



Eastern Equine Encephalitis Virus: A Case Report and Brief Literature Review of Current Therapeutic and Preventative Strategies

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Abstract

Background: Eastern equine encephalitis virus (EEEV) is a rare mosquito-borne illness exhibiting rapid neurological deterioration and permanent damage. Despite its >30% mortality and >60% long-term neurological damage, EEEV has no approved antiviral medication or vaccination. This report uniquely aims to describe a rare case of EEEV and provide a current literature review of therapeutic and preventative options from the clinical perspective to guide clinicians and public health workers, along with informing them about its impact and current knowledge gaps.

Methods: A retrospective chart review of the electronic medical record was performed for a patient's 10-day hospital admission in July 2021. In addition, PubMed was searched using relevant keywords for a literature review of EEEV.

Results: A 61-year-old woman presented with dysarthria and right-sided facial droop. Acute ischemic stroke was ruled out, and empiric intravenous (IV) antibiotics were initiated for possible infectious etiology. The patient developed worsening mental status and fever and was intubated, with antibiotics broadened with concern for meningitis along with tick-borne illness. The patient remained encephalopathic and febrile, and lumbar serologies were consistent with viral meningoencephalitis or acute disseminated encephalomyelitis. Several days after collection, quantitative antibody testing returned positive for EEEV. The patient was pronounced dead on hospital day 10. On review of the literature regarding EEEV, supportive care and prevention remain the cornerstone of management. Although early IV immunoglobulin and high-dose steroids have shown potential as treatments to reduce morbidity and mortality, no vaccines have been approved to date.

Conclusion: Prospective trials and further investigations into treatment and preventative options may be useful in reducing the morbidity and mortality associated with EEEV.

Keywords: case report, EEEV, IVIG, steroids, vaccine

Introduction

EASTERN EQUINE ENCEPHALITIS VIRUS (EEEV) is a rare but severe mosquito-borne illness that occurs at an average annual incidence of 11 cases in the United States, with 2 cases most recently in Georgia in 2021 (Centers for Disease Control and Prevention, 2022). As an alphavirus within the group of arboviruses, EEEV spreads through a single strand

of RNA commonly through *Culiseta melanura* mosquitoes, with various tree-perching birds in forested wetlands existing as part of the enzootic cycle (Morens et al., 2019; Powers, 2021). Although humans and horses are unable to develop sufficient viremia levels to infect other susceptible hosts and are, therefore, considered *dead-end hosts*, mosquito vectors can cause fatality from this arboviral encephalitis (Corrin et al., 2021; Millet et al., 2021; Morens et al., 2019).

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Hypothesized risk factors for contraction and severe disease include activity or habitation in boggy areas (particularly between July and September), pheasant farmers/handlers, immunocompromised states, male gender, and age <15 years or >50 years (Berlin et al., 2017; Centers for Disease Control and Prevention, 2022; Corrin et al., 2021; D’Onofrio, 2020; Pouch et al., 2019). Symptoms are often nonspecific, and laboratory testing may also be unremarkable, including EEEV-specific immunoglobulin M (IgM) (Morens et al., 2019).

Rapid neurological deterioration and permanent damage typically occur before definitive serological diagnosis through EEEV-specific IgM, immunoglobulin G (IgG), and neutralizing antibodies (D’Onofrio, 2020; Morens et al., 2019). Despite its >30% mortality and >60% long-term neurological damage—paralysis, cognitive impairment, and seizures—EEEV currently has no Food and Drug Administration (FDA)-approved antiviral medication or vaccination for its treatment or prevention (Corrin et al., 2021; D’Onofrio, 2020; Morens et al., 2019; Wilcox et al., 2021).

Methods

A retrospective chart review of the electronic medical record was performed for a singular patient’s 10-day hospital admission in July 2021. In addition, PubMed was searched from 1933 to 2022 using the following search terms: eastern equine encephalitis, EEEV, EEEV prevention, and EEEV treatment. Relevant articles were retrieved, and the results were used to delineate current therapeutic and preventative strategies regarding EEEV. Specifically, articles related to EEEV therapeutics in humans were utilized, with the aim of providing a focused literature review to guide clinicians involved in the care of patients with EEEV. Therefore, *in vitro* and animal studies on treatments for EEEV were excluded.

Furthermore, this is a retrospective case report with deidentified patient data. The institutional review board has, therefore, confirmed that no documentation of ethical approval is required.

Case Presentation

A 61-year-old woman with a medical history significant for tobacco use and coronary artery disease status post stent presented to the emergency department (ED) in July 2021 by ambulance where the ED triage nurse found her dysarthric with right-sided facial droop. Of note, her social history is significant for living in a heavily wooded area in Georgia near a lake. Her family states her symptoms began the night prior and have progressively worsened. The patient’s initial vitals were as follows: pulse rate 125 beats per minute, oxygen saturation 98% on room air, temperature 36.8°C, respiratory rate 20 breaths per minute, and blood pressure 145/75 mmHg.

Noncontrast computed tomography (CT) scan, CT angiography, and magnetic resonance imaging (MRI) of her head revealed no intracranial process. Laboratory results revealed a leukocytosis (white blood cell count 18,000 cells/mm³) with an increased neutrophil percent (90.6%). With acute ischemic stroke ruled out by neurology, intravenous (IV) fluids and IV vancomycin and piperacillin/tazobactam were initiated in the early resuscitation phase as empiric treatment

for possible infectious etiology. Shortly afterward, the patient became increasingly diaphoretic and was noted to be febrile (40.9°C).

Given worsening mental status and newfound fever, a bedside lumbar puncture (LP) was performed. Cerebral spinal fluid (CSF) was pertinent for elevated total nucleated cells of 1059 cells/ μ L, elevated neutrophil percent of 40%, normal glucose of 59 mg/dL, and elevated total protein of 130.6 mg/dL.

Once transferred to an intensive care unit (ICU), the patient’s oxygenation status worsened, and she was eventually intubated. The infectious disease (ID) team was consulted, and the team broadened her coverage from vancomycin and piperacillin/tazobactam to include IV ceftriaxone, ampicillin, and acyclovir for bacterial or viral meningitis. An Arctic SunTM was placed on the patient to reduce her core temperature.

The following day, doxycycline was added to the patient’s antibiotic regimen for coverage of tick-borne illness. Video electroencephalography (EEG) monitoring was performed to rule out seizure activity. The EEG was consistent with severe encephalopathy.

The patient remained febrile despite cooling blankets and antipyretics. Blood cultures remained negative at 72 h. On ICU day 4, the ID team raised concerns for an arboviral versus autoimmune etiology and ordered indirect fluorescent antibodies and serologies for West Nile virus, St. Louis encephalitis, California encephalitis, and EEEV. A repeat LP was performed that showed increased nucleated cells (223 cells/ μ L) and mostly lymphocytes (69%), consistent with viral meningoencephalitis or acute disseminated encephalomyelitis. IgM was negative in the CSF. All antibiotics were discontinued at this time except for doxycycline.

On day 10, 7 days after specimen collection, quantitative antibody testing for EEEV returned with IgG titer 1:2 and IgM titer 1:128. The patient remained unresponsive despite no sedation, was found to have fixed and dilated pupils along with an absent gag and corneal reflex, and was pronounced dead after being placed on comfort measures by family. Meningoencephalitis and acute respiratory failure were denoted as the official causes of death.

Literature Review

There are currently no FDA-approved antiviral medications or vaccinations for EEEV. Treatment remains largely supportive, including seizure management with antiepileptic therapies. In addition, patient isolation is not necessary, as patients are not contagious (D’Onofrio, 2020; Millet et al., 2021; Morens et al., 2019; Wendell et al., 2013).

Thus far, two treatments have been implemented in patients with EEEV: IV immunoglobulin (IVIG) and IV corticosteroids—both with mixed success in terms of morbidity, although with a possible mortality benefit (Cho et al., 2019; Wendell et al., 2013; Wilcox et al., 2021). In a case report by Cho et al. (2019), a 5-day course of 0.4 g/(kg·d) IVIG monotherapy was used; the patient survived but was ultimately nonverbal, unable to follow simple commands, unable to walk, and completely dependent in her activities of daily living (Cho et al., 2019).

In contrast, both Wendell et al. (2013) and Wilcox et al. (2021) used a combination of IVIG and corticosteroids.

In a case report by Wendell et al. (2013), a combination of 0.4 g/(kg·d) IVIG and high-dose (1 g/d) IV methylprednisolone was associated with a dramatic recovery and ultimate good outcome, including seizure prevention (Wendell et al., 2013). Furthermore, in a case series by Wilcox et al. (2021) of 17 patients with EEEV, a total of 11 patients (65%) received IVIG (typical dose 0.4 g/(kg·d) for 5 days), and a total of 8 patients (47%) received high-dose (>100 mg of prednisone equivalent per day) methylprednisolone or dexamethasone.

Six patients (35%) received both IVIG and steroids, five (29%) received IVIG alone, two (12%) received steroids alone, and four (24%) received supportive care alone. Mortality among the 17 patients was 12%, and all but 2 patients had improvement in their modified Rankin Scale scores by a median of one point between admission and follow-up, with the suggestion that early IVIG may correlate with a decrease in long-term disability ($r=0.72$, $p=0.02$)—although high-dose steroids were not correlated with disability (Wilcox et al., 2021).

Various mechanisms have been proposed for the benefit of IVIG and steroids in patients with EEEV. EEEV is thought to cause both direct neuronal injury and inflammatory damage, leading to necrosis and demyelination of neurons, and these agents are believed to act on these pathways, along with halting cytotoxic cerebral edema through the inflammatory cascade. Intracranial pressure monitoring with an external ventricular device may be useful for monitoring and intervening on this process (Wendell et al., 2013).

Regarding IVIG, the dimeric antigen-binding fragment, F(ab')₂, and the constant fragment (Fc) may provide the immunomodulatory effect. F(ab')₂-dependent mechanisms involve a reduction in inflammatory cells and anaphylatoxin, blockade of cellular receptors, and neutralization of auto-antibodies. Fc-dependent mechanisms involve saturation of the neonatal Fc receptor (FcRn), enhancement of expansion of regulatory T (Treg) cells, modulation of dendritic cells, prevention of immune complex binding to low-affinity Fcγ receptors (FcγRs), and modulation of activating and inhibitory FcγR expression on innate immune effector cells and B cells (Cho et al., 2019).

Although there are limited treatment options, several prevention strategies can be implemented. Education regarding mosquito bite prevention and mosquito-borne illness—including the use of insect repellents, insecticides, and larvicides; long-sleeved shirts and pants; and containment measures within homes to reduce aqueous mosquito breeding locations—remains a cornerstone of prevention strategies (Corrin et al., 2021; D'Onofrio, 2020).

In addition, state and local health departments can conduct surveillance of equids, birds, and mosquitos to provide early warnings of human infections (Morens et al., 2019). Providers can aid in this surveillance, as EEEV is a nationally notifiable condition, meaning that all cases should be immediately reported to local public health authorities (Centers for Disease Control and Prevention, 2022).

Lastly, several vaccine types against EEEV—including virus-like particles, subunit vaccines, vectored/chimeric vaccines, nucleic acid vaccines, and live attenuated vaccines—have so far been tested in animal models. However, the rarity, brevity, and unpredictability of the disease may prevent finalization and licensure of a vaccine, particularly for a

specific target population (Powers, 2021). Still, a vaccine against EEEV may be particularly useful for people at high occupational risk, such as laboratory workers (Morens et al., 2019; Powers, 2021).

Although decades of human data under a U.S. Army Investigational New Drug program have supported the use of an inactivated EEEV vaccine, full licensure has not been planned due to manufacturing constraints. In addition, alternatives are being developed, including two trivalent vaccines against all three encephalitic alphaviruses (EEEV, Venezuelan equine encephalitis virus, and western equine encephalitis virus), which have recently completed phase I trials (Pierson et al., 2021).

Discussion

This case report and literature review uniquely provides a case of EEEV along with details regarding the existing therapeutic and preventative options to guide clinicians and public health workers involved in the care of patients with EEEV, while informing them about both the impact and current knowledge gaps of the disease state. Despite the lack of FDA-approved antiviral medications or vaccinations for EEEV, there were various opportunities to possibly optimize care for this patient based on the present literature review.

Supportive care was appropriately provided throughout the patient's inpatient stay, as this currently remains the mainstay of treatment for EEEV. In addition, the appropriate laboratory tests and images were obtained, including CT scan, CT angiography, MRI of her head, CSF samples, EEG monitoring, viral serologies, and quantitative antibody testing. However, IVIG and/or IV corticosteroids could have been used to potentially optimize this patient's recovery.

IVIG and corticosteroids mechanistically have shown promise as therapeutic options for the treatment of EEEV (Cho et al., 2019; Wendell et al., 2013; Wilcox et al., 2021). Although both interventions have demonstrated mixed success regarding morbidity, they have the potential to improve mortality for patients with EEEV and could have improved the outcome for the patient described in the present case report. Various dosing schemes and therapeutic permutations have been utilized in the literature, with 0.4 g/(kg·d) IVIG for 5 days and high-dose steroids appearing to be consistent dosing schemes (Cho et al., 2019; Wendell et al., 2013; Wilcox et al., 2021).

Particularly, early IVIG seems to be beneficial for these patients, although the early initiation may be limited by the obtainment of serologies early in the disease course, along with the identification of positive serologies based on institutional laboratory limitations. In the present case, EEEV was not placed in the differential until day 4 of hospitalization, and serologies returned 7 days after specimen collection due to the need for an outside laboratory for these tests.

Because EEEV is a nationally notifiable condition, this case was reported to local public health authorities. For the health and well-being of the general population, education regarding mosquito bite prevention and mosquito-borne illness by public health authorities and providers can continue to be widely communicated, particularly during warmer seasons with increased outdoor activity. This is particularly pertinent for the patient presented, as her symptoms occurred

in July. Moreover, due to the geographic location of this patient within a heavily wooded area in Georgia near a lake, the patient could have benefited from a vaccine against EEEV had one been available.

Overall, to improve the morbidity and mortality of patients affected by EEEV, future studies would be useful in determining the most effective intervention—IVIG, steroids, or both—in treating EEEV, along with the safest and most efficacious dosing strategy. In addition to manufacture optimization, future studies would be useful in accelerating the approval of vaccines against EEEV. Unfortunately for now, clinicians must rely on supportive care, and public health authorities and providers have the responsibility in preventing further cases of EEEV through education and surveillance.

Conclusion

EEEV is a rare but severe and potentially deadly disease transmitted through mosquitos. Although supportive care and preventative measures remain the cornerstone of management, early IVIG and high-dose steroids have shown potential as treatments for this disease to reduce both morbidity and mortality. In addition, several vaccines are in development, although there are various barriers to their finalization and licensure. To further advances in the management of this disease, prospective trials and further investigations in potential treatment and preventative strategies may be useful in reducing this morbidity and mortality.

Authors' Contributions

C.R. carried out conceptualization (support), formal analysis (lead), investigation (support), methodology (lead), project administration (lead), supervision (lead), visualization (lead), writing—original draft preparation (lead), and writing—review and editing (lead). G.G. was involved in conceptualization (support), formal analysis (support), investigation (support), methodology (support), visualization (support), writing—original draft preparation (support), and writing—review and editing (support).

S.R. carried out investigation (lead), methodology (support), visualization (support), writing—original draft preparation (support), and writing—review and editing (support). K.F. was in charge of conceptualization (lead), formal analysis (support), investigation (support), methodology (support), visualization (support), writing—original draft preparation (support), and writing—review and editing (support).

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References

- Berlin D, Gilani AI, Grewal AK, et al. Eastern equine encephalitis. *Pract Neurol* 2017;17:387–391; doi: 10.1136/practneurol-2017-001659.
- Centers for Disease Control and Prevention. Eastern equine encephalitis (EEE). Atlanta, GA; 2022. Available from: <https://www.cdc.gov/easternequineencephalitis/index.html> [Last accessed: April 16, 2022].
- Cho JJ, Wong JK, Henkel J, et al. Acute seroconversion of eastern equine encephalitis coinfection with California serogroup encephalitis virus. *Front Neurol* 2019;10:242; doi: 10.3389/fneur.2019.00242.
- Corrin T, Ackford R, Mascarenhas M, et al. Eastern equine encephalitis virus: A scoping review of the global evidence. *Vector Borne Zoonotic Dis* 2021;21(5):305–320; doi: 10.1089/vbz.2020.2671.
- D'Onofrio LE. Eastern equine encephalitis virus: A current and future danger. *J Nurse Pract* 2020;16:744–746; doi: 10.1016/j.nurpra.2020.08.006.
- Millet N, Faiek S, Gurrieri D, et al. Deadly neuroinvasive mosquito-borne virus: A case of eastern equine encephalitis. *Perm J* 2021;25:1–4; doi: 10.7812/TPP/20.288.
- Morens DM, Folkers GK, Fauci AS. Eastern equine encephalitis virus—Another emergent arbovirus in the United States. *N Engl J Med* 2019;381:1989–1992; doi: 10.1056/NEJMp1914328.
- Pierson BC, Cardile AP, Okwesili AC, et al. Safety and immunogenicity of an inactivated eastern equine encephalitis virus vaccine. *Vaccine* 2021;39:2780–2790; doi: 10.1016/j.vaccine.2021.03.030.
- Pouch SM, Katugaha SB, Shieh W-J, et al. Transmission of eastern equine encephalitis virus from an organ donor to three transplant recipients. *Clin Infect Dis* 2019;69(3):450–458; doi: 10.1093/cid/ciy923.
- Powers AM. Resurgence of interest in eastern equine encephalitis virus vaccine development. *J Med Entomol* 2022;59(1):20–26; doi: 10.1093/jme/tjab135.
- Wendell LC, Potter NS, Roth JL, et al. Successful management of severe neuroinvasive eastern equine encephalitis. *Neurocrit Care* 2013;19:111–115; doi: 10.1007/s12028-013-9822-5.
- Wilcox DR, Collens SI, Solomon IH, et al. Eastern equine encephalitis and use of IV immunoglobulin therapy and high-dose steroids. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e917; doi: 10.1212/NXI.0000000000000917.

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