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Rhythmic EEG patterns in extremely preterm infants: Classification and association with brain injury and outcome

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HIGHLIGHTS

- Most rhythmic EEG patterns in extremely preterm infants related to head position.
- Clear ictal discharges were only observed in one out of 77 infants (1.3%).
- PEDs were prevalent, but their significance is not known.
- PEDs were not related to brain injury or poor cognition.

ABSTRACT

Objective: Classify rhythmic EEG patterns in extremely preterm infants and relate these to brain injury and outcome.
Methods: Retrospective analysis of 77 infants born <28 weeks gestational age (GA) who had a 2-channel EEG during the first 72 h after birth. Patterns detected by the BrainZ seizure detection algorithm were categorized: ictal discharges, periodic epileptiform discharges (PEDs) and other waveforms. Brain injury was assessed with sequential cranial ultrasound (cUS) and MRI at term-equivalent age. Neurodevelopmental outcome was assessed with the BSITD-III (2 years) and WPPSI-III-NL (5 years).
Results: Rhythmic patterns were observed in 62.3% (ictal 1.3%, PEDs 44%, other waveforms 86.3%) with multiple patterns in 36.4%. Ictal discharges were only observed in one and excluded from further analyses. The EEG location of the other waveforms ($p < 0.05$), but not PEDs ($p = 0.238$), was significantly associated with head position. No relation was found between the median total duration of each pattern and injury on cUS and MRI or cognition at 2 and 5 years.
Conclusions: Clear ictal discharges are rare in extremely preterm infants. PEDs are common but their significance is unclear. Rhythmic waveforms related to head position are likely artefacts.
Significance: Rhythmic EEG patterns may have a different significance in extremely preterm infants.

1. Introduction

In many units, neuro-monitoring with electroencephalography (EEG) during the first postnatal days has become part of standard care. Brain protection has become one of the main aims of neonatal intensive care, since the survival rate of extremely preterm infants (born <28 weeks gestational age) has increased due to major advances in perinatal care (Costeloe et al., 2012; Zegers et al., 2016).

Seizures have been related to adverse outcome in preterm infants (Davis et al., 2011; Pisani et al., 2008, 2004; Shah et al., 2010; Vesoulis et al., 2014). The incidence of seizures in preterm infants has been estimated at 4–48% (Scher et al., 1993; Vesoulis et al., 2014). This is higher than reported in full-term infants

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(Scher et al., 1993), while the response rate to antiepileptic drugs (AEDs) seems to be significantly lower in preterm infants (Weeke et al., 2016). The majority of seizures are subclinical, requiring continuous EEG for seizure detection (Patrizi et al., 2003). In the neonatal intensive care unit (NICU), detection of subclinical seizure patterns can be aided by automatic seizure detection algorithms (Navakatikyan et al., 2006).

However, little is known about EEG seizure morphology in extremely preterm infants. Clinicians are faced with a wide range of rhythmic EEG patterns that may be recognized by seizure detection algorithms as subclinical seizures. However, not all patterns seem to comply with the definition of an electroencephalographic seizure, which is rhythmic activity, lasting for at least 10 s, with a clear beginning, middle and end, and showing evolution in amplitude, frequency and/or morphology (Husain, 2005). This raises the question whether these patterns are subclinical seizures that require treatment and are related to poor outcome or whether they accompany normal brain development.

The aim of the present study was to classify all rhythmic EEG patterns, recognized by the BrainZ seizure detection algorithm, based on morphology and relate these different patterns to brain injury and neurodevelopmental outcome in a cohort of extremely preterm infants who were monitored with 2-channel EEG during the first 72 h after birth as standard of care. Our hypothesis was that ictal discharges and periodic epileptiform discharges (PEDs) would be associated with brain injury and poor cognitive outcome.

2. Methods

2.1. Patients

All infants born <28 weeks gestational age (GA) between May 2008 and December 2010 who had been admitted to the level III NICU of the Wilhelmina Children's Hospital in Utrecht, the Netherlands, and had a 2-channel EEG recording during the first 72 h after birth were retrospectively analyzed. Sixty-three infants were participants of a European multicenter study (Neonatal Estimation of Brain Damage Risk and Identification of Neuroprotectants [NeoBrain]) (Dammann et al., 2007). Clinical data, such as GA, birth weight, Apgar score, head position (side the infant's head was turned to) and morphine and AED administration, was obtained from the electronically available medical records. Head position was recorded in the electronic medical records by the nurses every time the infant's position was changed. Permission from the medical ethics committee and parental informed consent were obtained.

2.2. EEG monitoring

Patients were monitored using the BrainZ Monitor (BRM2 or 3 version, Natus, Seattle, USA). It records a two-channel amplitude-integrated EEG as well as a raw EEG from two needle electrodes over each hemisphere (F4-P4, F3-P3, according to the international 10–20 system of electrode placement modified for neonates) and has a built-in seizure detection algorithm (Navakatikyan et al., 2006).

2.3. EEG patterns

At the markers placed by the seizure detection algorithm of the BrainZ Monitor, the raw EEG was visually analyzed and categorized by consensus reading of five observers (AH, IO, LV, LH, LW). Rhythmic patterns were categorized into five different categories: ictal discharges, PEDs, PED-like waves, zeta waves and sinusoidal waves. These categories were based on patterns described in older children and adults (Deuschl and Eisen, 1999; Noachtar et al., 1999). The patterns that did not fit into these five categories or were clear artefacts caused by high-frequency ventilation or electrocardiography were discarded. For each EEG pattern that could be categorized into one of the five categories, the total duration in seconds (burden), the mean wavelength in seconds and the location on the EEG (left, right or bilateral) was determined for each infant.

Ictal discharges: have been described in neonates as rhythmic activity, lasting for at least 10 s, with a clear beginning, middle and end, and showing evolution in amplitude, frequency and/or morphology (Fig. 1A and B) (Husain, 2005). This activity can consist of spikes, sharp waves, spike-wave complexes or rhythmic delta or theta waves (Andre et al., 2010).

Periodic epileptiform discharges (PEDs): have been described in older infants and adults as sharp waves followed by a pronounced incision and a slow wave. These complexes repeat every 0.5–4 s, but do not show evolution (Fig. 1C and D) (Brenner and Schaul, 1990). They have been associated with brain lesions, epilepsy and poor outcome in children and adults (Chong and Hirsch, 2005; Hamano et al., 1994; Yemisci et al., 2003).

PED-like waves: these complexes were detected in our cohort but could not be related to a category described in the literature. They might be considered as PEDs in which the sharp waves are lacking. They consist of a positive sharp deflection from baseline forming an incision, followed by a periodic slow wave of generally more than one second (Fig. 1E and F).

Zeta waves: as described by Magnus and van der Holst (1987) consist of a slow wave with a rapid negative first phase, followed by a relatively slower positive second phase crossing the baseline. This wave is followed by a slow negative wave returning to baseline. Thus a Z-shaped complex appears with a duration of more than one second. Such complexes generally occur in trains of several seconds (Fig. 1G and H). In adults, zeta waves were associated with brain lesions with acute onset, such as intracranial hemorrhages (Magnus and van der Holst, 1987).

Sinusoidal waves: these waves resemble sine waves. They may occur in different, but generally low delta frequencies (Fig. 1I and J). In older children and adults frontal and occipital intermittent rhythmic delta waves have been described and related to deeply localized brain abnormalities (Watemberg et al., 2007, 2002) Sine waves were also thought to initiate seizures and metamorphose into other patterns as described by Blume et al. (1984).

2.4. Neuro-imaging

Cranial ultrasonography (cUS) was performed on admission to the NICU and repeated every day for the first 72 h and at weekly intervals thereafter until discharge. Magnetic resonance imaging (MRI) on a 3 T MR system was performed at term-equivalent age (39–43 weeks). The scanning protocol included T1-, T2-, diffusion- and susceptibility-weighted images. For each infant, it was determined whether abnormalities were seen on cUS or MRI and how severe these abnormalities were. Injury severity was categorized as mild (cUS: intraventricular hemorrhage [IVH] grade 1–2 according to Papile et al. (1978); MRI: IVH grade 1–2, <6 punctate white matter lesions [PWML], <6 punctate cerebellar lesions), moderate (cUS: IVH grade 3; MRI: IVH grade 3, $\geq$6 PWML, $\geq$6 punctate cerebellar lesions or a large unilateral lesion [<50% of the hemisphere]) or severe (cUS: IVH grade 4, infarction, periventricular hemorrhagic infarction, perforator stroke, cystic periventricular leukomalacia [cPVL], (de Vries et al., 1992) post-hemorrhagic ventricular dilatation [PHVD]; MRI: periventricular hemorrhagic infarction, cPVL (Martinez-Biarge et al., 2016), PHVD, large cerebellar hemorrhage [>50% of hemisphere]). The Kidokoro global score was calculated based on the MRI at term-equivalent