Case Reports of Neuroinvasive Manifestation of Viral Encephalitis

Hao Nguyen[1*], Kaushal Shah[1], Dean Markham[1] and Nada Fadul[1]

[1]*Department of Internal Medicine, Division of Infectious Diseases, The Brody School of Medicine at East Carolina University, USA.*

Authors' contributions

Author HN designed the study, managed the literature searches, and wrote the first draft of the manuscript. Authors KS, DM and NF performed further editing and proofreading for the manuscript. All authors read and approved the final manuscript.

Case Reports

ABSTRACT

West Nile virus (WNV) infection is a mosquito-borne viral disease, which can cause an inflammation of the brain and meningitis. WNV is commonly found in Africa, West Asia, the Middle East and Europe. For the first time in North America, WNV was confirmed in the New York metropolitan area during the summer and fall of 1999. Since then, WNV over-wintered in the northeastern United States and has been described in humans, horses, birds, and mosquitoes. It is estimated that more than 80% of infected persons remain asymptomatic. Of those who develop symptoms, 80–90% develop an uncomplicated, self-limited febrile illness ('West Nile fever'; WNF) while the remaining persons develop severe diseases including West Nile meningitis (WNM), West Nile encephalitis (WNE), or an acute poliomyelitis- like syndrome. In fact, less than 1% patients will develop neuroinvasive disease, which typically manifests as meningitis, encephalitis, or acute flaccid paralysis [1].
We are presenting two cases admitted at our tertiary medical center-Vidant Medical Center in Eastern North Carolina with neuroinvasive WNV manifestation. Both patients presented with fever, altered mental status, and proceeded to develop respiratory failure. One patient died thirty days after admission and the other survived with residual isolated right lower extremity weakness that required prolonged rehabilitation.

Corresponding author: Email: nguyenh@ecu.edu;

1. INTRODUCTION

West Nile Virus (WNV) is a flavivirus in the serocomplex that includes Japanese encephalitis virus, St. Louis encephalitis virus, and Murray Valley encephalitis virus. WNV is commonly found in Africa, West Asia, the Middle East, and Europe. WNV became of public health importance in 1950s when it was associated with epidemics of fever and encephalitis in the Middle East. For the first time in North America, WNV was confirmed in the New York metropolitan area during the summer and fall of 1999 [1]. Lindsey et al. in the surveillance for human West Nile virus infection in United States from 1999-2003, showed that the number of cases of WNV infections has increased from 62 cases to 9858 in 2003, and the number of deaths increased from 7 in 1999 to 264 in 2003. At present, WNV is recognized as the most widely distributed arbovirus in the world and also has become the most significant cause of epidemic encephalitis in the Western Hemisphere [2].

WNV is transmitted to humans by a mosquito bite that has become infectious after feeding on a bird infected with the virus. Birds serve that as the reservoir hosts of WNV, and humans and horses are known as dead end hosts. Currently, there are no vaccines or antiviral medications that have been developed for WNV, as supportive management remains the mainstay of treatment [3]. In North America, WNV genome was found in 58 mosquito species, the urban *Culex* species, *Cx pipiens* (the Northern house mosquito) and *Cx quinquefasciatus* (the Southern mosquito) being the two epidemiologically predominant vectors. Typical incubation period for infection ranges from 2-14 days although longer incubation periods have been observed among immunosuppressed hosts [2]. The objectives of these case reports are to describe the rare neuroinvasive manifestations of WNV infection and to review the relevant literature on these complications.

2. CASE SUMMARY

2.1 Case 1

A 68 year-old African American male presented to Vidant Medical Center, North Carolina around mid-August after being transferred from outside hospital for further evaluation and management of fever and mental status change. He had history of substance abuse, chronic obstructive lung disease, hepatitis C and cardiomyopathy with an ejection fraction of 20 percent. The patient was apparently in his usual health until one week prior to admission, when he started to have complaints of headache, dizziness and feeling of unsteadiness. The patient's daughter made note that he had been doing quite a bit of yard work and had sustained multiple mosquito bites during recent yard work. She denied any sick contacts nor any exposure to animals or exposure to sick children. She was unaware of any house pets. At outside hospital, he was found to have a fever of 38.5°C. He was noted to be hyponatremic with a serum sodium of 127 mEQ/L at admission. Lumbar puncture and cerebral spinal fluid (CSF) studies showed Red cell count (RBC) 0 (reference < 1/ UL), White cell count (WBC) 5 (reference 0-5 per UL) with neutrophils 80% and lymphocytes 20%, protein 65 (reference 15-45 mg/dl), Glucose 76 (reference 40-70 mg/dl). Gram stain, India ink stain, CSF Cryptococcal antigen, and bacterial cultures were negative. An HIV ELISA and serological studies for Ehrlichia, *R. rickettsia, B. burgdorferi* and influenza A&B were negative. The patient had computed tomography (CT) scans of the head which was negative for acute change. Portable Chest xray on admission showed no acute finding. Patient was treated with empirically with acyclovir, vancomycin and meropenem. After 3 days of hospitalization, he became unresponsive and required intubation. Broad spectrum antibiotics were continued. Acyclovir was discontinued when a CSF HSV PCR returned negative. He remained febrile through empiric antibiotics, and was therefore transferred to our hospital for further workup.

At our hospital, patient continued to have fever 38.5°C with leukocytosis of 35,000 cells/ml³ and remained unresponsive and intubated. Brain magnetic resonance image (MRI) was done which showed an abnormal increased T2-weighted signal in the deep cerebellar white matter and bilateral thalami without restricted diffusion, findings consistent with encephalitis. Electro-encephalogram (EEG) was done which showed some slowing but no clear cut focal or epileptiform features were noted.

Shortly after transfer, patient became hypotensive and went into septic shock. Norepinephrine drip was started. Broad spectrum

coverage was continued with meropenem and vancomycin, and doxycyline was added. Repeat lumbar cultures howed WBC 154 (93% lymphocytes), elevated glucose of 103 and protein of 209. CSF culture was negative for both viral and bacterial etiologies. Patient did not show any signs of improvement in mental status and required prolonged mechanical ventilation. Ten days after his transferred to our hospital, his serum West Nile serology by enzyme immunoassay came back positive for both IgM and IgG at 5.79 (normal < 0.9 index) and 2.24 (normal < 1.3 index) respectively. West Nile CSF (PCR), obtained after about 30 days of symptom onset, was negative. The CSF WNV serology was not sent. All the antibiotics were discontinued after 10 days. Patient, however, showed no improvement in his mental status and overall condition. After one month long of hospitalization, his family opted for comfort measures only and he expired shortly after that.

2.2 Case 2

A 55 years old African American male was transferred to Vidant Medical Center due to worsening mental status and progressive distal to proximal bilateral lower extremity weakness. He had a history of being mildly mentally challenged but was independent in activities of daily living. He initially presented in mid-September with the complaint of acute onset of bilateral leg weakness after working outside on his yard for several hours. The weakness occurred acutely and progressed to the point that he could not stand on his own. According to the patient, he had to "crawl out from his bathroom to get help". He also reported headache. Fever of 40°C was documented on admission. Non enhanced CT head was negative. He also had productive cough and was in mild respiratory distress. The patient underwent lumbar puncture which showed RBC < 1000, WBC 131 (54% neutrophils, 42% lymphocytes), elevated Protein of 77, and normal glucose of 88. The patient was treated empirically with acyclovir, doxycycline, ceftriaxone and vancomycin at the referring hospital. CSF cultures had no bacterial growth. HSV PCR in CSF came back negative so acyclovir was discontinued. Serological studies for Ehrlichia, *R. rickettsia*, *B. burgdorferi*, Cytomegalovirus and Epstein Bar virus were negative. Routine chest radiography on admission showed possible retro-cardiac infiltrate vs. atelectasis. MRI of the cervical, thoracic and lumbar spine did not reveal any epidural abscess. Three days into his stay at the outside hospital, patient continued to have worsening weakness, which was initially evident on his bilateral lower extremities but has now progressed proximally to involve the upper extremities as well.

On arrival at our hospital, he was febrile to 38.5°C and appeared lethargic. Empiric antibacterial coverage was continued with doxycyline, vancomycin and ceftriaxone. An MRI of the brain showed relatively symmetric T2 hyperintense signal in the basal ganglia and hippocampal formations, which were felt to be nonspecific, but encephalitis could not be excluded. Another lumbar puncture performed 9 days after the initial admission showed RBC 988, WBC 250 (96% lymphocytes), glucose of 60, and elevated protein of 397.

The hospital course included the development of respiratory failure due to mucous plugging, felt attributable to muscle weakness and an inability to clear secretions. Blood culture, urine culture and CSF culture did not show any bacterial growth, and therefore antibiotics were discontinued after total of 10 day course. The patient's muscle strength and respiratory status started to improve after 48 hours from transfer to our facility, but with persistent isolated flaccid paralysis of the right lower extremity. His mental status has significantly improved, and he was at his baseline 4 days after transfer. From outside hospital, serum WNV IgM and IgG serology collected 3 days after the onset of the symptoms were reported positive at 5.37 and 2.55 respectively. From our hospital, CSF WNV IgM came back > 5.0 (normal < 0.9 index) quantitatively and IgG also came back elevated at 3.68 (normal < 1.3 index) from repeated blood work. The CSF WNV PCR, which was collected 9 days after symptom onset, was negative. The patient progressed slowly and was discharged to the rehabilitation after 20-day hospital course.

3. DISCUSSION

At present, WNV is recognized as the most widely distributed Arbovirus in the world and has become one of the most significant causes of epidemic encephalitis in the western hemisphere [2]. For the first time in North America, WNV was confirmed in the New York metropolitan area during the summer and fall of 1999. Since then, WNV has been described in humans, horses, birds, and mosquitoes. The understanding of the spectrum of symptomatic infection with WNV in humans has expanded during the past few years,

and a number of previously under-recognized syndromes have been characterized.

WNE tends to occur during summer-early fall ranging from June to September with the peak around August [4] and is more commonly seen in persons over the age of 55 as occurred in both of our patients. Other underlying medical comorbidities include cardiovascular disease, hypertension and diabetes mellitus [1,3]. The most common signs and symptoms of WNE include fever, headache, altered mental status, neck pain, myalgia, tremor, nuchal rigidity, photophobia and dysphagia [2]. Patients with neuroinvasive disease have features of Parkinsonism and cerebellar ataxia with truncal instability and gait disturbance [3]. Sejvar et al. described the non-specific findings on EEG for those who developed seizure which include diffuse, non-specific slow wave abnormalities or anterior area predominance of slow wave similar to the EEG findings from our first patient. To date, there is no specific finding on EEG for WNV [5,6].

A retrospective study of 17 patients with confirmed WNV meningoencephalitis at the Cleveland Clinic Foundation showed that abnormal MRI findings are not uncommon but are nonspecific for encephalitis. Areas commonly affected are the basal ganglia, thalami, mesial temporal structure, brain stem, cerebellum, and cauda equina [7-9]. MRI of the brain in both of our patients showed some abnormal increased T2-weighted signal in the deep cerebellar white matter, basal ganglia and thalami which are consistent with MRI findings that have been reported with WVE.

Although the gold standard for diagnosis of WNV infection is isolation of virus from biological specimens, this is infrequent because the virus is often absent from the blood at the time of illness onset. Virus isolation by culture is difficult to perform, is of low yield, and can be performed only in laboratories with proper biosafety containment facilities. Consequently, diagnosis using isolation is not recommended especially if it is more than 5 days from symptom onset. Nucleic acid amplification tests (polymerase chain reaction techniques) are available for detection of WN virus nucleic acid in clinical samples, but are of limited sensitivity for many of the same reasons [3]. The persistence of WN virus-specific antibodies in CSF in persons with WNND is less clear, but they have been found to persist for at least 199 days in some cases; thus,

in endemic areas, findings of WN virus-specific IgM in CSF in persons with new-onset neurologic illness should, ideally, be corroborated with serologic data [4,10,11]. In majority cases, WNV IgM antibodies, in blood or cerebrospinal fluid, are positive in most infected people within 8 days of onset of symptoms and may remain detectable for months. In most laboratories, sera with reactive IgM are rerun in a modified test to rule out nonspecific reactions [4]. Lindsey at el in his review of WNV infection in the United States from 1999 to 2008 mentioned the diagnosis criteria for WNE including febrile illness with neurological manifestations (headache, aseptic meningitis, myelitis encephalitis) plus at least one of the followings: isolation of WNV from tissue, blood, CSF, or other body fluids; demonstration of WNV antigen in tissue, blood, CSF or body fluids, positive WNV IgM antibody in acute CSF sample, 4 fold change in Plaque reduction neutralization test; or both demonstration WNV specific IgM and IgG in a single serum sample [2]. In our cases, both of our patients have elevated IgM and IgG WNV specific in the serum. In addition, the second patient also had positive CSF WNV serology IgM and IgG.

Given the absence of definitive treatment of WN virus infection, prevention remains the cornerstone of management of human WN virus infection from a public health standpoint [3]. Efforts at mosquito control, including community-wide removal of mosquito breeding areas, larviciding and spraying for adult mosquitoes, can be effective at reducing mosquito populations, and is employed to different degrees in various communities.

Neuroinvasive WNV can present as West Nile poliomyelitis (WNP). Sejvar et al. [9] suggested that most cases of paralysis were due to viral involvement of the lower motor neurons of the spinal cord (anterior horn cells), resulting in poliomyelitis, a syndrome more typically associated with poliovirus infection. WNP generally has an early onset in the course of infection, often within the first 24 to 48 hours of illness. Limb paralysis can develop very rapidly, occasionally raising concern for stroke; weakness tends to be asymmetric, and often monoplegia. Central facial weakness, frequently bilateral, can also be seen. Sensory loss or numbness is generally absent, though some patients experience intense pain in the affected limbs [7]. Involvement of the respiratory muscle innervation may result in respiratory failure requiring emergent endotracheal intubation and

mechanical ventilation support and it is associated with high morbidity and mortality [6,7]. These clinical features were present in our second patient. Patients developing early bulbar findings, including dysarthria, dysphagia, and loss of gag reflex, in the setting of suspected WN virus infection should be monitored very closely for respiratory failure. Nerve conduction studies usually display findings consistent with a motor axonopathy with little or no demyelinating changes and preservation of sensory nerve potentials [8,9].

Besides poliomyelitis, Guillain-Barre´ syndrome (GBS) has also been associated with WNV infection but appears to be far less common than WNP. The weakness associated with the GBS is frequently symmetric and ascending in nature, and is associated with sensory and autonomic dysfunction. Additionally, CSF examination will generally show elevated protein in the absence of pleocytosis, and electro-diagnostics will be consistent with a predominantly demyelinating polyneuropathy [6,8,9].

The outcome of WNE neuroinvasive can range from sudden, rapid recovery to persistent neurologic dysfunction with movement disorder, chronic headache, or cognitive impairment. Sejvar et al. investigated the long-term outcome for WNV infection. Among 32 patients with WNV neuroinavsive disease, 27 patients with features of WVP, four with GBS like symptoms and one with brachial plexopathy, the distribution and severity of weakness at the time of acute illness was heterogeneous. Thirty eight percent of patients had respiratory failure, requiring intubation and mechanical ventilation. At four months follow-up, four patients, all of whom experienced respiratory failure, had died, and two remained intubated; the remaining 23 patients demonstrated varying degrees of strength improvement, ranging from minimal detectable improvement to complete recovery in two patients with GBS-like illness. Twenty five percent of patients continued to experience movement disorders at the 4-month follow-up visit. By one year, 3 more patients who had respiratory failure, had died; one patient with WNP had regained baseline strength, and the remainder continued to experience varying degrees of persistent weakness. In general, the greatest amount of strength recovery occurred between one and six months after acute illness; 41% of patients continued to experience other neurologic features [5,8,12]. By far, the primary

causes of death in WVN infections reported in North America are the cardiac and pulmonary complications. Other non-neurological illnesses that can also be associated with WNV infection include choreoretinits, rhabdomyolysis, viral myositis, orchitis, hepatitis, pancreatitis, myocarditis, fatal hemorrhagic fever with multi-organ failure, palpable purpura, and central diabetes insipidus [3].

There have been no studies investigating whether any particular immunosuppressive state or comorbidity may predispose patients to the WNV infection or predict the long term outcomes. However, WNE tends to occur more frequently in older persons (aged > 55 years) and in those with underlying immunosuppression. Patients with WNE neuroinvasive are hospitalized longer and experience medical complications at greater rates than do patients with other forms of WNV illness [12,13].

4. CONCLUSION

We presented two cases of WNV neuroinvasive diseases with two different outcomes. WNE is more commonly seen in persons over the age of 55. The most common signs and symptoms of WNE include fever, headache, alter mental status, neck pain, myalgia, tremor, nuchal rigidity, photophobia and dysphagia. The season for WNV neuroinvasive disease tends to occur during the summer early fall months ranging from June to September with the peak around August. Less than 1% patients will develop neuroinvasive disease, which typically manifests as meningitis, encephalitis, or acute flaccid paralysis. Recovery of limb strength in persons with WNV neuroinvasive is quite variable. However, persistent weakness and associated functional disability are the key factors influencing short term recovery, versus requirement for prolonged physical and occupational therapy, and prevention remains the cornerstone of management of human WN virus infection from a public health standpoint.

CONSENT

All authors declare that consent was obtained from the patient (or other approved parties) for publication of this case report.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Gubler DJ, Campbell GL, Nasci R, Komar N, Petersen L, Roehrig JT. Guideline for west Nile virus in the United States: Surveillance, prevention and control. Viral Immunol. 2000;13(4):469-75.
2. Lindsey NP, Staples JE, Lehman JA, Fischer M. Centers for disease control and prevention (CDC). Surveillance for human West Nile virus disease - United States, 1999-2008. MMWR Surveill Summ. 2010; 59(2):1-17.
3. James J Sejvar, Marfin AA. Manifestation of West Nile neuroinvasive disease. Rev Med Virol. 2006;16.
4. Lyle Petersen, Brault AC, Nasci RS. West Nile virus: Review of literature. JAMA. 2013:310(3):6. Kalliopi A Petropoulou, Gordon SM, Prayson RA, Ruggierri PM. West Nile virus encephalitis: MR imaging findings. Am J Neuroradiol. 2005;26:1986-1995.
5. Sejvar JJ, Bode AV, Marfin AA, Campbell GL, Ewing D, Mazowiecki M, Pavot PV, Schmitt J, Pape J, Biggerstaff BJ, Petersen LR. West Nile virus-associated flaccid paralysis. Emerg Infect Dis. 2005;11(7): 1021-1027.
6. Carson PJ, Steidler T, Patron R, Tate JM, Tight R, Smego RA Jr. Plasma cell pleocytosis in cerebral spinal fluid in patients with West Nile encephalitis. Clin Infect Dis. 2003;37(1).
7. Leis AA, Stokic DS, Webb RM, Slavinski SA, Fratkin J. Clinical spectrum of muscle weakness in human West Nile virus infection. Muscle Nerve. 2003;28(3):302–308.
8. Al-Shekhlee A, Katirji B. Electro-diagnostic features of acute paralytic poliomyelitis associated with West Nile virus infection. Muscle Nerve. 2004;29(3):376–380.
9. Park M, Hui JS, Bartt RE. Acute anterior radiculitis associated with West Nile virus infection. J Neurol Neurosurg Psychiatry. 2003;74(6):823–825.
10. Kapoor H, Signs K, Somsel P, Downes FP, Clark PA, Massey JP. Persistence of West Nile Virus (WNV) IgM antibodies in cerebrospinal fluid from patients with CNS disease. J Clin Virol. 2004;31(4):289–291.
11. Fan E, Needham DM, Brunton J, Kern RZ, Stewart TE. West Nile virus infection in the intensive care unit: a case series and literature review. Can Respir J. 2004;11(5): 354–358.
12. Sejvar JJ. The long term outcome of human West Nile virus infection. Clinical Infectious Diseases. 2007;44(12):1617-24.
13. Sejvar JJ, Lindsey NP, Campbell GL. Primary causes of death in reported cases of fatal West Nile fever, United States, 2002-2006. Vector Borne Zoonotic Dis. 2011;11(2):161-4.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/9841