An Unusual Case of Descending Paralysis Caused by West Nile Virus

Clinicians should consider a diagnosis of West Nile Virus in patients with acute flaccid paralysis, particularly those who come from areas where WNV is endemic.

BY CRAIG R. GROSSMAN MD, ALEXANDRA WALCZYSZYN MD, STEVEN MANDEL MD, DIALECTI VOUDOURIS, MD, LYNN RATNER, MD, NICKY BHATIA, AND SOUHEIL SAMAHA, MD

West Nile Virus (WNV) is a predominantly mosquito-borne illness that typically presents with a flu-like syndrome. A small percentage of patients can have more severe disease, manifesting as one of three presentations: acute flaccid paralysis, encephalitis, or meningitis. Ahead, we present an atypical case of neuroinvasive WNV infection distinguished by descending paralysis, which complicates the diagnosis.

CASE REPORT

A 51-year old female from New York City presented to the emergency department in September 2014 with complaints of fever, nausea, weakness, dizziness, difficulty ambulating, and visual disturbance, two weeks after chemotherapy for stage 2 gastric lymphoma that had been resected one month prior to admission.

In the emergency department, the patient was found to have low-grade fevers and orthostatic hypotension. Her review of systems was significant for blurred vision and headaches. Physical exam was unremarkable and no muscle weakness or respiratory distress was noted.

Shortly after admission, the patient developed fevers to 106.1F and tachycardia. Search for infectious etiology of symptoms was pursued, however no source was evident and fever of unknown origin work-up was initiated. There was no suggestion of any recent infection, though diagnostic studies were positive for H. pylori, and the patient did recall having sustained a bug bite in the weeks preceding admission.

On the third day of hospitalization, the patient developed dysarthria. MRI of the head at that time showed suspicion

for cerebellar stroke, but no other abnormalities. Supportive care and broad-spectrum antibiotics were initiated. The patient developed slurred speech, lethargy, and right upper extremity weakness over the next couple of days, which progressed to bilateral upper extremity weakness, and then quadriplegia. On the eighth day, the patient was noted to be severely lethargic with respiratory distress and hypotension, requiring emergent intubation and transfer to the ICU. At this juncture, which represents a nadir in the patient's clinical course, she exhibited no response to noxious stimuli, and no eye tracking, off sedation.

The patient was started on IVIG for presumed Guillain-Barre vs Bickerstaff encephalitis, while antibodies were pending. Initially, GQ1B IgG was borderline positive, suggesting a Guillain-Barre-like syndrome. (Repeat investigation, however, was negative.) The patient underwent three IVIG courses in total.

Lumbar puncture was initially negative for all studies. EEG showed generalized slowing but no epileptiform activity.

As the patient required mechanical ventilation for a period exceeding two weeks, a tracheostomy was placed, as well as a percutaneous endoscopic gastrostomy to facilitate feeding.

The patient gradually began to regain some motor function. EMG studies were performed on hospital day 44 and 74, and showed severely reduced median > ulnar motor amplitudes bilaterally with mildly diminished velocities. Right and left median, ulnar and radial sensory responses were intact. Left peroneal motor amplitude was severely reduced, left tibial motor amplitude was relatively normal. There was diffuse acute/active denervation with 1-2+ fibrillations seen at all
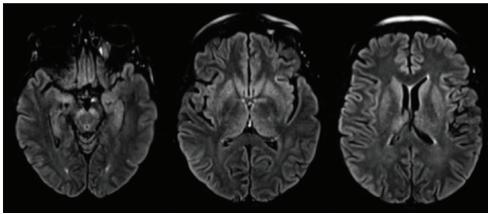
Figure 1: MRI of brain with intravenous gadolinium contrast, hospital day 8. Subtle T2 and flair symmetric hyperintensities in the bilateral basal ganglia, thalami, substantia nigra/cortical spinal tracts as well as mild patchy areas within the pons and medulla. No evidence of abnormal enhancement. No evidence of associated diffusion abnormality.

muscles tested of right upper and lower limbs proximal and distal (needle EMG not tolerated on left owing to severe pain). The overall impression from EMG testing was of a severe, acute, fairly symmetric motor axonopathy affecting lower and upper limbs.

Eventually, serum and CSF antibodies came back positive for West Nile Virus (see Table 1).

The patient continued to make gradual improvements in motor functioning, allowing for discharge to a rehabilitation facility after a 64-day hospital course. At the time of this writing, she was able to speak slowly, and was ambulatory with assistance.

DISCUSSION

West Nile Virus is a flavivirus first identified in Africa in the 1930s with the main route of transmission to humans via a Culex mosquito bite. It first appeared in the western hemisphere in 1999 and is now considered endemic to the US.[1] There are five lineages of WNV, with the most clinically important neuropathogen in lineage 1, clade 1a. Lineage 1, clade 1b and lineage 2 cause mostly self-limiting illnesses and the other lineages are even less well characterized in the literature.[2] Since the other forms are mostly self-limited viral disease states, it is important to discuss the more pathologic states that can result from infection with WNV. Approximately one percent of those infected with WNV go on to develop neurologic manifestations. These manifestations include meningitis, encephalitis, and acute flaccid paralysis

TABLE 1. AUTOIMMUNE AND INFECTIVE WORKUP			
Hospital day	Test	Result	Ref
3	Cryptococcal Ag level	Negative	Negative
3	EBV VCA IgM	Negative	Negative
3	EBV VCA IgG	Positive	Negative
3	EBNA Ab	Positive	Negative
3	IgG	684	694-1618
3	Parvovirus B19 Ab IgG	2.98	<0.9
3	Parvovirus B19 Ab IgM	0.07	<0.9
4	Urine - Legionella Ag	Negative	Negative
4	CMV DNA	Undetectable	Undetectable
5	Cocci Complement F	Negative	Negative
6	Cryptococcus AG Screen, Serum	Negative	Negative
7	RPR	Non-reactive	Non-reactive
7	Histoplasma Ab Screen, Serum	Negative	Negative
8	Blastomyces Ab, EIA, Serum	Negative	Negative
8	GQ1B IgG Antibody ELISA	1:100	<1:100
9	CSF - Epstein-Barr virus	Negative	Negative
9	CSF - Cryptococcal Ag screen	Negative	Negative
9	CSF- Varicella Zoster Virus	Negative	Negative
9	CSF - Protein 1433	<1.0	<1.5
9	CSF, CF - Coxsackie, Entovirus	Negative	Negative
9	CSF - VDRL	Negative	Negative
9	CSF – CMV	Negative	Negative
9	CSF - Bartonella PCR	Negative	Negative
9	HIV	Negative	Negative
9	LYME	Negative	Negative
9	CSF - Viral culture	Negative	Negative
9	IgG 1	1210	341-894
9	West Nile Ab IgG	Negative	Negative
10	IgG 2	665	171-632
10	West Nile Ab IgM	Negative	Negative
11	IgG 3	100	18.4-106
12	Aspergillus Ag, BAL	<0.500	<0.5
12	IgG 4	21.4	2.4-121
13	Mycoplasma Pneumoniae	Negative	Negative
13	CDiff PCR	Negative	Negative
13	Fungitell, BAL	>500pg/mL	<45pg/mL

TABLE 1. AUTOIMMUNE AND INFECTIVE WORKUP (CONT.)			
Hospital day	Test	Result	Ref
13	Legionella, BAL	Negative	Negative
13	Total IgG	2060	767-1590
14	T. Whipplei PCR	Negative	Negative
14	Bart Henselae IgG	<1:128	<1:128
14	Bart Henselae IgM	<1.20	<1.20
15	Bart Quintana IgG	<1:128	<1:128
16	Bart Quintana IgM	<1:20	<1.20
16	H pylori Ab IgG	85.2	<20
23	URine - LEgionella Ag	Negative	Negative
23	CDiff PCR	Negative	Negative
24	CMV DNA	Negative	Negative
25	GQ1B IgG Antibody ELISA	<1:100	<1:100
34	West Nile Ab IgM, CSF	4.46	<0.90
36	West Nile Ab IgG, CSF	1.39	<1.30
42	West Nile Ab IgG, Serum	Positive	Negative
42	West Nile Ab IgM, Serum	Positive	Negative

(AFP).[3] We present the only reported case of WNV in Manhattan in 2014 causing neuroinvasive symptoms.

West Nile Virus infects approximately one and a half million people in the US.[3] Of those infected, one in 140 individuals go on to develop neuroinvasive WNV infection, most commonly a nonspecific encephalitis. An even smaller percentage of patients develop AFP.[2] According to the CDC, risk factors for developing WNV neuroinvasive disease include older age, male sex, hypertension, and diabetes.[4] Both those with history of malignancy and subsequent chemotherapy as well as solid organ transplant recipients have been shown to have increased risk of neuroinvasive disease.[5]

Most of those infected with WNV are asymptomatic, however, those who develop symptoms most commonly present with fever, called West Nile Fever, which is indistinguishable from other viral syndromes. In addition to meningitis and encephalitis, neurologically WNV can cause AFP with many patterns of involvement ranging from monoplegia to quadriplegia, occasionally involving the brainstem, resulting in respiratory failure. Sensation is usually spared, however bowel and bladder function can be involved. Even rarer, some presentations include polyradiculitis, a Guillain-Barre like syndrome (GBS), brachial plexitis or dysautonomia secondary to involvement of the sympathetic neurons. Recovery from neurologic involvement,

especially AFP, is usually incomplete.[2] The case we present shows a descending flaccid paralysis, first involving the upper extremities and eventually resulting in quadriplegia and respiratory failure.

If suspicious for WNV, a serum WNV IgM antibody should be sent. This may not be detected early in the disease course or in those with only WNV fever. Seroconversion of the IgM antibody usually occurs four to 10 days after symptom onset.[9] CSF studies are critical in determining if neurologic symptoms are due to WNV versus other etiologies. In patients with WNV involving the CNS, the CSF usually has an elevated protein and lymphocytic predominance, except in early infections when neutrophils may predominate. Cytology may show plasmacytoid lymphocytes or large monocytic cells which may resemble Mollaret cells.[8] WNV IgM should also be sent from the CSF but it is important to note that IgM antibodies may persist for up to six months or longer.[10] Our patient initially had negative serum WNV antibodies, which on repeat testing several weeks later were positive in both the serum and CSF consistent with the pattern described above.

Neuroimaging studies may help clinicians in raising suspicion for WNV encephalitis. MRI is often used, however, the findings are not necessarily diagnostic, and even in cases of severe encephalitis, the MRI may be normal. Like the antibodies, abnormal imaging findings may not be apparent until several weeks after the onset of illness. In those with positive MRI findings, the most common characteristics are bilateral signal abnormalities located in the basal ganglia, thalami, brain stem, ventral horns and spinal cord. These findings are nonspecific and may be seen in other forms of encephalitis.[11,12] EEG studies may show generalized slowing and triphasic sharp waves, with prominence over the anterior regions. This finding also is nonspecific, but it has been suggested that any patient with encephalitis and an EEG showing anterior slowing should have WNV included on their differential.[11,13] Our patient had subtle T2 and FLAIR symmetric hyperintensities in the bilateral basal ganglia, thalami, substantia nigra and cortical spinal tracts. The EEG study was consistent with diffuse encephalopathy.

Impaired immunity, as seen in our case, may play a role in certain populations becoming symptomatic from WNV. For instance, Honig and Karussis presented a case of delayed-onset flaccid paralysis likely secondary to WNV reactivation following treatment with rituximab. They propose that the virus can be reactivated due to a delayed autoimmune process induced by recovering humoral
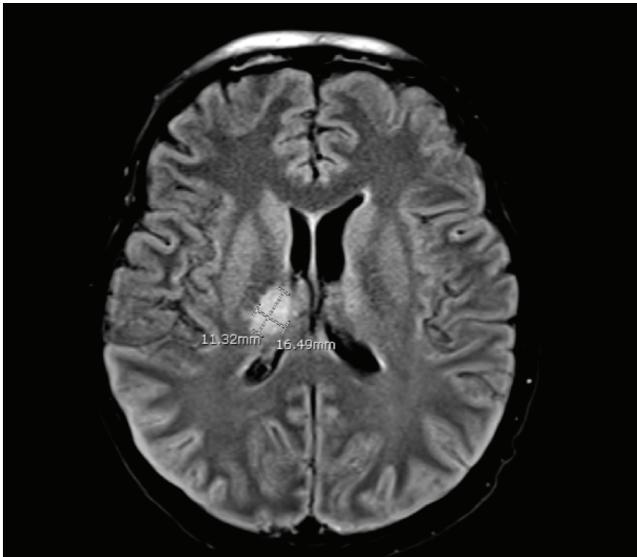
Figure 2: MRI of brain with intravenous gadolinium contrast, hospital day 13. Interval appearance of abnormal T2 and flair signal hyperintensity in the right thalamus. Subtle enlargement of the right thalamus. There has been also a smaller patchy area of T2 and flair signal hyperintensity in the left thalamus. Again noted are T2 and flair symmetric hyperintensities in the bilateral basal ganglia , thalami, substantia nigra/cortical spinal tracts as well as subtle patchy areas within the pons and medulla. There are abnormal mild patchy T2 and flair signal hyperintensities in the mesial temporal lobes similar to the prior study. There has been interval increased diffusion hyperintensity seen in the bilateral thalami, right greater than left.

immunity after being treated with the monoclonal antibody. A chronic infection or delayed neuroinvasion could explain the delayed WNV-poliomyelitis. Given that they found that WNV-ribonucleic acid may be detected in the urine of patients up to seven years following infection helps support this point. Despite the presence of the RNA in the urine, growth from these isolates was never obtained.[6] An additional hypothesis for the polyneuropathy seen in their patients include Acute Inflammatory Demyelinating Polyneuropathy (AIDP) related to the treatment with rituximab itself. Astor, et al. also presented a case of neuroinvasive WNV in a patient who received a solid organ transplant and was subsequently placed on rituximab therapy for organ rejection.[7] Our patient had received rituximab therapy for treatment of gastric lymphoma, with the most recent treatment two weeks prior to her presentation. Although the occurrence of the infection cannot with certainty be as a result of the treatment, the link between our case and the others in the literature is important to note.

There is no definitive treatment for WNV and supportive care is the mainstay of therapy.

Encephalitis caused by WNV has high morbidity, which may stem from inflammation caused by the disease process. Sirvastava, et al. studied the use of IVIG to treat the inflammatory effects causing encephalitis in patients with WNV. They found that "IVIG and pooled human WNV convalescent sera (WNV-IVIG) inhibited development of lethal WNE by suppressing CNS infiltration by CD45high leukocytes. Pathogenic Ly6Chigh CD11b+ monocytes were the major infiltrating subset in the CNS of infected control mice, whereas IVIG profoundly reduced infiltration of these pathogenic Ly6Chigh monocytes into the CNS of infected mice."[14]

Dampening the effect the virus may have on the nervous system is key to recovery. Our patient received both IVIG and plasmapheresis with notable clinical improvement and partial neurological recovery, which is still ongoing.

CONCLUSION

Despite having no known specific treatment currently available, and vaccines only in phase 1 clinical trials, clinicians must keep WNV on their differentials especially in those with recent mosquito exposure or in those who are immunocompromised in order to reach a correct diagnosis. Supportive therapy and IVIG can dampen the burden the virus takes on the body—especially the neurologic system—and can help patients begin their road to recovery. Any patient with a broad range of neurologic symptoms, including AFP, with no known cause could benefit from a workup for WNV. ■

1. Wilson, Carey A., and James F. Bale. "West Nile Virus Infections in Children." Current Infectious Disease Reports 16.3 (2014): 391.

2. Varkey Maramattom, Boby, et al. "Acute Flaccid Paralysis Due to West Nile Virus Infection in Adults: A Paradigm Shift Entity." Annals Indian Academy of Neurology 17.1 (2014): 85-88.

3. Mainali, Shraddha, Mansoor Afshani, James B. Wood, and Michael C. Levin. "The Natural History of West Nile Virus Infection Presenting with West Nile Virus Meningoencephalitis in a Man with a Prolonged Illness: A Case Report." Journal of Medical Case Reports 5.1 (2011): 204.

4. Risk Factors for West Nile Virus Neuroinvasive Disease, California, 2005 - Volume 13, Number 12-December 2007 - Emerging Infectious Disease Journal - CDC. http://wwwnc.cdc.gov/eid/article/13/12/06-1265_article. 17 May. 2015.

5. Patnaik JL, Harmon H, Vogt RL. Follow-up of 2003 Human West Nile Virus Infections, Denver, Colorado. Emerging Infectious Diseases. 2006;12(7):1129-1131. doi:10.3201/eid1207.051399.

6. Honig A, Karussis D. Delayed-onset flaccid paralysis related to west Nile virus reactivation following treatment with rituximab: a case report. BMC Research Notes. 2014;7:852. doi:10.1186/1756-0500-7-852.

7. Astor TL, Weill D, Cool C, Teitelbaum I, Schwarz MI, Zamora MR. Pulmonary capillaritis in lung transplant recipients: treatment and effect on allograft function. J Heart Lung Transplant. 2005;24:2091.

8. Procop GW, Yen-Lieberman B, Prayson RA, Gordon SM. Mollaret-like Cells in Patients with West Nile Virus Infection. Emerging Infectious Diseases. 2004;10(4):753-754. doi:10.3201/eid1004.030783.

9. Prince HE, Tobler LH, Lapé-Nixon M, Foster GA, Stramer SL, Busch MP. Development and Persistence of West Nile Virus-Specific Immunoglobulin M (IgM), IgA, and IgG in Viremic Blood Donors. Journal of Clinical Microbiology. 2005;43(9):4316-4320. doi:10.1128/JCM.43.9.4316-4320.2005.

10. Roehrig JT, Nash D, Maldin B, et al. Persistence of Virus-Reactive Serum Immunoglobulin M Antibody in Confirmed West Nile Virus Encephalitis Cases.Emerging Infectious Diseases. 2003;9(3):376-379. doi:10.3201/eid0903.020531.

11. Sejvar JJ. Clinical Manifestations and Outcomes of West Nile Virus Infection.Viruses. 2014;6(2):606-623. doi:10.3390/v6020606.

12. Rossi SL, Ross TM, Evans JD. West Nile Virus. Clinics in laboratory medicine. 2010;30(1):47-65. doi:10.1016/j.cll.2009.10.006.

13. Gandelman-Marton R, Kimiagar I, Itzhaki A, et al. Electroencephalography findings in adult patients with West Nile virus-associated meningitis and meningoencephalitis. Clin Infect Dis 2003; 37:1573.

14. Srivastava, R., C. Ramakrishna, and E. Cantin. "The Anti-inflammatory Activity of IVIG Protects against West Nile Virus Encephalitis." Journal of General Virology. 2015; 96(6):1347-357.