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Mild maturational delay of the brainstem at term in late preterm small-for-gestation age babies

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ABSTRACT

Aims: To detect any functional abnormality in the brainstem auditory pathway in late preterm babies born of small-for-gestational age (SGA) using maximum length sequence brainstem evoked response.
Study design: The response was recorded and analyzed at term in 38 SGA (birthweight <3rd centile) babies born at 33–36 week gestation. The results were compared with 40 age-matched babies born of appropriate-for-gestational age (AGA) (birthweight >10th centile). None of the subjects had major perinatal problems.
Results: All wave latencies and interpeak intervals in the SGA group were slightly longer than those in the AGA group at most click rates. Wave III latency was significantly longer than that in the AGA group at 227/s ($P < 0.05$), and wave V latency was at 227 and 910/s ($P < 0.05$ and 0.05). Of the interpeak intervals, only the I–V interval in the SGA group was significantly longer than that in the AGA group at the highest rate 910/s ($P < 0.05$). The amplitudes of waves I, III and V in the SGA group all tended to be smaller than those in the AGA group at all click rates 91–910/s. The wave V amplitude was significantly smaller at most click rates (227–910/s, all $P < 0.05$). The slopes of all wave latency–, interval–, and amplitude–rate functions were similar in SGA and AGA groups.
Conclusions: There were marginal abnormalities in MLS BAER of low-risk late preterm SGA babies, suggesting a mild degree of maturational delay in the brainstem. Intrauterine growth retardation occurring in late preterm babies has a minor effect on neural maturation of the immature brainstem.

1. Introduction

Neurodevelopment in babies born at 33–36 weeks gestation, or late preterm babies, has recently attracted considerable interest [1–6]. Of late preterm babies, most was born with a birthweight appropriate-for-gestational-age (AGA), while a small proportion was born with a birthweight small-for-gestational-age (SGA), suggesting possible intrauterine growth retardation (IUGR). There are previous authors who described neurodevelopment in SGA infants or children born at late preterm [7–11]. Some reported poor neurodevelopment [9], whereas others reported accelerated maturation of cognitive processing [10]. There are also authors who found that neurodevelopmental and cognitive outcomes are comparable in preterm and term SGA infants [11].

We previously found no noticeable abnormality in brainstem auditory evoked response (BAER) in low-risk late preterm babies, i.e., those without any major perinatal problems or conditions [12]. We further conducted a more detailed study in low-risk late preterm babies using a relatively new technique — the maximum length sequence brainstem auditory evoked response (MLS BAER). No major abnormalities were found in any MLS BAER variables, either [13]. It appears that there is no appreciable abnormality in neural maturation in late preterm babies who have no major perinatal conditions. There are a few authors who reported their BAER studies in SGA infants or children born at various gestations. Some of them found abnormalities (e.g., increase or shortening in wave latencies and interpeak intervals, although the others did not [14–22]). So far, there is no consensus with regard to the effect of SGA or IUGR on brainstem auditory function in infants.

It is presumable that IUGR might have differential effects on the immature brain in babies born at different gestations. Previous BAER studies in SGA preterm infants almost all included a wide range of gestation, with no reports of BAER specifically in late preterm SGA babies. There are no reports of SGA babies using MLS BAER. In this report, we describe our findings, specifically, in late preterm SGA babies using the MLS BAER, which has proven to enhance the detection of neuropathology that affects the brainstem auditory pathway in babies [23–27]. Any babies who had major perinatal problems or conditions had been excluded from study entry to minimize any confounding effects. The MLS BAER data from these SGA babies were compared with those in age-matched AGA babies to detect any differences. We aimed to identify any abnormalities in the SGA babies, contributing to the knowledge of whether IUGR affects brainstem auditory function in babies born at late preterm.

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2. Subjects and methods

2.1. Subjects

Two groups of low-risk late preterm babies, with matched gestational ages, were recruited from the Division of Neonatology, Children's Hospital, Fudan University in Shanghai. Informed consent of parents was obtained for each subject before the study entry. None had any major perinatal complications that may affect the brainstem auditory function, e.g., hypoxia–ischemia, hyperbilirubinemia at a serum level requiring exchange transfusion, bacterial meningitis, intraventricular hemorrhage and congenital malformation of the CNS [28].

2.1.1. Low-risk SGA late preterm babies (SGA group)

SGA status was defined as birthweight less than the 3rd centile for gestation using the Babson and Benda growth chart by Fenton [29]. We recruited 38 babies born between 33 and 36 weeks (34.6 ± 0.95 weeks) gestation, determined by the best estimate of the last menstrual period, obstetrical record, and clinical examination. Birthweight ranged between 783 and 1828 g (1468 ± 235 g). All SGA babies were examined at a postconceptional age (PCA) of 37–42 weeks (39.6 ± 1.91 weeks), i.e., term age.

2.1.2. Low-risk AGA late preterm babies (AGA group)

AGA status was defined as birthweight greater than 10th centile for gestation using the Babson and Benda growth chart by Fenton [29]. We recruited 40 AGA babies who had none of the above perinatal problems or conditions, with gestation between 33 and 36 weeks (34.3 ± 0.8 weeks, which did not differ significantly from that in SGA group). Their birthweight, ranging in 1505–3250 g (2144 ± 354 g), was significantly greater than that in the SGA group ($P < 0.001$). These babies, like SGA babies, were also examined at PCA 37–42 weeks (40.1 ± 1.1 weeks, which did not differ significantly from that in AGA babies).

Significant peripheral hearing problems are known to affect MLS BAER waveform morphology and make it difficult to accurately and reliably identify MLS BAER waves, particularly wave I [23]. Thus, we excluded any babies who had BAER threshold ≥40 dB normal hearing level (nHL) from study entry in both the SGA and AGA groups to minimize any significant effect of peripheral hearing loss on the measurements of MLS BAER wave components.

2.2. Procedures of BAER recording

The study procedures were approved by the Ethics Committee of the Children's Hospital of Fudan University. Recording and analyzing MLS BAER were conducted using a Nicolet Spirit 2000 Portable Evoked Potential System (Nicolet Biomedical Inc., Madison, WI, USA). As in our previous studies, recording of MLS BAER was done in the left ear for all babies to insure that estimates of population statistics were not biased by BAER ear difference, and to save recording time [23–27]. Following site skin preparation, three gold-plated disk electrodes were placed, respectively, at the middle forehead (positive), ipsilateral earlobe (negative) and contralateral earlobe (ground). The impedance between any two electrodes was kept at <5 kΩ. MLS BAER recording commenced shortly after the baby fell asleep naturally, often after feeding.

Rarefaction clicks with a duration of 100 μs were delivered monaurally through a TDH 39 headphone to the left ear. Click intensity was 60 dB nHL for babies who had a BAER threshold of 20 dB nHL or less. In 5 babies who had a BAER threshold of >20 dB nHL, higher intensities were also used: 70 dB nHL for a threshold of 25 dB nHL (1 in the SGA group and 1 in the AGA group), and 80 dB nHL for thresholds of 30 (1 in the SGA group and 1 in the AGA group) and 35 (1 in the SGA group) dB nHL. This allowed MLS BAER data to be collected at a hearing level slightly higher than 40 dB above the threshold for all babies, and MLS BAER data were compared between different groups of babies at comparable hearing levels [23–27]. Two runs of recordings to each stimulus condition were made to evaluate the reproducibility of recorded MLS BAER waveforms.

The clicks were presented at sequences of 91, 227, 455, and 910/s in the first run, and a reverse sequence in the second run, which was the same as we previously employed [23–28]. For each run, brain responses to 1500 trains of clicks were preamplified, bandpassed at 100–3,000 Hz, and then averaged. Sweep duration was 24 ms. During the signal averaging, amplitude artifact rejection was active to eliminate any on-line signals with amplitude exceeding ±25 μV.

2.3. Measurements of MLS BAER and data analysis

For each baby, the measurements of MLS BAER wave components from two replicated recordings to each stimulus condition were averaged for further data analysis. All these measurements were conducted blind to the medical history and clinical data of each subject. Detailed statistical analysis was performed in the MLS BAER data that were collected at a click intensity 50.6 ± 7.5 dB above the thresholds of individual babies in the SGA group and 50.3 ± 6.9 dB in the AGA group, which did not differ significantly between the two groups.

Mean and standard deviation of each BAER variable at each stimulus condition were obtained for each group of babies. The data were compared between the AGA and SGA groups using Student's t test. Correlation analysis was conducted between each MLS BAER variable and click rate, and correlation coefficient (two-tailed test of significance) was obtained. For those variables that were significantly correlated with click rate, regression analysis was carried out, and the latency-, and interval-rate functions were obtained. The slope for each of the latency-, and interval-rate function was then calculated. For those functions that were significantly greater than zero at the 0.05 level or better, comparison of the slopes between different groups of babies were made using Student's t test to detect any differences between the SGA and AGA babies in click rate-dependent changes. These statistical analyses were conducted using the SPSS package version 19 (Chicago, IL).

3. Results

3.1. MLS BAER wave latencies and intervals

Means and standard deviations of MLS BAER wave latencies and interpeak intervals are presented in Table 1. The results of statistical comparisons of the data between the SGA and AGA groups are also shown in the table. At almost all click rates of 91–910/s, the latencies of waves I, III and V in the SGA group tended to be slightly longer than

Table 1
Means and standard deviations (SD) of MLS BAER wave latencies and interpeak intervals (≥40 dB above the BAER threshold of each subject) and comparisons between SGA and AGA late preterm (LP) babies.

BAER Variables	Subjects	91/s Mean ± SD	227/s Mean ± SD	455/s Mean ± SD	910/s mean ± SD
I (ms)	AGA LP	2.39 ± 0.20	2.52 ± 0.22	2.68 ± 0.20	2.74 ± 0.20
	SGA LP	2.44 ± 0.31	2.62 ± 0.24	2.73 ± 0.22	2.75 ± 0.23
III (ms)	AGA LP	5.21 ± 0.24	5.50 ± 0.22	5.84 ± 0.29	5.91 ± 0.30
	SGA LP	5.27 ± 0.33	5.64 ± 0.24*	5.92 ± 0.24	5.96 ± 0.31
V (ms)	AGA LP	7.55 ± 0.26	8.12 ± 0.33	8.83 ± 0.37	8.88 ± 0.33
	SGA LP	7.64 ± 0.40	8.29 ± 0.29*	8.96 ± 0.27	9.01 ± 0.25*
I–V (ms)	AGA LP	5.16 ± 0.25	5.61 ± 0.31	6.15 ± 0.27	6.14 ± 0.23
	SGA LP	5.21 ± 0.24	5.71 ± 0.24	6.24 ± 0.24	6.26 ± 0.22*
I–III (ms)	AGA LP	2.82 ± 0.20	2.98 ± 0.18	3.16 ± 0.17	3.17 ± 0.18
	SGA LP	2.83 ± 0.17	3.04 ± 0.20	3.21 ± 0.23	3.22 ± 0.19
III–V (ms)	AGA LP	2.34 ± 0.14	2.63 ± 0.17	2.99 ± 0.17	2.97 ± 0.16
	SGA LP	2.38 ± 0.17	2.67 ± 0.17	3.02 ± 0.18	3.05 ± 0.22
III–V/I–III ratio	AGA LP	0.83 ± 0.08	0.88 ± 0.06	0.94 ± 0.06	0.94 ± 0.08
	SGA LP	0.85 ± 0.07	0.89 ± 0.09	0.95 ± 0.10	0.95 ± 0.09

* $P < 0.05$ in Student's t test for comparison between SGA and AGA late preterm (LP) babies.