Electroencephalographic Characteristics in Preterm Infants Born with Intrauterine Growth Restriction

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Objective To determine the impact of fetal growth on postnatal amplitude-integrated electroencephalography (aEEG) and power spectrum electroencephalography (EEG) data in preterm infants born with intrauterine growth restriction (IUGR).

Study design We defined IUGR as birth weight <10th percentile, and control as birth weight appropriate for gestational age (GA). We performed single-channel (C3-C4) EEG during the first 48 hours of life and measured the upper and lower margins of the aEEG trace width. EEG readings were analyzed by spectral analysis, and the relative power of the frequency bands was calculated. The Lacey Assessment of the Preterm Infant was administered before discharge.

Results We enrolled 14 infants with IUGR (mean GA, 34.3 ± 1.8 weeks; mean birth weight 1486 ± 304 g) and 16 appropriate for GA controls (mean GA, 33.7 ± 2 weeks; mean birth weight, 1978 ± 488 g). There were no significant between-group differences in perinatal complications. The mean aEEG trace width was 20.8 ± 1.4 μv in the infants with IUGR versus 17.3 ± 1.6 μv in controls ($P < .001$). The infants with IUGR also had significantly greater delta frequency activity and decreased theta, alpha, and beta frequency activities compared with controls. Delta frequency activity decreased with increasing GA ($r = -0.8$; $P = .001$ for infants with IUGR and $r = -0.9$; $P < .001$ for controls). The Lacey Assessment of the Preterm Infant developmental score was significantly lower in the infants with IUGR ($P < .02$) and was correlated with aEEG trace width ($r = -0.6$; $P = .002$) and with delta activity ($r = -0.5$; $P = .02$).

Conclusion Preterm infants with IUGR have delayed EEG maturation associated with delayed neuromotor development. The predictive value of these alterations regarding developmental deficits associated with IUGR remains undetermined, however. *(J Pediatr 2014;164:756-61)*.

Epidemiologic studies have identified strong associations between fetal growth and a number of common adult diseases, suggesting that fetal programming can alter long-term outcomes.[1] Multiple studies have shown that intrauterine growth restriction (IUGR) is associated with a higher incidence of neurodevelopmental sequelae, including visuospatial, coordination, attention, and learning difficulties.[2,3] The mechanisms of these neurocognitive sequelae have been extensively investigated in various animal models, particularly in models of placental vascular insufficiency, the most common type of IUGR, which results in chronically decreased oxygen and nutritional supplies to the growing fetus.[4-7] Reported histological characteristics of the animal IUGR brain include alterations in cell size and number, with an overall lower brain weight,[4,7,8] reduced connectivity,[6,9] delayed myelination, and white matter damage.[5,6] In some studies, IUGR also has been associated with altered electrophysiologic maturation in the form of prolonged latencies of visual evoked potentials,[10] shorter brainstem auditory evoked responses,[11] and prolonged somatosensory evoked potentials,[12] whereas other studies of evoked potentials yielded conflicting[13] or negative results.[14]

Although there are available data on neonatal electroencephalography (EEG),[15] amplitude-integrated EEG (aEEG),[16,17] and power spectrum EEG[18] in preterm and term infants, we are aware of only 1 previous study addressing the effects of IUGR on EEG findings.[19] Moreover, there are no reports on the impact of IUGR on neonatal aEEG data, despite the ostensibly reliable measures of neonatal cerebral function and maturation, as well as the ability to predict long-term outcomes.[16,17,20,21] Therefore, we evaluated the impact of fetal growth on early postnatal aEEG and on power spectrum EEG in preterm infants born with IUGR.

Methods

The study was conducted in the neonatal intensive care unit at Lis Maternity Hospital, Tel Aviv Sourasky Medical Center between 2011 and 2012. We prospectively recruited preterm infants (gestational age [GA] <37 weeks) who

aEEG	Amplitude-integrated electroencephalography
AGA	Appropriate for gestational age
EEG	Electroencephalography
GA	Gestational age
IUGR	Intrauterine growth restriction
LAPI	Lacey Assessment of the Preterm Infant

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were antenatally diagnosed with mid-second to third trimester late-onset IUGR and had a birth weight <10th percentile for GA, according to the Israeli percentile curves published by Dollberg et al.[22] Our control group comprised preterm appropriate for GA (AGA) infants. Each infant's estimated GA was calculated based on the date of the mother's last menstrual period.

All of the study participants were clinically stable, normoglycemic, and not receiving phototherapy, ventilation, or inotropic support. They all had normal standard neurologic examination findings and were free of cerebral pathology, such as intraventricular hemorrhage or white matter injury, as assessed by cranial sonography. They were all started on enteral feeding of breast milk and/or formula on the first or second day of life. Infants with a genetic syndrome, major malformation, congenital infection, or major respiratory or cardiac disease, as well as those receiving sedative drugs, were excluded from our analysis.

Once suitable candidates were identified, aEEG was performed within 48 hours of birth, and the relevant clinical data were collected prospectively. All infants also underwent a neuromotor evaluation on discharge, after reaching the 35th gestational week. All aEEG analyses and neuromotor evaluations were performed blinded to the infant's group and to all clinical variables. This study was approved by the Ethics Review Committee of the Tel Aviv Sourasky Medical Center, with informed consent provided by the parent(s) of each infant.

The relevant clinical data collected included maternal illness, use of medications, demographic data, labor and delivery information, cranial sonography, and postnatal course. Data on the presence of vascular abnormalities, defined as irregular perfusion, infarction, or small placental size, were collected from available placental pathology reports.[23]

During the first 48 hours after birth, single-channel EEG recording (C3-C4 scalp position, based on the 10-20 international scalp measurement system) was performed using a NicoletOne clinical EEG unit (VIASYS Healthcare, Conshohocken, Pennsylvania). The EEG study was performed in an environmentally controlled setting for approximately 3 hours. Both conventional EEG and processed aEEG tracings were acquired. All data were transmitted to a NicoletOne work station for further offline analysis.

The sleep-wake cycle for each study was classified as none, imminent/immature, or developed, according to the scheme of Hellström-Westas et al.[16] To record the continuity of an aEEG study, we divided each complete study into 10-minute epochs and then identified the lower and upper margins of each epoch by drawing lines on the peak and trough of the aEEG tracing. Based on a published classification scheme,[16] we recorded each epoch's aEEG background activity as continuous (lower amplitude of 5-10 μv and maximum amplitude of 10-50 μv) or discontinuous (lower amplitude <5 μv and maximum amplitude >10 μv).[16] We calculated the proportion of continuous versus total epochs (continuous and discontinuous) for each study, and defined this as percent aEEG continuity.

We then selected 10 artifact-free epochs from each study while maintaining the same ratio of continuous and discontinuous epochs as for the whole study. For each of the selected epochs, we recorded the difference between the lower and upper amplitude margins, defined as the trace width.

For spectral analysis, we used the previously chosen 10 artifact-free epochs from each study. We selected the first 4 seconds of each continuous epoch and the first 4 seconds of a burst of each discontinuous epoch. We performed power spectral analysis on the raw EEG signals thus obtained, applying fast Fourier transformation. Using the manufacturer's software, the analyzed power spectrum was divided into the following frequency bands: δ, 1-4 Hz; θ, 4-8 Hz; α, 8-13 Hz; and β, 13-30 Hz. We then converted power values to percent band power, defined as the ratio of absolute band power to total power of all frequency bands, expressed as a percentage. For each EEG study, we averaged the percent band power values from all analyzed segments for further statistical analysis.

For the neurodevelopmental assessment, a certified physical therapist administered the Lacey Assessment of the Preterm Infant (LAPI) to each study participant before discharge, after reaching the 35th gestational week. That assessment included motor (8 items), oral (2 items), and tone scores (4 items); total developmental score (the sum of those 3 scores); and a neurologic score (8 items) of atypical neuromotor responses.[24] The assessment was performed during the daytime, with the infant in a fully awake state, between 2 feedings, dressed lightly, and disconnected from other external monitoring.

Statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago, Illinois). Significance was set at $P < .05$. For all perinatal factors, dichotomous variables were analyzed using 2-group binominal comparisons (Fisher exact test), and all continuous variables were analyzed using the Student t test or the Wilcoxon 2-sample test. Group comparisons of aEEG and spectral variables in the IUGR and AGA control infants was performed by linear regression analysis, adjusted for postmenstrual age at the time of the examination. The relationships between several perinatal factors and both aEEG and spectrum variables was studied using partial Pearson correlation for continuous variables and logistic regression for dichotomous variables, both adjusted for postmenstrual age at the time of examination. A multivariate model was constructed by linear regression analysis to examine the independent effect of several explanatory variables associated with aEEG or power spectrum EEG.

Results

Our study cohort comprised 30 preterm infants with a mean ± SD GA of 34 ± 1.9 weeks (**Table I**). There were no significant differences in sex, maternal body mass index, and most perinatal complications between the IUGR and AGA groups. Cesarean delivery and antenatal steroid use were more frequent in the IUGR group than in the AGA group. Available placental pathology reports revealed