Eastern Equine Encephalitis and Use of Intravenous Immunoglobulin Therapy and High-Dose Steroids

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Background

Eastern equine encephalitis (EEE) is a mosquito-borne viral infection with significant neurological morbidity and mortality.

- In 2019, there were 37 confirmed cases of EEE in the United States and 12 in Massachusetts, with 15 deaths, making this the largest outbreak since 1959.
- EEE virus (EEEV) is one of the most virulent neurotropic viruses with an estimated 40% mortality rate observed in the past two decades.
- The clinical presentation and patient outcomes after treatment with IVIG, high-dose steroids, or standard of care alone in EEE remains unclear.
- While the majority of people infected with EEEV are suspected to be asymptomatic, the clinical presentation of symptomatic adults and children is characterized by acute onset of fever, headache, nausea, and encephalopathy with variable presence of meningismus, weakness, and seizure.
- There are no specific anti-viral treatments for EEE, unlike other viral encephalitides including herpes simplex virus, varicella zoster virus, and cytomegalovirus.
- Case reports suggest possible benefit from treatment with IVIG or negative outcomes with high-dose steroids, however, data are limited in EEE.

Methods

A retrospective observational study of patients admitted to two tertiary academic medical centers in Boston, Massachusetts with EEE from 2005 to 2019.

EEE cases were identified by searching the Partners Healthcare Research Patient Data Registry system using the *International Classification of Diseases (ICD) 9th and 10th edition* diagnostic codes for EEE

Patients evaluated at Massachusetts General Hospital or Brigham and Women's Hospital between January 1, 2005 and January 1, 2020 were included in the review

Data on clinical presentation, laboratory values, MRI and electroencephalogram (EEG) studies, treatment, and outcomes were collected until a censoring date of January 1, 2020

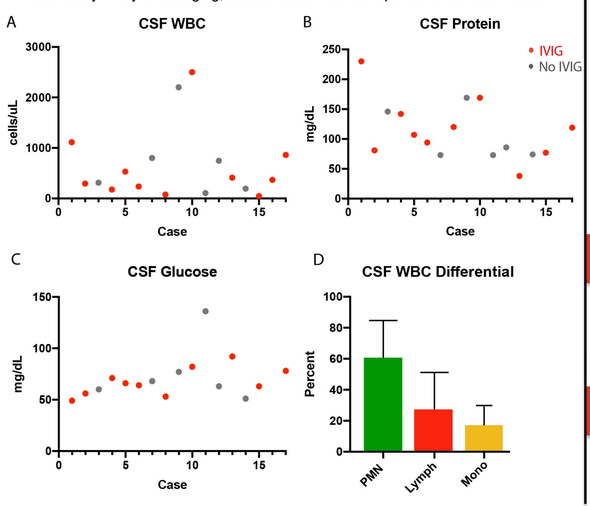
Study

We describe 17 cases of EEE diagnosed in the northeast over the past 15 years, including the most recent major outbreak in 2019. We also provide available data on post-discharge outcomes in patients treated with IVIG or steroids in addition to standard of care.

Results

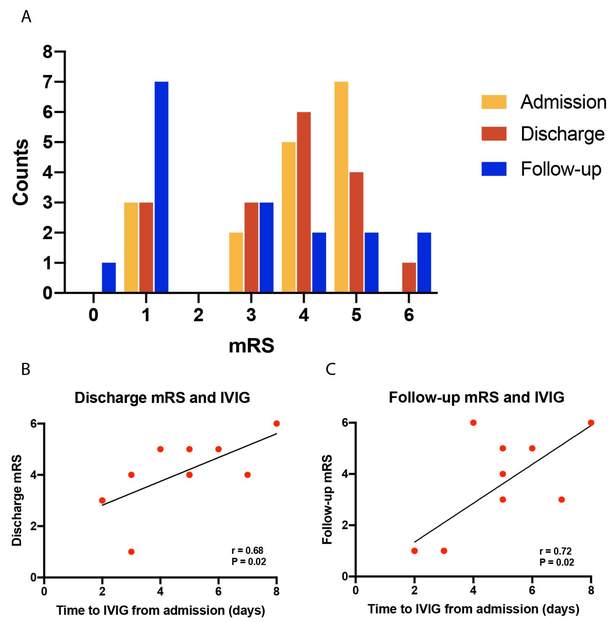
	Overall Prevalence (n=17)	Received IVIG (n=11)	Did Not Receive IVIG (n=6)
Demographics			
Age, years (median[IQR])	63 [36,70]	63 [52,72]	44 [22,61]
Race, n (%)			
White	16 (94)	11 (100)	5 (83)
Hispanic	1 (6)	0 (0)	1 (6)
Gender, n (%)			
Male	10 (59)	6 (55)	4 (67)
Female	7 (41)	5 (46)	2 (33)
Clinical Characteristics (n (%))			
Fever	17 (100)	11 (100)	6 (100)
Altered Mental Status	15 (88)	10 (91)	5 (83)
Headache	12 (71)	7 (64)	5 (83)
Photophobia	3 (18)	1 (9)	2 (33)
Neck Stiffness	3 (18)	2 (18)	1 (17)
Nausea	5 (29)	2 (18)	3 (50)
Vomiting	6 (35)	2 (18)	4 (67)
Abdominal Pain	3 (18)	0 (0)	3 (50)
Respiratory Symptoms	2 (12)	1 (9)	1 (17)
Tremor	6 (35)	6 (55)	0 (0)
Seizures	7 (41)	5 (46)	2 (33)
Abnormal EEG	10 (59)	7 (64)	3 (50)
Prodrome, days, mean (range)	3 (0-9)	3 (0-7)	3 (0-9)
Laboratory Characteristics (median[IQR])			
CSF WBC, cells, uL	369 [185,831]	369 [177,860]	529 [171,1152]
CSF Glucose, mg/dL	65 [57,78]	65 [55,79]	66 [58,92]
CSF Total Protein, mg/dL	100[75,145]	113 [80,149]	80 [73,152]
Serum WBC, K/uL	13[8,16]	13 [7,16]	11 [9,17]
Sodium, mmol/L	135 [133,138]	135 [132,138]	136 [134,139]
Platelets, K/uL	187 [158,236]	171 [142,217]	215 174,252]
ALT, U/L	22 [16,57]	22 [19,57]	18 [13,137]
AST, U/L	36 [19,70]	26 [24,73]	37 [11,68]
Alk Phos, U/L	59 [50,68]	62 [45,69]	54 [49,77]
Length of Stay, days (median(range))			
Hospital LOS	18 (5-38)	18 (6-38)	16 (5-35)
ICU LOS	10 (0-34)	12 (1-34)	5 (0-14)
Outcomes, n (%)			
Survival	15 (88)	9 (82)	6 (100)
Death	2 (12)	2 (18)	0 (0)
mRS, median (range)			
Admission mRS	4 (1-5)	4 (1-5)	4 (1-5)
Discharge mRS	4 (1-6)	4 (1-6)	4 (1-5)
Follow-up mRS	3 (0-6)	3 (1-6)	1 (0-4)

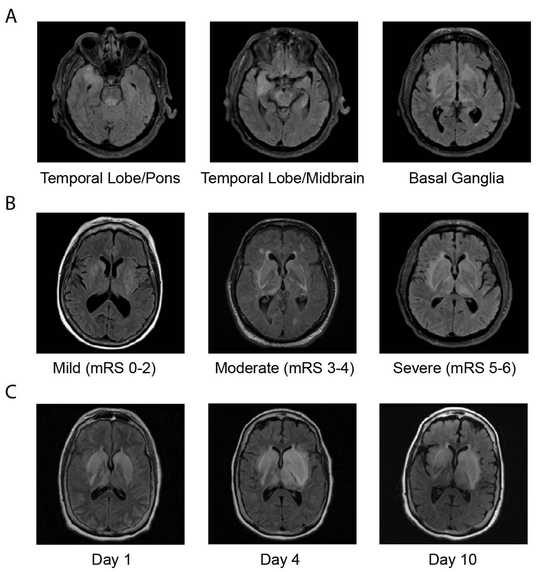
Table 1. Demographics, Clinical Characteristics, Laboratory Data, and Outcomes in Patients with Eastern Equine Encephalitis. Abbreviations: CSF = cerebrospinal fluid, WBC = white blood count, EEG = electroencephalogram, ALT = alanine aminotransferase, AST = aspartate transaminase, IVIG = intravenous immunoglobulin; LOS = Length of Stay; ICU = intensive care unit; mRS = modified Rankin Scale. Demographic data was collected for all patients with confirmed EEE. Altered mental status included any description of encephalopathy, confusion, or difficulty with attention. Seizures were defined as clinical events with a high-degree of suspicion to be true seizures and were entirely comprised of generalized tonic-colonic seizures. High-dose steroids included methylprednisolone and dexamethasone. The typical dose used in the treatment of adult patients was 0.4 grams of IVIG per kilogram of patient body weight for a duration of 5 days; one adult patient received 1g/kg IVIG for 2 days. One pediatric case received an initial loading dose of 2g/kg IVIG for 1 day, followed by 1 day of 0.5mg/kg, and the dose was not reported in the other case.

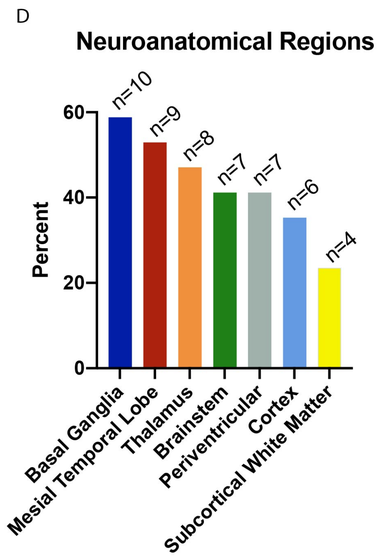


Results

- Of 17 patients (median [IQR] age, 63 [36,70] years; 10 (59%) male, and 16 (94%) White race), 17 patients had fever (100%), 15 had encephalopathy (88%), and 12 had headache (71%).
- Eleven of 14 patients with cerebrospinal fluid (CSF) cell count differential had a neutrophil predominance (mean=60.6% of white blood cells) with an elevated protein level (median [IQR], 100 mg/dL [75,145]).
- Affected neuroanatomical regions included the basal ganglia (n=9/17), thalamus (n=7/17), and mesial temporal lobe (n=7/17).
- A total of 11 patients (65%) received IVIG; 8 (47%) received steroids.
- Of the patients who received IVIG, increased time from hospital admission to IVIG administration correlated with worse long-term disability as assessed by modified Rankin Score (mRS) (r=0.72, p=0.02); steroid use was not associated with mRS score.
- The mortality was 12%.







Conclusions

Clinicians should suspect EEE in immunocompetent patients with early subcortical neuroimaging abnormalities and CSF neutrophilic predominance. This study suggests a lower mortality than previously reported, but a high morbidity rate in EEE. IVIG as an adjunctive to standard of care may be considered early during hospitalization.

Acknowledgements

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