CASE REPORT

West Nile virus-associated acute flaccid paralysis

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SUMMARY

A 43-year-old woman presented to George Washington emergency department with 48 h of new-onset inguinal pain. Physical examination revealed a diffuse maculopapular rash involving the palms and soles, as well as inguinal lymphadenopathy. The patient denied recent travel outside of Washington, DC, and had no known sick contacts. She was admitted to the hospital for observation. Within 24 h of admission she developed left lower extremity flaccid paralysis, with loss of left patellar and Achilles reflexes. cerebrospinal fluid was positive for West Nile virus IgG and IgM antibodies, so methylprednisone 125 mg intravenously two times per day was started. On day 7, the patient recovered reflexes and continued to regain strength in the left lower extremity. She was discharged on day 9 on prednisone taper, with outpatient follow-up.

BACKGROUND

West Nile virus (WNV) is the leading cause of arboviral disease in the USA, with 39 557 cases reported to the Centers for Disease Control and Prevention (CDC) since 1999. The infection can present with extremely varied symptomatology, including rare central nervous system presentations. With the increasing incidence of WNV infections, it is important that physicians recognise the rare presentations of WNV, in order to avoid iatrogenic complications from incorrect diagnoses and subsequent treatments.

This case report illustrates a rare neurological presentation of WNV.

CASE PRESENTATION

A 43-year-old woman presented to George Washington emergency department with new-onset inguinal pain for the past 48 h. She had no significant medical history and had been exceptionally healthy as a professional athlete most of her life. She had received the recommended childhood vaccinations, denied recent travel outside of Washington, DC, and had no known sick contacts.

Physical examination revealed centrifugal maculopapular rash including on the palms and soles, with no mucosal membrane involvement, accompanied by painful inguinal lymphadenopathy. The rash was characterised by paresthesia, but without pain or pruritus.

The patient was admitted to the hospital for observation. A punch biopsy of the rash identified non-specific inflammation suggestive of viral exanthema. Within 24 h after admission patient developed left lower extremity flaccid paralysis (2/5 strength), with loss of left patellar and Achilles reflexes.

INVESTIGATIONS

Emergency room vitals on presentation: blood pressure 136/83 mm Hg, heart rate 65 bpm, respiratory rate 19 rpm, temperature 36.8°C, weight 67.1 kg and height 178 cm.

Emergency room complete blood count: white cell count (WCC) 3.53 (L), red blood cell (RBC) 4.28, haemoglobin 13.6, haematocrit 40.8, mean corpuscular volume 95.3, red cell distribution width-SD 44.3, platelet 149, neutrophils 44%, lymphocytes 41%, monocytes 14% (H), eosinophils 1%, basophils 0%; Chem7 WNL.

Lumbar puncture (postonset of flaccid paralysis): cerebrospinal fluid (CSF) WCC 180 (H), RBC 11 (H), neutrophils 29% (H), lymphocytes 66% (H), monocytes 4%, eosinophils 1% (H), glucose 92 (H), LD 283, TP 166 (H).

MRI (72 h postonset of flaccid paralysis): Extensive abnormal signal is seen throughout the thoracic spinal cord, in the central region involving the grey matter. This may be caused by inflammation or ischaemia.

CSF studies: WNV IgG/IgM positive, varicella zoster virus PCR negative, herpes simplex virus 1 and 2 negative, PCR negative, enterovirus panel PCR negative, human herpes virus 6 PCR negative, *Borrelia* spp PCR negative and cytomegalovirus PCR negative.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for asymmetrical flaccid paralysis includes, but is not limited to: WNV paralysis, Guillain-Barré variant, lyme disease, heavy metal toxicity, multiple sclerosis, cauda equina syndrome, botulism, rocky-mountain spotted fever, syphilis, hand, foot and mouth disease and poliomyelitis.

TREATMENT

There is no current treatment for WNV infection and clinical management is supportive.¹ This includes pain management and antiemetic therapy for those with severe meningeal disease, and close monitoring for encephalopathy symptoms of increased intracranial pressure, airway instability and seizures. Acute neuromuscular respiratory failure may require ventilator support.

There is no Food and Drug Association-approved treatment of WNV infection-associated acute flaccid paralysis. Empiric pharmaceutical management, such as corticosteroids and WNV intravenous IgG antibody, has shown efficacy.²

Select clinical trials for WNV infection treatment can be found at <http://clinicaltrials.gov/ct2/home>.³

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OUTCOME AND FOLLOW-UP

On day 7 the patient recovered reflexes and continued to regain strength in the left lower extremity. She was discharged with corticosteroids on day 9, and given follow-up appointments with infectious disease, neurology and physical therapy. She continues to recover strength, but has 4/5 strength in the left lower extremity at 1 year follow-up.

DISCUSSION

WNV is a zoonotic flavivirus carried by over 50 species of mosquitoes in the USA, but most commonly by the *Culex* spp mosquito.⁴ The first human case of WNV infection described was during 1937, in Uganda. The virus spread to the Middle East and, likely via bird migration, to Eastern Europe, causing the 1996 epidemic of human encephalitis in Romania.⁵ The 1999 transatlantic jump to New York City enabled the impressive dissemination of the virus throughout two continents in less than 10 years. Since the initial case, it has been estimated that over 3 million infections have resulted in 780 000 illnesses.⁶

The clinical presentation of WNV infection is highly variable. The CDC approximates 80% of WNV infections to be subclinical, with the remaining patients commonly presenting with an acute systemic febrile illness and maculopapular rash.⁷ Less than 1% of infected patients develop severe neurological illness, such as meningitis, encephalitis and acute flaccid paralysis.⁷

Clinical presentation of WNV acute flaccid paralysis is identical to poliovirus-associated poliomyelitis. The paralysis classically presents as isolated, asymmetric limb paralysis, with or without apparent viral prodrome.⁸ During the acute process, the affected limb exhibits weakness, hypotonia and diminished or absent deep tendon reflexes, without sensory loss. At this point, CSF will demonstrate IgM for WNV.⁹ Rarely, this weakness may progress to respiratory paralysis requiring mechanical ventilation. WNV is infrequently associated with Guillain-Barré syndrome, distinguished from WNV poliomyelitis by clinical symptoms and electrophysiological testing.

The development of WNV neuroinvasive disease is host and viral variant dependent. In murine studies, select North American WNV genetic variants have been shown to have attenuated neuroinvasiveness.¹⁰ Additionally, the risk for neuroinvasive disease increases with age and in organ transplant recipients,^{11 12} while it remains unclear if those with immunodeficiency, diabetes, hypertension and cerebrovascular disease have increased risk.¹³ Finally, murine models have identified a

possible genetic susceptibility to neuroinvasive disease, due to a deficiency in 2'-5'-oligoadenylate synthetase.¹⁴

WNV pathophysiology has yet to be fully elucidated. The virus replicates at the site of inoculation and then spreads systemically to lymph nodes and bloodstream. Murine models have shown neuroinvasive disease can be accomplished through WNV stimulation of neuronal toll-like receptor 3, leading to a tumour necrosis factor α mediated increased blood-brain barrier permeability.¹⁵ WNV causes immune-mediated damage of neurons as well as directly infecting deep neurons of the grey matter.¹⁵ WNV acute flaccid paralysis pathology is identical to poliovirus-associated poliomyelitis; targeting spinal cord grey matter of the anterior horn.⁸

Diagnosis of WNV flaccid paralysis relies on CSF serological demonstration of IgM antibody presence,⁹ but there may be indicators of neuroinvasive earlier than IgM production. While routine clinical laboratory studies are often normal, CSF cytology and MRI of the spine have shown specific patterns in disease.

The CSF cytology of our patients exhibits a pleocytosis, namely, a lymphocyte predominance with significant increase in neutrophils (figure 1), as seen in the other literature on neuroinvasive WNV.¹⁶ The significance of CSF lymphocyte predominant pleocytosis in neuroinvasive WNV is still being debated.^{17 18}

The presence of MRI findings in WNV acute flaccid paralysis is varied in the literature.¹⁹ Our MRI findings show hyperintense T2 signal involving the grey matter of the thoracic spine (figure 2). These findings are in concordance with the patient's symptoms and are seen in similar cases within the literature.²⁰ It should be noted that the MRI was performed 72 h after the onset of paralysis. As many WNV acute flaccid paralysis patients have normal MRIs, there may be a time sensitivity to establishing MRI findings, or perhaps the pathophysiology of disease varies in these patients.

In the recovery phase, the virus appears to be cleared by host immune response in non-fatal WNV infections; WNV paralysis

Figure 1 Cerebrospinal fluid pleocytosis with neutrophilia.

Figure 2 Sagittal T2-weighted MRI of the thoracic spine showing hyperintensity.

patients do not classically regain complete strength in the affected muscle.^{21 22} For muscles experiencing WNV flaccid paralysis, it has been shown that the motor unit number estimation correlates directly with the degree of regained muscle strength, as a 50% survival of motor units can compensate for lost neurons using collaterals.²³

Patient's perspective

- ▶ After my initial discharge from the hospital on 29 September 2013, I experienced severe side effects (insomnia and water retention in the abdomen and thighs) from the steroid treatment and had a persistent lower back pain, which was attributed to the lumbar puncture.
- ▶ I started physical therapy in conjunction with acupuncture almost immediately, yet my progress was slow due to lack of muscle–nerve communication in my left leg. My overall energy level was extremely low and I had difficulty concentrating or reading.
- ▶ I consulted a biochemist and nutritionist to help with the side effects of the steroid treatment as well as support my adrenal gland function, which had consequently suffered, as well as to educate me on how to support my nerve function through nutrition and food supplements.
- ▶ Despite my best efforts, I noticed a steady decline in my leg strength over a period of 7 days and was readmitted to the hospital on 11 November 2013, by my neurologist. He had performed the baseline exam during my initial hospital stay in September, and found that I had no reflexes in my left leg and that I was significantly weaker than a month earlier. With the consultation of an Infectious Disease Physician, another MRI was performed, that showed improvement in the region where the initial inflammation was, but also indicated that the inflammation had 'settled' or moved. A second lumbar puncture showed no acute viral infection. Overall vital signs were good.
- ▶ After some debate, the teams (Neurology, Infectious Disease) decided on a second steroid treatment since I had responded well to it the first time around. Nobody was able to offer any insight as to why I was experiencing this relapse. There was also disagreement on whether or not another round of steroids should be prescribed since it is so invasive and since there was so little insight into the cause for my relapse. I was discharged after 4 days with a steroid taper that lasted for another 10 days.
- ▶ I responded almost immediately to the steroid treatment and started seeing improvements. Aside from insomnia, I experienced no other side effects this time around.
- ▶ Within 2 weeks, I started up my rehab routine and in addition to a modified diet, this has been my rehab plan.
- ▶ I bought a minitrampoline, which allowed me to do cardiovascular exercise without impact. It also triggered nerve–muscle communication and thus muscle growth in my left leg. Over the months, I improved from simple bouncing to now 'running' on the trampoline. The lymphatic system is stimulated through the bouncing, which helped my body flush the toxins from the steroid treatment.

- ▶ I started daily meditation and QiGong in order to support my mental well-being. One of my physicians from the CDC had told me that one of the most challenging issues in overcoming this diagnosis is to maintain a positive outlook. I have to admit that it has been challenging and I definitely recognised depressive phases over the past months.
- ▶ For the past 5 months, I have been seeing a private instructor for a weekly Gyrotonics session. It is an exercise routine developed by a former dancer with influences from dance, yoga and Pilates. The focus is on precise muscle movement with emphasis of developing and strengthening the psoas muscle (incidentally, the MRI showed the most significant abnormal signal in the exact area where the psoas muscle attaches!!) and hamstrings (as opposed to the overused quadriceps). I have learned more and seen more progress in my weekly sessions than in any conventional physical rehab!
- ▶ I use a Power Plate machine, which was initially developed by NASA to prepare astronauts for space travel, in helping build muscle and bone density. <http://www.powerplate.com/us/>
- ▶ I see a Chinese acupuncturist who is also a trained Western medical doctor, monthly.
- ▶ I have made impressive progress according to my neurologist, who performed a baseline exam on me on 24 June 2014. I am scheduled today, 2 July 2014, for an EMG to explore the nerve health of my left leg. I am walking with only a slight indication of a limp. I still cannot run but am hoping to start water running next week in combination with easy treadmill running.

Learning points

- ▶ West Nile virus (WNV) can present as acute asymmetric flaccid paralysis.
- ▶ Diagnosis of WNV is dependent on cerebrospinal fluid (CSF) positivity for WNV IgM.
- ▶ CSF cytology will often include neutrophilia and lymphocytosis.
- ▶ MRI of WNV spinal cord involvement will variably demonstrate T2 hyperintensity in the affected region, but may show normal MRI findings.

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