Opsoclonus myoclonus syndrome: an unusual presentation for West Nile virus encephalitis

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A record number of West Nile virus (WNV) cases and fatalities seen in 2012 have brought to light the numerous manifestations of neuroinvasive disease. We report a case of opsoclonus myoclonus syndrome attributed to WNV and its clinical course after treatment with a combination of steroids and intravenous immunoglobulin. Our objective is to highlight opsoclonus myoclonus syndrome as a potential manifestation of WNV encephalitis.

West Nile virus (WNV) is a mosquito-borne arbovirus belonging to the genus *Flavivirus*. It is more common in temperate and tropical regions of the world. Before the 1990s, it was not considered a big threat to the human population. However, WNV has now spread all over the world. The first case of WNV in the United States was reported in New York City in 1999; over the next 5 years, it spread across the nation (1). The main mode of transmission is mosquitoes, which are the prime vector, whereas birds are the prime reservoir host. WNV is also found in ticks, but they are not important vectors. WNV can also be spread by blood transfusion, organ transplantation, and breastfeeding (2). WNV infects various mammals, reptilian species, as well as amphibians (3).

CASE PRESENTATION

A 43-year-old Caucasian woman presented to an outside facility in the fall of 2012 with a 10-day history of dizziness, worsening headaches, nausea, fever, and myalgias. Early in the course, she developed a raised nonerythematous rash on her neck that spread in a craniocaudal fashion. One week after developing the rash, she started having involuntary multidirectional jerky saccadic eye movements with superimposed fluttering eyelid movements consistent with opsoclonus myoclonus syndrome (OMS).

The patient's past medical history was insignificant except for a cesarean section. She mentioned a family history of recurrent meningitis in her son, breast cancer in her mother, and prostate cancer in her father. Her social history was significant only for exposure to WNV, as she was a rancher in a neighborhood where others had been diagnosed with WNV. Her medications included occasional nonsteroidal antiinflammatory drugs and oral contraceptives.

At the time of admission, she appeared very uncomfortable and kept her eyes closed with myoclonic jerking of the eyelids whenever she tried to open them. Her vital signs revealed only low-grade fever, which resolved spontaneously. She had difficulty keeping her eyes open, and her eyes initially had to be pried open to examine her severe OMS. She had good muscle strength but her gait was ataxic. Opening her eyes or any movement triggered severe nausea and episodes of emesis. She stayed in bed in a dark room with her eyes clenched shut with a constant look of distress. However, her cognition remained unaffected.

A thorough evaluation was done for the possibility of malignancies, paraneoplastic syndromes, autoimmune processes, and infectious etiologies as the cause of OMS. Her cerebrospinal fluid (CSF) was xanthochromic with lymphocytic pleocytosis *(Table 1)*. Among the imaging studies performed at the outside facility, magnetic resonance (MR) imaging with contrast and MR angiography of the brain were nonrevealing. Computed tomography with contrast of the chest, abdomen, and pelvis

Table 1. Results of laboratory tests of the patient's cerebrospinal fluid

Test	Result
Color	Xanthochromic 49K RBC
Lymphocyte (per µL)	30
Neutrophil (per µL)	62
Glucose (mg/dL)	47
Protein (mg/dL)	110
Culture	No organisms
Fungal culture	Negative
Paraneoplastic panel	Negative
HSV/HHV6/Coxsackie A-B/GQ1b Ab/VGCC/WNV IgM	Negative

HSV indicates herpes simplex virus; HHV6, human herpesvirus 6; Ab, antibody; VGCC, voltage-gated calcium channel; WNV, West Nile virus.

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Table 2. Results of other laboratory tests

Blood test	Results
Antimitochondrial antibody	Absent
Antinuclear antibodies	Absent
Coccidioides/Rocky Mountain spotted fever antibody	Negative
C-reactive protein	<0. 3
Creatine kinase	24
Blood culture	Negative
Paraneoplastic panel	Negative
Enterovirus/herpes simplex virus	Negative
West Nile virus IgM	Positive

showed small bilateral pleural effusions and a small amount of free fluid in the pelvis but no signs of primary malignancy. Laboratory test results were remarkable for the presence of WNV immunoglobulin (Ig) M in the blood, with negative IgG and negative polymerase chain reaction results *(Table 2)*. Although CSF WNV IgM titers were below the assay cutoff, they were in fact found to be present at low levels. CSF WNV IgM was tested after completion of intravenous immunoglobulin (IVIG) treatment and while on high-dose steroids. Based on the clinical presentation and these laboratory findings, the diagnosis of acute WNV meningoencephalitis was made. CSF and blood cultures drawn prior to antibiotics were without any growths.

Prior to transfer to Baylor University Medical Center, the patient was started on broad-spectrum antibiotics and antiviral coverage with doxycycline, meropenem, vancomycin, and acyclovir but showed no signs of improvement. She was also started on gabapentin and diazepam for nystagmus symptom relief. Nausea and emesis were controlled with promethazine and ondansetron. Upon transfer, the patient was immediately started on IVIG with a total of 2 g/kg administered over 3 days. On day 2 of IVIG, she was started on intravenous methylprednisolone 125 mg twice a day, which was later transitioned to oral prednisone after 5 days. Within a couple of days of starting IVIG and intravenous steroids, her symptoms of nystagmus and ataxia showed visible improvement. On day 5, her symptoms of headache, nausea, vomiting, and nystagmus had improved significantly such that she was finally able to open her eyes and eat. On day 6, oral prednisone, memantine, and oxcarbazepine were started. Due to drowsiness, memantine and oxcarbazepine were discontinued fairly quickly after initiation. By day 10, the patient had full range of motion in all extremities, and OMS had nearly resolved to the untrained eye.

The patient had become very deconditioned from being bedbound for nearly 2 weeks with poor nourishment, requiring inpatient rehabilitation. Over the course of a year, she has improved to the extent of being able to get groceries and take care of her children. Using her eyes for prolonged tasks will still cause her to be nauseated and worsen her headache. Although her opsoclonic-nystagmoid movements are not visible outside of ophthalmological evaluations, which do show small continued movement not obvious to the naked eye, she does have difficulty with reading. She also has intermittent problems with urinary retention.

DISCUSSION

West Nile virus

According to the Centers for Disease Control and Prevention, in 2012, there were 5674 WNV cases in the United States (4). Texas was particularly hit hard, with 1739 (32%) cases reported (3). Severe cases of neuroinvasive WNV were initially reported in 2002 and 2003 but have been increasing in frequency over the past several years. Just in 2012 alone, 2873 of the reported WNV cases were neuroinvasive, with 286 reported fatalities (4). The risk factors that contribute to the more severe form of disease are HIV infection, chemotherapy, organ transplant, immunosuppression, young or old age, and pregnancy.

WNV infection usually presents with fever and nonspecific symptoms such as abdominal pain, nausea, emesis, and diarrhea. Rash is also often described. These symptoms can last anywhere from 3 to 6 days to about a month. WNV can cause inflammation in a wide variety of organs in the body with variable manifestations. Notable complications of WNV are fulminant hepatitis, pancreatitis, myocarditis, rhabdomyolysis, chorioretinitis, orchitis, nephritis, optic neuritis, cardiac arrhythmias, and hemorrhagic fever with coagulopathy (5–7). The more severe neuroinvasive form of disease manifests as meningitis or encephalitis. Seizures are also often seen. Patients can present with confusion, loss of consciousness, coma, stiff neck, permanent brain damage, and muscle weakness that resembles polio and on rare occasions with OMS. Neurological complications are often fatal. Previous reports have suggested that 1 out of 10 patients presenting with encephalitis due to WNV do not survive (2). Therefore, it is prudent to evaluate for WNV exposure in patients presenting with neurological symptoms in endemic areas during late summer.

Opsoclonus myoclonus syndrome

OMS is an unusual presentation of WNV infection. Only two cases of OMS were reported in the 2003 outbreak of WNV, with another similar case reported in 2006 (8). One of the cases reported occurred in a patient who was potentially immunocompromised with non–small cell lung cancer, which makes it difficult to attribute OMS solely to WNV infection (9).

OMS is a rare autoimmune condition characterized by cerebellar degeneration and is seen in patients with encephalitis secondary to various etiologies such as cancers, toxins, autoimmune diseases, and viral infections (10). It occurs most often as a paraneoplastic syndrome when a cancer remote to the brain induces cerebellar dysfunction that is unrelated to metastasis. Half of the cases occur in children with neuroblastoma. In some cases, OMS has been successfully treated with immunotherapy, as the presence of widespread CNS lymphocytic infiltrates in autopsy studies indicates that an autoimmune pathogenesis is likely (11). In some cases of OMS, symptoms are believed to develop after intracellular and surface binding (IgG3) antibodies in serum and CSF specifically bind to and damage inhibitory Purkinje cells and

granular neurons in the dorsal vermis of the cerebellum. Because the antibodies can vary widely and sometimes are not found at all, the exact mechanism is not entirely clear (10).

OMS has horizontal and vertical saccades. Horizontal saccades are generated by burst neurons in the paramedian pons, and vertical saccades are caused by burst neurons in the rostral midbrain. The activity of these burst neurons is controlled by omnipause neurons in the pontine raphe. It is suggested that OMS is caused by the failure of omnipause neurons to control burst neurons (8). The omnipause neurons are affected in brainstem encephalitis and also when there is impaired control of the brainstem saccade generating network by the cerebellum. Patients with OMS should undergo a complete evaluation for cancer and infection. Abnormal immunoglobulin analysis and other laboratory findings may be nonspecific, since there are no diagnostic biomarkers for paraneoplastic OMS. Blood or CSF analysis may assist in identifying an infectious etiology. While they neither diagnose nor exclude a paraneoplastic or autoimmune etiology, CSF studies often document paraneoplastic antibodies, mild increases in proteins, and a lymphocytic pleocytosis consistent with inflammatory changes (10).

The exact role of IVIG and high-dose steroids in the treatment of WNV has not been studied. However, improvements have been reported in several instances for severe cases of human enteroviral encephalitis. Sequelae such as hearing loss of infectious aseptic meningitides in general have been shown to be reduced in children with steroid treatment. IVIG products prepared in areas where WNV is endemic such as Texas have been shown to have high titer levels to WNV. The timing and route of administration of IVIG also appears to be important (9). In the case presented, IVIG was administered 5 days after onset of OMS (12 days after the rash and fever), along with high-dose intravenous steroids and antivirals with initial rapid improvement followed by very slow improvement and plateauing. It is impossible to determine the exact role of acute use of IVIG and steroids in the recovery of our patient.

In general, neuroinvasive WNV infections can have numerous presentations. Patients who present with OMS with signs of an infective process should be checked for WNV infection especially if they live in endemic areas. Patients surviving WNV neuroinvasive disease often suffer long-term neurological sequelae (4), and it is unclear if therapies offered for other aseptic meningitides would apply. As is the case with meningitis in general, it may be reasonable to consider steroids or other immunomodulatory therapies to limit neuronal injury in WNV neuroinvasive disease as well.

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