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ORIGINAL ARTICLE

Can We Predict Functional Outcome in Neonates with Hypoxic Ischemic Encephalopathy by the Combination of Neuroimaging and Electroencephalography?

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Key Words
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Background: Neonatal hypoxic ischemic encephalopathy (HIE) is a major cause of mortality, morbidity, and long-term neurological deficits. Despite the availability of neuroimaging and neurophysiological testing, tools for accurate early diagnosis and prediction of developmental outcome are still lacking. The goal of this study was to determine if combined use of magnetic resonance imaging (MRI) and electroencephalography (EEG) findings could support outcome prediction.
Methods: We retrospectively reviewed records of 17 HIE neonates, classified brain MRI and EEG findings based on severity, and assessed clinical outcome up to 48 months. We determined the relation between MRI/EEG findings and clinical outcome.
Results: We demonstrated a significant relationship between MRI findings and clinical outcome (Fisher's exact test, $p = 0.017$). EEG provided no additional information about the outcome beyond that contained in the MRI score. The statistical model for outcome prediction based on random forests suggested that EEG readings at 24 hours and 72 hours could be important variables for outcome prediction, but this needs to be investigated further.
Conclusion: Caution should be used when discussing prognosis for neonates with mild-to-moderate HIE based on early MR imaging and EEG findings. A robust, quantitative marker of HIE severity that allows for accurate prediction of long-term outcome, particularly for mild-to-moderate cases, is still needed.

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1. Introduction

Neonatal hypoxic ischemic encephalopathy (HIE) occurs in 1–2/1000 live births, accounts for 23% of neonatal deaths, and is the fifth largest cause of death in children under 5 years.[1]

Brain hypoxia triggers a cascade of events leading to neuronal death 12–36 hours after the initial ischemic insult,[2] so prompt recognition is imperative for early, effective interventions that will prevent loss of neurons, including therapeutic hypothermia.[3] In addition, identification of HIE and accurate classification of severity are important for reliable prediction of clinical outcome and long-term planning. Routine diagnostic modalities including electroencephalography (EEG) and magnetic resonance imaging (MRI) are somewhat limited tools, particularly in cases of moderate severity.

We investigated the relationship between EEG and MRI findings and outcome in infants with HIE who underwent therapeutic hypothermia. As a secondary investigation, we considered the predictive utility of EEG and MRI findings at 24 hours and 72 hours for determining the clinical outcome.

2. Methods

This study was approved by the West Virginia University Institutional Review Board (Morgantown, WV, USA). All newborns with HIE who underwent therapeutic hypothermia (total body cooling) at West Virginia University Hospital (WVUH) between 2009 and 2013 were included in this retrospective study. Clinical data were obtained from electronic medical records (Table 1).

2.1. Cooling protocol

The decision to cool infants was based on inclusion/exclusion criteria as published (Appendix 1).[4] Cooling was achieved by a cooling blanket to an esophageal temperature of 33.5°C for 72 hours, followed by slow rewarming by 0.5°C/h.

2.2. Neurodevelopmental outcome

Outcome was monitored at 6 months, 12 months, 24 months, or 36 months by neurologic examination, Denver developmental scales (DDST).[7] Pediatric Stroke Outcome Measure (PSOM)[9] and, when possible, Bayley Scales of Infant Development (BSID).[8] All evaluations were performed by a certified pediatric neurologist, or by neurodevelopmental specialists as part of routine clinical assessments for patients followed in the high-risk neonatal clinic at WVU. Most recent assessments are reported for each individual (Table 2). All neurological evaluations were assigned a numeric value of progressive severity (Table 3). DDST scores were as follows: 1, normal; 2, mild delay; 3, moderate delay; and 4, severe delay for each category (personal/social, language, fine motor/adaptive, gross motor). PSOM scale includes sensorimotor, language, and cognitive/behavioral evaluation with a maximum total score of 10. BSID includes scoring for motor development index (MDI) and psychomotor development index (PDI) with 1–4 scoring levels of progressive severity. The above scores were averaged in a Global Outcome Score (Tables 2 and 3). All assessments were performed by a certified pediatric neurologist and/or by a child development specialist.

2.3. MRI

Brain MRI (1.5 or 3 Tesla) was obtained within 1 week after birth including T1-and T2-weighted images, Fluid Attenuated Inversion Recovery(FLAIR), diffusion weighted imaging (DWI), and apparent diffusion coefficient (ADC) sequences. Contrast was used in all patients (0.8 mL Magnevist, Bayer, Toronto, Ontario, Canada). MRI images were evaluated by board-certified neuroradiologists and classified into three groups: 1 = normal; 2 = mild restricted diffusion in cortical gray matter or deep nuclei; and 3 = severe restricted diffusion with or without cystic encephalomalacia. This classification was based on a previously published scoring method,[10] but given the small number of participants in this report, mild and moderate MRI abnormalities were merged as level 2.

2.4. EEG findings

Continuous electroencephalogram monitoring was obtained for 72 hours. Findings were evaluated by a board-certified epileptologist and classified at 24 hours and 72 hours into four groups of increasing severity: 1 = normal; 2 = rare spikes and/or sharp waves; 3 = moderate slowing with or without epileptiform discharges; and 4 = low voltage or severe suppression, with or without prolonged or multiple seizures. Seizures were defined as electrographic seizures detected on EEG according to the definition of Classen and co-workers[5] of "rhythmic discharge or spike and wave pattern with definite evolution in frequency, location, or morphology lasting at least 10 sec". Electrographic definition of seizures was deemed necessary as it has been reported that only one-third of neonatal EEG seizures displays clinical signs on simultaneous video recordings.[5,6]

2.5. Statistical analysis

Positive and negative predictive values, sensitivity, and specificity were calculated for EEG and MRI findings and clinical outcome; positive or negative test and normal/abnormal outcome were used for these calculations, without characterization of levels of severity.

We used Spearman's rank correlation (r_s) for a nonparametric assessment of the association between MRI and EEG on day of life (DOL) 1 (24 hours), and DOL 3 (72 hours). Fisher's exact test was used to assess the relationship between MRI and EEG with the clinical outcome (normal, mild delay, moderate delay, and deceased). Multinomial logistic regression and log-linear regression were used to assess the combined association of MRI and EEG with the clinical outcome.

We explored the predictive ability of EEG and MRI scales using random forests. We performed data preprocessing[11]