Electroencephalographic characteristics of epileptic seizures in preterm neonates

Soňa Janáčková MD PhD (1,2), Steward Boyd MD (1,3), Elissa Yozawitz MD (4), Tammy Tsuchida MD PhD (5), Marie-Dominique Lamblin MD (6), Sophie Gueden MD (6), Ronit Pressler MD PhD (1,3)

(1) Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

(2) Neurophysiology department, Hôpital Trousseau, Assistance Publique Hôpitaux de Paris, Paris, France

(3) Clinical Neuroscience, Institute of Child Health, University College London, London, UK

(4) Saul R. Korey Department of Neurology, Department of Pediatrics. Montefiore/Einstein Epilepsy Management Center, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, USA

(5) Division of Neurophysiology, Epilepsy and Neurocritical Care Children's National Health System, George Washington University School of Medicine

(6) Neurophysiology department, CHRU Roger-Salengro, Lille, France

Corresponding author: Soňa Janáčková MD PhD
Great Ormond Street Hospital for Children
Great Ormond Street
London WC1N JH
United Kingdom

Present address:
Hôpital Trousseau APHP
26 av du Docteur Arnold-Netter
75012 Paris
France
Tel: +33 1 44 73 64 52
Fax: + 33 1 44 73 68 04
E-mail address: sona.janackova@aphp.fr

Running head: Seizures in preterm neonates

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

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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.

Key words: preterm, neonate, epileptic seizures, electroencephalography

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.

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 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;Pisani et al., 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;Scher et al., 1993b) 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 minutes, severe encephalopathy) was monitored from birth for 48 hours 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 synchronized 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 minutes or multiple shorter ictal discharges occupying more than 50 % of time for at least 30 minutes 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 across the ipsilateral or to the contralateral hemisphere. The proportion of propagating seizures of each type was calculated for each neonate prior to establishing group values.

2.3. Statistical analysis

Bi-variate associations were assessed with χ^2 or Fisher's exact test. Student's t-test was used to compare continuous variables of normal distribution. Correlation between corrected age and maximal frequency of the ictal discharge was modelled by linear regression. The results were considered significant if $\alpha < 5$ %. Non-Gaussian distributed continuous variables were described using median and interquartile range (IQR).

3. Results

3.1. Baseline characteristics

Between 2004 and 2013, 56 neonates (34 boys; sex ratio 1.54) met the inclusion criteria, 24 from GOSH, 6 from UCLH, 9 from Albert Einstein College, 12 from Children's National Health System and 5 from CHRU Lille. Neonates were born between 24 and 36 weeks of GA (median 32 weeks, IQR 9 weeks) and seizures were recorded between 27 and 39 weeks of CA (median 35 weeks, IQR 6.5weeks). Preterm neonates were monitored for a duration of recording between 16 minutes and 126 hours; 1069 seizures (range 1-198 per neonate) and 10 episodes of status epilepticus were captured.

Forty-five full-term neonates from GOSH born between 37 and 42 weeks constituted a control group. They were recorded between 16 minutes and 21 hours; 152 seizures were analysed (range 1-14 per neonate).

Seventy percent of preterm and 50 % of term neonates were treated with at least one antiepileptic drug at the time of EEG recording which captured a seizure (Supplementary Table 1). Five (9 %) preterm and seven (16 %) term neonates were pharmacologically paralysed in order to facilitate ventilatory support.

3.2. Aetiology

A single cause could be identified in the majority of the neonates, despite the frequent occurrence of several risk factors (Supplementary Table 2). Vascular aetiologies were the most common cause of seizures; periventricular haemorrhage was the most common cause in the preterm group and hypoxic ischaemic encephalopathy in the term group. Infections, metabolic and structural causes had similar incidence in both groups. Inborn errors of metabolism, chromosomal abnormalities and neonatal epileptic syndromes were almost exclusively observed in term neonates (one preterm neonate born at 36 weeks GA was affected by molybdenum cofactor deficiency).

3.3. Seizure duration

Seizures were significantly shorter in preterm neonates compared to the term born group (χ^2, p=0.005) (Fig. 1). In less mature preterm neonates the seizures tended to be shorter, but the sample was insufficient for statistical analysis of subgroups of preterm neonates. By contrast, one extremely premature neonate had seizures lasting unusually long, around 5 minutes, with a distinctive electrographic pattern with spike frequency < 1 Hz.

3.4. Localisation of seizure onset

In prematurely born neonates, focal onset was seen in 85 % of seizures, 15 % started unilaterally and one (0.1 %) bilaterally. The most common onset was over the central region (40 %); frontal, temporal and posterior regions each represented about 20 % (Fig. 2a). There were, however, differences between age groups. The central region onset predominated in neonates older than 32 weeks of CA; in the younger groups, the occipital onset predominated, whereas frontal onset was not seen before 29 weeks of CA (Fig. 2b).

The majority of neonates with more than one seizure (32/43) had variables areas of onset. There was no preference for a hemisphere (left 48 %, right 52 %, t-test not significant).

In term born neonates, focal onset was observed in 47 %, unilateral in 33 % and bilateral in 24 % of seizures. Within the focal seizures the central onset was the most common (66 %). There was no preference for a hemisphere (left 52 %, right 48 %, t-test not significant).

3.5. Spatial propagation

Before 28 weeks CA, only about 1 % of seizures propagated. After 28 weeks CA, the incidence of propagation was between 30-47 %. Independently of corrected age, contralateral propagation between homologous regions predominated (Fig. 3a).

In focal seizures, we assessed whether there were preferential pathways of spread depending on age. Before 28 weeks CA, spread to the other hemisphere was only seen between the temporal regions, whereas afterwards the interhemispheric propagation occurred between any homologous regions. Before 28 weeks CA the propagation within hemispheres did not involve the frontal lobes, whereas after 28 weeks CA until full term, it could take place between any adjacent regions (Fig. 3b).

In term born neonates, 30 out of 115 (26 %) seizures which had focal or unilateral onset propagated. Seizures with onset over one region typically did not propagate. Seizures with onset wider than one region frequently propagated over the homologous contralateral regions or widely over both hemispheres.

3.6. Electrographic pattern

In preterm neonates the most common electrographic pattern was repetitive sharp waves; most frequently within delta-theta frequency range; ictal discharge slower than 1 Hz- the low frequency discharge pattern- was observed in four preterm neonates. Other patterns observed were rhythmic oscillation, and arrhythmic activity. An electrodecremental onset pattern was only observed at age of 39 weeks CA. A pattern with spike-wave complexes was seen in seven neonates. Five of them were older than 36 weeks CA and two were

younger. The maximal frequency of the ictal discharge for each subject was faster in more mature neonates (Fig. 4a).

We observed three patterns of discharge frequency at ictal onset: 1) deceleration, 2) essentially unchanged frequency and 3) acceleration (Fig. 4b). Acceleration and minimal changes in frequency were frequent and were seen at all corrected ages; deceleration was seen infrequently and only in more mature neonates.

3.7. Clinical manifestations of seizures

Clinical manifestations of seizures were seen in 14 (25 %) preterm and 22 (49 %) term neonates. We investigated whether it was more likely that clinical ictal changes were noted when the seizure discharge involved the central region (at onset or following propagation) (Table 1). In thirty-six preterm neonates the ictal discharge involved the central region at some point, in at least some of the seizures captured. Twelve of these 36 neonates had associated clinical manifestation. Two other preterm neonates presented some clinical ictal manifestation; the ictal discharge was localized over the frontal region (χ^2, $p=5*10^{-2}$). Two of the 24 preterm neonates with central discharge without motor signs received muscle relaxing drug. From the 40 term neonates with discharges over the central region, 22 had clinical manifestation associated. None of the term neonates without involvement of central region had ictal clinical manifestation (Fisher exact test, $p<5*10^{-2}$). A muscle relaxant drug was used in five of those with subclinical seizures over the central region.

4. Discussion

This study is the first to characterise electrographic features of seizures in preterm neonates according to corrected age and it showed a number of differences compared to term neonates. The study has shown that most seizures in preterm neonates are subclinical, have smaller areas of onset and propagate less readily than those in term neonates.

In two previous series, seizures were recorded earlier in more mature preterm neonates than in the less mature.(Pisani et al., 2008a;Scher et al., 1993a) Both, different aetiologies and under-recognition of seizures in less mature neonates could contribute to this effect.

We showed that involvement of central regions correlates with motor manifestations. In preterm neonates the percentage of neonates in which at least some seizures involved the central regions at some point was 64 %. The proportion of term neonates having seizures involving central regions was as high as 89 %, an incidence similar to a previous study which found that in 94 % of neonates at least one seizure involved the C3 –C4 channel.(Shellhaas et al., 2007) This finding may have implications in using devices with restricted number of channels in preterm neonates.

We found that the majority of seizures in preterm neonates had a focal onset, unlike Patrizi, who found that regional onset occurred in 75 % of preterm neonates.(Patrizi et al., 2003) Patrizi argued that focal onset would be expected in immature brain with lower connectivity and myelination. Multiple onset zones were common – in 74% of neonates in whom more than one seizure was captured. Nagarajan found a lower proportion, however she reviewed standard 1-h recordings. This value could increase, to some extent, with recording duration. In this study, central region was more often involved in neonates approaching term, which is in keeping with a previous study of term neonates. However, some authors have found the temporal lobe the most likely onset zone.(Nagarajan et al., 2011;Okumura et al., 2008;Shellhaas and Clancy, 2007) We found occipital predominance in the youngest ages, and did not observe frontal onset before 29 weeks CA. One could speculate that the onset zone follows the postero-anterior pattern of maturation. Structural hemispheric asymmetry emerges at the beginning of the second half of gestation and underlies future functional specialisation ; however, like Nagarajan, we did not observe any impact on hemispheric lateralisation of seizure onset.(Chi et al., 1977;Habas et al., 2012)

Spatial propagation of seizures was very rare before 28 weeks CA. The frontal lobes were not found to be involved in seizure propagation before 28 weeks CA (nor was seizure onset). Interestingly, the only interhemispheric propagation occurred via the temporal lobes, suggesting earlier maturation of this path, although due to small numbers a selection bias cannot be excluded. After 28 weeks CA, propagation of ictal discharges was seen in approximately 1/3 of seizures – possibly reflecting progress of synaptogenesis and

myelination. Propagation occurred more frequently between homologous regions of the hemispheres than within the same hemisphere. However, the different sets of recording electrodes used in the participating centres did not allow further splitting of the areas to evaluate local spreading in more detail.

One of the aims of the study was to investigate a possible correlation between corrected age and electrographic patterns of ictal activity. The commonest pattern was repetitive sharp waves (similarly to a previous study in preterm neonates).(Okumura et al., 2008) We observed an evolution towards higher frequencies with increasing corrected age. We hypothesise that these higher frequencies of firing become possible only with sufficient synaptogenesis and ion channel expression as well as with maturation of fast kinetics excitatory and inhibitory ion channels.(Kobayashi and Himwich, 1962;Owens and Kriegstein, 2001) However, slow (delta) frequencies were the sole manifestation of seizures in some near term neonates. The significance of this finding is unknown, but exploring whether persistence of an earlier pattern of the ictal discharge could be a supplementary marker of brain dysfunction, would be an interesting path for future studies. A recent study of rat models of temporal lobe epilepsy showed that the pathophysiological mechanism of seizure genesis determines the electrographic pattern.(Salami et al., 2015) Lack of GABA inhibition in early stage of development or in pathological circumstances would be an analogous situation and analysis of seizure patterns could help elucidate when GABA becomes inhibitory and in which circumstances it can become excitatory again.

Onset pattern of the ictal discharge in preterm neonates also differed significantly from those met in older children. Electrodecremental onset, which may consist of low-voltage rapid oscillations not captured by conventional EEG, constitutes a characteristic electrophysiological pattern in focal seizures in older children and adults independently of the underlining pathology. (Bancaud et al., 1973;Perucca et al., 2014;Wendling et al., 2003) Animal studies and computational models suggest that fast oscillations are generated by rhythmically discharging inhibitory interneurons. (Penttonen et al., 1998;Wendling et al., 2002) In our cohort of premature neonates, an electrodecremental/high frequency onset was first seen only after 38 weeks CA. Conversely, spike-wave complex appeared only in neonates approaching full term - the slow wave of such complexes is thought to represent repolarisation and hyperpolarisation after the depolarisation during the spike. (Charpier et al., 1999;Neckelmann et al., 2000) We can speculate that these particular patterns emerge

only when the inhibitory mechanisms have matured, which would happen in the last month of pregnancy.

There are a number of limitations to our study. It was retrospective and because of recordings prompted in most cases by clinical suspicion of seizures, it might lead to a selection bias. Multicentre study also implied inclusion of recordings with slightly different sets of electrodes and of different durations. Even with multichannel EEG described here, the spatial sampling is limited and seizures may have been missed. In principle, prospective study which would have to be multicentre, but counteracting the limitations, might get more unified information; however, the clinical reality of unstable neonate has to be taken into account.

Despite the limitations, analysis of ictal EEG can contribute to better understanding of maturation of neuronal networks. It would be useful, in future studies, to evaluate whether persistence of some type of ictal pattern or absence of emergence of another could discern emergence of abnormalities of maturation and thus help predict the neurodevelopmental outcome.

In conclusion, the results of this study indicate, that in contrast to term neonates, in preterm neonates the seizures are shorter, begin over a more localised region and propagate less. In preterm neonates higher proportion of seizures are subclinical, thus EEG is essential for diagnosis.

Tables and figure legend

Supplementary table 1: Antiepileptic and paralysing treatments received during EEG recording.

AEDs	**Preterm n=56**	**Term n=45**
Phenobarbital	25	17
Phenytoin/fosphenytoin	11	4
Benzodiazepines	10	9
Levetiracetam	3	0
Topiramate	1	0
Lidocaine	1	0
Thiopentone	1	1
Pyridoxine	1	2
Vigabatrin	0	1
Valproate	1	1
No AEDs	17	23
Curare derivatives	5	7

Supplementary table 2: Aetiology of seizures. Total exceeds 100 % as some children accumulated several comorbidities which were plausible causes of seizures.

Aetiology		**Preterm n=56**	**Term n=45**
Vascular/circulatory		**46**	**21**
	Hypoxic injury	16	10
	Periventricular haemorrhage	20	0
	Intracranial haemorrhage	6	6
	Cerebral infarction	4	5
Infection		**12**	**9**
Metabolic		**11**	**7**
	Na, Ca, Mg, glucose	7	5
	Multiorgan failure	4	2
Inborn error of metabolism		**1**	**3**
Structural		**8**	**6**
	Trauma	1	1
	Malformative syndrome	7	5
Neonatal epileptic syndrome		**0**	**2**
Chromosomal abnormality		**0**	**3**

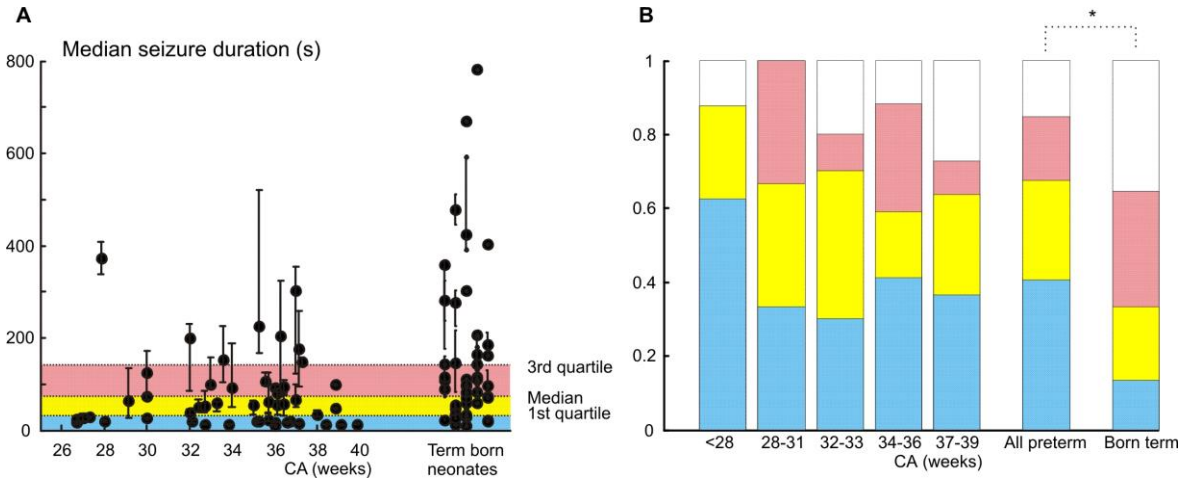

Figure 1: Duration of seizures. **A** Median and interquartile range of each child is represented as function of corrected age when the seizures were captured. **B** Distribution of seizure duration in quartiles depending on corrected age. Seizures were shorter in preterm neonates than in full term neonates (χ^2, $p<5*10^{-3}$).

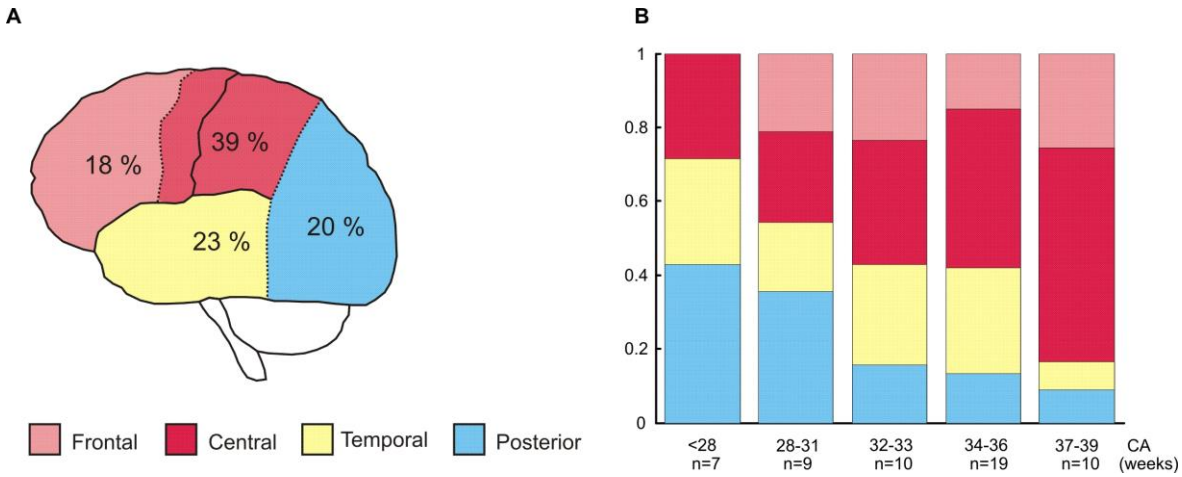

Figure 2: Localisation of seizure onset. A Onset of focal seizures was observed in all cerebral regions and on the whole, the central regions predominated. **B** We observed differences depending on age. In the youngest neonates, the onset over posterior regions predominated, whereas frontal onset was observed only after 28 weeks CA.

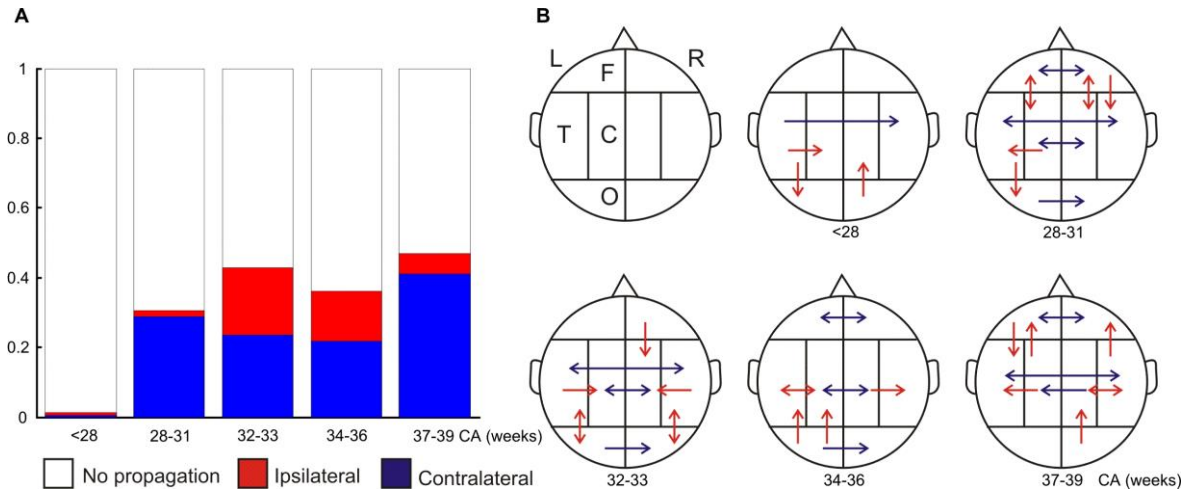

Figure 3: Spatial propagation. A Spreading from the region of onset was extremely rare prior to corrected age of 28 weeks. Afterwards, the proportion of propagation rose to 30-45 %, of which the propagation to homologous regions of the opposite hemisphere predominated independently of age. **B** Pathways of propagation involved only the posterior, central and temporal lobes before 28 weeks CA and the interhemispheric propagation was limited to propagation between temporal lobes. Later on, the seizures could propagate between any lobes within and between hemispheres.

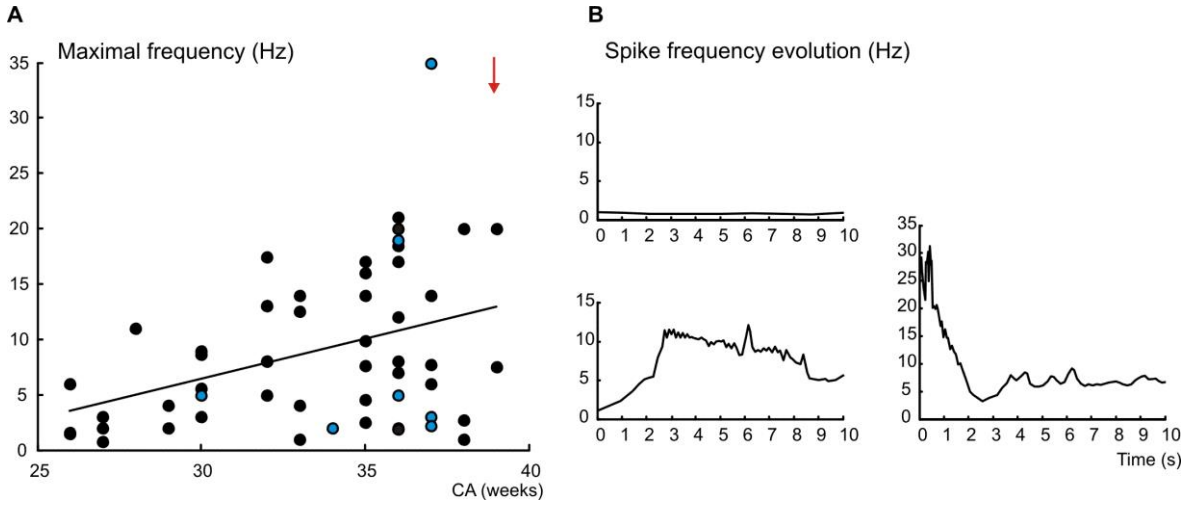

Figure 4: Frequency of ictal discharge. A Each point represents maximal frequency found within seizures recorded in each child. Linear regression of maximal frequency depending on corrected age shows increase of maximal frequency with increasing corrected age; test of slope of linear regression $p < 5*10^{-2}$. Blue dots represent neonates in whom spike-waves pattern was recorded (the spike-wave intra-train frequency was not necessarily the highest frequency of the ictal discharge found in a given subject). Red arrow represents the age of appearance of electrodecremental onset – the exact maximal frequency of the ictal discharge cannot be determined in those cases. **B** Examples of changes of frequency of the ictal discharge at the onset of the seizure. (1) Subset of seizures did not exhibit marked changes in the frequency of the discharge. (2) Most

frequently the onset was marked by progressive increase of the frequency of the discharge. (3) Infrequently, a progressive deceleration was observed in neonates close to term.

Table 1: Ictal clinical manifestation depending on localisation of ictal discharge. Central +/- ictal discharge involving/not involving the central region; EC electro-clinical seizure; E electrographic only seizure; in parenthesis is the subset receiving muscle relaxing drug

Preterm neonates				**Term neonates**			
	EC	E			EC	E	
central +	12	24(2)	36	central +	22	18(5)	40
central -	2	18	20	central -	0	5	5
	14	42	56		22	23	45

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