Case Report

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Parkinsonian Symptoms with Fever

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Abstract

Introduction: West Nile virus (WNV) is the most common arthropod borne virus and is the leading cause of domestically acquired disease in the United States.

Case Description: A 75-year-old man presented in August 2015 with sepsis and one day of confusion, fever of 104°F, a white blood cell count (WBC) of 19.80, and blood pressure of 204/91, in the setting of a recent admission for small bowel obstruction. On exam, he was only oriented to self with slurred speech, tongue and bilateral quadriceps fasciculations, cogwheel rigidity and tremor of bilateral upper arms, and dysmetria. He did not have skin changes, no meningeal signs, or visual problems. Initially, he was treated empirically for meningitis. Head computed tomography (CT), magnetic resonance imaging (MRI), abdominal CT, chest X-ray (CXR) were negative. He remained febrile and hypertensive for four days, with worsening Parkinson's features. Blood and urine cultures were negative and antibiotics were stopped. Neurology started a Sinemet trial. Lumbar puncture (LP) revealed mild pleocytosis and no detectable WNV. On day six, his white blood cell count (WBC) resolved, blood pressures were under control, and defervesced-only with supportive care. All of his Parkinson's symptoms resolved. On day seven, serum WNV IgM was positively elevated >5.00. One week later, he had seroconverted.

Discussion: The first case of WNV was isolated in 1937 in Uganda. This case report reminds us of the necessity to heighten public health awareness for WNV. It also portends the need for WNV surveillance in order to control disease spread. Our priorities need to shift toward early disease identification and implementation of control measures. Reporting databases like ArboNET are effective, however, as it currently stands, the onus of reporting lies in the hands of health care professionals. This leads to an underestimate of the actual disease prevalence and burden. Frequently, WNV cannot be detected in serum because the viremia is short lived and peaks before clinical symptoms are present. Case reports have documented that WNV can present as Parkinsonian symptoms including hypomimia, bradykinesia and postural instability. Persistent fever without a known source should initiate a search for the cause, and merits a thorough review of the patient's social history. Treatment should be focused on supportive care while pending laboratory confirmation of WNV, and irrespective of imaging studies. Consistent with the literature, our patient did not have significant imaging findings. WNV can be a preventable disease if preventative measures are taken. Thus, the long-term sequelae of WNV, which include depression, fatigue, headaches, cognitive and muscular deficits, can be potentially avoided.

Keywords: Parkinsonian; Arthropod borne virus; West Nile Virus (WNV); Fever; Parkinson and fever

Introduction

West Nile virus (WNV) is the most common arthropod borne virus and is the leading cause of domestically acquired disease in the United States. It was formerly thought to only have been endemic to Africa and the Middle East, but reached the United States in 1999. The first case was described in the West Nile district of Uganda in 1937 [1]. Some 60 years later, outbreaks revealed that WNV could be a potentially lethal pathogen by invading the nervous system.

The Japanese encephalitis virus sero-complex includes Japanese encephalitis virus, St. Louis, Murray Valley virus and West Nile virus. West Nile virus is an RNA virus and a member of the flavivirus family. It is transmitted by arthropods with mosquitoes serving as the vector. Without a high index of clinical suspicion, the diagnosis is often missed. WNV has an incubation period of 2-14 days [1]. The majority of individuals infected with WNV, with some studies reporting up to 80%, are asymptomatic [2]. Symptoms can include neuro-invasive disease (meningitis, encephalitis, acute flaccid paralysis). 1 in 150 experience encephalitis, while 1 in 5 solely present with fever [3]. Other manifestations include ataxia, seizures, optic neuritis. Very rarely can it cause fulminant hepatitis, pancreatitis, and myocarditis [4]. It also has a significant mortality rate. Over 1300 deaths have been reported to the CDC from 1999 until 2010 [3]. Risk factors for WNV associated deaths include increased age, organ transplantation, hypertension, cerebrovascular disease, renal disease and diabetes.

Case reports from Serbia, Italy, Tunisia, Germany and the U.S. have contributed to the growing knowledge base of WNV [5-7].

A Serbian study reported on the functional status of WNV after hospital discharge [2]. Of the 52 patients included in their analysis, 13 developed respiratory failure ultimately requiring mechanical ventilation. In this study, WNV was confirmed by anti-WNV IgM antibody in the serum and cerebrospinal fluid (CSF) using IgG and IgM ELISA. The CSF had pleocytosis and high protein defined as values over 0.45 g/L with signs of meningitis, headache, vomiting, photophobia, phonophobia, encephalopathy, focal neurologic signs, ataxia, wide based gait and dysmetria which suggested involvement of the cerebellum. Acute flaccid paralysis in this study was defined as limb weakness and at least two of the following: asymmetry of weakness, areflexia, lack of pain or sensation changes in the limbs, CSF pleocytosis and high protein, or abnormal anterior grey matter on MRI.

This Serbian study reported an average length of stay of 18 days. Several patients had a kinetic tremor in the upper extremities. Head CT showed old lacunar infarcts and hypointense pons lesions, with MRI showing hyperintense lesions on T2 in the basal ganglia, pons, and temporal lobe. They found predictors of fatal outcomes to include the presence of acute flaccid paralysis, respiratory failure and impaired consciousness.

The IgM response in CSF or serum remains the most reliable means of detection. This can detect the virus up to 47 or 199 days post infection in the serum and CSF, respectively with 91.7% and 99.2% sensitivity and specificity [8]. Confirmatory testing includes a 4 fold increase in serum antibodies. Plaque reduction neutralization test (PRNT) is another means of confirmation, but is not always available because processing involves a high biosafety level laboratory.

A case report of an Italian man in 2009 with WNV revealed colorless CSF with 2 cells/mL and protein 74 mg/dL [8]. He had positive serum antibodies but negative CSF antibodies.

In one study of a Crohn's patient with WNV, the CSF studies showed white blood cell count (WBC) of 84 cells/mm^3 with 21% neutrophils, 53% lymphocytes, 26% monocytes, 27 RBCs/mm^3, with normal glucose and protein levels, and WNV was identified in the CSF by PCR. This patient also had a normal magnetic resonance imaging (MRI). The patient did not have sequelae at the 6-month follow up after discharge [1].

A study of 113 patients in 2003 in Tunisia were found to have CSF showing pleocytosis with a mean white cell count of 5-490, lymphocytic predominance, with high protein, mild leukocytosis >145, normal glucose and hyponatremia [4].

Another case of a young woman with meningoencephalitis diagnosed in Germany in 2011 presented with leukocytosis to 15K and CSF findings of pleocytosis, 430 cells, 72% granulocytes, 27% lymphocytes, and 1% monocytes with elevated protein to 1023, and also with a normal MRI. She had an 8 and 32-fold increase in serum titers from day 4 to 26 with IgM, and IgG, respectively [9].

A case report in Dallas, Texas noted that WNV PCR testing is discouraged because of the transient viremia and low sensitivity of this particular test. Thus, it should only be used in instances where the serology is negative but there remains high suspicion, if the patient presents early in the course of infection, or in immunocompromised patients [10].

Frequently, patients can present with a coarse bilateral tremor and myoclonus in the upper extremities. Case reports have also documented parkinsonian symptoms including hypomimia, bradykinesia and postural instability.

Currently, there is no treatment for WNV. Therapy is aimed at symptomatic management and supportive care. There has been some success with IV Immunoglobulin (IVIG) but the literature is scarce given the impracticality of performing a randomized control trial [3].

Case Presentation

A 75-year-old man presented to the Inova Fairfax emergency department in August 2015 with sepsis and one day of confusion, fever to 104F and white blood cell count (WBC) of 19.80. He was admitted a month prior for small bowel obstruction, which had since resolved. Three days prior, he was constipated and taking magnesium and miralax. His family members noted severe lethargy and marked weakness and urine incontinence. His past medical history includes prostate cancer, hypertension, paroxysmal atrial fibrillation, hyperlipidemia, and mild cognitive impairment. His surgical history includes colon surgery and external beam radiation for prostate cancer. His medications include hydralazine, nebivolol, diovan, and terazosin for hypertension, pravastatin for hyperlipidemia, memantine for mild cognitive impairment, and Coumadin for atrial fibrillation. He presented with a blood pressure of 204/91 mmHg, temperature of 104.2F. On physical exam, he was only oriented to self and had slurred speech. He had fasciculations of bilateral anterior quadriceps, and tongue. He had cogwheel rigidity in bilateral upper extremities. He also had a severe intention tremor and dysmetria as it was difficult for him to perform the finger-to-nose test. He did not have any skin changes.

At bedside, his wife was able to report that the patient had been suffering from headaches for weeks, without reports of stiff neck, vision changes, or cardiopulmonary changes. He also is a gardener living in Northern Virginia and had not traveled in many years.

Hospital Course

Initial work-up and treatment was focused on meningitis. Subsequently, he was empirically treated with vancomycin, ceftriaxone and ampicillin given his fevers, altered mental status, and history of headaches, albeit a lack of neck stiffness. Head CT was negative for intracranial bleed or masses. The MRI findings did not reveal enhancements that would be consistent with acute encephalitis. Urine and blood cultures were negative. Chest X-ray was only significant for cardiomegaly. He was influenza negative. Complement, ANA,

and Rheumatoid Factor were negative. We consulted Infectious Disease, who thought that the source of infection was intra-abdominal given his recent history of small bowel obstruction (SBO). An abdominal CT was done that was without significance. He was febrile and hypertensive for the first four days of hospitalization. Given the low probability of meningitis, his medications were changed to vancomycin and meropenem on the second day. As the cultures came back negative, both of these antibiotics were eventually discontinued.

We then consulted Neurology who believed that this patient was manifesting early signs of Parkinson's disease. Again, we emphasize that he presented with bilateral tremors and cogwheel rigidity. In addition, he had signs of bradykinesia and the classic expressionless face commonly associated with Parkinson's. Although it would be peculiar for Parkinson's to present this acutely, a Sinemet trial was started nonetheless. He continued to have low-grade fevers. This is inconsistent with Parkinson's and thus raised questions and concerns for other possible etiologies.

For his fasciculations, an electromyography study was performed and significant for left hand carpal tunnel syndrome. On hospital day three, interventional radiology performed a lumbar puncture showing mild pleocytosis, but no bacteria suggesting an acute infection. There was only enough CSF to fill two tubes. The results were as following: Tube 1: WBC 17, RBC 1130, (both high), Neutrophil 24, Lymphocyte 49, Macrophage 27, Tube 2: WBC 26, RBC 3900, (high), Neutrophil 21, Lymphocyte 59, Macrophage 20, with protein of 53.4 (high). WNV could not be detected in the CSF (**Table 1**). At this time, we continued evaluations which revealed a negative serum EBV, CSF enterovirus, HSV and Lyme. Furthermore, RPR was negative, and B12, folate and ammonia were all normal. Thyroid stimulating hormone was mildly decreased at 0.18 with a normal free T4 and T3. By hospital day six, his mental status was improving, with a resolved WBC, controlled blood pressures, and he had defervesced. In addition, his slurred speech, fasciculations, tremors and rigidity all improved. However, on hospital day 7, West Nile Virus serum serologies provided us with an answer. The IgG was undetectable (<1.30) but the IgM was positively elevated (> 5.00). We repeated this test. At follow-up one week later, IgG was 2.35, and IgM was again > 5.00. This time, the IgG was unequivocally positive (**Table 2**). He had seroconverted. Interestingly, although a sensitive test, the WNV RNA was undetectable. This lab however, was drawn after the patient had recovered and was no longer showing signs and symptoms consistent with WNV.

Discussion

The first case of WNV was isolated in 1937 in Uganda [1]. Since then, several epidemics have resulted in financial and social impacts on the medical community. Outbreaks have occurred in the United States, Romania, Russia, Israel, Hungary, Italy and Greece. This case report reminds us of the necessity to heighten public health awareness of WNV. It also portends the ongoing need for WNV surveillance in order to control the spread of this disease. Although several case reports have demonstrated that infected individuals have low mortality rates, the focus should be on prevention. It is evident that reporting databases like ArboNET are effective, however as it currently stands, the onus of reporting lies in the hands of health care professionals. This leads to an underestimate of the actual disease prevalence and thus decreases the actual disease burden.

Table 1 Interventional radiology performed a lumbar puncture showing mild pleocytosis

CSF Tubes	Tube # 1	Tube # 2
WBC	17	26
RBC	1130	3900
Neutrophil	24	21
Lymphocyte	49	59
Macrophage	27	20
Protein	N/A	53.4
WNV	Not Detected	Not Detected

Table 2 WNV Serology Results

WNV Serology Results			
Inpatient*		**Outpatient****	
IgG	<1.30	IgG	2.35
IgM	>5.00	IgM	>5.00
*Hospital Day 7			
**Follow-up 1 week after the first set of results			

We bring your attention to several key factors that can influence prognosis in those affected with WNV. The Serbian study proposed that these are the presence of AFP, respiratory failure or impaired consciousness [2]. Thus, it is imperative to monitor respiratory status and maintain efforts to re-orient those who present with altered mental status. This will effectively decrease mortality and post-discharge complications.

Our priorities need to shift toward early disease identification, with a focus on surveillance and implementation of control measures and public education. As healthcare providers, we must also be sensitive to providing empathic care to our patients. In our case, it was difficult for the family members to understand the breadth of work-up given the nonspecific presentation of illness. It is important to bear in mind that the severity of presentation has no bearing on functional outcomes. This message should be relayed to patients and their family members.

Frequently, WNV cannot be detected in serum because the viremia is short lived and peaks before clinical symptoms are present. The value of imaging, such as head CT and MRI, in those presenting with neurological symptoms is of questionable significance. The literature has not established a

concrete pattern that is associated with WNV. In our case report, we present a patient with no acute intracranial findings. The take home point is that treatment should be focused on supportive care while pending laboratory confirmation of WNV, and irrespective of imaging studies.

Several studies have proposed a correlation between increasing age and disease severity. Subsequently, harboring the WNV places the elderly at a higher risk of death. Although the mechanism is unclear, this may be in part secondary to the decrease in the integrity of the blood brain barrier that occurs with aging [4]. The elderly or immunocompromised are most prone to developing neuroinvasive disease. Thus, there needs to be close follow up because the disease can lasts for weeks to months with a high mortality rate.

Neurologists should consider WNV in those who present with ataxia, unsteady gait, muscle weakness even without meningeal or encephalitic signs in the summer and early fall. Particular attention should be drawn to those who present with acute onset of Parkinsonian features. The presentation of Parkinsonian features in patients infected with WNV can be explained by the virus's neurotropism for extrapyramidal structures [2]. Interestingly, our patient did not have any significant head MRI or CT findings. This was consistent with the literature. Post-mortem studies of those who die from WNV could offer insight into the regions of brain infiltrated by the virus. This could potentially add an imaging component to the diagnostic criteria beyond the serum and CSF antibody testing that exists now. Parkinsonian features appear to be transient and resolve with time. In our case, our Neurology consultants believed this to be a case of early onset Parkinson's disease and started a trial of Sinemet. The patient's symptoms improved drastically over the course of a few days, with improved upper extremity tremors, cogwheel rigidity and bradykinesia. In retrospect, this was not due to the immediate effects of Sinemet, but rather the resolution of WNV symptoms. Thus, medical professionals will need to continue to maintain a high index of suspicion for WNV based on knowledge of symptoms, geographic and seasonal distributions.

It is evident that if the index of suspicion is low amongst clinicians, the diagnosis of WNV could potentially be missed. However, WNV could also be mistaken for autoimmune neuropathic disease such as Guillane-Barre syndrome. The AFP of WNV presents with hypo- or areflexia without sensory loss, however GBS has symmetric weakness and sensory loss. In addition, WNV has pleocytosis without albuminocytologic dissociation unlike that of the CSF in GBS.

Public health education should include recommending people who spend a great deal of time outdoors to wear long sleeved pants and shirts, to use insect repellants and to install screens at home. WNV can be thought of as a preventable disease if preventative measures are taken. Thus, the long-term sequelae of WNV, which include depression, fatigue, headaches, cognitive and muscular deficits can be potentially avoided [11].

With regards to treatment, INF alpha has been shown to inhibit in vitro cytotoxicity of WNV but has not been studied in animal models [12]. It has been studied in Japanese encephalitis without benefit. Animal models have examined the benefit of WNV specific IV Immunoglobulin (IVIG) and humanized monoclonal antibodies targeting viral envelope proteins. Future studies should examine the efficacy of novel agents in providing more permanent therapies rather than supportive, temporizing measures of managing WNV.

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