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Original Article

Prediction of Neonatal Seizures in Hypoxic-Ischemic Encephalopathy Using Electroencephalograph Power Analyses

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ABSTRACT

BACKGROUND: The severity of the initial encephalopathy in neonatal hypoxic-ischemic encephalopathy correlates with seizure burden. Early electroencephalograph (EEG) background activity reflects the severity of encephalopathy. Thus, we hypothesized that early EEG background would be predictive of subsequent seizures in neonatal hypoxic-ischemic encephalopathy. **METHODS:** This study included infants undergoing therapeutic hypothermia at St. Louis Children's Hospital between January 2009 and April 2013. Two pediatric epilepsy specialists independently characterized EEG background qualitatively using amplitude-integrated EEG trends. Total EEG power in the 1-20 Hz frequency band was calculated for quantitative EEG background assessment. Seizures were identified on conventional full montage EEG. Statistical analysis was performed using logistic regression. **RESULTS:** Seventy-eight of the 93 eligible infants had artifact-free EEG data; 23 of 78 infants (29%) developed seizures, and of these, 11 developed status epilepticus. The best predictors of subsequent seizures during the first hour of EEG recording were a flat tracing pattern on amplitude-integrated EEG (sensitivity 26%, specificity 98%, likelihood ratio 13, positive predictive value 85%) and the total EEG power less than 10 μV^2 (sensitivity 52%, specificity 98%, likelihood ratio 30, positive predictive value 92%). **CONCLUSIONS:** Early EEG biomarkers predict subsequent seizures in infants with hypoxic-ischemic encephalopathy. Compared with the qualitative amplitude-integrated EEG background, total EEG power improves our ability to identify high-risk infants from the first hour of EEG recording. Infants with a total EEG power of less than 10 μV^2 have a 90% risk of subsequent seizures. Quantitative EEG measures could stratify cohorts while evaluating novel neuroprotective strategies in neonatal hypoxic-ischemic encephalopathy.

Keywords: neonatal seizures, hypoxic-ischemic encephalopathy, aEEG, quantitative EEG, total EEG power, seizure prediction, neonatal EEG

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Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) is a leading cause of mortality and long-term neurological morbidity. Although therapeutic hypothermia has improved prognosis in some individuals, it does not prevent all HIE-related injuries and more than a third of survivors still experience neurological disability.[1,2] Seizures complicate the acute clinical course in 30% to 65% of infants with HIE and may cause secondary injury. Early identification of infants at risk for seizures could pave the way for evaluation and institution of complementary therapies in addition to therapeutic hypothermia in these babies.

Conventional electroencephalography (EEG), with its established role in current management protocols for neonatal HIE, offers a practical bedside stratification tool for early identification of at-risk infants.[3] Qualitative assessment of the conventional EEG background, mainly based on low EEG amplitude and excessive discontinuity, correlates with the severity of cerebral injury and neurodevelopmental outcome in neonates with HIE.[4] However, conventional qualitative EEG analysis is subjective and is limited by the lack of emergency access to neonatal neurophysiology services in many neonatal intensive care units.

Quantitative analysis of EEG background provides the objectivity and reproducibility needed for reliable risk identification. Amplitude-integrated EEG (aEEG) is a commonly employed, semiquantitative EEG monitoring tool, used independently or in conjunction with conventional EEG recording in neonatal intensive care units.[5,6] EEG spectral power derived from conventional EEG recordings predicts seizures in adult and pediatric EEGs[7,8] but needs evaluation in neonates.

In this study, we assess and compare early qualitative aEEG background and quantitatively calculated total EEG power (TEP) from conventional EEG in infants with and without seizures undergoing therapeutic hypothermia for HIE.

Methods

Participants and research design

This single-center retrospective cohort study included encephalopathic term neonates undergoing therapeutic hypothermia at St. Louis Children's Hospital from January 2009 until April 2013. At least 24 hours of conventional full montage EEG video study was performed with Stellate Harmonie (Natus Medical Incorporated, San Carlos, CA, USA) sampled at 200 Hz using Grass gold disc electrodes placed according to the conventional 10-20 electrode measurement system. Exclusion criteria included either absence of at least one hour of EEG recording free of significant artifacts in the first 24 hours after birth or status epilepticus in the initial hour of EEG recording. The Human Research Protection Office at Washington University in St. Louis reviewed and approved this study and waived the requirement of informed consent.

Clinical variables such as gender, birth weight, gestational age, Apgar scores at one and five minutes of life, cord arterial pH, base deficit, Sarnat stage and clinical risk index for babies score at admission, age at full feeding, and length of stay were obtained from the patient's medical records.

Procedures

EEG video analysis

Seizures and status epilepticus were determined using conventional EEG recording in a blinded fashion by pediatric epilepsy specialists (S.J. and J.M.Z.). An electrographic seizure was defined as a sudden and repetitive evolving stereotypical EEG waveform with a definite start and end lasting for at least ten seconds arising from at least one EEG electrode. Electrographic status epilepticus was defined as continuous or cumulative electrographic ictal activity lasting for at least one-half of each one-hour period. A consensus on a single seizure was enough to classify infants with subsequent seizures with a 100% agreement between the two physicians. Interrater reliability for seizure detection was not needed for this study design.

Spectral data extraction and TEP calculation

TEP was calculated from the first hour of artifact-free EEG data, in C3-P3 and C4-P4 electrode pairs using Polytrends EEG software version 7 (Stellate, Montreal, Canada). EEG band power was calculated after band-pass filtering the raw data (high-pass infinite impulse response filter of order 2 and low-pass infinite impulse response filter of order 4) between 1 and 20 Hz using the fast Fourier transform algorithm (FFT length 512, 30-second epochs, no overlap). An average of the median value of the EEG band power (1 to 20 Hz, μV^2) from both channels yielded the TEP. In addition, epochs with median power values not corresponding to artifact-free and seizure-free sections on visual analyses were rejected and the next hour similarly evaluated. Since status epilepticus would raise background EEG power, epochs with status epilepticus were excluded (Fig 1).

We chose to calculate TEP over central-parietal channels as they overlie the watershed regions of the brain preferentially affected in neonatal HIE. Limited channel aEEG monitoring also utilizes these regions for EEG background evaluation and seizures in many neonatal intensive units around the world. In addition, a limited channel algorithm simplifies the analysis allowing for a rapid bedside estimation of the predictive variable. However, full conventional EEG recordings were used for seizure detection.

aEEG pattern classification

aEEG trends from both centroparietal channels (Polytrends EEG trending software version 7, Stellate, Montreal, Canada) were classified as continuous normal voltage, discontinuous normal voltage, burst suppression, low voltage, and flat tracing, as described by Hellström-Westas et al.[6] Low-voltage burst suppression was an additional pattern used for characterization of a burst suppression pattern with lower amplitude bursts (<10 μV) as the traditionally described burst suppression pattern has higher amplitude bursts (>25 μV). There was a 96% agreement in the background aEEG classification between the two interpreting physicians. The differences were resolved by discussion.

Statistical analysis

Logistic regression analysis was used to compare EEG measures between infant cohorts with and without seizures and status epilepticus. Continuous demographic variables were compared using Student *t* tests and Mann-Whitney U, whereas chi-square tests were used to compare categorical variables. A receiver-operating curve was generated for TEP, which provided the likelihood ratios to help determine thresholds for further analyses using PRISM6 (GraphPad Software, Inc, La Jolla, CA, USA).

Results

Descriptive results

Ninety-three infants underwent therapeutic hypothermia at St. Louis Children's Hospital between January 2009 and April 2013. Of these, 78 infants (42 males) had EEG data available for analysis of which 23 had seizures (12 infants had no EEG data and two had uninterpretable EEGs in the first 24 hours after birth; one had status epilepticus at onset of EEG recording). Excluded infants were similar in seizure incidence (7 of 15) compared with the study cohort (23 of 78).

More females than males had seizures ($P = 0.029$) (Table 1). Infants with seizures had higher Sarnat stage, base