ABSTRACT: Background: Patients infected with West Nile virus (WNV) may develop acute neurologic disease, which can be severe or even fatal, including WNV meningitis, encephalitis, and an irreversible acute flaccid paralysis or poliomyelitis-like syndrome. Movement disorders have also been described. Report: We report combined neuronal loss, gliosis, and neurofibrillary tangle formation in the substantia nigra of a 41-year-old man with a history of WNV encephalomyelitis and poliomyelitis-like paralysis. Conclusions: Clinically our patient did not display parkinsonism, however, it is interesting to speculate whether, in the absence of the residual subacute poliomyelitis-like syndrome, the neuropathologic findings could have eventually evolved clinically into WNV-associated post-encephalitic parkinsonism.

RÉSUMÉ: Encéphalomyélite due au virus du Nil occidental avec paralysie ressemblant à une poliomyélite et dégénérescence nigrale. Contexte : On peut observer une atteinte neurologique aiguë, parfois sévère et même fatale, chez les patients infectés par le virus du Nil occidental. Il peut s’agir d’une méningite ou d’une encéphalite avec paralysie flasque aiguë ou syndrome ressemblant à une poliomyélite irréversible. Des troubles du mouvement ont également été rapportés. Observation : Nous décrivons le cas d’un patient de 41 ans ayant une histoire d’encéphalomyélite et de paralysie ressemblant à une poliomyélite chez qui nous avons observé une perte neuronale combinée, une gliose et des amas neurofibrillaires dans la substance noire. Conclusions : Ce patient n’avait pas de manifestations cliniques de parkinsonisme. Cependant, on peut se demander si, en l’absence du syndrome résiduel subaigu ressemblant à une poliomyélite, cette atteinte neuropathologique aurait pu causer éventuellement un parkinsonisme post-encéphalitique associé au VNO chez ce patient.


West Nile virus (WNV) is a mosquito-borne RNA virus in the genus Flavivirus (family Flaviviridae), and a member of the Japanese encephalitis serological group which comprises eight virus species including Japanese encephalitis virus (JEV) and St. Louis encephalitis virus (SLEV), and two subtype viruses. Although most cases of WNV infection are subclinical or result in a mild, self-limited febrile illness known as West Nile fever, a minority of patients (<1%) develop acute neurologic disease, which can be severe and even fatal. West Nile virus meningitis and encephalitis are often associated with favorable outcomes, but when infection results in spinal anterior horn cell destruction it can cause an irreversible acute flaccid paralysis or poliomyelitis-like syndrome. Movement disorders including parkinsonism, tremor and myoclonus have also been described.

We present the clinical and neuropathologic findings in a patient who developed a poliomyelitis-like syndrome and was found at autopsy to have severe neuronal loss and gliosis in the spinal cord anterior horns with associated severe atrophy of the anterior nerve roots, as well as moderate neuronal loss and gliosis in the substantia nigra along with nigral neurofibrillary tangle formation.
CASE REPORT

A 41-year-old white male was admitted in late September 2002 with a two-week history of diffuse myalgias, fever, nausea, headache and photophobia. There was no recent history of rash, travel or insect bites, and past medical history was significant only for resection of a thymoma five years earlier. Physical examination revealed the following pertinent findings: a weak general appearance, temperature of 38.3°C, lungs clear to auscultation bilaterally but with weak inspiratory effort, a distended non-tender abdomen, motor deficits (power 2/5 in all four extremities) without sensory deficits, and reflexes 1/4 bilaterally in all four extremities except brachioradialis (2/4 bilaterally). An EMG was not performed.

Cerebrospinal fluid (CSF) was obtained by lumbar puncture, and cell count showed 1,400 white blood cells/ml with 80% neutrophils, a protein level of 140 mg/dL and glucose of 54 mg/dL. Cerebrospinal fluid was also sent to the Illinois Department of Public Health for serologic testing.

Empiric therapy was instituted with ceftriaxone, vancomycin and acyclovir. While awaiting the serology results, the patient’s mental status declined and his weakness progressed, and he was intubated for impending respiratory failure.

The WNV-specific IgM antibodies were detected in the cerebrospinal fluid (CSF) by enzyme-linked immunosorbent assay and the patient was diagnosed with poliomyelitis due to WNV infection; antimicrobial coverage was stopped. His respiratory status and strength slowly improved. However, long-term ventilatory support was still required and he was transferred to a rehabilitation facility at the end of October. In April 2003, he was briefly admitted because of gradual-onset dyspnea/increasing oxygen requirements and mucus plugging, in addition to chronic left lower lobe consolidation and pleural effusion, and he was treated presumptively for pneumonia. In May 2003, the patient died of hypoxic respiratory failure. A complete autopsy was performed.

At autopsy, external examination of the body was remarkable for marked muscular atrophy of the upper and lower extremities bilaterally and thenar wasting. Internal examination revealed residual thymoma (which was clinically inapparent), bibasilar congestion of the lungs and left lower lobe atelectasis, mild chronic bronchitis and marked mucostasis, and a staghorn calculus in the collecting system of the left kidney.

The femoral nerve showed no significant pathology, however the psoas muscle showed group atrophy and angular atrophic fibers, consistent with chronic and ongoing denervation atrophy. There were focal aggregates of lymphocytes but no myopathic alterations.

The fresh brain weighed 1,680 g. External examination showed flattening of gyri compatible with cerebral edema. Following formalin fixation, the brain was step-sectioned. The gray-white matter interface was indistinct, compatible with mild cerebral edema. Moderate pallor was noted in the substantia nigra and locus coeruleus. The anterior roots of the spinal cord demonstrated severe atrophy with myelin loss, and a few foamy macrophages containing PAS positive myelin debris, due to descending Wallerian degeneration [Figure 1].

Microscopically, rare subtle microglial nodules were seen in the caudate nucleus, thalamus, centrum semiovale, cerebellum, and brainstem. There was mild cerebellar Purkinje cell loss, and mild neuronal loss and gliosis in the hippocampus, neocortex, and locus coeruleus. In the substantia nigra, the neuronal loss and gliosis was moderate (estimated at ~50% neuronal loss compared to three age- and sex-matched controls) [Figure 2]. Cell loss was not apparent in the globus pallidus, subthalamic nucleus or nuclei basis pontis. There was mild to moderate white matter rarefaction in the centrum semiovale, corticospinal tracts in the pons and spinal cord, and dorsal columns. Neuronal loss and gliosis in spinal cord anterior horns was severe, and patchy perivascular lymphocytes and macrophages were present in spinal cord sections.

Rare neurofibrillary tangle formation was noted in the substantia nigra, and was confirmed by immunohistochemistry with AT8, an antibody to abnormally phosphorylated tau protein (Pierce-Endogen, Figure 2).
The substantia nigra. Almost one-half of patients from the 1917-1928 Spanish influenza pandemic developed ‘encephalitis lethargica,’ or parkinsonism with severe nigral cell loss, often during the post-encephalitic phase and sometimes years later. Post-encephalitic parkinsonism (PEP) has been described after infection with non-WNV flaviviruses, including JEV, SLEV, and rubella. In fact, a group of investigators has used JEV to induce a Parkinson’s disease model in rats, with the major resultant neuropathologic changes comprising neuronal loss and gliosis mainly confined to the substantia nigra pars compacta.

While it is not our intention to overemphasize our patient’s neurofibrillary tangle formation, a few aspects caused us to reflect on its possible significance in this setting. Neurofibrillary tangles (NFTs) are seen in normal aging, but our patient was relatively young (41-years-old). Moreover, in normal aging, NFTs are observed in the entorhinal cortex and hippocampus (not a feature of the present case), but are generally not seen in the substantia nigra. Neurofibrillary tangles in the substantia nigra are a well-known feature of severe Alzheimer disease (AD), progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis-parkinson dementia complex of Guam (ALS-PDC), and PEP. Unlike in AD, tangles in the midbrain of patients with PEP are not accompanied by deposition of β-amyloid. There are a number of similarities between PEP and PSP. Clinical similarities have caused speculation regarding a relationship between encephalitis lethargica and PSP. The same has been said for PEP and Guamanian ALS-PDC. Pathologic similarities between PEP and PSP include the distribution of neurofibrillary tangles and the absence of Lewy bodies and senile plaques.

In summary, we report for the first time combined neuronal loss, gliosis, and neurofibrillary tangle formation in the substantia nigra of a patient with a history of WNV infection. Perhaps because of residual subacute poliomyelitis-like syndrome, our patient did not display features of parkinsonism. However, it is interesting to speculate whether, in the absence of the residual subacute poliomyelitis-like syndrome, the neuropathologic findings (depletion of approximately one-half of the nigral neurons, and neurofibrillary tangles), could have eventually evolved clinically into WNV-associated post-encephalitic parkinsonism.

**REFERENCES**


