Empirical Treatment of West Nile Neuroinvasive Disease with IVIG

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Abstract—West Nile Neuroinvasive disease (WNND) is associated with high mortality and morbidity. Currently, there is no proven therapy. Animal studies and anecdotal reports suggested potential benefit of intravenous immune globulin (IVIG). We report our experience of IVIG for WNND. We retrospectively reviewed the clinical features and outcome of four consecutive patients with WNND who were admitted to our Neuro ICU between September 1 and October 31 of 2014. The diagnosis was confirmed with CSF and serum antibodies or PCR. Two patients with severe encephalitis and one with acute myelitis were treated with IVIG intravenously at 400mg/kg daily for 5 days. One patient with milder symptoms was managed with supportive care only. There was significant improvement in all 3 cases treated with IVIG. The patient with most severe WNND recovered from coma, quadriplegia and respiratory failure with good cognitive function and reasonable motor strength. In conclusion, all patients with severe WNND survived following IVIG therapy. Randomized control study is warranted to evaluate the efficacy of IVIG for WNND.

Keywords — West Nile; Encephalitis; Myelitis; IVIG; West Nile Neuroinvasive Disease (WNND).

I. INTRODUCTION

West Nile virus (WNV) is an arbovirus primarily transmitted to humans through mosquito bites.1 WNV is endemic to the Middle East, West Asia, and Africa. Increasing numbers of cases are being reported in the United States. The first reported cases in the United States were a localized epidemic of encephalitis in New York City in 1999.1,2 The usual flu-like febrile symptoms are self-limiting. However, meningitis, encephalitis and acute flaccid paralysis (AFP) are manifestations of West Nile Neuroinvasive disease (WNND).3 In 2012, of the 5674 cases reported in the United States, 51% of these were neuroinvasive.4 Twenty-eight percent of neuroinvasive cases were reported to have WN Encephalitis (WNE), 18% to have meningitis, and 4% to have acute flaccid paralysis (AFP). The mortality rate of WNND was as high as 30%.3,4,5 Severe residual weakness is very common, with only 21% WNE survivors returning to a prehospitalization level of function.3,5,6

In spite of significant morbidity and mortality, the treatment for WNND is mainly supportive. High-titer WNV-specific intravenous immunoglobulin (IVIG) was initially used for the treatment of neuroinvasive disease in Israel.7,8 Makhoul et al. reported a case series of 8 patients and showed that earlier treatment with IVIG led to better and faster neurologic recovery.7 Shimoni et al. then reported their case series of 12 patients and showed more rapid recovery and better outcome in patients treated with IVIG as compared to the those not treated with IVIG.8 There were 5 case reports on the treatment of WNND with IVIG in the U.S.9-13 There were a total of 8 solid organ transplant patients with WNND who were treated with IVIG.9,10,12,13,14 Five of the 8 patients survived. Haley et al. described a case of fatal WNE in a patient with Chronic Lymphocytic Leukemia despite of IVIG treatment.11 Here we report 4 cases of WNND treated at our Neurointensive Care Unit. To our knowledge, this is the first reported case series of WNND treated with IVIG in non-solid organ transplant patients in the US.

II. CASE SERIES

The demographics, clinical feature, treatment and outcome of the 4 consecutive patients treated at our Neuro ICU between September 1 and October 31 of 2014 are summarized in Table 1.

Patient #1 is a 62 year-old male with past medical history of hypertension, hypercholesterolemia, and diverticulitis who presented with agitation and a fall. His initial neurological examination was only significant for confusion. Imaging study
showed traumatic compression fracture of 12th thoracic vertebra. He became delirious and more agitated on hospital day 4. He was therefore transferred to Neuro ICU for further evaluation. On arrival in the ICU, he was non-verbal but followed simple commands. He was intubated on hospital day 6 for worsening mental status and inability to protect airway. MRI scan of brain revealed mild atrophy and periventricular white matter changes. Both serum and CSF were positive for WNV IgG and IgM. He was empirically treated with IVIG for 5 days from hospital day 8 to day 12. Despite complicated hospital course from the development of deep venous thrombosis in bilateral lower extremities, acute tubular necrosis and urinary tract infection (UTI), his mental status improved after empirical therapy with IVIG. He underwent tracheostomy on hospital day 15, and tolerated being on a trach collar prior to transfer to Long Term Acute Care facility after 21 days in the ICU.

Patient #2 is a 61 year-old male with a history of Follicular Lymphoma in remission (on Rituxan infusion every 2 months) who presented with fever, body aches, and watery stools for 3 days. He was oriented to time, place and name with good strength in both arms and legs at admission. He deteriorated gradually and became unresponsive with quadriplegia and respiratory distress over the next few days. He was therefore transferred to Neuro ICU on hospital day 8 for higher level of care. He was emergently intubated for aspiration pneumonia and severe ARDS. MRI Brain revealed bilateral cerebellar hyperintensities on FLAIR sequence suggestive of edema. The polymerase chain reaction (PCR) assay for West Nile viral RNA in the serum was positive. He was treated with IVIG from hospital day 10 to day 15. A repeat MRI brain one week after IVIG therapy showed decreased cerebellar edema. He underwent tracheostomy for prolonged ventilator dependence. His hospital course was also complicated by deep venous thrombosis in both lower extremities and segmental pulmonary embolism. He was treated with long-term anticoagulation. After tolerating weaning of ventilator support, he was transferred to long-term subacute care facility on hospital day 40. He was awake, following commands and moving all extremities with generalized weakness at the time of hospital discharge.

Patient #3 is an 82 year-old male with history of coronary artery disease, hypercholesterolemia, chronic kidney disease, and obstructive sleep apnea who presented with fever for 10 days. He developed new left arm weakness and became somnolent after admission. He was intubated for airway protection and transferred to the neuro ICU for further evaluation. Extensive work-up showed positive West Nile IgM in serum and CSF. MRI scan of the brain did not show any significant abnormality. His hospital course was complicated
by generalized weakness, aspiration pneumonia, and UTI. He received antibiotics for infection and methylprednisolone for 5 days. He subsequently improved and tolerated extubation on hospital day 9. He was transferred out of the ICU on hospital day 13.

Patient #4 is a 63-year-old right-handed man with history of right knee arthritis who was transferred from outside hospital for evaluation of progressive bilateral asymmetric lower extremity weakness, numbness, burning pain in his pelvis, urinary and fecal incontinence for 6 days. On arrival, he had normal mental status, and normal strength in upper extremities. His strength was 4/5 in right lower extremity, and 3/5 in left lower extremity with foot drop. MRI of thoracolumbar spine showed cord edema at T11-L1 levels with extension into nerve roots. Lab test showed WNV IgG and IgM in CSF and serum. He was treated with IVIG for 5 days. He showed improvement in motor and sensory exam, urinary retention and fecal incontinence. He was discharged home on hospital day 21.

III. DISCUSSION

Since the first outbreak of WNV in 1999, there have been epidemic WNV spikes across the United States. Neuroinvasive west nile infection portents significant risk of morbidity and mortality. Supportive care is the only recommended treatment per CDC guideline. Despite of anecdotal reports of potential benefit, IVIG is not recommended as a therapy. This poses a great challenge to physicians who take care of patients with life threatening WNN. Should we treat or not treat WNN with IVIG? To err on the safe side, it is reasonable to treat a life threatening condition with potentially effective therapy if the risk of devastating side effect is low.

Considering high morbidity and mortality of WNN and potential benefit of IVIG without significant adversary effect, we treated 3 patients with severe WNN with IVIG. There was significant improvement in mental status, respiratory function, or symptoms of myelitis in all 3 patients treated with IVIG. One recovered from coma and quadriplegia. Although there were only 4 patients in this case series, we demonstrated that all 3 patients with severe WNN survived after aggressive therapy including empirical IVIG.

IV. CONCLUSION

In this case series, we report that 3 patients with severe WNN survived with reasonable good recovery following IVIG therapy. Randomized control study is warranted to evaluate the efficacy of IVIG for WNN.

REFERENCES
4. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6225a1.htm?s_cid=mm6225a1_e

Questions (please choose one single answer):
1) What is the most common form of WNND in US?
   a) Encephalitis
   b) Acute flaccid paralysis
   c) Meningitis
2) The mortality rate of WNND has been reported to be as high as?
   a) 5%
   b) 15%
   c) 30%
   d) 50%
3) What proportion of reported West Nile cases are Neuroinvasive?
   a) 20%
   b) 30%
   c) 50%
   d) 70%
4) What is the mode of transmission of West Nile virus to humans?
   a) Tick bite
   b) Food borne
   c) Transmission via aerosol
   d) Mosquito bite
Answers

1) a) 28% percent of neuroinvasive cases were reported to have West Nile Encephalitis, 18% to have meningitis, and 4% to have acute flaccid paralysis (AFP). 3,4,5

2) c) The mortality rate of WNND was as high as 30%. 3,4,5

3) c) In 2012, of the 5674 cases reported in the United States, 51% were neuroinvasive. 4

4) d) West Nile virus (WNV) is an arbovirus primarily transmitted to humans through mosquito bites. 1