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Short Report

Clinical Spectrum of West Nile Virus Neuroinvasive Disease

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Abstract

West Nile virus (WNV) is the most common arbovirus infection in the United States. The diagnosis requires consideration of not only a broad spectrum of presenting symptoms, ranging from a mild febrile illness to severe encephalitis and acute flaccid paralysis, but also public health risk factors and seasonality. There is no approved targeted therapy for WNV, so treatment relies on supportive care, management of neurologic sequelae and airway, treatment of other systems including the eye, and aggressive rehabilitation. Here, we describe a series of 3 cases of WNV encountered in September 2018 at one institution. First, we describe a case of WNV encephalitis with worsened dyskinesias and a relatively good recovery. Second, we describe a severe WNV encephalitis with overlying motor neuron involvement with a poor outcome. Finally, we describe a case of a WNV meningitis with significant bilateral chorioretinitis, an underappreciated complication of WNV infections. Through these cases, we review the epidemiology of WNV, risk factors for infection, the neurologic sequalae and long-term outcomes, and the importance of recognizing ocular involvement to prevent ophthalmologic complications.

Keywords

West Nile virus, meningitis, encephalitis, chorioretinitis

Introduction

West Nile virus (WNV) infection accounts for the vast majority of the arboviral disease burden in the United States.[1] Since its first description in the United States after an outbreak in New York City in 1999, WNV has continued to present both a diagnostic challenge for physicians and a public health concern.[2] It is therefore essential for neurologists to be familiar with the epidemiology, seasonality, wide spectrum of manifestations, complications, and prognosis of the disease. Here, we present 3 cases encountered at our institution during September 2018. Institutional review board was consulted, and review and approval were deemed not necessary. These cases show a range of presenting symptoms, clinical courses, and sequelae.

Case 1

A 73-year-old male with long-standing mild cognitive impairment and parkinsonism (on rasagiline) presented with 2 days of fever (Tmax on admission 101.9°F), fatigue, weakness, and drifting to the left when walking. He was diagnosed with parkinsonism (suspected Lewy body dementia) or Parkinson disease 1 year prior to presentation based on a history of falls, a mild tremor, and a positive dopamine transporter protein scan. His examination during hospitalization was notable for both his baseline resting tremor, and high amplitude, postural tremors of the head, neck, and bilateral upper extremities, which were different from baseline. No maculopapular rash was observed. His course was complicated by decreasing verbal output and inability to follow commands. A magnetic resonance imaging (MRI) of the brain with contrast showed chronic white matter disease. Electroencephalogram (EEG) showed generalized delta slowing without seizures. Initial lumbar puncture (LP) showed cell count 550 cells/μL (76% neutrophils, 16% lymphocytes, and 8% monocytes; see Table 1), protein 91 mg/dL, and glucose 108 mg/dL. He was started on antibiotics and acyclovir for presumed infectious meningitis. His laboratory work showed serum Lyme testing immunoglobulin M (IgM) negative/IgG positive, C-reactive protein (CRP) 106.4 mg/L, erythrocyte sedimentation rate (ESR) 21 mm/h, and negative cerebrospinal fluid (CSF)

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Table 1. Cerebral Spinal Fluid Analysis Results.

	Case 1 (Day 1)	Case 1 (Day 6)	Case 2 (Day 1)	Case 2 (Day 4)	Case 3
Nucleated cells, cells/μL	550	5	768	123	18
Neutrophils, %	76	2	69	0	20
Lymphocytes, %	16	57	17	89	68
Monocytes, %	8	2	7	9	12
Protein, mg/dL	108	57	138	82	108
Glucose, mg/dL	90.6	97	75	70	58
Red blood cells, cells/μL	10	162	171	139	7
CSF WNV IgM index ELISA	>5		-		-
CSF WNV PCR	Negative		Negative		Negative

Abbreviations: CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; IgM, immunoglobulin M; PCR, polymerase chain reaction; WNV, West Nile virus.

cultures. On day 3, he was intubated due to worsening mental status, hypoxia, and tachycardia. Repeat CSF on day 6 showed a cell count of 5 cells/μL (2% neutrophils, 57% lymphocytes, and 2% monocytes; see Table 1). His CSF WNV IgM index via enzyme-linked immunosorbent assay (ELISA; sent to Quest Diagnostics, Chantilly, Virginia, USA using the WNV IgM Capture DxSelect ELISA kit from DiaSorin, formerly Focus Diagnostics, Saluggia, Italy) returned >5 (IgG <1.3) and CSF WNV polymerase chain reaction (PCR) returned negative. Given the CSF pleocytosis with a shift toward lymphotic predominance and the positive serology without clear confirmatory testing, he was diagnosed with probable neuroinvasive WNV disease. With supportive treatment, he had improvement in his mental status, was extubated on day 13, and discharged on day 18 to a rehabilitation hospital. He was seen in clinic 24 days after discharge. He was fully orientated, had fluent speech, intact attention, and only mild memory impairment. He had a mild right-sided rest tremor, left upper extremity bradykinesia with fine finger movements, and mild left-sided upper extremity ataxia, with an ataxic gait.

Case 2

A 56-year-old male with a history of hypertension presented with 3 days of fever (Tmax 101.8°F), fatigue, headache, and confusion (answering questions inappropriately and speaking nonsensically). On examination, he was somnolent, oriented to person and place, able to move all his extremities spontaneously, but could only follow 1-step commands. No rash was observed. Magnetic resonance imaging of the brain with contrast was normal. Initial LP showed cell count of 768 cells/μL (69% neutrophils, 17% lymphocytes, and 7% monocytes; see Table 1), protein 138 mg/dL, and glucose 75 mg/dL. The EEG showed delta slowing without seizures. On day 3, he developed worsening tachypnea due to pulmonary edema and declining mental status prompting transfer to the intensive care unit. Repeat LP on day 4 showed cell count 123/μL (0% neutrophils, 89% lymphocytes, and 9% monocytes; see Table 1), protein 82 mg/dL, and glucose 70 mg/dL. His serum WNV IgM returned positive via ELISA and confirmed via plaque reduction neutralizing tests with negative Eastern Equine Encephalitis IgM ELISA; CSF WNV PCR returned negative. Given the clinical and CSF evidence of meningoencephalitis with a shift toward a lymphocytic predominance in the CSF and confirmatory IgM antibodies with neutralizing antibodies, he was diagnosed with confirmed neuroinvasive WNV disease. His course was complicated by severe widespread muscle and diaphragmatic weakness, and he underwent tracheostomy and gastrostomy tube placement. Toward the end of his acute hospitalization, his examination showed reduced tone and absent reflexes (aside from a trace right biceps) in all extremities, trace proximal and 2/5 distal upper extremity strength, and only trace hip flexion bilaterally. An MRI of the cervical spine with contrast only showed multilevel degenerative changes without spinal stenosis, cord signal, or abnormal enhancement. Electromyogram (EMG) at day 23 showed markedly reduced compound muscle action potentials with normal distal latency and conduction velocities, fibrillation potentials, and positive sharp waves in all muscles tested. By day 25, he had improved mental status but had reduced tone in all extremities with 2/5 weakness in all extremities, most severe in shoulder abduction and hip flexion. While at rehab, nearly 2 months postdischarge, the patient's examination was notable for normal tone and reflexes (aside from 1+ at the Achilles tendon bilaterally) in all extremities and at least 3/5 strength in all muscle groups aside from the left deltoid.

Case 3

A 60-year-old male without past medical history presented with 5 days of fever (Tmax 102°F), chills, myalgias, nausea, vomiting, diarrhea, and a moderate right-sided throbbing headache. On day 2, he developed visual abnormalities described as "hundreds of moving black spots," which first affected his right eye, then progressed to his left eye.

On admission, he reported bilateral blurred vision. No maculopapular rash was observed. Neurologic examination was notable for inability to tandem walk. Magnetic resonance imaging of the brain and orbit with contrast was normal.

Figure 1. Color fundus photo of the right eye showing mild media opacity due to vitreous inflammation and multiple round chorioretinal lesions in a curvilinear pattern (black arrows).

Blood work showed no antibodies for Lyme disease, ESR 10 mm/h, CRP 24.8 mg/L; LP showed CSF cell count 18 cells/μL (18% neutrophils, 68% lymphocytes, and 12% monocytes; see Table 1), protein 108 mg/dL, and glucose 58 mg/dL. Ophthalmologic examination was notable for best-corrected visual acuity (BCVA) of 20/100 in each eye, normal intraocular pressures, bilateral inflammatory cells in the anterior chamber, bilateral vitreous inflammation, and multiple round chorioretinal lesions in a curvilinear pattern predominantly affecting the nasal retina in the right eye more than the left eye (Figure 1). Fluorescein angiography confirmed these lesions to be "target" lesions, characteristic of WNV chorioretinitis (Figure 2). Serum WNV IgM index was 4.77 and IgG index was 2.85 via ELISA (sent to Quest Diagnostics, as in case 1). The CSF WNV PCR returned negative. Given the clinical and serologic findings, without known confirmatory testing, he was diagnosed with probable neuroinvasive WNV disease. He was started on prednisolone acetate and atropine eye drops, and at follow-up 18 days postdischarge, his BCVA improved to 20/40 OD and 20/25 OS.

Discussion

The Centers for Disease Control and Prevention (CDC) reported nearly 2300 cases of non-neuroinvasive and neuroinvasive arboviral disease during 2017 across the 48 continental states and Washington DC, over 90% of which was represented by non-neuroinvasive and neuroinvasive WNV.[1] West Nile virus is predominantly diagnosed in the summer months of July to September, although cases have been reported year-round. Although the number of WNV cases had remained relatively stable since 2012, there was an uptick in 2018 (2544 in 2018; 2097 in 2017), when Massachusetts reported

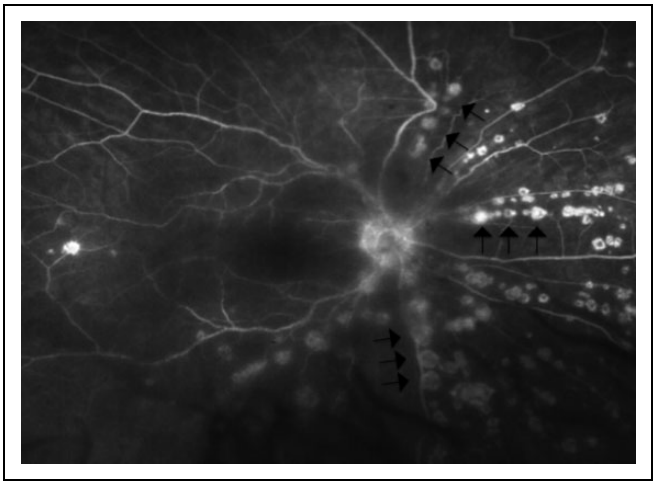

Figure 2. Fluorescein angiogram of the right eye showing multiple "target" lesions with hypofluorescent centers and hyperfluorescent edges (black arrows).

the highest number of neuroinvasive WNV in 2018 (42) since the CDC began collecting data through ArboNET in 1999.[3]

It is estimated that 10% of patients infected with WNV are symptomatic, and of that subset, 10% present with neuroinvasive disease, which includes encephalitis (50%), meningitis (37%), and acute flaccid paralysis (AFP; 6%).[1] The greatest risk factors for acquiring WNV meningoencephalitis include age (>50), diabetes, and immunosuppression.[4] Genetic variants have also been found to influence risk of WNV infection.[5] Cases of WNV meningoencephalitis have also been described after organ transplantation.[6] Clinically, the diagnosis of WNV relies on serology, specifically IgM, as the replication in the CSF is only present for 2 to 3 days before becoming undetectable through PCR, as seen in our patients. Because of this, CSF WNV PCR may often be negative, although in patients with immunosuppression, PCR may remain positive while serologies are negative.[7] In the early stage of the disease, the CSF differential may be neutrophilic or mixed before becoming lymphocytic predominant.[8] Although none of our patients were found to have a rash, a maculopapular rash may also be seen on examination. In addition, all of our patients exhibited normal MRI of the brain. However, it is important to recognize a spectrum of MRI brain findings in WNV meningoencephalitis, most commonly deep gray matter and brain stem involvement (Figure 3).[9] Epidemiological risk factors for WNV infection revolve around exposure to mosquitoes; in association with mosquito life cycle, one study found that the most significant risk factor for an epidemic is warmer than expected weather in January.[10]

In case 1, our patient was diagnosed with WNV meningoencephalitis, complicated by new dyskinesias, but went on to have good cognitive recovery with only residual parkinsonism on examination (2+ right-sided rest tremor, 2+ left-sided distal bradykinesia). In this case, it was difficult to differentiate between worsening parkinsonism in the setting of acute

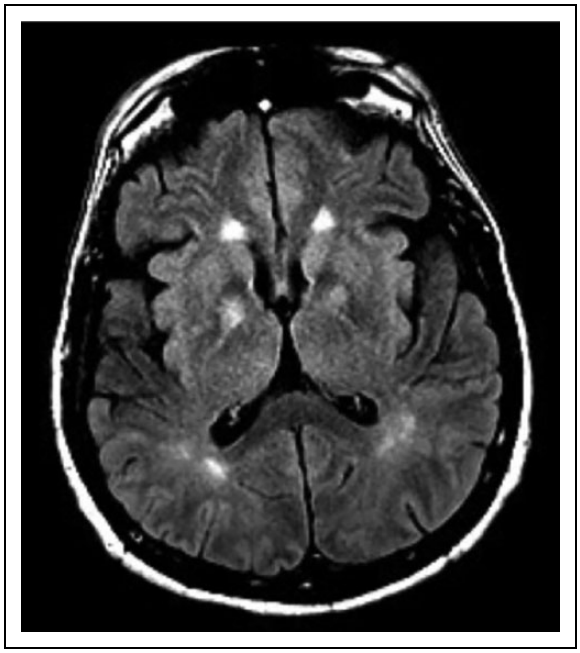

Figure 3. Magnetic resonance imaging (MRI) of the brain T2-Flair sequence of a patient with neuroinvasive West Nile virus (WNV) showing T2-FLAIR hyperintensities of the bilateral globus pallidi. (Courtesy of Dr Shibani Mukerji—MGH Prospective Encephalitis and Meningitis Study [PEMS] cohort).

illness and WNV-related deep nuclei involvement (there was no radiographic evidence on MRI). In a cohort of 16 patients with WNV infection from Louisiana who were followed for repeat neurologic evaluation, 15 patients had evidence of a dyskinesia (tremor, myoclonus, parkinsonism). Interestingly, the tremors were either static or kinetic, but none were rest tremors.[11] Eleven of 16 patients showed signs of parkinsonism, particularly rigidity and bradykinesia, which may reflect the known propensity of the virus to affect the deep nuclei, although many patients with tremor had negative MRI findings. One in vitro study of Parkinson therapies showed that amantadine significantly reduced WNV RNA replication, raising interest in exploring this class of medications as potential therapeutics for WNV.[12]

In case 2, we observed a younger male with WNV meningoencephalitis whose course was complicated by severe and diffuse weakness and a significantly prolonged rehabilitation. His EMG findings were consistent with an AFP, as can be seen in WNV.[4] Studies evaluating long-term outcomes can be difficult to interpret based on differing definitions of recovery. In a prospective study from Louisiana, 5 of 7 patients with severe meningoencephalitis were able to achieve their prior level of functioning at 8 months.[11] In a cohort of 157 patients, 62% had neuroinvasive disease and 40% were reporting symptoms such as fatigue, weakness, depression, and pain, up to 8 years after infection.[13] In a cohort of 35 patients, 19 (54%) were diagnosed with WNV meningoencephalitis; 6 (31.6%) of these patients achieved full recovery at 12 months.[14] The number of patients reporting residual symptoms after WNV seemed to plateau after approximately 2 years.[13] Those with WNV meningitis typically have excellent recovery. Those with AFP will likely have minimal to no improvement in motor function of the affected limb.[11] In terms of mortality, one study following a Colorado cohort from 2003 found a delayed mortality up to 3 years after hospitalization, with a 1-year mortality of 4% and a 4-year mortality of 12%.[15]

In case 3, we observed a patient with meningitis, complicated by bilateral multifocal chorioretinitis with remarkable recovery in the following weeks. In a case series of 29 patients, investigators found that when WNV affects the eye, it most commonly presents as a multifocal chorioretinitis. These lesions, frequently referred to as "target" lesions, typically cluster in a linear pattern parallel to the vessels; nearly half of this cohort had over 50 identifiable lesions. Other features include retinal hemorrhages and white-centered hemorrhages.[16] A prospective cohort study of 111 patients found that 27 (24%) had evidence of WNV retinopathy; however, in those patients with WNV meningoencephalitis, this percentage rose to nearly 50%. Patients with WNV retinopathy had similar long-term visual acuity outcomes compared to those without WNV retinopathy; however, as was noted in case 3, visual acuity can be limited by the ocular inflammation in the acute setting and thus should be treated to prevent sequela of persistent ocular inflammation such as posterior synechiae, cataracts, and cystoid macular edema. Although the ophthalmological findings can be striking, the diagnosis of WNV retinopathy may be easily missed, especially in patients who present with meningoencephalitis and who are unable to verbalize their visual symptoms.

In pursuing a workup for a meningoencephalitis, AFP, or chorioretinitis, a broad differential should be considered. For meningoencephalitis, testing will hinge upon the CSF differential, protein, and glucose but will likely include diseases from 3 main categories: infectious (including herpes simplex virus [HSV], varicella zoster virus [VZV], other flaviviruses, Lyme disease, ehrlichiosis, and listeria), inflammatory (systemic lupus erythematous, Sjögren syndrome, Hashimoto encephalitis, and primary central nervous system vasculitis), and neoplastic (leptomeningeal disease). Laboratory work should include but is not limited to CSF HSV PCR, CSF VZV PCR, serum VZV IgM and IgG, CSF enterovirus PCR, and autoimmune markers (antinuclear antibody, double-stranded DNA antibodies, anti-Ro/La antibodies). When evaluating AFP, greater consideration should be given to spinal cord, neuromuscular junction, and peripheral pathologies. The differential diagnosis includes but is not limited to poliomyelitis, botulism, Guillain-Barre syndrome, transverse myelitis, myasthenia gravis, and critical illness polyneuromyopathy. In this setting, MRI with contrast of the corresponding spinal segments and EMG should be strongly considered. For a chorioretinitis, one should further broaden their differential for a meningoencephalitis by including cytomegalovirus, HIV, rheumatoid arthritis, inflammatory bowel disease, and

sarcoidosis. An ophthalmology consultation is necessary, especially to consider additional testing including fluorescein angiography, optical coherence tomography, and a B-scan ocular ultrasound.[17]

The diagnosis of WNV is challenging as it requires knowledge of geographic and seasonal preponderance, as well as a wide range of clinical manifestations, including neurologic and ophthalmologic complications. The management hinges on early recognition, supportive care with particular attention to airway protection in those with severe meningoencephalitis, and careful prognostication and counseling for patients.

Declaration of Conflicting Interests

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