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Electroencephalography for diagnosis and prognosis of acute encephalitis ☆

Raoul Sutter [a,b,c,d,*], Peter W. Kaplan [b], Mackenzie C. Cervenka [e], Kiran T. Thakur [f], Anthony O. Asemota [f], Arun Venkatesan [f], Romergryko G. Geocadin [a,f]

[a] Division of Neurosciences Critical Care, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[b] Department of Neurology, Johns Hopkins Bayview Medical Center, Baltimore, MD, USA
[c] Department of Neurology University Hospital Basel, Basel, Switzerland
[d] Clinic of Intensive Care Medicine, University Hospital Basel, Basel, Switzerland
[e] Division of Epilepsy, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[f] Johns Hopkins Encephalitis Center, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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HIGHLIGHTS

- EEG provides significant diagnostic and prognostic information in acute encephalitis.
- Periodic discharges and focal slowing were associated with *Herpes Simplex* encephalitis.
- Normal EEG was the strongest association with survival independently from possible confounders.

ABSTRACT

Objectives: To confirm the previously identified EEG characteristics for HSV encephalitis and to determine the diagnostic and predictive value of electroencephalography (EEG) features for etiology and outcome of acute encephalitis in adults. In addition, we sought to investigate their independence from possible clinical confounders.
Methods: This study was performed in the Intensive Care Units of two academic tertiary care centers. From 1997 to 2011, all consecutive patients with acute encephalitis who received one or more EEGs were included. Examination of the diagnostic and predictive value of EEG patterns regarding etiology, clinical conditions, and survival was performed. The main outcome measure was in-hospital death.
Results: Of 103 patients with encephalitis, EEGs were performed in 76 within a median of 1 day (inter quartile range 0.5–3) after admission. Mortality was 19.7%. Higher proportions of periodic discharges (PDs) ($p = 0.029$) and focal slowing ($p = 0.017$) were detected in *Herpes Simplex virus* (HSV) encephalitis as compared to non-HSV encephalitis, while clinical characteristics did not differ. Normal EEG remained the strongest association with a low relative risk for death in multivariable analyses (RR < 0.001, $p < 0.001$) adjusting for confounders as coma, global cerebral edema and mechanical ventilation. None of the patients with a normal EEG had a GCS of 15.
Conclusions: Normal EEG predicted survival independently from possible confounders, highlighting the prognostic value of EEG in evaluating patients with encephalitis. EEG revealed higher proportions of PDs along with focal slowing in HSV encephalitis as compared to other etiologies.
Significance: EEG significantly adds to clinical, diagnostic and prognostic information in patients with acute encephalitis.

1. Introduction

Acute encephalitis is a life-threatening neurologic condition with an incidence of 12/100,000 cases per year, characterized by inflammation of the brain (Granerod et al., 2010b). Symptoms

☆ Institutions where the work was performed: The Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center.

* Corresponding author at: Department of Neurology and Intensive Care Units, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland. Tel.: +41 61 265 25 25.
E-mail address: Raoul.Sutter@usb.ch (R. Sutter).

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usually emerge over hours to days and include fever, headache, altered consciousness, seizures, and focal neurologic deficits (Davies et al., 2006; Koskiniemi et al., 1981). Approximately one-third of acute encephalitis cases are thought to be immune-mediated (Granerod et al., 2010a) and etiology frequently remains undetermined in >50% of cases in some studies (Koskiniemi et al., 1981). The most frequently identified etiologies are infections, with viruses representing the predominant pathogens, although recognition of autoimmune causes is increasing. Mortality is high, ranging up to 20% in patients with *Herpes Simplex virus* (HSV) encephalitis (Whitley and Lakeman, 1995). Although electroencephalography (EEG) is typically recommended in the evaluation of patients with suspected encephalitis (Venkatesan et al., 2013), the contribution of EEG to diagnosis and prognosis has not been well characterized. The EEG features mostly described in association with HSV encephalitis, a type of encephalitis best examined with EEG, are uni- or bilateral periodic discharges, focal or generalized slow waves, and electrical seizures (Al-Shekhlee et al., 2006; Brodtkorb et al., 1982; Ch'ien et al., 1977; Illis and Taylor, 1972; Lai and Gragasin, 1988; Upton and Gumpert, 1970). However, investigations regarding the independent diagnostic and predictive value of EEG patterns are lacking.

We aimed to confirm the previously identified EEG characteristics for HSV encephalitis and to further determine the diagnostic and predictive value of EEG features for different underlying etiologies and short-term outcome in the first week of acute encephalitis in adults. In addition, we sought to investigate their independence from possible clinical confounders.

2. Materials and methods

This study was performed at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center, two academic tertiary care centers in Baltimore, USA. All neurocritical care units (NCCU), medical ICUs, coronary care units (CCU), and surgical ICUs were screened. The study was approved by the institutional review boards; patient consent was waived.

2.1. Patients and data collection

From January 1997 to July 2011, all consecutive patients older than 16 years of age with the diagnosis of acute encephalitis requiring critical care for more than 48 h and who had an EEG in the first week following admission were included. The first EEG was assessed. Cases were identified using *ICD-9* diagnosis codes corresponding to encephalitis. Diagnoses were confirmed by neurologists' review of patient charts including physicians' notes, laboratory results, neuroimaging studies, and other supporting data. Detailed information regarding clinical data collection was described previously (Thakur et al., 2013).

2.2. Definition of encephalitis

According to the consensus statement of the international encephalitis consortium and population-based studies (Granerod et al., 2010a; Venkatesan et al., 2013), encephalitis was diagnosed if a patient was encephalopathic (defined by depressed or altered level of consciousness, lethargy, or personality change lasting at least 24 h) with at least two of the following characteristics: fever, seizure, focal neurologic deficit, central spinal fluid (CSF) pleocytosis (white blood cell count >5 cells/mm^3), and EEG or neuroimaging findings consistent with encephalitis. Active malignancy, HIV infection/AIDS, or use of chronic immunosuppressants defined an immunocompromised state.

2.3. Clinical categories

Patients were categorized as having an infectious encephalitis (i.e., viral, bacterial and fungal), autoimmune encephalitis, or encephalitis of unknown etiology as previously reported (Thakur et al., 2013). Infectious encephalitides were defined by serology, positive polymerase chain reaction, culture, or histopathology. Autoimmune encephalitis was defined by the presence of antigen-specific antibodies in the serum and/or CSF or cases with a clinically recognized autoimmune syndrome and supportive histopathologic evidence. Cases of acute disseminated encephalomyelitis were categorized as autoimmune etiology and defined by clinical features and imaging characteristics of acute disseminated encephalomyelitis or histology-proven cases (Tenembaum et al., 2007).

2.4. Electroencephalography

EEGs were recorded in the first week following admission with silver–silver chloride disk scalp electrodes placed according to the International 10–20-System. All patients had one or more EEGs recorded for at least 30 min. EEGs were analyzed by three neurologists' board certified in epilepsy and/or clinical neurophysiology [RS, PWK, MCC] and blinded to clinical or radiologic information. Inter-rater agreement was assessed and if divergent, subsequent critical review was performed to reach agreement. Background activity was categorized into alpha, alpha/theta, theta, theta/delta, and delta activity during arousal as defined elsewhere (Sutter et al., 2013a). As periodic discharges (PDs) have been described in association with HSV encephalitis in prior case series and smaller studies (Al-Shekhlee et al., 2006; Brodtkorb et al., 1982; Illis et al., 1972; Upton et al., 1970), we assessed the occurrence of episodic EEG transients, such as periodic discharges (PDs) according to the definition provided by Chatrian et al. (1964), frontal intermittent rhythmic delta activity (FIRDA), and triphasic waves (TWs) as defined elsewhere (Sutter et al., 2013a). In addition, seizures and status epilepticus were noted as defined previously (Ozuna, 2000; Sutter and Kaplan, 2012). As a standard procedure, patients without arousals were stimulated by an EEG technician who was trained to first give verbal commands, open the patients' eyes, and if still no arousal was registered, to apply a noxious stimulation. Arousals were defined according to standard criteria as an abrupt shift in the frequency range of EEG background activity lasting $\geqslant$3 s that may include alpha, theta and/or frequencies greater than 16 Hz, but not spindles (American Sleep Disorders Association, 1992). EEG background reactivity to stimuli was defined as an abrupt, intermittent shift from the baseline frequency and/or amplitude ranges towards higher or lower ranges immediately following arousal, acoustic (call) or noxious stimulation.

2.5. Outcome

The principal outcome measure was in-hospital death. Secondary outcomes were length of hospital and ICU stay, Glasgow Coma Scale (GCS) on the day of EEG and the modified Rankin Scale (mRS) at discharge.

2.6. Statistics

Patients were categorized into the following three groups of acute encephalitis: infectious encephalitis, autoimmune encephalitis and encephalitis of unknown etiology. Subsequently, patients were dichotomized into additional subgroups: patients with HSV-encephalitis and non-HSV-encephalitis, and into survivors and non-survivors. Fisher's exact test was used for comparisons of proportions. For continuous variables, the Shapiro–Wilk test was used to distinguish between normal and abnormal