Neurologic Manifestations and Outcome of West Nile Virus Infection

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Most human infections with West Nile virus (WNV) are subclinical or manifest as a mild febrile illness, but a small proportion of patients (<1%) develop acute neurologic illness. Although recent WNV outbreaks have been associated with severe neurologic disease, retrospective studies have failed to identify clinical features that distinguish WNV from other viral encephalitides. The US outbreak of WNV in 2002 presented an opportunity to assess neurologic manifestations, laboratory and neurodiagnostic findings, and outcome associated with WNV infection.

Methods
From August 1 to September 2, 2002, patients from St Tammany Parish, La, with suspected WNV infection were identified through state-based surveillance at local hospitals and regional medical centers. Suspected WNV infection was defined as illness with evidence of an acute infectious process (eg, temperature ≥39°C; elevated white blood cell count; or cerebrospinal fluid [CSF] pleocytosis) along with clinical evidence of meningitis, encephalitis, or acute focal weakness (Box). Infection with WNV was confirmed if WNV-specific antibodies were detected in acute-phase serum or CSF samples by IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) and were confirmed by plaque-reduction neutralization assay.

Eligible enrollees were assessed on presentation to medical care. Patients were approached under the auspices of a public health event; oral consent was obtained. Standardized case histories and initial symptoms and signs were collected. One neurologist (J.J.S.) examined each patient; a second neurologist verified findings for 7 patients. Laboratory results, neuroimaging and electrophysiologic findings were recorded and updated 1 week following initial assessment, during repeat neurologic evaluation.

Approximately 8 months later (March 15-April 4, 2003), patients with confirmed WNV infection were reexamined. The Centers for Disease Control and Prevention institutional review board approved the study. The anonymous individual participant identifiers were maintained by the study institution. The report conforms to the Strengthening the Reporting of Observational Studies in Epidemiology, and the Neurology Reporting Standards (NeurologeRs) guidelines for observational studies.

Results
Sixteen (37%) of 39 suspected cases had antibodies against WNV; 5 had meningitis, 8 had encephalitis, and 3 had poliomyelitis-like acute flaccid paralysis. Movement disorders, including tremor (15 [94%]), myoclonus (5 [31%]), and parkinsonism (11 [69%]), were common among WNV-seropositive patients. One patient died. At 8-month follow-up, fatigue, headache, and myalgias were persistent symptoms; gait and movement disorders persisted in 6 patients. Patients with WNV meningitis or encephalitis had favorable outcomes, although patients with acute flaccid paralysis did not recover limb strength.

Conclusions
Movement disorders, including tremor, myoclonus, and parkinsonism, may be present during acute illness with WNV infection. Some patients with WNV infection and meningitis or encephalitis ultimately may have good long-term outcome, although an irreversible poliomyelitis-like syndrome may result.
**NEUROLOGIC MANIFESTATIONS OF WEST NILE VIRUS INFECTION**

**Box. Diagnostic Criteria**

**West Nile Meningitis**
- A. Clinical signs of meningeal inflammation, including nuchal rigidity, Kernig or Brudzinski sign, or photophobia or phonophobia.
- B. Additional evidence of acute infection, including 1 or more of the following: fever (>38°C) or hypothermia (<35°C); cerebrospinal fluid pleocytosis (>5 leukocytes/mm³); peripheral leukocyte count >10,000/mm³; neuroimaging findings consistent with acute meningitis inflammation.

**West Nile Encephalitis**
- A. Encephalopathy (depressed or altered level of consciousness, lethargy, or personality change lasting ≥24 hours).
- B. Additional evidence of central nervous system inflammation, including 2 or more of the following: fever (>38°C) or hypothermia (<35°C); cerebrospinal fluid pleocytosis (>5 leukocytes/mm³); peripheral leukocyte count >10,000/mm³; neuroimaging findings consistent with acute inflammation (with or without involvement of the meninges) or acute demyelination; presence of focal neurologic deficit; meningismus (as defined in A); electroencephalography findings consistent with encephalitis; seizures, either new onset or exacerbation of previously controlled.

**Acute Flaccid Paralysis**
- A. Acute onset of limb weakness with marked progression over 48 hours.
- B. At least 2 of the following: asymmetry to weakness; areflexia/hyporeflexia of affected limb(s); absence of pain, paresthesia, or numbness in affected limb(s); cerebrospinal fluid pleocytosis (≥5 leukocytes/mm³) and elevated protein levels (≥45 mg/dL); electrodiagnostic studies consistent with an anterior horn cell process; spinal cord magnetic resonance imaging documenting abnormal increased signal in the anterior gray matter.

The 8 patients with WNE had a mean admission Glasgow Coma Scale score of 11 (range, 4T [intubated] to 15). A median of 3 days passed between symptom onset and changes in mental status. Cranial nerve and bulbar abnormalities were observed in several patients with WNE. Results of formal strength testing displayed mild-to-moderate diffuse weakness in 4 patients and focal weakness in the 3 patients with AFP. New sensory abnormalities were not observed. Four patients with WNE and 1 patient with WNM displayed abnormal hyperreflexia; the 3 patients with AFP had increased signal or hyporeflexia of the affected limbs.

Dyskinesias (ie, movements including tremor, myoclonus, and features of parkinsonism) were observed in 15 of the 16 WNV-seropositive patients (Table). Tremor was observed in 15 patients; 9 had onset of tremor after day 5 of illness. Tremor in all 15 patients was static or kinetic, asymmetric, and involved the upper extremities. Two patients additionally displayed intentional movement dysmetria. Myoclonus was directly observed in 10 patients. Parkinsonism was observed in all 3 patients with AFP, 6 of 8 patients with WNE, and 2 of 5 patients with WNM. Resting tremor was not observed. Seizures were documented using electroencephalography in 1 patient with WNE.

All 3 patients with AFP had asymmetric limb weakness within 48 hours of initial symptom onset. Pain, pares-
Neuroimaging and Electrophysiologic Studies

None of the WNV-seropositive patients showed acute abnormalities on computed tomography. Magnetic resonance imaging of the brain was performed on 10 of the 16 patients: the findings showed nonacute abnormalities in 8 patients and bilateral, focal lesions in the basal ganglia, thalamus, and pons on T2- and diffusion-weighted sequences in 2 severely ill patients with WNE (Figure). Findings of magnetic resonance imaging of the cervical, thoracic, and lumbar spine for the 2 patients with AFP with lower extremity involvement showed diffuse degenerative changes without spinal cord abnormalities.

Electroencephalograms were obtained for 7 patients with WNE. Abnormal findings included electrographic seizures in 1 patient, focal sharp waves in 1 patient, and diffuse irregular slow waves in 6 patients. No correlation between electroencephalographic findings and the presence of myoclonus or tremor was observed.

Electromyographs and nerve conduction studies were performed on the 3 WNV-seropositive patients and 1 WNV-seronegative patient with asymmetric weakness from 3 to 42 days after onset.

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Laboratory results

Leukocyte count at admission, 10<sup>9</sup>/mm<sup>3</sup> 13.9 (9.8 to 17.1) 7.6 (3.5 to 18.2) 11.8 (9.5 to 13.0) 9.9 (3.5 to 18.2) 7.3 (5.6 to 16.2)

Initial CSF leukocyte count, cells/mm<sup>3</sup> 24 (1 to 231) 62 (0 to 1168)§ 143 (140 to 329) 140 (0 to 2317) 2 (0 to 189)‡

Initial CSF protein, mg/dL 57 (40 to 157) 78 (51 to 194)§ 116 (75 to 234) 78 (40 to 234) 45 (13 to 295)§

Initial CSF glucose, mg/dL 68 (44 to 113) 54 (37 to 102)§ 74 (60 to 119) 60 (37 to 119) 86 (54 to 156)§

Initial CSF lymphocytes, % 21 (2 to 57) 25 (0 to 83)§ 68 (42 to 95) 26 (0 to 95) 63 (4 to 100)§

Days hospitalized, median (range) 5 (4 to 8) 15.5 (5 to 35) 14 (7 to 19) 12 (4 to 36) 7 (1 to 66)

Abbreviation: CSF, cerebrospinal fluid. SI conversion: For glucose, to convert mg/dL to mmol/L, multiply by 0.06556.

* Patient hospitalized for unrelated condition before onset of symptoms associated with acute West Nile virus infection.
† Patients who were comatose were not assessed (n = 22).
‡ Patients who were comatose were not assessed (n = 7).
§ n = 7.

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Follow-up neurologic examination of the 15 WNV-seropositive patients who survived revealed no neurologic deficits in the 5 patients with WNM. Among patients with WNE and AFP, tremor was present in 5 patients and parkinsonism in 5. A postural and/or kinetic tremor was observed in 5 patients following recovery from WNE, and in 1 patient, it was severe enough to interfere with grooming and eating. Parkinsonism persisted in 5 of the 11 patients. In all but 1 patient (the patient with underlying systemic lupus erythematosus), parkinsonism was mild and did not interfere with daily activities. One patient with WNE with severe initial parkinsonism and postural instability was ambulatory with a walker for 4 months following illness onset, but by 6 months was able to climb ladders at work. Eight-month follow-up examination demonstrated only minimal postural instability and bradykinesia. The 8-month follow-up examination revealed 2 patients who demonstrated myoclonus of the upper extremities and face.

Five of 7 patients with severe encephalitis, as characterized by an initial Glasgow Coma Scale score of 12 or less or an initial mental status score of 2 SDs below normal for age, had favorable outcomes, defined as achieving or exceeding their level of functioning before illness. Two patients with particularly guarded prognoses during acute illness were functioning at baseline level by 6 months, with no residual symptoms. Recovery to normal or near-normal functioning occurred within 4 months in all cases of improvement.

Patients with AFP showed no improvement in limb weakness. Bladder symptoms in the patients with AFP had resolved. Electromyographs and nerve conduction studies performed at the 8-month follow-up examination revealed chronic denervation and motor axon loss in affected limbs. One patient with AFP experienced continued severe dyspnea. Chest and diaphragmatic fluoroscopy performed 3 months after illness onset revealed right hemidiaphragmatic paralysis consistent with central nervous system etiologic findings.

Patients with AFP reported the lowest overall functioning scores and had the lowest scores on both Barthel and modified Rankin scoring systems (data not shown). Five of 7 patients who survived WNE and 4 of 5 patients who survived WNM reported normal functional scores (data not shown). Seven of the 10 patients who were employed before WNV infection returned to work within 4 months following hospital discharge. Five patients, including all 3 with AFP, described continuing difficulties with daily activities, such as grooming, housekeeping, and mobility. All patients with AFP required use of a wheelchair for ambulation, and 2 patients who had been independently mobile before infection required walkers following recovery from WNE.

**COMMENT**

Movement disorders, in particular tremor, myoclonus, and parkinsonism, were prominent among WNV-seropositive patients, but uncommon among WNV-seronegative patients. While tremor and myoclonus have been documented prospectively in patients with St Louis encephalitis virus, other viral infections, they have not been described in contemporary WNV studies. Documentation of these findings in 15 of 16 WNV-seropositive patients suggests that these findings have diagnostic relevance.

Previous immunohistological assessments have detected WNV in the basal ganglia, thalamus, and pons in patients with severe encephalitis, suggesting the possibility of viral involvement of these structures with resultant parkinsonism and tremor. Magnetic resonance imaging findings in 2 patients correlated clinically with the findings of parkinsonism and tremor; however, in 8 patients, parkinsonian features were present without abnormal findings on magnetic resonance imaging. Parkinsonism has been observed with Japanese encephalitis virus infection, a related flavivirus. Some prior studies have suggested long-term persistence of signs, while others have reported parkinsonism as a more transient feature. In our study, the pa...
tient with severe persistent parkinsonism at 8-month follow-up had shown persistence of abnormalities in the basal ganglia, thalamus, and substantia nigra on magnetic resonance imaging. All patients with WNM had favorable outcome; all returned to work and reported normal or near-normal functioning at 8-month follow-up. In addition, 5 patients with severe WNE had excellent outcomes, achieving premorbid levels of functioning without residual disability within 4 months of illness. Severe parkinsonism associated with WNE is variable, and severe initial manifestations of acute WNV infection may necessitate near- or long-term supportive care in all patients.

Two of the 3 patients with AFP developed AFP without associated encephalopathy or meningismus. Clinical findings and electrodiagnostic data suggested involvement of anterior horn cells of the spinal cord, resulting in a poliomyelitis-like syndrome.19,31,32 At 8 months, none of the patients had improvement in weakness, and electromyographic data suggested permanent motor neuron loss, indicating that significant recovery in weakness is unlikely. Persistent dyspnea in 1 patient with AFP is most likely due to poliomyelitis-like diaphragmatic and intercostal muscle weakness with respiratory failure.3-5

We conclude that movement disorders, particularly tremor, myoclonus, and parkinsonism, may be underrecognized manifestations of acute WNV illness and have a generally favorable prognosis. However, complaints of persistent fatigue, headache, and myalgia are common. Long-term outcome of patients with WNE is variable, and severe initial encephalopathy did not necessarily portend poor prognosis. A poliomyelitis-like syndrome can occur without associated meningitis or encephalitis and has poor long-term outcome.

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REFERENCES