Acute Parkinsonism with West Nile Virus Infection

West Nile virus (WNV) is a mosquito-borne single-stranded RNA flavivirus related to Japanese encephalitis (JE) Murray valley and St. Louis encephalitis viruses. WNV is maintained in an enzootic transmission cycle between mosquitoes (usually *Culex*) and birds, although it occasionally infects human beings and horses as end hosts. WNV infection usually presents with systemic symptoms such as fever, fatigue, myalgia, rash, arthralgia, or headache. Less than 1% of WNV-infected patients develop neurological manifestations. However, this subgroup can develop severe neurological complications such as meningitis, encephalitis, ataxia, or movement disorders. Rarer presentations include Guillain-Barre syndrome (GBS) mimics, brachial plexitis, or acute pan dysautonomia. WNV produces sporadic outbreaks in India, and we have previously reported a cluster of WNV-associated acute flaccid paralysis (AFP) resembling poliomyelitis in Kerala.[1] We now report a case of WNV encephalitis from India with acute parkinsonism and impaired dopaminergic transmission, demonstrated with a ^{99m}Tc-TRODAT-1 SPECT scan.

A 76-year-old man presented to us with a history of low-grade fever and altered sensorium of 3 days duration. He had a past medical history of bronchial asthma, type 2 diabetes mellitus, and systemic hypertension. There was no history of cough, vomiting, or diarrhea. There was no past history of tremors or parkinsonism. He had been fully vaccinated for coronavirus disease 2019 (COVID-19). On examination, he was drowsy and had no focal neurological signs. He was

started on IV ceftriaxone, azithromycin, acyclovir, antipyretics, and supportive management. On day 2, he was intubated for airway protection. MRI brain showed FLAIR hyperintensities in the subcortical white matter of the left frontal lobe [Figure 1]. Restricted diffusion was observed in the dependent portions of the occipital horn of the lateral ventricles suggestive of ventriculitis. Lumbar puncture showed 420 cells (lymphocytes 97, monocytes 1), protein 191 mg/dl, and glucose 88 mg/dl. CSF meningoencephalitis PCR panel, GeneExpert for Mycobacterium tuberculosis, influenza, lyme, paraneoplastic neuronal antibodies, and GAD 65 antibody were negative. On day 5, he developed hypotension requiring noradrenaline and vasopressin infusions. His blood culture grew Staphylococcus epidermidis resistant to the MEC-A gene, and antibiotics were hiked to meropenem and teicoplanin.

On day 10, a neurological consult revealed a stuporous patient with severe generalized rigidity and generalized stimulus-sensitive myoclonus. He was started on 400/100 mg of levodopa/carbidopa per day. A repeat MRI showed the same restricted diffusion in the dependent portions of the occipital horn of the lateral ventricles. Because of worsening renal function and oliguria, he was initiated on hemodialysis. Repeat lumbar puncture on day 11 showed a decrease in the total white blood cell count to 107 cells (1 neutrophil, 99 lymphocytes) with protein 124 mg/dl and glucose 124 mg/dl. On day 17, serum West Nile IgM was positive [IgM capture enzyme-linked immunosorbent assay (ELISA), confirmed by micro-neutralization assay showing a high titer of neutralizing antibodies to WNV (titer: 40)].

In the 3rd week, ^{99m}Tc-TRODAT-1 SPECT showed significant dopaminergic transporter abnormalities in both putamens (right > left) with reduced dopaminergic transporter uptake in the left caudate nucleus. ^{18}FDG PET-CT scan showed global brain hypometabolism. He was tracheostomized and weaned off to a portable ventilator and transferred to rehabilitation. The dose of levodopa/carbidopa was increased to 500/125 mg. On day 60, his cognition had normalized and he could stand with support. However, he had mild residual bilateral upper > lower limb rest and intention tremors along with mild rigidity and bradykinesia.

Movement disorders and acute parkinsonism have been reported following viral infections with West Nile virus (WNV), SARS-CoV-2, influenza virus, Coxsackievirus, Powassan virus, Japanese encephalitis virus (JEV), St. Louis encephalitis virus, and human immunodeficiency virus (HIV). Neuro-invasive WNV infection can cause a variety of movement disorders, including tremor (rest tremor, postural tremor, or intention tremor), opsoclonus–myoclonus, parkinsonism, myoclonus, ataxia, and chorea.[2-4] In most cases, these movement disorders improve over time.[5] Myoclonus and parkinsonism can also occur together in WNV. Nevertheless, WNV neuro-invasive disease survivors often regain functional independence over the following years in spite of having severe disability at discharge.

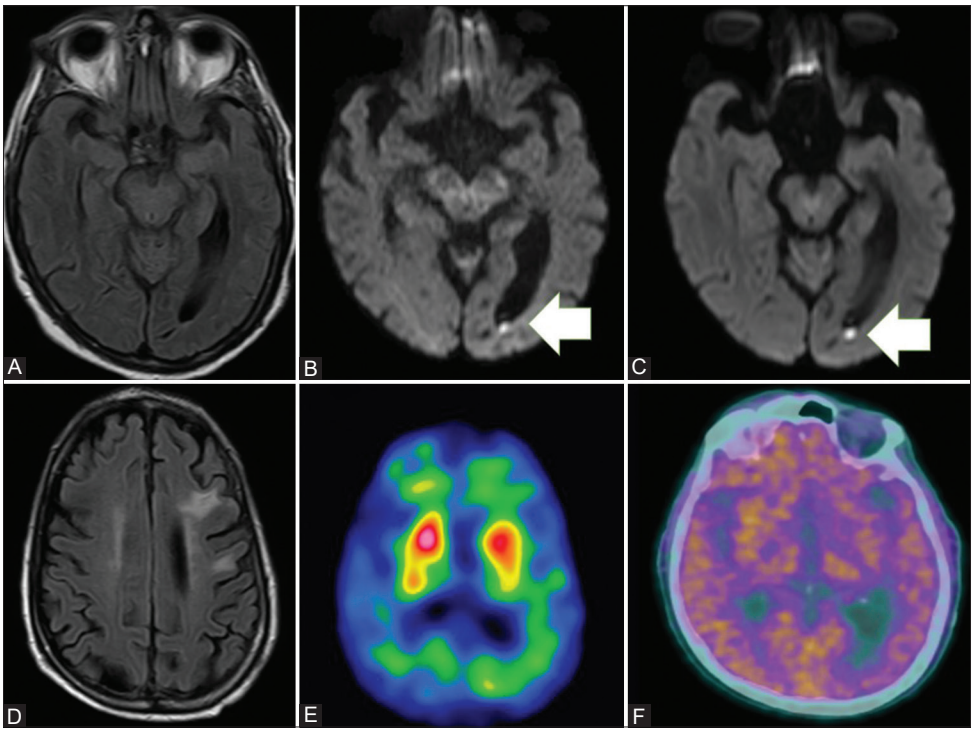

Figure 1: Panel A: FLAIR MRI image – normal on day 2. Panel B: DWMRI on day 2 shows restricted diffusion in the dependent portions of the occipital horn of the lateral ventricle. (White arrow) Panel C: DWMRI on day 10 shows persistent restricted diffusion in the left occipital horn of the lateral ventricle. (White arrow) Panel D: Stable old left sub-cortical white matter hyperintensities. Panel E: 99mTc-TRODAT SPECT scan – significantly reduced tracer uptake noted in both putamens (right > left). Mildly reduced tracer uptake in the left caudate nucleus. Panel F: 18FDG PET-CT image – diffusely reduced FDG uptake in both cerebral and cerebellar hemispheres, basal ganglia, and thalami

Therefore, aggressive treatment during the acute phase of WNV and intensive rehabilitation thereafter is justified. MRI in WNV is non-specific or can even be normal. Some cases show diffusion restriction or FLAIR hyperintensities in the white matter, lobar or deep-gray matter (basal ganglia, thalamus), brainstem, cerebellum, or leptomeningeal enhancement.[1] The cervical cord or spinal cord anterior horns can show T2 hyperintensities with contrast enhancement of the conus medullaris or cauda equina. Patients with polyradiculitis may demonstrate gadolinium contrast enhancement of the anterior roots. Intra-ventricular restricted diffusion (often the dependent portions of both occipital horns of the lateral ventricle) mimicking ventriculitis is a newly described finding of WNV infection.[6]

Technetium-99m-labeled tropane derivative, 99mTc-TRODAT-1, is a radioligand that binds selectively to dopamine transporters (DATs) in the brain. DAT is responsible for dopamine reuptake at the presynaptic membrane on the nigrostriatal dopaminergic projections, which extend from the substantia nigra pars compacta (SNc) in the midbrain to the dorsal striatum (caudate nucleus and putamen) in the forebrain. 99mTc-TRODAT-1 is a useful imaging modality for visualizing dopamine terminal innervation as it binds to DAT.

In the early stages of Parkinson's disease, nigrostriatal dopaminergic neurons are reduced. The putamen is affected earlier than the caudate nucleus, with the posterior putamen showing the greatest decrease in specific DAT binding. This is reflected by a lower presynaptic dopaminergic terminal density and reduced TRODAT uptake in the striatum.

Like JEV, WNV is capable of inducing dopaminergic neuron cell death by involving the SNc and its nigrostriatal dopaminergic projections. 99mTc-TRODAT-1 SPECT imaging has demonstrated positive findings (significantly decreased uptake in bilateral striata) in a case of JEV-induced parkinsonism.[7]

Previous reports of WNV-associated parkinsonism have demonstrated post-mortem nigrostriatal involvement. However, we were able to demonstrate nigrostriatal involvement, antemortem. WNV-induced dopaminergic nigrostriatal involvement was confirmed by 99mTc-TRODAT-1 SPECT imaging.[8]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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