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Cerebral maturation on amplitude-integrated electroencephalography and perinatal exposures in preterm infants

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Abstract

Aim—To determine the associations between perinatal exposures, cerebral maturation on amplitude-integrated encephalography (aEEG) and outcome.

Methods—During this prospective cohort study, 136 infants ≤30 weeks estimated gestational age received four hours of aEEG at four time points (between the first two weeks of life and term equivalent age) during hospitalisation. Perinatal factors were documented. Associations between perinatal exposures and Burdjalov-scores were investigated. Neurodevelopmental outcome was assessed at the age of two.

Results—Immature cyclicity on the initial aEEG recording was associated with higher CRIB score (p=0.01), vaginal delivery (p= 0.02), male gender (p<0.01) and death (p=0.01). Perinatal factors associated with lower Burdjalov-scores included cerebral injury (p<0.01), sepsis (p<0.01), lower caffeine dose (p=0.006), prolonged mechanical ventilation (p=0.002) and death (p<0.01). Burdjalov-scores at 30 (β=2.62, p<0.01) and 34 weeks post-menstrual age (β=2.89, p=0.05) predicted motor scores.

Conclusion—aEEG measures of cyclicity and Burdjalov-scores in the first six weeks of life, with an emphasis on 30 and 34 weeks post-menstrual age, demonstrated associations with perinatal factors known to predict adverse neurodevelopmental outcome.

Keywords

neonatal intensive care; preterm infant; aEEG; cerebral maturation; perinatal exposure

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INTRODUCTION

Preterm infants face a high risk of adverse neurodevelopmental outcome. The contributors to such adverse outcomes include brain injury, such as intraventricular hemorrhage and periventricular leukomalacia (1) and/or altered regional brain development (2). While cranial ultrasound (CUS) or magnetic resonance imaging (MRI) have predictive value for later outcome (3), there remains a subset of infants with impairments in childhood who demonstrate no significant brain injury or alterations on neuroimaging (4). The relationship between cerebral maturation on EEG, neuroimaging and neurodevelopmental outcome is unclear.

Although several methods are available to measure cerebral function, amplitudeintegrated encephalography (aEEG) is becoming utilized more frequently in the neonatal intensive care unit (NICU) (5) to obtain information about the immature brain (6). The very preterm infant, born <30 weeks gestation, has a discontinuous pattern with immature cyclicity when present. With cerebral maturation, the baseline variability rises, bandwidth decreases, and cyclicity becomes regular (7). Based on these features, measures of the aEEG background patterns for preterm infants have been developed (8) with normative values for gestational age (9) and a global scoring system (10). Cyclicity appears to be an important independent marker of cerebral function. The absence of cyclicity in the first 24 hours of life in preterm infants appears to be a marker for brain injury(11) and adverse neurodevelopmental outcomes at 12 months (11). The pattern of aEEG background activity, including seizure burden, appears related to neurodevelopmental outcome at three years of age (12). While there is research supporting associations between medical factors in the NICU and childhood outcome in preterm infants with early cerebral function on aEEG, there remains limited data on whether aEEG may help identify infants most at risk for adverse development. Our primary aim in this study was to investigate the associations between serial aEEG and: 1) perinatal exposures and 2) early childhood outcome aEEG.

PATIENTS AND METHODS

This was a prospective cohort study, which took place in a level III, 75-bed NICU in the Midwestern United States, which has a large population of patients with diverse socioeconomic status. Participants were preterm infants born ≤30 weeks estimated gestational age (EGA), free of congenital anomalies and enrolled within the first 72 hours of life following informed parental consent. Infants received aEEG within the first two weeks after birth, 30 and 34 weeks post menstrual age (PMA), and term-equivalent age (TEA). Infants underwent cranial ultrasound (CUS) and magnetic resonance imaging (MRI) within the first two weeks of life and TEA, respectively. Medical exposures were collected from the hospital record. This study was approved by the Human Research Protection Office at the study site.

Primary Outcome variables

AEEG in the NICU—The BrainZ (™BRM2, BrainZ instruments, Natus Medical Incorporated, Natus Europe, Munich, Germany), a two-channel bedside aEEG monitor that displays raw and amplitude-compressed recordings for each hemisphere, was used in this study. AEEG occurred up to four time points during each infant's NICU stay. The first recording occurred over a 72-hour period within the first two weeks of life (of which a 4-hour midpoint was analysed), while subsequent recordings were conducted for 4 hours at 30 and 34 weeks PMA, and at TEA (37–41 PMA). For each recording, a trained research assistant placed 4 gel electrodes on the infant's scalp using the central (C3-C4) and parietal (P3-P4) locations. Continuous cerebral activity was obtained and stored in the BrainZ Monitor, then evaluated with Analyze (BrainZ) software. Impedance, defined as artifact or

interference, was identified by Analyze, and recordings with moderate-high impedance throughout were excluded. Recordings at all time points were evaluated for background pattern, onset and appearance of cyclicity, and lower amplitude border and bandwidth, which were used to derive a composite Burdjalov score (10) The score ranges from 0–13, and increases with age. At the time points aEEG was collected, the normative scores for the first two weeks after birth, 30, 34 weeks and TEA are 2–6, 8, and 11 and 13, respectively. In addition, cyclicity was also recorded as a dichotomous variable and recorded as present or absent at each timepoint. It was defined as at least one cycle of sinusoidal variations in minimum amplitude, alternating between narrow and broad bandwidths. All recordings were analysed by one aEEG analyst, who was blinded to medical course. Another aEEG analyst completed a reliability check by randomly selecting 5 recordings, scoring them independently and then checking the scoring against the primary analyst. There was 100% inter-rater reliability in determining the aEEG measures.

Developmental Testing at age Two Years—Infants were assessed with the Bayley Scales of Infant Development, 3rd edition (Bayley-III) (13) at two years corrected age. The Bayley is considered the gold standard for assessment of development in early childhood. Composite subscores for language, motor and cognition were used as the primary outcome at two years.

Independent Variables – Medical Factors

Baseline medical factors included initial severity of illness (The Critical Risk Index for Babies (CRIB) score)(14), gestational age at birth, gender and mode of delivery (vaginal or caesarean). Medical interventions in the NICU were collected including total sedative dose received for each infant (fentanyl), days of ventilation (categorized according to quartiles), total caffeine dose, days on total parenteral nutrition, and the use of inotropic drugs. Factors extracted from the medical records included presence or absence of patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), necrotizing enterocolitis (Bells stage II or greater) and sepsis. In addition, cerebral injury was defined by CUS and MRI and dichotomized into ‘moderate to severe injury‘ (cerebellar hemorrhage, grades 3–4 intraventricular hemorrhage and/or cystic periventricular leukomalacia) or ‘no to mild injury’ (the absence of the aforementioned injuries).

Statistical Analysis

Statistical analyses were conducted using the IBM SPSS (version 20) software programme. Independent variables were investigated for associations with Burdjalov-scores, onset of cyclicity and Bayley-III scores. Burdjalov-scores were the primary outcome of interest; and secondary to the high number of comparisons, a Bonferroni correction was made for all subsequent analyses ($p=0.025$). Initial univariate analyses were significant at $p<0.05$. Data was analysed using multivariate linear mixed models and logistic regression to determine associations between the independent and dependent variables. Gestational age at birth, PMA at the time of each recording and gender were controlled for in all data analyses, in addition to insurance status, as a sociodemographic marker, in the outcome analyses.

RESULTS

Between 2007 and 2010, 136 infants were enrolled in the study. Among these infants, seven were withdrawn, one transferred and one was excluded due to a congenital anomaly. Out of 127 infants, 118 infants had at least one aEEG recording between birth and TEA. Of note, 14/17 infants who expired did so before the second recording, all of whom were ≤ 27 weeks EGA at birth. The average EGA at birth was 26.3 ± 1.8 weeks [23–30 weeks]. See Table 1 (in supporting information) for additional population demographics.

The first recording commenced at a median 26 weeks PMA (range 23–30) and postnatal age of median 59.1 hours (range 6–272), the second recording occurred at a median 30 weeks PMA (range 28–32) (n=66), the third recording occurred at a median 34 weeks PMA (range 32–36) (n=57) and the fourth recording occurred at a median 38 weeks PMA (range 37–42) (n=57). The numbers of recordings either missing (due to medical status or procedures) or discarded due to impedance are as follows: first recording (n=11), second recording (n= 52); third recording (n= 61) and fourth recording (n= 61).

Burdjalov-scores and Perinatal Exposures

Perinatal factors associated with lower Burdjalov-scores included cerebral injury ($p<0.01$), sepsis ($p<0.01$), caffeine dose ($p=0.006$), prolonged mechanical ventilation ($p=0.002$) and death ($p<0.01$). None of these factors had persisting effects on Burdjalov-scores by TEA. The strongest predictors for lower Burdjalov-scores at 30 weeks PMA included the presence of severe cerebral injury and inotropes. Lower Burdjalov-scores at 30 and 34 weeks were also associated with ROP diagnosed later in the NICU hospitalization. The associations between medical factors and Burdjalovscores are shown in Table 2 (in supporting information).

Cyclicity and background pattern were separately analyzed. Absence of cyclicity on initial recording was associated with higher CRIB score ($p=0.01$), vaginal delivery ($p= 0.02$), male gender ($p<0.01$) and death ($p=0.01$). Gestational age at birth was not significantly associated with cyclicity, however, gestational age at time of first scan was significantly different for infants who did and did not demonstrate cyclicity (PMA = 27.4, 25.5 respectively). There were no associations between background pattern (as measured by Burdjalov-scores), perinatal factors, and neurodevelopment. The associations between medical factors and the onset of cyclicity are shown in Table 3 (in supporting information).

Burdjalov-scores and developmental outcome

At the age of two, 73% (n=73) of the infants with aEEG recordings returned for developmental follow-up assessment. Burdjalov-scores at 30 ($\beta=2.62$, $p<0.01$) and 34 weeks PMA ($\beta=2.89$, $p=0.05$) predicted the Bayley-III motor composite score at the age of two years. Burdjalovscores were not significantly associated with language or cognitive scores on the Bayley-III.

DISCUSSION

The key finding in this study is that aEEG measures of cerebral maturation measured by Burdjalov-scores and onset of cyclicity during the early NICU course (prior to 35 weeks gestation) were associated with cerebral injury and other perinatal exposures. We identified associations between moderate to severe cerebral injury and lower Burdjalov-scores at 30 weeks PMA, and delayed onset of cyclicity, as previously reported (8). We also demonstrated associations between altered aEEG activity during the NICU hospitalization and perinatal/demographic factors including CRIB score and vaginal delivery. These early aEEG measures were predictive of motor outcome at two years. Previous studies have demonstrated links between initial medical severity and vaginal delivery with neurodevelopmental outcome in preterm infants (15–17). However, the associations between aEEG measures and perinatal exposures and outcome were no longer detectable by TEA. Marked increases in Burdjalov-scores via aEEG were observed throughout the NICU stay, which has been previously reported(7) and is consistent with a period of rapid cerebral development (1, 18). There was also evidence of elevation in the lower amplitude border, narrowing bandwidth and increased continuity as infants advanced in postnatal age. The dominant background pattern matured from discontinuous within two weeks of birth to

continuous by TEA. In addition, the Burdjalov scoring system classified the majority of infants as having immature cyclicity during the first two weeks of life, some degree of cyclicity at 33 weeks PMA (as previously reported)(18) and there was uniform presence of mature cyclicity by TEA. There was no association between gestational age at birth and any of the aEEG measures, suggesting that cerebral electrophysiological function may be more affected by postnatal events rather than age of prematurity itself, or possibly the wide range of post-natal ages at the first recording. For example, therapy for PDA and use of inotropes were associated with lower Burdjalov-scores during the early period. Decreased cardiac output has been previously demonstrated to alter aEEG measures in the very preterm infant (19). The presence of a hemodynamically significant PDA therefore may lead to impaired cerebral perfusion and altered cerebral activity. In addition, mechanical ventilation showed a trend toward lower Burdjalov-scores early in the hospitalization in our cohort, consistent with other research showing that the mechanical ventilation was associated with decreased mental developmental index scores (20). Thus, abnormalities in cerebral maturation detected on aEEG are consistent with the concerns of these exposures on the development of the immature brain from birth through early childhood. Of note, the amount of caffeine exposure was positively associated with increased cerebral maturity at 30 weeks PMA. In general, infants who received larger doses of caffeine were sicker, defined by lower CRIB score, which contrasted with our initial thoughts that we would find an association with delayed cerebral maturation due to their decreased general health status. In contrast, infants exposed to more caffeine demonstrated increased Burdjalov-scores. Previous research has also demonstrated that caffeine is associated with increased maturation of aEEG activity (21). Whether acceleration of maturation measured by aEEG represents an atypical or typical accelerated pattern remains unknown and will be assisted by the later neurodevelopmental sequelae in this cohort, which are still to be evaluated.

It is worth noting that the period of greatest association between aEEG measures and perinatal factors differed between cyclicity and Burdjalov-scores. The early period (first two weeks of life) demonstrated associations with aEEG measures of cyclicity, whereas the middle period of the NICU admission (30 and 34 weeks PMA) displayed associations with Burdjalov-scores. This finding may guide clinical investigators as to the sensitivity of these two measures. It is plausible that the Burdjalov-scores within the first two weeks vary greatly due to the instability of the infant. A more detailed analysis of the evolutional patterns of the individual features of the Burdjalov score may assist in an understanding of the variability. Of importance, neither cyclicity nor the Burdjalov-scores demonstrated any associations with medical factors at TEA, with the exception of PDA. This may reflect that both scoring systems have matured to such an extent that there is less sensitivity for variation. These findings can assist the clinical investigator in the application of aEEG measures in the preterm infant.

In addition to relationships between early medical factors in the NICU and aEEG measures, Burdjalov-scores were found to be predictive of motor outcome at age two years. Thirty and 34 weeks gestation were the most significant time points to assess Burdjalov-scores in relation to short-term neurodevelopmental outcome. The associations between aEEG and motor outcome are supported by other research that has documented associations between aEEG and outcome (22, 23), however, the timing of aEEG assessment differs among the two studies. There are several limitations in this study including impedance or artifact that is often noted on aEEG recordings resulting in limited data and reduced sample size power. In addition, the electrode placement differs slightly from the initial study by Burdjalov et. al. This study relied on multiple comparisons to determine which factors were associated with cerebral aEEG measures. Although all factors investigated were unique, the use of multiple comparisons has the potential to increase the error rate within results.

In conclusion, evaluation of cerebral maturation and brain function by serial aEEG has great clinical utility in preterm management along with neuroimaging of the brain. These functional measures appear to be influenced by factors known to be associated with altered neurodevelopmental outcome including cerebral injury and neonatal factors (medication use and prolonged ventilation) rather than gestational age at birth. The impact appears most notable at 30 and 34 weeks PMA outside of the immediate acute phase of the neonatal stay, yet prior to maturation of electrocortical activity at TEA. Our results continue to support the value of aEEG as a bedside cerebral monitor, especially in the youngest and most vulnerable infants. With aEEG background maturation and cyclicity as signs of cerebral health and well-being, serial monitoring, especially following acute clinical deterioration can show response to treatment and recovery of brain activity. Future research should be directed to more prolonged frequent recordings, with aEEG to map the evolution of aEEG measures in the preterm infant and fully interrogate the impact of perinatal exposures on cerebral maturation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NICU	Neonatal intensive care unit
TEA	Term-equivalent age
aEEG	Amplitude-integrated electroencephalography
PMA	Post-Menstrual Age
CRIB	Critical Risk Index for Babies
CUS	Cranial ultrasound
MRI	Magnetic resonance imaging

REFERENCES

1. Olischar M, Klebermass K, Waldhoer T, Pollak A, Weninger M. Background patterns and sleep wake cycles on amplitude integrated electroencephalography in preterms younger than 30 weeks gestational age with peri /intraventricular haemorrhage. Acta Pædiatr. 2007; 96:1743–1750.
2. Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E, et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics. 2003; 111:939. [PubMed: 12728069]
3. Leijser L, Liauw L, Veen S, de Boer I, Walther F, van Wezel-Meijler G. Comparing brain white matter on sequential cranial ultrasound and MRI in very preterm infants. Neuroradiology. 2008; 50:799–811. [PubMed: 18545992]
4. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med. 2006; 355:685–694. [PubMed: 16914704]

5. Foreman SW, Thorngate L. Amplitude-integrated Electroencephalography: A New Approach to Enhancing Neurologic Nursing Care in the Neonatal Intensive Care Unit. Newborn Infant Nurs Rev. 2011; 11:134–140.
6. Rosen I. The physiological basis for continuous electroencephalogram monitoring in the neonate. Clin Perinatol. 2006; 33:593–611. v. [PubMed: 16950313]
7. Sisman J, Campbell DE, Brion LP. Amplitude-integrated EEG in preterm infants: maturation of background pattern and amplitude voltage with postmenstrual age and gestational age. J Perinatol. 2005; 25:391–396. [PubMed: 15815708]
8. Hellstrom-Westas L, Rosen I, De Vries L, Greisen G. Amplitude-integrated EEG classification and interpretation in preterm and term infants. NeoReviews. 2006; 7:e76.
9. Olischar M, Klebermass K, Kuhle S, Hulek M, Kohlhauser C, Rücklinger E, et al. Reference values for amplitude-integrated electroencephalographic activity in preterm infants younger than 30 weeks' gestational age. Pediatrics. 2004; 113:e61. [PubMed: 14702497]
10. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. Pediatrics. 2003; 112:855. [PubMed: 14523177]
11. Kidokoro H, Kubota T, Hayashi N, Hayakawa M, Takemoto K, Kato Y, et al. Absent cyclicity on aEEG within the first 24 h is associated with brain damage in preterm infants. Neuropediatrics. 2010; 41:241–245. Epub 2011/03/30. [PubMed: 21445813]
12. Klebermass K, Olischar M, Waldhoer T, Fuiko R, Pollak A, Weninger M. Amplitude-Integrated EEG Pattern Predicts Further Outcome in Preterm Infants. Pediatr Res. 2011; 70:102. [PubMed: 21436758]
13. Bayley N. Bayley Scales of Infant and Toddler Development® 3rd Edition (Bayley-III®). 1969
14. Cockburn F, Cooke R. The CRIB (clinical risk index for babies) score: A tool for assessing initial neonatal risk. Lancet. 1993; 342:193–198. [PubMed: 8100927]
15. Bührer C, Grimmer I, Metze B, Obladen M. The CRIB (Clinical Risk Index for Babies) score and neurodevelopmental impairment at one year corrected age in very low birth weight infants. Intensive Care Med. 2000; 26:325–329. [PubMed: 10823390]
16. Deulofeut R, Sola A, Lee B, Buchter S, Rahman M, Rogido M. The impact of vaginal delivery in premature infants weighing less than 1,251 grams. Obstet Gynecol. 2005; 105:525. [PubMed: 15738019]
17. Herbst A, Thorngren-Jerneck K. Mode of delivery in breech presentation at term: increased neonatal morbidity with vaginal delivery. Acta obstet gynecol Scand. 2001; 80:731–737. [PubMed: 11531616]
18. Soubasi V, Mitsakis K, Nakas CT, Petridou S, Sarafidis K, Griva M, et al. The influence of extrauterine life on the aEEG maturation in normal preterm infants. Early hum dev. 2009; 85:761–765. [PubMed: 19919892]
19. West CR, Groves AM, Williams CE, Harding JE, Skinner JR, Kuschel CA, et al. Early low cardiac output is associated with compromised electroencephalographic activity in very preterm infants. Pediatr res. 2006; 59:610–615. [PubMed: 16549539]
20. Barrington K, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. 2007; 3
21. Supcun S, Kutz P, Pielemeier W, Roll C. Caffeine increases cerebral cortical activity in preterm infants. J pediatr. 2010; 156:490–491. [PubMed: 20176190]
22. Soubasi V, Mitsakis K, Sarafidis K, Griva M, Nakas CT, Drossou V. Early abnormal amplitude-integrated electroencephalography (aEEG) is associated with adverse short-term outcome in premature infants. Eur J Paediatr Neuro. 2012
23. Wikström, S. Background aEEG/EEG measures in very preterm infants: Relation to physiology and outcome. Umeå University; 2011.

Key notes

- While amplitude-integrated encephalography (aEEG) in preterm infants has known associations with brain injury and later outcome, the relationship between early cerebral maturation and perinatal exposures is unclear.
- This study adds knowledge regarding the associations between early cerebral maturation measured by aEEG and perinatal exposures during the hospitalisation.
- In addition, investigations into aEEG and early neurodevelopment found an association between early aEEG and motor outcomes at the age of two.