Electrographic Seizures during the Early Postnatal Period in Preterm Infants

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Objective To investigate the frequency and characteristics of electrographic seizures in preterm infants in the early postnatal period.

Study design Infants <32 weeks gestational age (GA) (n = 120) were enrolled for continuous multichannel electroencephalography (EEG) recording initiated as soon as possible after birth and continued for approximately up to 72 hours of age. Electrographic seizures were identified visually, annotated, and analyzed. Quantitative descriptors of the temporal evolution of seizures, including total seizure burden, seizure duration, and maximum seizure burden, were calculated.

Results Median GA was 28.9 weeks (IQR, 26.6-30.3 weeks) and median birth weight was 1125 g (IQR, 848-1440 g). Six infants (5%; 95% CI, 1.9-10.6%) had electrographic seizures. Median total seizure burden, seizure duration, and maximum seizure burden were 40.3 minutes (IQR, 5.0-117.5 minutes), 49.6 seconds (IQR, 43.4-76.6 seconds), and 10.8 minutes/hour (IQR, 1.6-20.2 minutes/hour), respectively. Seizure burden was highest in 2 infants with significant abnormalities on neuroimaging.

Conclusion Electrographic seizures are infrequent within the first few days of birth in very preterm infants. Seizures in this population are difficult to detect accurately without continuous multichannel EEG monitoring. *(J Pediatr 2017;187:18-25).*

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Seizures are a hallmark of neurologic dysfunction but can be difficult to detect and treat in newborns.[1] Seizures are an even greater diagnostic challenge in preterm infants, in whom the vast repertoire of normal general movements can be difficult to distinguish from the often subtle movements of clinical seizures.[2-5] This challenge is further compounded by the high rate of electroclinical dissociation in infants with seizures.[6] The early postnatal period, or transitional period, in preterm infants is of particular concern because the brain is vulnerable to injury, and the risk increases with decreasing gestational age (GA).[7]

Continuous electroencephalography (EEG) monitoring is the only way to reliably monitor and then treat seizures in newborns, but because interpretation is difficult, real-time results are rarely acutely available.[8,9] Many centers rely instead on amplitude-integrated EEG (aEEG) because of its ease of application, maintenance, and interpretation.[10] aEEG is a useful tool for assessing neurologic function in newborn infants[11] and identifying generalized seizures,[10,12] but it does have limitations. These limitations are greater in the preterm population, in whom the baseline EEG changes continuously with GA[13] and seizures are less generalized with shorter duration.[14] Studies reporting only a clinical diagnosis of seizure frequency in preterm infants have reported values ranging from 3.9 to 57.5 per 1000 births.[15-17] In very preterm infants, seizure frequency of 0.9%-8.7% has been reported in EEG studies, but recordings have been short in duration or have targeted only infants with risk factors.[3,18-20] Much higher seizure frequencies (22%-48%) have been reported in the first few days in preterm infants using aEEG.[21-23]

We applied continuous, long-duration video-EEG monitoring within the first few days of birth in a sample of infants <32 weeks GA, regardless of their clinical status. We aimed to describe the frequency and characteristics of seizures in preterm infants

AED	Antiepileptic drug
aEEG	Amplitude-integrated electroencephalography
BW	Birth weight
cPVL	Cystic periventricular leukomalacia
CRIB	Clinical Risk Index for Babies
CUS	Cranial ultrasound
EEG	Electroencephalography
GA	Gestational age
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit

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Funded by a Science Foundation Research Centre Award (INFANT-12/RC/2272). J.O.T. received financial support from the Irish Research Council (GOIPD/2014/396). Some data collection was also supported by the Wellcome Trust UK (085249). The authors have no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.03.004

of <32 weeks GA during the early postnatal period using continuous video-EEG monitoring.

Methods

Infants <32 weeks GA born at Cork University Maternity Hospital were enrolled in this study between April 2009 and March 2011 and between March 2013 and April 2014. Cork University Maternity Hospital delivers approximately 8500 infants annually, including 100-120 infants of <32 weeks GA, and contains a level 3 neonatal intensive care unit (NICU). Infants with congenital anomalies were excluded prospectively, and infants with EEG recordings <24 hours in duration were excluded retrospectively to optimize the time window for seizure detection. Ethical approval for the collection and analysis of data was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Ireland. Written informed parental consent was obtained for each infant before the initiation of EEG recordings.

EEG Recording

A continuous multichannel video-EEG was initiated as soon as possible after birth when the infant was stable and maintained for up to approximately 72 hours of age, or longer if requested by the clinical team. Three EEG machines were used: the NicoletOne EEG system (CareFusion, San Diego, California), the NeuroFax EEG-1200 (Nihon Kohden, Tokyo, Japan), and the CNS-200 EEG and Multimodal Monitor (Moberg ICU Solutions, Ambler, Pennsylvania). All of these EEG systems display continuous multichannel video-EEG and a 2-channel aEEG trend (F4-C4 and F3-C3). F3 and F4 locations were used instead of Fp1/Fp2[24] because they are less susceptible to fall off during long-term monitoring in the NICU. Disposable single-patient surface electrodes (Neuroline 700; Ambu, Ballerup, Denmark) were used for EEG recordings. The active electrodes were applied at positions F4, F3, C4, Cz, C3, T4, T3, O2, and O1, with a reference electrode at Fz and a ground electrode behind the ear, using a modified neonatal version of the international 10/20 system.[24,25] The midline central electrode (Cz) was occasionally omitted owing to an extremely small head size. An impedance <5 kΩ was maintained throughout the recording. Clinical staff used the aEEG as an aid for clinical assessment. During monitoring, if there were any concerns about suspicious clinical behaviors or aEEG patterns, a neurophysiologist was asked to review the continuous multichannel EEG if possible, but this was dependent on staff availability. An EEG application approach for preterm infants has been developed that limits the need to reposition or adjust the electrodes.[25] Following this approach, we were able to minimize handling of the infants. Moreover, surface disposable electrodes did not cause any small scalp lesions.

Seizure Analysis

The entire video-EEG recording for each infant was reviewed, and all seizures were identified and annotated independently by an electroencephalographer. Another electroencephalographer also annotated all EEGs demonstrating seizures. A third electroencephalographer reviewed a subset of all recordings and evaluated any seizures for which disagreement existed to provide a consensus. A seizure was defined as a clear ictal event comprising of a sudden, repetitive, evolving stereotyped waveform with a definite start, middle, and end and lasting for at least 10 seconds.[26] The onset and offset of each electrographic seizure was annotated and exported to text files for further analysis.

Seizure Characteristics

Several seizure characteristics were calculated from the annotation text files. These metrics are illustrated in **Figure 1** (available at www.jpeds.com) and described as follows. Total seizure number is the total number of seizures over the entire recording. Mean seizure duration is the mean duration of all seizures in the EEG record. Total seizure burden is the total duration of all seizures in the entire recording. Seizure onset is the start time of the first recorded seizure. Total seizure period is the interval between seizure onset and the end of the last recorded seizure. Maximum seizure burden and time of maximum seizure burden are the maximum point, and time (postnatal age) of the maximum point, of the temporal distribution of seizure burden. This distribution, also known as instantaneous seizure burden, is calculated as the midpoint of a 1-hour window (seizure burden per hour) shifted in time, by 1 second, across the entire EEG record.[27,28] Seizure burden per hour is the total seizure duration, in minutes, within a 1-hour window.

For each seizure, the onset location, morphology, and evolution were described.[29] Video-EEG analysis provided information on clinical seizure manifestations and allowed categorization of events as either electrographic or electroclinical. Electroclinical seizures were described as clonic, tonic, myoclonic, spasms, autonomic, or subtle (boxing, pedaling, oral automatisms, ocular movements), following Volpe modified classification system.[1,30] Annotations also allowed the identification of any periods of status epilepticus, defined as continuous or accumulative electrographic seizures present in >50% of a 1-hour period.[31]

Additional Data Collection

Serial cranial ultrasound (CUS) scans were collected for intraventricular hemorrhage (IVH) grading or presence of cystic periventricular leukomalacia (cPVL). Grade 3 or 4 IVH and cPVL were considered significant brain abnormalities. In accordance with our standard clinical practice, all scans were officially performed and reported by a pediatric radiologist who was not involved in the study and was blinded to EEG data. Infants had the first CUS within the first 72 hours of birth where possible, with repeat scans between 7-10 days of age and at 1 month of age. Timing varied slightly depending on the radiologist's availability and the infants' clinical condition. Each infant's GA, birth weight (BW), Apgar scores at 1 and 5 minutes, and mechanical ventilation (intubation in the delivery suite and mechanical ventilation over the first 3 days of age) were collected. In addition, the Clinical Risk Index for Babies (CRIB