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Case report

Case of fatal eastern equine encephalitis

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ABSTRACT

Eastern Equine Encephalitis (EEE) is a rare and very serious arbovirus that is transmitted to humans through the bite of infected mosquitoes. When symptomatic, patients with this condition are typically seriously ill and the fatality rate is high. We present a fatal case of EEE that exhibited classic symptoms and findings. Included are high quality MRI images that show the classic radiographic findings of this infection. In addition to confirmatory laboratory findings, the case report includes pathologic specimens from brain tissue obtained at autopsy. Perhaps due to climate change and human encroachment on mosquito habitat, there is a westward spread of EEE in the United States.

Introduction

Eastern Equine Encephalitis (EEE) is a rare arbovirus infection that is predominantly found in the eastern United States. It is most commonly seen in the summer months, consistent with the presence of mosquito activity. Classic symptoms include fever, meningismus, altered mental status and seizures. Laboratory findings include serum hyponatremia, leukocytosis, positive inflammatory markers, and an abnormal CSF with pleocytosis, often with a neutrophilic predominance, increased protein and normal glucose. Antibody testing is typically positive in serum and CSF, however conversion may be delayed. Currently, there are no effective treatments and when symptomatic, the case fatality rate is high. High index of clinical suspicion is required, particularly as this disease is spreading westward through the United States.

Case report

A 64-year-old Caucasian woman from Nevada was vacationing in northwest Wisconsin starting in mid-June of 2020. She had a history of chronic pain treated with chronic opioids, tobacco use, COPD, hypertension, type 2 diabetes, morbid obesity and hypertension. In late July 2021, EMS was activated for an episode of decreased responsiveness with retained consciousness. At that time, her family reported a 3 week history of nonspecific illness with ataxia and malaise. They reported she had stated she felt as though she was poisoned, had phantosmia and generalized shortness of breath. A friend who is a registered nurse had been worried she had COVID-19 and provided her with antimicrobials (amoxicillin) that had been obtained in Mexico. There was no history of alcohol use, any illicit drug use or overuse of her chronic opioids. After approximately 20 min of observation the patient regained the ability to communicate and refused transport to the hospital. Early the next morning, however, she was found on the ground outside of her camper and was transported to the emergency room at a regional hospital. During her evaluation 2 generalized tonic-clonic seizures were observed and she was treated with lorazepam and levetiracetam. The seizures ceased and she was transferred to our hospital.

On arrival the patient was obtunded and unable to provide any additional details of the history. Blood pressure was 128/68, pulse 95, respiratory rate 18, temperature of 38.6° and oxygen saturation of 98%. She was able to track with her eyes intermittently, her pupils were 3 mm and reactive and her funduscopic examination was grossly normal. There was no gross focal asymmetry on testing and no nuchal rigidity but she did have bilateral Babinski responses. Initial laboratory studies revealed hemoglobin of 11.5 g/L, white count 9700/μL and a platelet count of 185,000/μL, sodium 120 mmol/L, potassium 4.3 mmol/L, creatinine

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0.85 mg/dL, calcium was 8.3 mg/dL and glucose of 132 mg/dL. Liver function tests were normal. PH was 7.38, pCO2 43 mm Hg and PO2 was 96 mm Hg with a bicarb of 25.

CT scan of the brain revealed no acute intracranial pathology. No abnormalities of the cervical spine were noted. Electroencephalogram showed diffuse slowing but no epileptiform abnormalities. Initial MRI without contrast was read as showing only nonspecific abnormalities but on subsequent review FLAIR abnormalities in the basal ganglia more on the right than the left were present. Due to difficulty protecting the airway the patient was intubated. CSF evaluation showed 837 white blood cells/μL with 59% neutrophils. Protein was elevated at 88 mg/dL and the glucose was 82 mg/dL with a serum glucose of 150. Gram stain on a cytospin showed white blood cells and no organism seen. Initial CSF and serum evaluation for tick-borne disease and arbovirus were negative. SARS-CoV-2 RT-PCR testing was negative. Repeat electroencephalogram 2 days after admission showed a burst suppression pattern but no evidence of seizures. However, on hospital day 6 repeat electroencephalogram showed nonconvulsive status epilepticus. Repeat MRI showed increased foci of hyperintense FLAIR and T2 signal throughout the thalami and basal ganglia bilaterally with a band of increased signal extending along the medial aspect of the temporal lobes bilaterally (Fig. 1). Due to intractable status epilepticus and worsening clinical status the patient was transferred to a tertiary care center on hospital day 7.

MRI scan showed more prominent changes consistent with diffuse encephalitis (Fig. 2). Repeat serum serology for Eastern equine encephalitis on day 11 after initial admission showed positive conversion with greater than 1:40 IgG and 1:4 IgM in the CSF confirming recent infection. Prolonged electroencephalogram the recording showed persistent bilateral lateralized discharges maximum over the bitemporal regions with moderate to severe generalized delta slowing suppression. Despite aggressive supportive care the patient showed no signs of improvement and the family elected to withdraw care on hospital day 24.

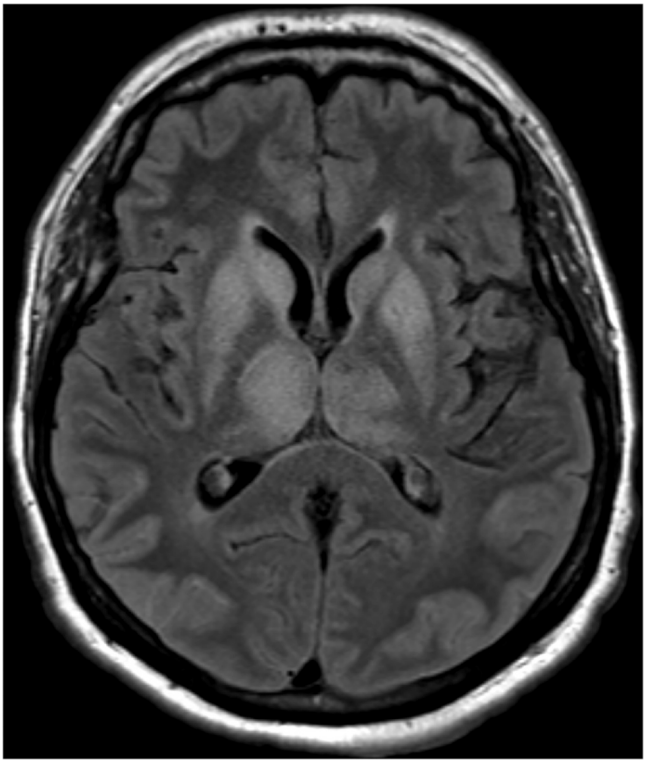

Fig. 1. Axial FLAIR MRI image showing confluent hyperintense signal abnormality involving the bilateral thalamus, caudate and putamen.

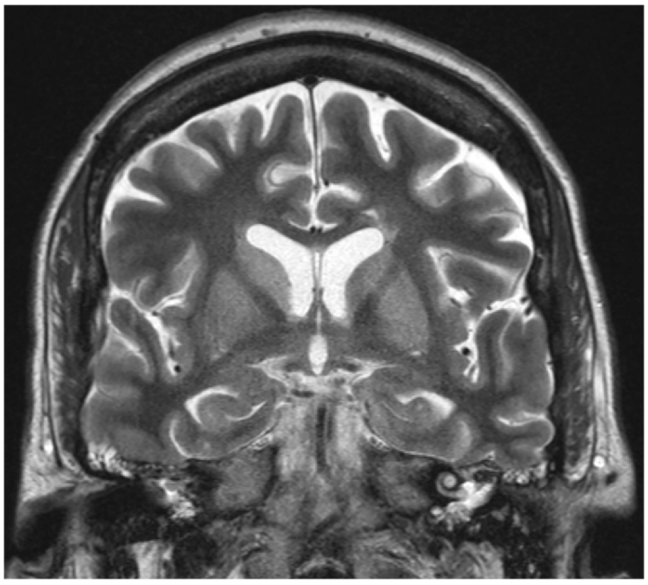

Fig. 2. Confluent T2 hyperintense signal abnormality involving the bilateral thalamus, caudate, putamen and hippocampus.

At autopsy, the brain was grossly normal. Microscopic evaluation, however, revealed lesions in the distribution and with the characteristic features of a viral encephalitis. Specifically, extensive foci of organizing necrosis with neuronal loss were present throughout the brainstem and thalamus with associated macrophage infiltrates and associated reactive astrogliosis. Perivascular and leptomeningeal inflammation that was predominantly CD3 positive was also identified throughout the brain and brainstem. Areas of active neuronophagia and scattered microglial nodules were present throughout, including the brainstem and neocortex (Fig. 3). The neuropathological examination revealed findings of organizing lesions consistent with chronicity of the patient's clinical course, as well as features of a persistent viral infection. There was minimal aging-related changes characterized by sparse hippocampal and entorhinal tau immunoreactive pretangles. No neurofibrillary tangles, beta-amyloid pathology, TDP-43 lesions, or, alpha synuclein pathology was identified.

Discussion

First identified in Massachusetts in 1831, EEE was known to infect horses. The first identified case in humans was in 1938 with between three and fifteen cases reported annually between 2009 and 2018 [1]. In recent years, the disease has seen a westward expansion with cases appearing as far as Texas and Wisconsin. Diagnosis can be difficult due to the similarity of symptoms to other illnesses and infected humans can be asymptomatic. There is no predilection between males and females, and all ages are affected.

Originating from different species of birds, the virus is only transmittable to humans through mosquitoes. EEE is transmitted in a cycle from bird to *Culiseta melanura,* a species of mosquito, amplifying the virus [2]. The virus will stay in a closed mosquito-bird cycle until a bridge vector species of mosquito is infected by feeding on a bird. These bridge vector species are then able to transmit EEE to humans through bites. The virus is unable to be transmitted between humans. Awareness and avoidance of mosquitoes is the best method of prevention. The risk for infection is greatest during the summer months, especially near wetlands or swamps. Use of mosquito repellant and wearing clothing that covers more areas of skin are important preventative measures especially when in a high risk environment, particularly during times when mosquitoes are most active.

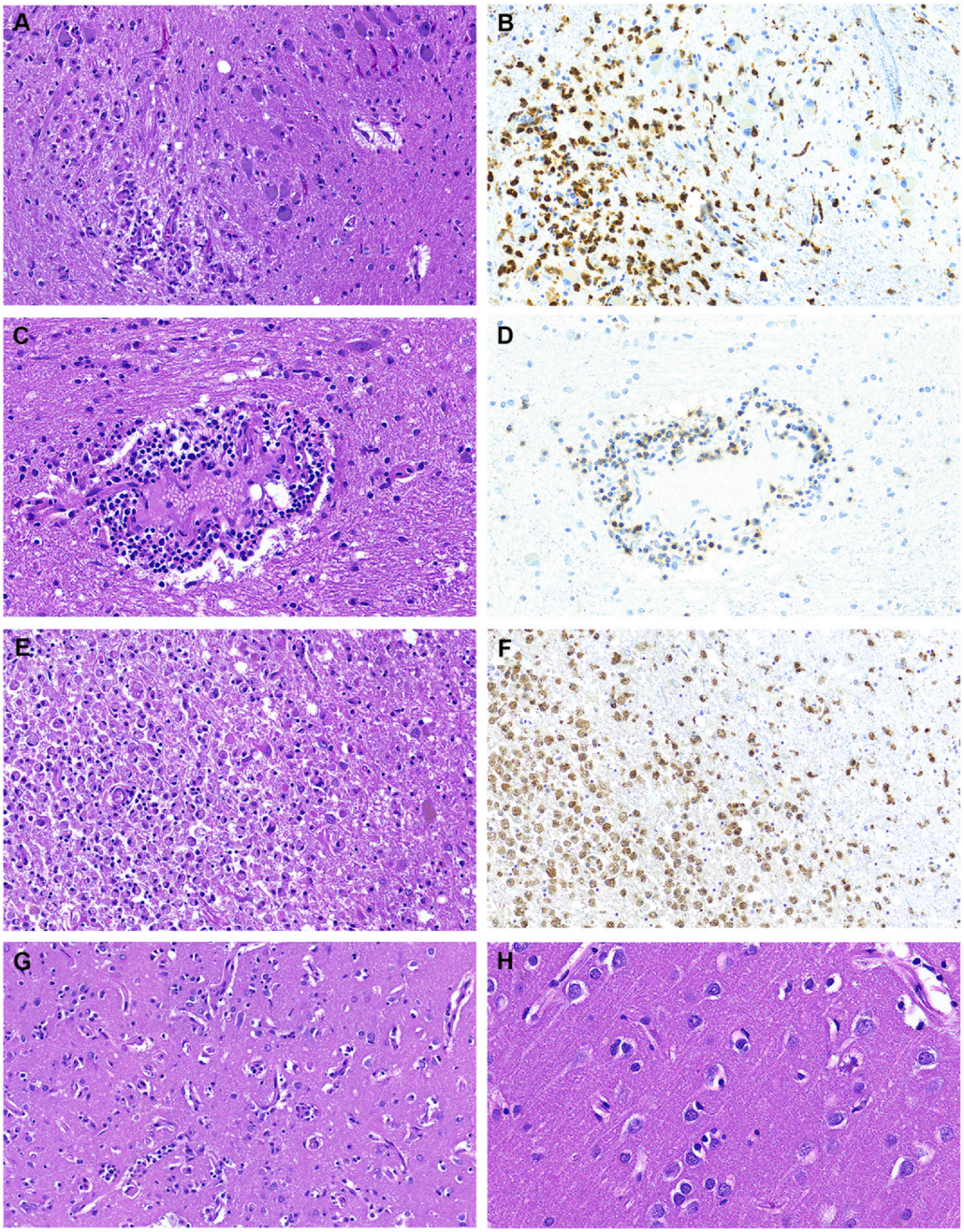

Fig. 3. Inferior medullary olive with neuronophagia and microglial nodules (A) that is highlighted by a CD68 (microglial/macrophage marker) immunostains (B). Patchy leptomeningeal and intraparenchymal perivascular lymphocytic infiltrates were present (C) and predominately consisted of CD3 cells (D). Organizing lesions were identified in the thalamus (E) that were characterized by collections of CD68-positive macrophages (F). The neocortex had patchy regions of active neuronophagia (G) characterized by macrophages surrounding individual neurons (H).

Symptoms of EEE are nonspecific and include fever, headache, nausea, malaise, meningismus and seizures. Altered mental status is an important distinguishing symptom of EEE, as disruption of higher cortical function serves to distinguish encephalitis from meningitis. Due to the nature of the general symptoms, this distinction of altered mental status is crucial for increasing clinical suspicion for EEE [3–5].

Laboratory findings in serum are nonspecific with hyponatremia, leukocytosis (median: 14,500 cells/μL, range: 3800–23,900) and positive inflammatory markers. Spinal fluid findings include elevated white blood cell count (median: 370 cells per cubic milliliter, range: 0–2400) with neutrophil predominance (median 70%) [5]. Specific testing for EEE is performed with demonstration of IgM antibody in CSF or a four-fold rise in serum antibodies.

Neuroradiologic studies can be helpful, although CT scans are often unremarkable. MRI findings are often classic and include confluent FLAIR and T2 hyperintense signal changes in the basal ganglia, thalamus and cortex. Since the virus is an obligate intracellular pathogen, primarily gray matter signal abnormalities are common. Contrast enhancement is variable [6,7].

It is estimated that 96% of people infected with EEE are asymptomatic. In those that show symptoms, roughly 33% die and a majority of those who survive will suffer permanent neurologic damage. The fatality percentage of 33% is the highest among arboviruses identified in the United States [5].

There have been reports of successful treatment of this infection with aggressive supportive therapies and other interventions

including intravenous immunoglobulins [8,9]. Further research into treatment regimens would be important to pursue.

Summary

Eastern Equine Encephalitis is a rare but potentially serious disease as shown in this case report. The best strategy is prevention, by use of mosquito repellant, avoiding high activity mosquito areas and times of day. Clinicians should be aware of the physical, laboratory and imaging manifestations of this disorder. This is particularly important as the range of the disease begins to spread westward, perhaps due to climate change and human encroachment on previously wild areas. Ongoing research into effective treatments or vaccinations will be important to reduce morbidity and mortality.

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Author contributions

Evan P. Dexter, Wrote introduction, discussion, and summary. Donn D. Dexter, MD, wrote case report, help with editing. Christopher W. Lindsay, MD, contributed MRI images and description of radiologic findings. Reichard, R. Ross, MD, contributed pathology images and descriptions. Larry Lutwick, MD, Advice and editing of manuscript.

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