West Nile Virus Encephalitis Involving the Substantia Nigra

Neuroimaging and Pathologic Findings With Literature Review

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West Nile virus has become a medically important arbovirus in the continental United States with its debut in 1999 in the New York City area. We present neuroimaging features and pathologic findings in 2 patients who were severely affected out of the more than 100 documented cases at our institution. Both patients showed striking involvement of the substantia nigra, a finding not previously reported for West Nile virus.

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The awareness of unusual infectious diseases in the continental United States has been enhanced by reports of West Nile virus (WNV) encephalitis, which occurred in the New York City area during 1999. The increasing mobility of our society and potential threat of germ warfare mandate that we stay informed and aware of such “exotic” diseases. Most articles have dealt with the clinical manifestations of the disease and its epidemiology. Few articles have addressed the appearance of WNV on imaging studies. We present the clinical features and neuroimaging findings in 2 cases of WNV encephalitis in which the virus showed a predilection for substantia nigra involvement, which has been previously reported for the Flaviviridae family of viruses but not for WNV. This pattern of involvement seems to indicate a more severe disease course, as was alluded to in previous Flaviviridae virus case reports.

CASE REPORTS

CASE 1

A 39-year-old man known to have adult polycystic kidney disease and previous cadaveric renal transplant for which he received cyclosporin A developed fever, chills, headache, and myalgia. At hospital admission, his cerebrospinal fluid (CSF) showed lymphocytic pleocytosis. The CSF cell count was abnormal, with a total of 41/µL (0.041 × 10⁹/L) white blood cells and 4/µL (0.004 × 10⁹/L) red blood cells. There were 67% lymphocytes and 30% mononuclear cells in the CSF. The CSF protein level was markedly elevated at 115 mg/mL, and the CSF glucose level was mildly elevated at 8.7 mg/dL (0.5 mmol/L). The CSF virus study results were positive for WNV by IgM-capture enzyme-linked immunosorbent assay. The head computed tomographic (CT) scan obtained hospital day 3 was unremarkable. On hospital day 4, the patient developed slurred speech, decreased responsiveness, lethargy, and respiratory failure that required intubation. No seizure activity was present. Brain magnetic resonance (MR) images demonstrated subtle abnormal signal intensity in the thalami (Figure 1). The hospital day 8 head CT scan showed development of hydrocephalus (Figure 2).

On hospital day 9, the patient had an abrupt mental status change with the development of status epilepticus, which was controlled with induction of a pentobarbital coma. Brain MR images demonstrated marked worsening of the initial hyperintensity involving the bilateral thalami and the presence of subtle petechial hemorrhage on the cerebellar cortical surface, thalami, and subthalamic areas bilaterally (Figure 3 and Figure 4).

The patient remained in a coma with occasional partial seizure activity that
manifested as rhythmic clonic movements. This partial seizure activity diminished and ceased after repeated intravenous injections of diazepam.

On hospital day 21, brain MR images (Figure 5) demonstrated improvement of the previously noted areas of abnormal hyperintensity, but the petechial hemorrhage was much more prominent and extensive (Figure 6). There were no further seizures. The patient remained intubated owing to respiratory failure that improved slowly during the next 2 weeks. His involuntary tremor was replaced by bilateral ballistic movements, which failed to respond to a series of medications. However, the involuntary movements gradually resolved during several weeks and was replaced by tremor affecting the fingers bilaterally and associated with occasional myoclonic jerks. Six months after initial hospital admission, the patient demonstrated continued improvement of his extrapyramidal movement disorders. He had normal strength in his upper limbs bilaterally but remained paraparetic in the lower limbs. He demonstrated some ataxia with intention tremor. His judgment, retention, recall, and memory improved enough to allow independent functioning in an assisted rehabilitation setting.

CASE 2
A 75-year-old woman had been in her usual baseline state of health after returning from a visit to northern Michigan, when she developed difficulty walking and was noted by her husband to have some difficulty initiating movements. She complained of upper extremity tremors that were present at rest and worsened with activity. She had been symptomatic for approximately 4 to 5 days prior to hospital admission. At hospital admission, a masked facies and bilateral upper and lower extremity cogwheel rigidity were present. She developed fever after admission to the hospital; head CT scans were remarkable for hydrocephalus (Figure 7). She became obtunded and died on hospital day 4. An autopsy was performed.

At external inspection, the brain showed diffuse cerebral edema and a known prior remote infarct with associated white matter track degeneration in the brainstem. The leptomeninges were unremarkable. Bilateral pallor of the substantia nigra was noted.

The CSF obtained from cisterna magna aspirate obtained after the patient's death showed moderate num-
Numbers of neutrophils. Results of bacterial cultures and IgG immunoblot for herpes virus 1 and 2 were negative.

Microscopic examination showed nonspecific changes of a viral meningoencephalomyelitis. Mild to moderate chronic inflammation was seen in the leptomeninges and perivascular spaces. Numerous microglial nodules were present in both the gray and white matter and involved the entire neuraxis. In the gray matter, the microglial nodules were often associated with neuronophagia. The substantia nigra showed particularly severe involvement, with patchy marked loss of neurons and pigment incontinence in the pars compacta (Figures 8, 9, and 10). This severe involvement of the substantia nigra correlated with the patient’s clinical parkinsonian features. No Lewy bodies were present. No viral cytopathic inclusions were
Results of subsequent IgM-capture enzyme-linked immunosorbent assay on remaining CSF were positive for WNV.

The WNV is a single-stranded RNA virus of the family Flaviviridae, which includes Japanese encephalitis (JE) and St Louis encephalitis, some medically important viruses that are also associated with human encephalitis. The WNV is a type of arbovirus transmitted to humans by infected mosquitoes. Until the 1999 outbreak in New York City, WNV was primarily found in the eastern hemisphere in Africa, Asia, and the Middle East. The original WNV isolate was reported in Uganda in 1937.2,3

Specific viral cause in encephalitis may be difficult to infer from the location of brain lesions on imaging studies. There are a few viral encephalitides in which a characteristic pattern of brain involvement has been described. Authors of previous articles have documented the propensity of St Louis encephalitis and JE to involve the substantia nigra.7-11 In our 2 cases, WNV showed a similar potential for particularly severe involvement of the substantia nigra, specifically the pars compacta. The abnormalities seen at gross and microscopic examination in case 2 correlate with the abnormal signal intensity seen at MR imaging in the substantia nigra in case 1. Although previous pathology reports of WNV fatalities

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**Figure 7.** Axial nonenhanced computed tomographic images of the head reveal hydrocephalus with subependymal edema and subtle fullness of the pons and brainstem filling the basal peripontine cistern.

**Figure 8.** The substantia nigra demonstrates numerous microglial nodules, scattered mononuclear cells, and extensive patchy loss of neurons. The microglial nodules are composed of many macrophages and microglia with some lymphocytes. There is a moderate perivascular lymphocytic infiltrate. No viral cytopathic inclusions are seen (hematoxylin-eosin, original magnification ×250).

**Figure 9.** The striking involvement of the substantia nigra is demonstrated with stain that highlights the numerous macrophages and microglia (CD68 KP1 immunoperoxidase stain, original magnification ×250).

**Figure 10.** High-power micrograph of the substantia nigra demonstrates microglial nodules and focal neuronophagia (CD68 immunoperoxidase stain, original magnification ×500).

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**COMMENT**

The WNV is a single-stranded RNA virus of the family Flaviviridae, which includes Japanese encephalitis (JE) and St Louis encephalitis, some medically important viruses that are also associated with human encephalitis. The WNV is a type of arbovirus transmitted to humans by infected mosquitoes. Until the 1999 outbreak in New York City, WNV was primarily found in the eastern hemisphere in Africa, Asia, and the Middle East. The original WNV isolate was reported in Uganda in 1937.2,3

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have described the brainstem, particularly the medulla, to be the site of most extensive inflammatory involvement by the virus, to our knowledge, striking involvement of the substantia nigra as seen in our 2 cases has not been previously reported.12,13

In addition, JE may show characteristic bilateral thalamic involvement with a strong tendency to be hemorrhagic, as demonstrated at MR imaging.10 Case 1 demonstrated this finding, with additional petechial hemorrhages of the upper half of the cerebellum, hippocampi, and corticospinal tracts. These features were not seen grossly or microscopically in case 2. The hemorrhagic involvement of the thalamus in JE was reported to not correlate with severity of illness or with outcome and was possibly related to a more virulent strain.10

Movement disorders as sequelae of JE have also been reported.10,14 The patient in case 1 manifested choreiform movements of the tongue and face and then bilateral ballistic movements during recovery. Cell injury to the basal ganglia and substantia nigra from viral encephalitis may have been the cause. The patient in case 2 came to the hospital with a sudden onset of parkinsonian movements that corresponded to viral damage to the dopaminergic substantia nigra.

The patient in case 1 required phenobarbital coma for seizure control, which has been previously reported in a patient with St Louis encephalitis.13 His second brain MR examination results were so strikingly symmetrically abnormal that there was initial concern as to how much of the abnormal areas of MR signal intensity was caused by hypoxia from status epilepticus and how much by viral encephalitis.

Head CT scans may be normal in patients with enzyme-linked immunosorbent assay results positive for WNV. There have been no reports of a specific abnormality at head CT in WNV encephalitides.2,3 Computed tomography may not be sensitive enough to demonstrate an abnormality, even when early encephalitis is clinically suspected. In hindsight, head CT results in case 2 demonstrated abnormalities that may have suggested involvement by WNV, which was unsuspected clinically.

In our institution, with more than 100 documented cases of WNV infection, the neuroimaging pattern we have discussed was present only in the most severe course of the infection. Whether this potential tropism of WNV for the substantia nigra will lead to an increase in postencephalitic parkinsonism in patients with or without clinical symptoms is unclear at this time.

There are few descriptions of neuroimaging findings in WNV encephalitis. The pattern of brain involvement we have discussed is rare and seems to mimic that of other Flaviviridae during a clinically severe course of this infectious agent.

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