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Etiological associations and outcome predictors of acute electroencephalography in childhood encephalitis

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HIGHLIGHTS

- A non-reactive EEG background on early EEG predicts abnormal outcome in children with encephalitis.
- Seizures with shifting ictal focality predict drug resistant epilepsy in children with encephalitis.
- Children with NMDAR encephalitis have reactive early EEG background & demonstrate extreme spindles.

ABSTRACT

Objectives: To examine EEG features in a retrospective 13-year cohort of children with encephalitis.
Methods: 354 EEGs from 119 patients during their admission were rated blind using a proforma with demonstrated inter-rater reliability (mean $k = 0.78$). Patients belonged to 12 etiological groups that could be grouped into infectious and infection-associated ($n = 47$), immune-mediated ($n = 36$) and unknown ($n = 33$). EEG features were analyzed between groups and for risk of abnormal Liverpool Outcome Score and drug resistant epilepsy (DRE) at last follow up.
Results: 86% children had an abnormal first EEG and 89% had at least one abnormal EEG. 55% had an abnormal outcome, and 13% had DRE after median follow-up of 7.3 years (2.0–15.8 years). Reactive background on first EEGs (9/11, $p = 0.04$) and extreme spindles (4/11, $p < 0.001$) distinguished patients with anti-N-Methyl-D-Aspartate Receptor encephalitis. Non-reactive EEG background (48% first EEGs) predicted abnormal outcome (OR 3.8, $p < 0.001$). A shifting focal seizure pattern, seen in FIRES (4/5), anti-voltage gated potassium channel (2/3), *Mycoplasma* (1/10), other viral (1/10) and other unknown (1/28) encephalitis, was most predictive of DRE after multivariable analysis (OR 11.9, $p < 0.001$).
Conclusions: Non-reactive EEG background and the presence of shifting focal seizures resembling migrating partial seizures of infancy are predictors of abnormal outcome and DRE respectively in childhood encephalitis.
Significance: EEG is a sensitive but non-discriminatory marker of childhood encephalitis. We highlight the EEG features that predict abnormal outcome and DRE.

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; CSF, cerebrospinal fluid; D2R, dopamine-2 receptor; DRE, drug resistant epilepsy; EEG, electroencephalogram; HSE, Herpes simplex encephalitis; MRI, magnetic resonance imaging; *M. pneumoniae*, *Mycoplasma pneumoniae*; NMDAR, N-Methyl-D-Aspartate Receptor; PED, periodic epileptiform discharges; VGKC, voltage-gated potassium channel.

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1. Introduction

Abnormalities on electroencephalography (EEG) comprise one of the diagnostic criteria for encephalitis (Granerod et al., 2010). However, EEG features that suggest encephalitis, such as slowing of the background, remain non-specific. Some EEG features have proposed etiological associations, such as extreme delta brush in anti-N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis (Schmitt et al., 2012), periodic discharges in Herpes simplex encephalitis (HSE) (Lai and Gragasin, 1988; Kim et al., 2016) and temporal slowing and epileptic discharges in limbic encephalitis (Kaplan and Sutter, 2013). However, these features have not been examined blinded in a cohort of children with encephalitis. Recent work suggested that epileptic changes in EEG are a risk factor for drug resistant epilepsy (DRE) (Pillai et al., 2015b) in children with encephalitis, but the nature of these changes was not defined further and this was based on retrospective clinical reports. The clinical utility of EEG as a diagnostic criterion is further complicated by the highly variable and often modest inter-rater agreement in EEG ratings in research and clinical practice (Grant et al., 2014; Gilbert et al., 2003). We designed a retrospective study with a standardized proforma to examine EEG features on first and subsequent recordings in children with various etiological categories grouped under infectious and infection-associated, immune-mediated and unknown encephalitides.

2. Methods

We undertook a blinded review of 354 EEGs from 119 patients with encephalitis of varying etiologies. The study was approved by the institutional ethics committee (09/CHW/56) at the Children's Hospital at Westmead in Sydney, Australia - the largest referral centre for children in New South Wales, Australia. The clinical features and outcome for many of these children were recently reported (Pillai et al., 2015a). 170 patients who fulfilled the Granerod case definitions for encephalitis (Granerod et al., 2010) were identified from a retrospective cohort referred to the hospital from 1998 to 2010. 119 patients who had readable EEGs in a digital format were included. Included patients were divided into twelve etiological categories (Table 1) grouped as infectious and infection-associated ($n = 47$), immune-mediated ($n = 36$) and unknown ($n = 33$), as previously described (Pillai et al., 2015a). Infection-associated encephalopathy syndromes such as acute necrotizing encephalopathy (ANE), influenza-associated encephalopathy and febrile infection-related encephalopathy syndrome (FIRES) were included, as previously described (Pillai et al., 2015a). Liverpool Outcome Scores (LOS) (Lewthwaite et al., 2010) were obtained from a recent study at our institution (Pillai et al., 2015a) and were updated using the most recent medical records. DRE was defined as in a previous study (Pillai et al., 2015b) as the persistence of seizures despite two or more appropriate anti-epileptic medications at last follow-up.

2.1. EEG recording and selection

Digital video EEG was performed using 25 scalp silver/silver chloride electrodes, which were placed according to the international 10–20 system. A reduced array of electrodes was used for children younger than eight weeks of age or with a head circumference less than 40 cm according to electrode placement methodology proposed by the International Federation of Societies for Encephalography and Clinical Neurophysiology. The *Stellate Harmonie*™ EEG system from Natus medical Inc. USA was used to record, archive and review EEGs. We included the first EEG for all patients during their initial presentation with encephalitis and then selected the longest daily EEG from the first week of admission, if available. Two EEGs/week were selected from week 2 to 4 of admission (the longest in duration). Where possible, these were selected with an interval of two or more days in between. For subsequent weeks, one EEG was chosen per week (the longest in duration) till the patient was discharged. EEGs during subsequent outpatient follow-up and relapses were not included. With this selection method, all EEGs performed during the admission with acute encephalitis were included for 82% (97/119) patients.

2.2. Blinding

All identifying information was digitally removed during export of EEGs from the digital archives. Each individual EEG was assigned a unique random four-digit code prior to rating. Annotations made during EEG recording were not removed. Digital videos were only available with some archived recordings and were not reviewed as part of this study.

2.3. EEG rating

The EEGs were reviewed using the *Harmonie 7.0* reviewer from Natus medical Inc., which allowed viewing in a variety of customizable bipolar and reference montages. A structured electronic proforma (Appendix A) was developed for EEG rating. Each proforma was identified by the unique patient code. The proforma was divided into major categories of state of consciousness, awake and sleep background, non-epileptiform interictal abnormalities, interictal epileptiform discharges, ictal recording, photic stimulation and hyperventilation. Each major category had several subdescriptors that detailed topographical distribution of EEG changes, nature of EEG discharges and correlation with clinical events. All terminology used in the proforma (Appendix B) was based on standard usage in clinical practice and research adapted from the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology (Hirsch et al., 2013), Fisch & Spehlmann's EEG Primer (Fisch, 1999) and Niedermeyer's Electroencephalography (Donald et al., 2010). Each patient's age at the time of EEG was provided to the raters linked to the unique EEG code. Other information added to the database after completion of the EEG rating included diagnosis, timing of symptom onset and hospital admission relative to timing of each EEG, location of EEG recording, duration of EEG recording, details of each medication administered in the 24 h preceding each EEG, MRI abnormalities noted, duration of follow-up, LOS on last follow-up and whether the patient was categorized as having DRE as per a recent study of this cohort (Pillai et al., 2015b).

2.4. Inter and intra-rater reliability

Paediatric EEGs in Australia are routinely reported by paediatric neurologists. In order to determine inter-rater reliability (IRR), and improve the proforma, 30 randomly selected EEGs were independently reviewed by each of three blinded expert raters – DG (paediatric epileptologist), SS (senior neurophysiology scientist), SM (paediatric neurologist) – using a pilot version of the proforma. Mean IRR analyzed using Fleiss' modification of Cohen's kappa (K) (Fleiss, 1971) was 0.6 (95% CI = 0.39–0.78), which can be regarded as "moderate agreement" using Landis and Koch's interpretation of kappa (Landis and Koch, 1977). The proforma was modified in a consensus meeting according to noted areas of poor IRR by simplifying use of terminology, removing or combining categories with duplication and adding easily accessible pop-up definitions of various terms to the proforma (Appendices A & B). A further 40 randomly selected EEGs were then rated by each rater and IRR was again calculated in the same categories with