Seizure: European Journal of Epilepsy 61 (2018) 221–226

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

High electroencephalographic seizure exposure is associated with unfavorable outcomes in neonates with hypoxic-ischemic encephalopathy

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ARTICLE INFO

Keywords:
Therapeutic hypothermia
Neonatal seizures
Seizure exposure
Neurodevelopmental outcome
Electroencephalography

ABSTRACT

Purpose: Electroencephalographic seizures (ES) are common among neonates with hypoxic-ischemic encephalopathy (HIE), and they represent a treatable complication that might improve neurodevelopmental outcomes. We aimed to establish whether higher ES exposure was predictive of unfavorable outcomes while adjusting for other important clinical and electroencephalographic parameters.

Methods: We performed a single-center, retrospective study of consecutive neonates with HIE managed with therapeutic hypothermia from June 2010 through December 2016. Neonates underwent continuous electroencephalographic (cEEG) monitoring during and after therapeutic hypothermia. Outcome measures included abnormal MRIs after rewarming and abnormal motor and language development.

Results: Clinical data from the perinatal period were available for 116 neonates. Follow-up data were available for 93 of 116 (80%) neonates who survived to discharge, with a median follow-up period of 23 months (interquartile range 1236 months). Multivariate analysis demonstrated that high ES exposure (OR 5.2, 95% CI 1.3–21.2, p = 0.02) and moderate/severely abnormal EEG background (OR 8.3, 95% CI 1.6–43.9, p = 0.01) were independent predictors of abnormal motor development. High ES exposure was an independent predictor of abnormal language development (OR 4.2, 95% CI 1.1–15.9, p = 0.04). High ES exposure (OR 7.0, 95% CI 2.2–22.5, p = 0.01) and severe encephalopathy (OR 7.9, 95% CI 1.5–42.7, p = 0.02) were independent predictors of abnormal MRIs.

Conclusions: Among neonates with HIE managed with therapeutic hypothermia, high ES exposure was the most important predictor of abnormal developmental and neuroimaging outcomes, even after adjustment for multiple clinical and EEG variables. Adequate identification and management of ES with judicious use of anti-seizure medications may optimize outcomes.

1. Introduction

Hypoxic-ischemic encephalopathy (HIE) is a common cause of clinical and non-convulsive (subclinical) electroencephalographic seizures (ES) among neonates and remains a substantial cause of death and neurodevelopmental disability [1]. Historically, morbidity and mortality from HIE were high; however, the implementation of therapeutic hypothermia has led to significant reductions in death and neurodevelopmental disability [2–8]. Since therapeutic hypothermia became the standard of care for neonatal HIE treatment, studies have identified several factors that are predictive of unfavorable neurodevelopmental outcomes, including the clinically assessed degree of encephalopathy, the amount of brain injury evident on MRI, abnormal EEG background features, and high seizure exposure [9–15]. Moreover, seizures are correlated with more severe abnormalities on brain MRI [16,17]. Importantly, these studies adjusted for only a subset of potentially important clinical, EEG, and neuroimaging parameters, which complicates their interpretation. Additionally, to assess seizure exposure, several studies utilized clinical or amplitude integrated EEG assessment rather than the gold standard of conventional EEG assessment [14,17–19]. This study evaluated multiple clinical and conventional EEG features to determine which are predictive of abnormal neurodevelopmental and

Abbreviations: cEEG, continuous EEG; EEG, electroencephalographic; ES, electroencephalographic seizures; HIE, hypoxic-ischemic encephalopathy; SE, status epilepticus

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https://doi.org/10.1016/j.seizure.2018.09.003
Received 7 June 2018; Received in revised form 2 August 2018; Accepted 10 September 2018

neuroimaging outcomes. We hypothesized that high ES exposure would be associated with abnormal motor, language, and MRI outcomes after adjustment for other relevant clinical and EEG variables.

2. Patients and methods

The Children's Hospital of Philadelphia (CHOP) Institutional Review Board approved this study. We performed a single-center, retrospective study of consecutive neonates with HIE treated with therapeutic hypothermia from June 2010 through December 2016. No neonates treated during this period were excluded. Subjects were identified using a database maintained by the Neonatal Intensive Care Unit (NICU) that catalogues clinical data on all patients. Based on an institutional pathway, whole-body therapeutic hypothermia was initiated on all appropriate infants within six hours of birth. Clinical variables were defined as published previously [20]. Degree of encephalopathy was determined prior to therapeutic hypothermia initiation by the admitting neonatologist using a structured clinical examination to assess the degree of encephalopathy.

Given that these neonates have a high incidence of ES and guidelines recommend continuous EEG monitoring (cEEG), an institutional clinical pathway specified that all neonates with HIE undergoing therapeutic hypothermia underwent cEEG during therapeutic hypothermia and through rewarming, or for 24–48 h after the cessation of the last seizure. EEG monitoring was performed using Grass-Telefactor video EEG equipment with a standard 10–20 electrode montage. All EEG data were interpreted by trained pediatric electroencephalographers. Data regarding cEEG findings were obtained by reviewing reports in the electronic medical record. EEG background was classified as: (1) mildly abnormal if the record demonstrated discontinuity with either interburst amplitudes $< 25\,\mu V$ or duration that is prolonged for corrected age [21]; (2) moderately abnormal if the record demonstrated discontinuity with both interburst amplitudes $< 25\,\mu V$ and prolonged for gestational age with duration < 30 s; or (3) severely abnormal if the record was severely attenuated/featureless or if there was discontinuity with interburst intervals that lasted ≥ 30 s or if burst-suppression was present. EEG background classification was performed based on the initial 24 h of recording. ES were defined according to neonatal EEG standardized terminology from the American Clinical Neurophysiology Society [21]. ES exposure was defined as the number of seizures during the entire period of cEEG, from initiation of monitoring through rewarming. ES exposure thresholds were determined using a threshold analysis that varied the definition of high ES exposure from ≥ 1 ES through ≥ 20 ES. High ES exposure was defined as the lowest number of ES that was predictive of outcome (motor: ≥ 4, language: ≥ 3, MRI abnormality: ≥ 2). Low ES exposure was defined as ES less than this cutoff. This type of analysis was performed in an effort to avoid an arbitrary definition of high ES exposure. Patients experiencing status epilepticus were included with the high ES exposure group. Status epilepticus was not included as a separate group given the very small numbers of patients who experienced this ES exposure.

MRI scans were typically performed within 24–48 h of rewarming unless neonates were too medically unstable for transport to MRI at that time. Data regarding MRI findings were obtained by reviewing reports in the electronic medical record. MRI images were reviewed when the reports were not sufficiently clear for scoring. MRI reports and images when necessary were reviewed by one clinician (MPF) blinded to clinical and EEG data on two occasions spaced more than one month apart. MRI injury distribution was scored using published methods, modified to include DWI signal abnormality in addition to abnormalities on T1 and T2 weighted images [22,23].

Neurodevelopmental outcomes were abstracted from clinical care notes from routine follow-up appointments in the Neurology Clinic and from structured follow-up appointments with the Neonatal Neurodevelopmental Follow-up Clinic at 3, 6, 12, 18, and 24 months of age. Clinicians assessed for neurodevelopmental delays using clinical interviews frequently supplemented by the Bayley Scales of Infant Development Third Edition (BSID-III). Neurodevelopmental outcomes from the most recent clinic assessment were utilized in the analyses.

For the purposes of logistic regression analyses, several clinical variables were converted to categorical variables. Birth weight was categorized as low (< 2500 g), normal (2500–4000 g) and high (> 4000 g). Gestational age was categorized as premature (34–37 weeks), term (38–40 weeks), and post-term (≥ 41 weeks). Apgar score at 10 min was categorized as ≤ 5 or > 5. EEG background was categorized as normal/mildly abnormal or moderately/severely abnormal. Neurodevelopmental outcomes in the motor and language domains were categorized as normal or abnormal. Abnormal motor development was defined as any delays in gross motor and/or fine motor skills. Abnormal language development was defined as any delays in expressive and/or receptive language skills. Not all patients were assessed with the BSID-III; therefore, neurodevelopmental outcomes were not defined based on specific Bayley score cutoffs. MRI scans were categorized as normal or abnormal. Abnormal MRI scans were defined as those with a basal ganglia/watershed score of ≥ 1 [22].

Data were summarized using descriptive statistics including medians with interquartile range (IQR) or means with standard deviation (SD) for continuous variables, or as percentages for categorical variables. Univariate logistic regression analyses compared potential predictor variables to neurodevelopmental and neuroimaging outcomes. Variables with $p < 0.2$ on univariate analysis were included in multivariate logistic regression to determine which clinical and EEG variables were independent predictors of motor delay, language delay, and MRI abnormality. After creation of the multivariate models, an analysis was performed in which variables were sequentially removed from the overall model to verify the predictive value of statistically significant variables in the model.

3. Results

During the study period, 132 neonates with HIE underwent therapeutic hypothermia. Of these neonates, 70% were term, 20% were preterm ($\leq$ 37 weeks), and 10% were postterm (≥ 41 weeks). Sixteen neonates (12%) died prior to discharge due to withdrawal of technological support, and 116 neonates (88%) survived to hospital discharge. MRI results were available for 118 neonates (89%). Among the 116 neonates who survived to discharge, 93 (80%) had follow-up neurodevelopmental data available. The median follow-up interval was 23 months (IQR 1236; range 2–72 and 90% had a minimum follow-up duration of 6 months).

Table 1 provides the clinical characteristics of the cohort stratified according to the presence or absence of motor delay, language delay, and abnormalities on MRI. Neonates with motor delays in follow-up demonstrated statistically significant differences in gestational age (38.2 versus 38.9, $p = 0.03$), birthweight (3575 g versus 3273 g, $p = 0.05$), Apgar score at 10 min (3 versus 5, $p = 0.01$), ES exposure (no seizures: 50% versus 73%; low ES (< 4 seizures): 9% versus 15%; high ES (≥ 4 seizures): 41% versus 11%; $p < 0.01$), and abnormal EEG background (moderate: 36% versus 30%; severe: 45% versus 10%; $p = 0.01$). Neonates with language delays in follow-up demonstrated a statistically significant difference in male sex (74% versus 49%, $p = 0.04$), Apgar score at 10 min (3 versus 5, $p = 0.02$), degree of encephalopathy (moderate/severe: 87% versus 70%, $p = 0.01$), ES exposure (no seizures: 43% versus 76%; low ES (< 3 seizures): 17% versus 7%; high ES (≥ 3 seizures): 39% versus 17%; $p = 0.02$), abnormal EEG background (moderate: 22% versus 35%; severe: 43% versus 10%; $p = 0.01$), and duration of follow-up (29 months versus 19 months, $p = 0.02$). The only variable associated with a statistically significant increase in the likelihood of having an abnormal MRI was ES exposure (no seizures: 59% versus 84%; low ES (< 2 seizures): 3% versus 7%; high ES (≥ 2 seizures): 83% versus 17%; $p < 0.01$). No significant differences were noted with other clinical variables,