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Term-equivalent functional brain maturational measures predict neurodevelopmental outcomes in premature infants

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ABSTRACT

Background: Term equivalent age (TEA) brain MRI identifies preterm infants at risk for adverse neurodevelopmental outcomes. But some infants may experience neurodevelopmental impairments even in the absence of neuroimaging abnormalities.

Objective: Evaluate the association of TEA amplitude-integrated EEG (aEEG) measures with neurodevelopmental outcomes at 24–36 months corrected age.

Methods: We performed aEEG recordings and brain MRI at TEA (mean post-menstrual age of 39 (± 2) weeks in a cohort of 60 preterm infants born at a mean gestational age of 26 (± 2) weeks. Forty-four infants underwent Bayley Scales of Infant Development, 3rd Edition (BSID-III) testing at 24–36 months corrected age. Developmental delay was defined by a score greater than one standard deviation below the mean (< 85) in *any* domain. An ROC curve was constructed and a value of $SEF_{90} < 9.2$, yielded the highest sensitivity and specificity for moderate/severe brain injury on MRI. The association between aEEG measures and neurodevelopmental outcomes was assessed using odds ratio, then adjusted for confounding variables using logistic regression.

Results: Infants with developmental delay in any domain had significantly lower values of SEF_{90}. Absent cyclicity was more prevalent in infants with cognitive and motor delay. Both left and right $SEF_{90} < 9.2$ were associated with motor delay (OR left: 4.7(1.2–18.3), $p = 0.02$, OR right: 7.9 (1.8–34.5), $p < 0.01$). Left SEF_{90} and right SEF_{90} were associated with cognitive delay and language delay respectively. Absent cyclicity was associated with motor and cognitive delay (OR for motor delay: 5.8 (1.3–25.1), $p = 0.01$; OR for cognitive delay: 16.8 (3.1–91.8), $p < 0.01$). These associations remained significant after correcting for social risk index score and confounding variables.

Conclusions: aEEG may be used at TEA as a new tool for risk stratification of infants at higher risk of poor neurodevelopmental outcomes. Therefore, a larger study is needed to validate these results in premature infants at low and high risk of brain injury.

1. Background

Preterm birth remains a significant problem in the United States, with a current rate of 11%. Multiple efforts are being directed towards decreasing the preterm birth incidence to a rate of 9.6% by 2020 [1]. There is a trend towards increase in survival of very preterm infants at the expense of increased long-term morbidities and disabilities [2]. Intraventricular hemorrhage (IVH) and white matter injury (WMI) continue to be important contributors of poor neurodevelopmental outcomes in this population. Primary care physicians and parents seek information on prediction of psychomotor and cognitive outcomes, both at discharge or early during follow up, for early institution of intervention services and helping this subset of population to achieve their best potential.

Magnetic resonance imaging (MRI) has emerged as an important tool for prediction of neurodevelopmental outcomes. White and gray matter abnormalities on MRI correlate well with childhood diagnoses of cerebral palsy and cognitive impairment with a reasonable specificity of

Abbreviations: aEEG, Amplitude-integrated EEG; (SEF_{90}), Spectral edge frequency; BSID-III, Bayley Scales of Infant Development, 3rd Edition,; TEA, Term equivalent age; MRI, Magnetic resonance imaging; NICU, Neonatal Intensive care unit; IVH, Intraventricular hemorrhage; WMI, White matter injury; GA, Gestational age; PMA, Post-menstrual age

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76–89% [3,4]. Despite this, a significant number of preterm infants experience neurodevelopmental impairments even in the absence of neuroimaging abnormalities, reflecting the importance of exploring other measures that may help with prediction of outcomes. In addition, MRI acquisition poses some practical issues such as transport of preterm infants out of the neonatal intensive care unit (NICU), the high cost of MRI, required personnel to perform and read the imaging studies.

An additional tool that accurately identifies brain injury and predicts neurodevelopmental outcomes at term equivalent age (TEA) would allow for better stratification of infants at risk of disability or developmental delay. Electroencephalography (EEG) and amplitude-integrated EEG (aEEG) are additional tools commonly used in the NICU to study the functional maturation of the preterm brain. They allow for objective measurements of brain function and may aid in accurate and reproducible assessment of the brain function.

The utility of amplitude-integrated EEG has been studied extensively in preterm infants. Measures from studies performed in the first days of life, such as continuity, cyclicity, and spectral edge frequency (SEF_{90}), correlate with short- and long-term neurodevelopmental outcomes [5–7]. Early absence of cyclicity and lower SEF_{90} in the first week of life are predictive of intraventricular hemorrhage and white matter damage [7,8]. Other authors studied the predictive value of early aEEG (background pattern, cyclicity and presence of seizures) for neurodevelopmental outcomes at 3 years of age. Some of these studies did not take into account the various clinical confounders in the NICU, as well as the socio-economic status after discharge, both of which may affect outcomes [9]. A recent study showed that brain injury on MRI at TEA in premature infants is closely correlated with delay in brain functional maturation on term aEEG measures [10]. In addition, no prior studies have evaluated the role of aEEG at TEA for prognostication.

Therefore, the objective of this study is to evaluate the association of maturational measures as assessed by aEEG at TEA, with neurodevelopmental outcomes at 24–36 months corrected age in preterm infants born at < 30 weeks of gestational age (GA). We hypothesized that delayed maturation of aEEG measures such as cyclicity and SEF_{90} at TEA are associated with developmental delay at 24–36 months corrected age.

2. Methods

2.1. Study population

Infants in this study were selected from a cohort of babies recruited into a TEA neuroimaging study. To meet criteria for recruitment, infants had to meet the following criteria: 1-born at < 30 weeks GA, 2-TEA MRI with moderate to severe injury, 3-TEA aEEG on same day as MRI. Infants were excluded if they were diagnosed with congenital infections or congenital brain malformations. The remaining 28/60 infants in the cohort were matched by gestational age at birth and enrolled from a control group of premature infants with none/mild injury on a TEA MRI as part of the same neuroimaging study.

Then, they were evaluated at 24–36 months corrected age using the Bayley Scales of Infant Development, 3rd edition. The study was conducted with approval from Washington University School of Medicine Human Research Protection Office.

Data regarding perinatal and neonatal factors were collected from each infant's medical record including: gestational age at birth, birth weight, small for gestational age status, and clinical risk index for babies (CRIB-II) score [11]. Clinical variables included the use of oxygen therapy at 36 weeks post menstrual age (PMA), patent ductus arteriosus requiring treatment, postnatal steroids (hydrocortisone or dexamethasone), retinopathy of prematurity requiring surgery, surgical necrotizing enterocolitis, inotrope use (dopamine or dobutamine), sedative exposure (fentanyl, midazolam or morphine) at TEA (Table 1).

Five measures of the overall socio-economic status of each child's family were collected from the mother's medical record, including ethnicity, marital status, maternal illicit drug use, maternal age (early motherhood < 20 y of age), and insurance type as an indicator for family income. These five variables were combined to form a social risk index score [12,13].

Table 1
Clinical characteristics of the cohort.

Variable	Cohort (N = 44)
Maternal characteristics	
Ethnicity	Caucasian: 23 (52.3%), Black: 21 (47.7%)
Maternal age	< 20 years: 7 (15.9%), > 20 years: 37 (84.1%)
Illicit drug use	None: 40 (91%), at least one: 4 (9%)
Marital status	Married: 17 (38.6%), Single: 27 (61.4%)
Insurance	Private: 20 (45.5%), Public: 24 (54.5%)
Birth weight in grams (mean ± sd)	856 (± 280)
Gestational age (mean ± sd)	26 (± 2)
PMA at study (mean ± sd)	39 (± 2)
SGA status, n (%)	6 (13.6%)
Antenatal steroids, n (%)	29 (66%)
CRIB-II score (mean ± sd)	11 (± 3)
NEC surgery, n (%)	7 (15.9%)
PDA ligation, n (%)	6 (13.6%)
ROP surgery, n (%)	13 (29.5%)
Post-natal steroids, n (%)	15 (34.1%)
Oxygen therapy at 36 wk., n (%)	34 (77.3%)
Inotropes, n (%)	21 (47.7%)
IVH grade 3–4, n (%)	19 (43.2%)
Moderate/severe injury on MRI at TEA, n (%)	25 (56.8%)
Motor delay, n (%)	27 (61%)
Language delay, n (%)	23 (52%)
Cognitive delay, n (%)	24 (54%)

PMA: Post-menstrual age, SGA: Small for gestational age, CRIB-II score: clinical risk index for babies score, NEC: necrotizing enterocolitis, PDA: Patent ductus arteriosus, ROP: retinopathy of prematurity, IVH: Intraventricular hemorrhage, diagnosed by cranial ultrasound.

2.2. aEEG recordings

Two sets of hydrogel electrodes (Natus Newborn Care, San Carlos, CA) were applied in the C3–P3 and C4–P4 positions for the newborn infant according to the International 10–20 system. Tracings were recorded using the BrainZ BRM3 monitor (Natus Newborn Care, San Carlos, CA) and analyzed offline using the software AnalyZe (Natus Newborn Care, San Carlos, CA). The median length of the aEEG recordings was 3 h (range: 1.5–5 h). Quantitative and qualitative analysis was performed. Spectral edge frequency (SEF_{90}: defined as the frequency below which 90% of the spectral power is present) was computed using AnalyZe software.

Visual inspection of the tracings for presence or absence of cyclicity was performed according to Hellstrom-Westas [14]. The tracings were classified into the presence or absence of fully developed sleep-wake cycling defined as clear sinusoidal variations between discontinuous and more continuous background activity, with cycle duration ≥ 20 min. This qualitative analysis was computed by two independent, trained and blinded observers (N.E. and S.L.) and an interclass correlation coefficient was computed.

2.3. Neuroimaging

On the same day of the aEEG recording, infants underwent a non-sedated, non-contrast brain MRI following our institutional neonatal MRI guidelines [15]. Patients were fed and wrapped prior to placement

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