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In and ex utero maturation of premature infants electroencephalographic indices

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HIGHLIGHTS

- Neonatal EEG indices follow a well described maturation changes.
- Conceptional age predicts Delta and Theta wavelength amplitudes of the neonatal EEG better than interburst interval.
- The effect of ex-utero maturation is not readily discernible when using specific neonatal EEG indices.

ABSTRACT

Objectives: To assess the effect of extra uterine life on continuity and amplitude of premature infants' cerebral activity at different gestational age as compared to soon after birth.
Methods: Stable infants less than 34 weeks gestation were prospectively recruited and EEG was recorded bi-weekly. Interburst interval and different wavelength amplitudes were digitally measured during the most discontinuous and most continuous (periods with longest and shortest interburst intervals, respectively) parts of the tracings. Linear regression was used to assess conceptional age prediction of interburst interval and wavelength amplitudes. Significant regression results were compared to the group of babies recorded close to delivery (newborn group).
Results: 144 EEG tracings from 59 infants were analyzed. Interburst intervals were significantly predicted by conceptional age in the newborn group only ($p \leqslant 0.002$). Delta and theta amplitudes were significantly predicted by conceptional age in the newborn group and most of the other conceptional age groups ($p < 0.004$). No significant differences were detected between the different groups.
Conclusions: Our data reiterates the normal maturation of cerebral activity in the premature infant and support the concept of similar in and ex-utero maturation of cerebral activity in stable premature infants.
Significance: The effect of ex-utero maturation on the brain of stable premature infant is not readily discernible when using specific neonatal EEG indices.

1. Introduction

During the third trimester of pregnancy the human brain is undergoing fast structural and functional changes. On the structural level the brain surface folds, neuronal and glial cells differentiate, mature and migrate until the term infant brain architecture is fully developed (Volpe, 2008). Concomitantly with structural changes functional changes are taking place. One of the reliable methods to monitor these changes is electroencephalographic (EEG) recordings. Typical maturational changes of cerebral activity consisting of increasing continuity and decreasing amplitude and wave length were consistently described (Monod and Tharp, 1977; Dreyfus-Brisac, 1979; Lamblin et al., 1999; Shany and Berger, 2011; Kato et al., 2011). Beside these general developments, specific electroencephalographic wave patterns were described in conjunction with specific conceptional age (CA) (e.g. appearance of delta brushes at 29–30 weeks CA and appearance of frontal transients at 34 weeks CA (Lamblin et al., 1999; Shany and Berger, 2011). Recent studies exploring the maturation of cerebral activity in the neonate (Nunes et al., 1997; Scher et al., 2003; Flores

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Guevara et al., 2008; Conde et al., 2005; Biagioni et al., 2005; Soubasi et al., 2009; Klebermass et al., 2006; Kato et al., 2011) questioned the generally held concept of similar intra and extra uterine maturation in the healthy premature neonate (Parmelee et al., 1968) but reached different conclusions.

We hypothesized that the basic maturational development of continuity and amplitude of different wavelength along conceptional age do not differ significantly in the extra uterine environment of the stable, low risk premature infant as compared to the intrauterine environment.

The objective of this study was to assess the effect of extra uterine life on continuity and amplitude of premature infants' cerebral activity at different gestational age as compared to soon after birth using a novel signal processing software.

2. Patients and methods

This was a prospective cohort study. Included in the study were infants born before 34 weeks completed gestation. Excluded were infants that suffered from intraventricular hemorrhage grade 3, intraparenchimal hemorrhage, cystic periventricular leukomalacia or did not survive to discharge. Infants with unreliable gestational age (GA) were also excluded from the cohort. Pathologic EEG studies and those recorded while infants needed assisted ventilation and/or were under sedation were excluded from analysis.

The study protocol was approved by Soroka Medical Center ethics committee and guardians of recruited infants signed an informed consent form.

2.1. Gestational and conceptional age

Gestational age (GA) was set as the average between the assessment by early prenatal ultrasound scan and the calculation from the first day of the last menstrual period. GA was considered reliable if no more than one week difference was detected between the two methods. Conceptional age was defined as GA plus postnatal age.

2.2. EEG recordings and ultrasound scanning

EEG recordings were carried out with a Netlink biologic (Natus) recorder. Recordings started as soon as possible after scheduled care of the infant for a duration of an hour and half. The following bipolar montage was used: Fp2-T4, T4-O2, Fp2-C2, C2-O2, Fp1-C1, C1-O1, Fp1-T3, and T3-O1 according to the 10–20 international system. We preferred the bipolar montage, as most of the literature pertaining to neonatal EEG measurements, including studies on maturation referenced in our discussion, used bipolar montages. Impedance below 10 KOhms were reached before initiation of the EEG recording, high pass filter was set at 0.1 Hz and low pass filter to 100 Hz, sampling rate was 256 Hz. Additionally, ECG and respiratory signals were collected. The first EEG was carried out during the first 14 days of life and then bi-weekly until 36 weeks post conception or discharge. All EEGs were clinically assessed by the first author (ES), soon after recording. Cranial ultrasound examination was performed and evaluated by one of the investigators (ES or IM) on the day of the EEG recording.

2.3. EEG signal processing softwares and artifacts detection

Digital data of each EEG was split into 4 s segments that were processed by two different software modules developed by two of the authors (SG and ES).

2.3.1. Interburst interval (IBI) module (Fig. 1A)

This module detects the length of time between the decrease of the EEG signal below a threshold voltage in a pre-specified number of channels for more than two seconds and the increase of the voltage above the threshold in a pre-specified number of channels. As no accepted definition IBI is available (Tich et al., 2007) and discussion four different preset definitions of IBI were used.

a. 30 micV-0 channel: the most stringent definition set the activity threshold to 30 micV with the end of an IBI defined as at least one channel activity exceeding this threshold.
b. 30 micV-2 channel: a slightly less stringent definition with an activity threshold of 30 micV, but allowing for up to two channels voltage increase above threshold for up to 2 s.
c. 50 micV-0 channels: another less stringent definition similar to (a) but with a 50 micV threshold.
d. 50 micV-2 channels: a tolerant definition similar to (c) but with a 50 micV threshold.

2.3.2. Maximal amplitude module (Fig. 1B)

This module calculates the maximal amplitude of different wavelengths (Delta (0.25–3.75 Hz), Theta (4–7.45 Hz), Alpha (8–11.75 Hz) and Beta (12–25 Hz) for each 4 s segments. The software uses a band pass filter for the above bandwidths using filters for the shorter wavelengths as it proceeds to the longer ones, then for each 4 s interval the algorithm of the software identifies the first through and a maximal point following that trough located no more than half the wavelength of the pre-specified bandwidth. In order not to miss possible maximal points occurring after the 4 s segments, the algorithm seeks maximal points in first second of the following segment. The output is a list of maximal trough to peak maximal amplitudes per wavelength group per each 4 s interval.

2.3.3. Artifact detection

As the software does not differentiate artifacts from normal EEG waves, all recordings were visually inspected by two investigators (IM, ES) that were blinded to the groups. Timing of artifacts was marked with 4 s margins and deleted from further analysis. Furthermore, for each wavelength, amplitude outliers above a set threshold (500 micV for Delta, 300 micV for Theta, 200 micV for Alpha and 100 micV for Beta) identified by the software as maximal amplitudes were visualized on the EEG viewer and in case the first author (ES) considered them as artifacts, they were deleted from the data base with 4 s margins.

2.4. EEG data processing

Average and maximum of maximal amplitudes for each wavelength as well as the total IBI for the four preset definitions were retrieved with the above software for each 10 min interval.

For statistical analysis two datasets were assessed separately: data originating from the 10 min interval with the longest total IBI (the most discontinuous period of the EEG according to the most stringent criteria (30 micV-0 channel)) and data originating from the 10 min interval with the shortest total IBI periods (the most continuous part of the recording according to the most tolerant criteria (50 micV-2 channel)).

2.5. Data analysis

Since 75% (45) of the infants had a recording in the first 10 days of life, this time interval was used to form the different groups as follows. The first group of recording from the first 10 days of life was used as a reference group (In utero maturation/Newborn group). Groups 2, 3 and 4 consisted of recordings done between the 11–20, 21–30 and 31–40th day of life, respectively. Group 5