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Electroencephalographic characteristics of epileptic seizures in preterm neonates

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HIGHLIGHTS

- Most seizures in preterm newborns are subclinical, thus EEG is required for diagnosis.
- Seizures in preterm neonates have smaller regions of onset and propagate less frequently.
- Ictal EEG features undergo changes depending on corrected age likely reflecting maturational changes.

ABSTRACT

Objective: Although seizures are more common in the neonatal period than in any other stage of childhood, those in preterm neonates are still poorly described. The aim of this study was to assess electro-clinical characteristics of seizures occurring before a corrected age of 40 weeks in neonates born prematurely.
Method: Retrospective analysis of EEG-documented seizures in neonates born prematurely. Seizures in a group of term neonates served as controls.
Results: Fifty-six prematurely born and 46 term born neonates were included. Median duration of seizures was 52 s in preterm and 96 s in term neonates. Seizures were focal or multifocal. In least mature neonates, they involved smaller regions of onset and remained localised. With increasing corrected age, propagation became more frequent. The electrographic pattern – maximal frequency of oscillation and the onset pattern also evolved with age. Electro-clinical seizures were observed in 25% of preterm versus 50% of term neonates; almost all electro-clinical seizures involved the central (motor) regions.
Conclusion: Ictal EEG features undergo changes depending on corrected age. Most seizures are subclinical, thus EEG is essential for diagnosis.
Significance: Relating ictal EEG pattern to corrected age can improve diagnosis and ultimately management.

1. Introduction

Seizures are more common in the neonatal period than during any other time throughout childhood. They are reportedly even more prevalent in preterm neonates (Ronen et al., 1999; Vesoulis et al., 2014). Previous studies of neonatal seizures concentrated

Abbreviations: EEG, electroencephalogram; GA, gestational age (weeks); CA, corrected age (weeks).

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mainly on term newborns and definitions were established in this population (Boylan et al., 1999; Mizrahi and Kellaway, 1987). Seizures in term as well as preterm neonates were associated with a significantly worse neurodevelopmental outcome (Brunquell et al., 2002; Bye et al., 1997; Davis et al., 2010; Painter et al., 2012; Pisani et al., 2008b, 2016).

Diagnosing seizures can be challenging, even in term neonates. Clinical manifestations are often subtle and similar behaviours can be observed in healthy newborns, making clinical diagnosis unreliable (Mizrahi and Kellaway, 1987; Malone et al., 2009; Murray et al., 2008; Rennie et al., 2004). In addition, use of sedative, paralysing and antiepileptic drugs increases the incidence of purely electrographic seizures (Clancy et al., 1988; Lawrence et al., 2009; Scher et al., 2003).

Characteristics of immature neurotransmission, overabundance of connections and small neuronal size in this age group contribute to a relative excess of excitation and thus propensity to seizures (Holmes and Ben-Ari, 2001; Swann et al., 1991; Tsumoto et al., 1987; Brady et al., 1991; Low and Cheng, 2006). This may affect clinical and electrographic properties of seizures in preterm neonates.

Important differences between seizure characteristics in preterm and term born neonates, however, may exist due to gestational maturation. Studies on preterm infants are sparse and focused mainly on neuro-developmental outcome rather than on electro-clinical characteristics (Okumura et al., 2008; Pavlidis et al., 2015; Pisani et al., 2008a; Scher et al., 1993a,b). Few studies describe ictal EEG characteristics in preterm neonates and compare them to seizure characteristics in term neonates (Patrizi et al., 2003; Scher et al., 1993b). We retrospectively analysed EEG-documented seizures in prematurely born neonates aiming to describe the changes in electrographic patterns and clinical manifestations and to compare them with seizures in term born neonates.

The aim of the study was to describe clinical and electrographic characteristics of seizures in relation to the corrected age of the neonates to

(1) describe the evolution of clinical characteristics to help improve the yield of diagnostic EEGs
(2) describe the evolution of the electrographic patterns to infer the underlying pathophysiological mechanisms, which could ultimately lead to improvement in management of seizures.

2. Methods

2.1. Patients

Neonates born before 37 weeks of GA were recruited from Great Ormond Street Hospital (GOSH) between 2005 and 2014, University College London Hospital (UCLH) 2010–2012, United Kingdom, Albert Einstein College of Medicine, NY, USA, 2007–2013, Children's National Health System, Washington, USA 2006–2012 and Centre hospitalier régional universitaire (CHRU) Lille, France 2005. Preterm born neonates with electro-clinical and/or electrographic seizures recorded before 40 weeks of CA were included. A group of term-born neonates (37–42 GA) was recruited for comparison at GOSH (2005–2014). In term born neonates, seizures recorded in the neonatal period (under 28 days of age) were included. Electro-clinical and/or electrographic seizures were included. Paroxysmal clinical events without ictal EEG changes were excluded.

2.2. Electrophysiological explorations

In all centres, the indication for EEG was clinical suspicion of seizures. At Albert Einstein College and Children's National Health System, a subset of neonates with high risk of seizures (e.g. acidosis at birth, need for resuscitation for more than 5 min, severe encephalopathy) was monitored from birth for 48 h or more to assess the seizure burden and evolution of background activity (Sarnat and Sarnat, 1976; Shankaran et al., 2005). In addition, systematic EEG investigations assessing cerebral maturation at given corrected age were performed in CHRU Lille.

EEGs were recorded on digital systems (XLtek, Nicolet, Nihon-Kohden, Deltamed, Natus Neurology), with synchronised video recording. Sampling rate was at least 200 Hz. In neonates recorded at GOSH 12 electrodes (F4, F3, A2, T4, C4, Cz, C3, T3, A1, P8, P7 and Oz) were placed according to the modified Maudsley system (Pampiglione, 1956). All other centres used the international 10–20 system. At UCLH 11 electrodes (F4, F3, T4, C4, Cz, C3, T3, P4, P3, O2 and O1), Albert Einstein College 17 electrodes (Fp2, Fp1, F8, F4, Fz, F3, F7, T4, C4, Cz, C3, T3, T6, Pz, T5, O2 and O1) and Children's National 11 electrodes (Fp2, Fp1, T4, C4, Cz, C3, T3, P4, P3, O2 and O1) were placed and 8 in Lille (Fp2, Fp1, T4, C4, C3, T3, O2 and O1). Polygraphic recording included ECG lead I, and depending on centre, surface EMG over deltoid muscles, respiratory movements and oxygen saturation were measured. Video monitoring was used to determine whether clinical signs were associated with electrographic events.

A seizure was defined as abnormal electrographic activity with peak to peak amplitude of at least 2 μV and lasting at least 10 s with plausible electrographic distribution that evolved in morphology and frequency (Abend and Wusthoff, 2012; Tsuchida et al., 2013). Status epilepticus was defined as a single long seizure lasting more than 30 min or multiple shorter ictal discharges occupying more than 50% of time for at least 30 min of recording time (Tsuchida et al., 2013; Wusthoff et al., 2011). Ictal discharges were evaluated for location of onset, spread, duration and pattern of activity (Andre et al., 2010).

An electrographic seizure was defined as an EEG event without clinical accompaniment (motor or autonomic). Electro-clinical seizures were defined as seizures with both electrographic and clinical correlate.

The number of recorded seizures varied widely between patients. Therefore, to reduce the bias introduced by patients with a large number of seizures, we assessed median seizure duration and interquartile range for each child. To compare the duration between preterm and term born neonates, quartiles were established for the group of all neonates and number of neonates in each interval delimited by the quartiles was counted in the different age groups.

We assessed whether a preferential onset zone of seizures existed and whether it depended on corrected age. As each centre used a slightly different subset of recording electrodes, we grouped them into regions (frontal, central, temporal and posterior; posterior region included parietal, posterior temporal and occipital electrodes). Onset over one region of electrodes was considered focal, over several regions of electrodes over one hemisphere unilateral and when seizure started over both hemispheres the onset was called bilateral. We also assessed lateralisation of seizure onset. Left-right ratio was calculated for each neonate and the individual ratios were averaged.

Maximal frequency of ictal discharge was determined in each neonate by measuring the period between rhythmic ictal components/spikes over the fastest segment of the seizure, which was chosen visually. If several seizures were recorded, the fastest segment within them was taken for maximal frequency. For example, if spikes at 30 Hz were mixed with slow components at 1 Hz, the frequency was taken as 30 Hz, and if there were spike-wave complexes at 2 Hz, the frequency was 2 Hz.

Propagation of the ictal activity was classified in three categories; absence of propagation from the onset region, propagation