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Authors
Mukerji, Shibani S
Lam, Alice D
Wilson, Michael R

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Eastern Equine Encephalitis Treated With Intravenous Immunoglobulins

Shibani S. Mukerji, MD, PhD1, Alice D. Lam, MD, PhD1, and Michael R. Wilson, MD2

Abstract
We report the case of a 68-year-old man from southeastern Massachusetts presenting with encephalitis due to eastern equine encephalitis (EEE) virus. Despite the high morbidity and mortality rate of EEE, the patient made a near complete recovery in the setting of receiving early intravenous immunoglobulins.

Keywords
encephalitis, central nervous system infections, central nervous system, viral diseases, movement disorders

Case
A 68-year-old man from southeastern Massachusetts presented to the emergency department (ED) in early September, with 4 days of fever, headache, fatigue, generalized weakness, nausea, vomiting, neck discomfort, and 1 day of inattention and difficulty putting on his clothes after camping in a Massachusetts state park 6 days previously. He had a temperature of 104.8°F, pulse of 95 beats/min, blood pressure of 134/74 mm Hg, and respiratory rate of 18 breaths/min with an oxygen saturation of 96% on room air. In the ED, he was lethargic and inattentive but still recognized his family and knew the name of the president and the Republican presidential nominee. The family confirmed there was no relevant exposure history aside from the recent camping trip where he was bitten by mosquitoes. He had no exposures to tuberculosis and no known exposures to rodents, or wild game. His hometown had been sprayed a second time for mosquitoes 3 weeks prior due to rising pools of eastern equine encephalitis (EEE)-infected mosquitoes. Laboratory workup demonstrated a peripheral white blood cell (WBC) count of 13.4 K/μL (96% neutrophils and 3% lymphocytes) and serum sodium of 132 mEq/L. The cerebrospinal fluid (CSF) had 330 nucleated cells/mm³ (11% neutrophils, 68% lymphocytes, and 21% monocytes), 30 red blood cells/mm³, protein 94 mg/dL, and glucose 64 mg/dL. An opening pressure was not documented. The patient was started on broad-spectrum antibiotics and intravenous acyclovir.

The next day, the patient was transferred to the intensive care unit with persistent fevers over 104°F and neurological decline characterized by coarse tremors, delirium, and agitation requiring intubation. On examination, he was comatose with intact brain stem reflexes, decerebrate posturing of the arms, triple flexion of the legs, and diffuse hyperreflexia. Magnetic resonance imaging (MRI) demonstrated extensive T2-weighted hyperintensities in the midbrain, insula, basal ganglia, and thalamus bilaterally (Figure 1A and B); diffusion-weighted image sequences were normal. Cerebrospinal fluid Gram stain, aerobic cultures, and herpes simplex virus 1 and 2, and polymerase chain reaction (PCR) were negative. Cerebrospinal fluid Lyme immunoglobulin (Ig) G and IgM antibodies were <1:4 and <1:1, respectively. A CSF sample sent to the Massachusetts Department of Public Health to test for EEE virus and West Nile virus (WNV) returned a positive IgM enzyme-linked immunosorbent assay (ELISA) for EEE virus that was confirmed by plaque reduction neutralization assay. The ELISAs for WNV IgG, IgM, and EEE IgG were negative (titers not reported). Antimicrobials were discontinued. After extensive discussion with the family about EEE’s high morbidity and mortality, the family opted for empiric treatment with intravenous immunoglobulin (IVIg) based on limited case report data.1

The patient started IVIg (0.4 g/kg/d) on day 2 of admission (6 days after symptoms began). On treatment day...
(TD) 3, he opened his eyes to voice and protruded his tongue to command. On TD 4, he had purposeful movements of the arms and spontaneous movement of the legs. Prominent bilateral upper extremity myoclonus was present (Video 1). He was discharged to rehab 3 weeks after presentation, with severe inattention and minimal vocalization. Strength was antigravity in all limbs, and the myoclonus had resolved.

One month later, he returned home with improvement in communication and memory skills, scoring 28 of 30 on the Montreal Cognitive Assessment. Three months later, his repeat MRI demonstrated marked improvement (Figure 1C and D). Nine months after his acute illness, he returned to driving, cooking meals for a group of 50 veterans, and singing Irish ballads to his family. His Mini-Mental State Examination was 29 of 30.

**Discussion**

Eastern equine encephalitis virus is an alphavirus and is the most severe neuroinvasive arboviral infection in the United States, frequently progressing to coma and death. The virus is endemic along the eastern seaboard and Gulf coast. The disease prodrome is characterized by headache, malaise, nausea and vomiting, confusion, and meningeal signs. In a recent case series, the median CSF WBC count was 370 cells/mm$^3$ (median 70% neutrophils). The median total protein was 97 mg/dL, and hypoglycorrhachia was typically absent. Diagnosis of EEE encephalitis relies upon the detection of IgM antibodies in the serum and/or CSF. An EEE virus PCR test is also available, and virus isolation from CSF or brain remains the diagnostic gold standard.

Our patient had a remarkable and rare neurological recovery. Several favorable factors included a CSF WBC count of less than 500 cell/mm$^3$ and minimal hyponatremia. His brain MRI did not show evidence of restricted diffusion, indicating that severe tissue destruction including ischemic changes was not present prior to initiating IVIg. The mechanism of neurological injury in EEE is likely a combination of direct cytolysis viral injury and extensive inflammatory reaction, although the exact mechanisms remain unclear. In this case, IVIg was given early, approximately 48 hours after neurological symptoms developed and prior to a confirmed diagnosis of EEE, although EEE was strongly suspected, given the patient’s risk factors as well as his high fever and classic brain MRI and CSF profiles. Intravenous immunoglobulin has been used to treat many immune-mediated neurological diseases as it inactivates or silences autoreactive T cells, neutralizes pathogenic antibodies by anti-idiotypic antibodies, and downregulates the production of antibodies. Intravenous immunoglobulin has 2 principal components: the antigen-binding domains that are involved in adaptive immunity and the Fc fraction involved in innate immunity. The use of IVIg for viral encephalitis remains controversial. Multiple case reports suggest improved clinical outcomes following IVIg treatment for viral encephalitis including WNV and Japanese encephalitis virus summarized in a recent review by Ruzek et al. A randomized placebo-controlled clinical trial for the treatment of WNV neuroinvasive disease with IVIg that contains antibodies specific to WNV (Omr-IgG-am) was completed in 2007. However, the trial results have not been reported (ClinicalTrials.gov Identifier: NCT00068055). Eastern equine encephalitis is a rare disease, and it remains unclear whether this successful outcome is due to host factors, natural variability in EEE outcomes, or due to early IVIg intervention. This is the third report of a patient with EEE virus encephalitis treated with IVIg who made an excellent recovery. While there is no rigorous evidence that IVIg alters the natural history of EEE infections, IVIg is a well-tolerated treatment strategy that remains a reasonable consideration, given the high morbidity and mortality of EEE encephalitis, especially in elderly individuals.

**Authors’ Note Contributions**

S. S. Mukerji drafted/revised the manuscript, including medical writing for content, study concept or design, analysis, or interpretation of data. A. D. Lam drafted/ revised the manuscript for content.
including medical writing for content. M. R. Wilson drafted/revised
the manuscript, including medical writing for content, study concept
or design, analysis of interpretation of data, and study supervision or
coordination.

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