WNV polioencephalomyelitis [12] have been associated with histopathologically demonstrated anterior horn cell destruction. With regard to humans, a case report from 1979 described a patient with WNV infection who developed an acute syndrome resembling poliomyelitis [13].

Flaccid paralysis associated with WNV infection has previously been attributed to demyelinating polyneuropathy, thought to be similar to Guillain-Barré syndrome [1], or to axonal polyneuropathy [14] in the few patients studied with electromyography and nerve conduction studies. Our patient’s asymmetric weakness, which progressed to flaccid paralysis, was shown by electrophysiological testing to be due to severe losses of motor nerve fibers and diffuse denervation in the muscles, which suggested a poliomyelitis-like syndrome. However, electrophysiologic testing alone is not sufficient to distinguish anterior horn cell loss from motor axonopathy. Our report links the electrophysiological evidence suggesting poliomyelitis with histopathological evidence.

The severe sensory fiber losses shown by electrophysiological studies of this patient have not been previously associated with WNV infection. A possible explanation for these losses that invokes WNV infection is that an inflammatory attack occurred on the sensory neurons in the dorsal root ganglia and the second-order sensory neurons within the CNS, as occurred with the lower motor neurons. WNV can infect dorsal root ganglion neurons and axonal myelin sheaths in vitro [15]. However, unlike in the ventral roots, no inflammatory infiltrate was found in the dorsal roots. Because peripheral nerve and dorsal root ganglia specimens were not available for pathological examination, the cause of the sensory fiber losses remains unknown.

Rhabdomyolysis with elevation of CK levels is also an unusual finding in cases of WNV infection. Although it is possible that a component of viral myositis may have contributed to the development of weakness in this patient, we found no evidence of muscle necrosis. Only a small specimen of fixed skeletal muscle was available for testing and microscopic examination, and a more extensive examination of skeletal muscle might have yielded positive findings. The lack of virus in the muscle tissue is similar to findings in lung, liver, spleen, and kidney tissue examined during the 1999 New York outbreak of WNV infection. During that outbreak, immunohistochemical staining revealed no viral antigen except in samples of neurons, neuronal processes, and areas of necrosis in the gray matter [14]. Motor neuron disease, including acute poliomyelitis, and acute axonal neuropathies can be associated with mild-to-moderate elevations of CK levels [16–20].

In conclusion, WNV infection may be associated with acute flaccid paralysis, and, in some unusual cases, the clinical state may progress to resemble brain death. Several critical findings led to the diagnosis of WNV infection in this patient. First, the pupillary response to light was questionable, which was incompatible with a diagnosis of brain death. Second, electrophysiological testing with electromyography, nerve conduction studies, and EEG supplied crucial evidence of the lower motor neuron etiology of the paralysis. WNV infection must be considered in cases of febrile illness associated with meningoencephalitis and weakness or cranial neuropathies, and it may be confused with other acute paralytic disorders of the central or peripheral nervous system. Recent electrophysiological and histopathological reports point to motor neuron involvement in the anterior horn of the spinal cord and brainstem as targets of severe WNV infection.

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