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Case report

A case of West Nile virus encephalitis accompanied by diabetic ketoacidosis and rhabdomyolysis

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ABSTRACT

Introduction: We present here a case of West Nile Virus (WNV) encephalitis that initially presented with diabetic ketoacidosis and rhabdomyolysis.
Case presentation: A 35-year-old male with no past medical history presented to the emergency department complaining of polydipsia, generalized weakness, lightheadedness, and visual disturbances of one week duration. He was found to be in diabetic ketoacidosis. His hemoglobin A1c was 11%. The patient was appropriately treated for diabetic ketoacidosis and it resolved on hospital day 1. On hospital day 2, the patient developed a fever of 101.6 °F and his mental status became severely altered. He developed auditory and visual hallucinations. IgM and IgG antibodies to West Nile Virus were positive in the cerebral spinal fluid (CSF). The patient's creatine kinase level rose to 118,400 U/L during his hospitalization and eventually returned to baseline. The patient made a full recovery with no residual neurologic deficits after an 11 day hospital course.
Discussion: In this patient, neuroinvasive WNV was confirmed with positive CSF IgM. The patient's newly diagnosed diabetes likely contributed to his susceptibility to neuroinvasive disease. Furthermore, WNV encephalitis in a background of DKA has not been previously described in the literature and this case demonstrates WNV neuroinvasive disease should be in the differential diagnosis for patients presenting with unexplained neurological symptoms.
Conclusion: Diagnosis of neuroinvasive WNV is imperative to stop unnecessary therapies, limit further diagnostic evaluation, help predict patient outcomes, direct public health prevention measures, and further provide investigations into the clinical conditions that define the spectrum of WNV disease.

Introduction

Since its first isolation originating from the West Nile province in Uganda in 1937, West Nile Virus (WNV) has historically been known to be the least virulent of the Japanese serogroup viruses of the arthropod-born flaviviruses. This perception changed in the 1990's with the westward expansion of an epidemic subtype of the virus associated with greater virulence and severe neurologic disease. The WNV outbreak in Queens, New York in 1999 resulted in 59 cases of neuroinvasive disease, 7 deaths, and the migration of the virulent strain to the rest of the country [1]. A total of 49 states and the District of Columbia have reported WNV infections in people, birds, or mosquitoes as of November 2018. Neuroinvasive disease accounted for 61% of the reported 2323 cases of WNV in the year 2018 alone [2]. WNV is now one of the most widely distributed arboviruses worldwide [3,4]. We present here a case of WNV encephalitis that initially presented to the hospital with diabetic ketoacidosis and rhabdomyolysis.

Case presentation

A 35-year-old male with no past medical history presented to the emergency department complaining of polydipsia, generalized weakness, light headedness, and visual disturbances of one week duration. On initial laboratory assessment, he was found to be in diabetic ketoacidosis with a blood glucose of 600 mg/dL, arterial blood pH of 7.26, a beta-hydroxybutyrate level of greater than 46.8 mg/dL and an anion gap of 27 mmol/L. His hemoglobin A1c was 11%. He was also found to have a mild leukocytosis at 12,250 cells/mcl. He was admitted to the intensive care unit and treated with intravenous fluids and an insulin infusion.

On hospital day 2, he was transferred to the medical floor after being transitioned to subcutaneous insulin. He developed a fever of 101.6 °F and his mental status became severely altered. The patient

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was unable to follow multistep commands, he was unable to tell time on a standard clock, and was unaware of where he was, details regarding his hospitalization, or the current President of the United States. He developed auditory and visual hallucinations despite having no prior psychiatric history. The patient only complained of generalized muscle soreness and neck stiffness. Physical exam was notable for impaired finger to nose testing in both right and left upper extremities and he developed an intermittent dysconjugate gaze during extraocular eye movements that would correct nearly immediately after eye movement stopped. He had no nuchal rigidity. Kernig's and Brudzinski's signs were negative. Chest radiograph showed no acute cardiopulmonary pathology. Computed tomography imaging of the head was negative for any acute intracranial process. Magnetic resonance imaging of the brain with and without contrast was also negative. A lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis showed elevated protein at 74 mg/dL, normal glucose of 95 mg/dL, 14 red blood cells and 10 white blood cells per microliter, all lymphocytes. Gram stain of CSF showed no organisms. Herpes virus PCR and Enterovirus PCR in CSF were both negative. Blood and urine cultures were sent. Urine analysis revealed large blood and only 2 red blood cells per high power field which raised the possibility of myoglobinuria. Initial creatine kinase was measured at 19,154 U/L. Due to persistent fever, he was empirically started on vancomycin and cefepime for concerns of possible bacterial sepsis.

Over the next four days, his mental status gradually improved and his hallucinations resolved, while his creatine kinase rose to 118,400 U/L despite aggressive fluid resuscitation. During this time, his weakness improved, and the muscle tenderness was mild and only reproducible with deep palpation. Due to his rising creatine kinase, a vastus lateralis muscle biopsy was obtained showing only rare hypotrophic fibers, without evidence of rhabdomyolysis or myopathy. A muscle viral myositis and paraneoplastic panel were also sent. When his CSF, blood and urine culture results were finalized as negative, vancomycin and cefepime were stopped. He continued to improve despite discontinuation of antibiotics, without recurrence of his fever. Creatine kinase started to gradually decrease over the next few days. Muscle tenderness resolved. On hospital day eleven, he was discharged home without any neurological deficits. After discharge, CSF results returned positive for both IgM and IgG antibodies to West Nile Virus while the muscle viral and paraneoplastic panel returned negative.

Discussion

The natural transmission cycle of WNV involves birds as the amplifying host and mosquitoes of the Culex species as vectors [1]. Domestic animals and humans serve as incidental hosts with manifestations of the virus ranging from asymptomatic infection to fatal neurologic disease. Dissemination of the virus begins with suppression of immune effector cell trafficking at the site of inoculation and introduction of mosquito salivary components that modulate infection of local cells including keratinocytes and dendritic cells [2]. Viremia develops with the migration of these cells to draining lymph nodes, with subsequent infection of visceral organs and central nervous system via postulated neuroinvasive mechanisms: direct viral crossing through the blood brain barrier due to increased vascular permeability, trafficking of infected tissue macrophages across the blood brain barrier, and/or direct axonal retrograde transport from infected peripheral neurons [2,3].

The human incubation period of WNV is 2 to 14 days. Approximately 80% of infected patients are asymptomatic while 20% develop West Nile Fever. This presents as a nonspecific mild febrile illness with malaise, myalgias, headache, lymphadenopathy, and a pruritic maculopapular rash in up to 50% of these patients. Acute symptoms can last from 3 to 10 days, however prolonged recovery with fatigue and weakness has been reported in some patients weeks to months after incubation [3]. 1 in 150 infected patients with WNV develop neuroinvasive disease which typically comprises of meningitis, encephalitis, or acute flaccid paralysis and has a mortality rate of about 10% [4–6].

Fever, headache, photophobia, and meningismus are consistent with WNV meningitis whereas mild self-limited confusion to severe encephalopathy can indicate WNV encephalitis. Additional evidence of encephalopathy include lethargy, personality changes focal neurologic deficits, new onset or exacerbation of seizures, tremor, myoclonus, and Parkinsonian features. Functional and cognitive difficulties may persist for up to one year following infection, however it has also been shown that the severity of initial encephalopathy does not necessarily result in poor long-term outcomes [6]. Acute flaccid paralysis typically presents without meningitis/encephalitis but is associated with poor long-term outcomes. It involves acute onset of asymmetric limb weakness with marked progression over 48 h, hyporeflexia, and paresthesia [5,7]. Quadriplegia and respiratory failure are associated with high morbidity and mortality, however it has been shown that some patients with initial severe neurological dysfunction have experienced profound recovery [5,8,9].

Other manifestations of WNV-associated neurologic disease include chorioretinitis, myasthenia gravis, seizures, facial weakness, bulbar palsy and disorders similar in presentation to Guillain-Barré syndrome [2,10]. It is imperative that appropriate diagnostic testing, including lumbar puncture, electromyography, and nerve conduction studies be obtained to rule out inflammatory neuropathies prior to initiating therapies.

There have also been reported rare cases of hepatitis, pancreatitis, myocarditis and rhabdomyolysis, as seen in our patient [11]. Muscle weakness or pain has been reported with WNV but reports of rhabdomyolysis in patients with flavivirus infections are rare and creatine kinase elevations are not usually documented [7,8,11]. Risk factors for rhabdomyolysis in patients with WNV illnesses include chronic alcohol abuse or the use of statins for hyperlipidemia. WNV encephalitis patients with involuntary movement disorders are at risk for trauma from falls and immobility which can lead to rhabdomyolysis [11]. Risk factors for developing neuroinvasive disease include advanced age, which is the most important risk factor, hypertension, diabetes, cancer history, and chronic renal disease. Underlying illnesses associated with an increased probability of death include past history of stroke, cardiovascular disease, kidney disease, hepatitis C infection, and diabetes [3,5,12,13].

The diagnosis of WNV includes identification of immunoglobulin M (IgM) antibodies in serum or CSF in patients with neurologic symptoms. Indications for testing include patients who present with unexplained febrile illnesses, encephalitis, meningitis, or flaccid paralysis in regions of WNV activity and during mosquito season of summer and early fall [3]. Warmer climates where year-round transmission is possible should also be considered [3]. IgM and IgG antibodies can be detected by day 4 and day 8 after onset of symptoms, respectively [14]. The relatively short timeframe for IgG antibodies to appear after onset of symptoms explains why our patient had both IgM and IgG antibodies detected in his CSF. In the vast majority of patients, a positive MAC-ELISA test with IgM on CSF or serum is sufficient to make the diagnosis, since IgG can indicate previous infection and provide false positives. However, the role of plaque reduction neutralization tests (PRNT) to validate the initial results is considered the gold standard for diagnosis of WNV infection, since IgM can persist in serum for months to years after infection and cross reactivity exists between all flaviviruses in patients with recent immunization against other flaviviruses [15]. Viral detection methods with PCR is useful in

immunocompromised patients since the development of IgM may be delayed or absent in such patients [16].

Treatment of WNV is primarily supportive. Several investigated therapeutic approaches include immune-gamma-globulin, ribavirin, intravenous immunoglobulin, and corticosteroids [2]. However, due to the highly variable clinical course of WNV infection, no study has documented efficacy of these therapies. Studies of different vaccines in animals suggest efficacy, however no vaccine is licensed for humans [17]. WNV prevention relies in part on methods to reduce the numbers of WNV-infected mosquitoes, including community-based mosquito control programs and blood donor screening programs [18]. Elimination of breeding sites with insecticides, especially with strategically timed early-season control of adult mosquitoes, and public education regarding personal protective equipment has been associated with reduced WNV infection risk [18].

In this case of WNV encephalitis, our patient presented with auditory and visual hallucinations after resolution of diabetic ketoacidosis and eventual progression to severe rhabdomyolysis. Further radiologic examination and muscle biopsy with virology was unremarkable, but the diagnosis of neuroinvasive WNV was confirmed with positive CSF IgM. The patient's newly diagnosed diabetes likely contributed to his susceptibility to neuroinvasive disease; however, WNV encephalitis in a background of DKA has not been previously described and further reiterates that, in the appropriate setting, WNV neuroinvasive disease should be in the differential diagnosis for patients presenting with unexplained neurological symptoms.

Conclusion

The emergence and geographical spread of WNV in recent years suggests that WNV will continue to produce unpredictable outbreaks in the United States. The presentation of WNV infection is highly variable. In this case we describe a patient with neuroinvasive WNV disease that presented in DKA and developed neuropsychiatric symptoms with rhabdomyolysis. This unique presentation reiterates the need for a high index of suspicion in endemic areas to correctly diagnosis this disease and to limit unnecessary diagnostic tests and treatments.

Listed below are the author contributions for this submission

Zachary Burden, MD was the senior resident leading the care of this patient while hospitalized and was instrumental to the discovery of the diagnosis of West Nile Virus infection. Dr. Burden contributed to the manuscript by writing the abstract and editing the manuscript.

Madeline Fasen, DO was the intern responsible for the care of patient while hospitalized and

contributed by writing the discussion portion of the manuscript.

Benjamin Judkins was a medical student that assisted in the care of the patient while hospitalized as well as follow up with the patient after hospital discharge. Mr. Judkins wrote the case presentation

Carmen Isache, MD was the attending physician for the patient and oversaw all clinical care for the patient. Dr. Isache edited the manuscript and wrote the conclusion.

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