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Auditory brainstem response in premature and full-term children

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KEYWORDS
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Summary

Objectives: To compare the absolute latencies of peaks I, III and V and interpeak intervals of premature and full-term children.
Methods: Prospective, comparative cohort study. Study subjects were premature and full-term children with auditory brainstem response (ABR) measured at ages 4, 12 and 20 months. The children had previously undergone otorhinolaryngolic and audiologic evaluations to exclude those with altered hearing.
Results: One hundred and twenty-four children were included in the study (73 premature). No differences were found between children of different sexes nor between the right and left ears of the individual children, so the statistical unit sed for the study was the ear. Using the *t*-test for independent samples, the absolute latencies of peaks I, III and IV and the interpeak intervals I—III, I—IV and III—V presented statistically significant differences between the groups at ages 4 and 12 months. At 20 months, only peak I failed to show a difference in absolute latency. Strong inverse correlation was found (Pearson's coefficient) between gestational age and absolute peak latency, as well as for interpeak intervals.
Conclusions: Maturation of the auditory system, as measured by ABR, occurs differently between premature and full-term children, suggesting that gestational age be taken into consideration when using ABR in premature children younger than 20 months old.

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1. Introduction

The neurological maturation of the auditory system occurs in two phases. The first, peripheral maturation, takes place around the 6th month of fetal development. The second phase, which begins after birth and concludes within about 18 months, involves the myelination of the auditory pathways throughout the central nervous system [1—4].

Brainstem auditory evoked potentials (ABR) enable neurophysiologic analysis of the auditory pathways between the inner ear and the upper brainstem. Many authors have reported that ABR results are influenced by the auditory maturation process and that their characteristics differ between premature and full-term babies [2,4—10].

This test has been widely promoted for use in newborns due to the impossibility of obtaining reliable results in subjective examinations and because it is a very useful clinical instrument for evaluating maturation of the auditory system. Due to the great value and applicability of the test, it is important that each hospital develop their own norms to improve the precision of audiological diagnosis.

In an effort to aid in the understanding of the neurophysiological maturation process of the auditory pathways, this study observed the functional behavior of the auditory system through ABR analysis in premature and full-term children in three age groups, comparing the absolute latencies of peaks I, III and V and the interpeak intervals I—III, III—V and I—V, as well as analyzing the difference between the peak and interpeak latencies for the right and left ears of the children.

2. Methods

An observational, comparative, prospective cohort study was carried out, in which the subjects were premature and full-term children and the clinical outcome was the observation of the functional behavior of the auditory system through analysis of auditory brainstem response (ABR).

The study population was comprised of premature children referred from the Outpatient Clinic for Growth and Development of At-Risk Children of the Hospital de Clínicas de Porto Alegre, Brazil (a specialized service for premature children) and full-term children between 4 and 20 months old who were born at the same hospital.

The research plan was approved by the Graduate Research Group of the Hospital de Clínicas de Porto Alegre (HCPA). The objectives of the study were explained to the adult companions of children accompanied by the institution, and those children whose legal guardians agreed to sign the informed consent form were included in the study.

Children were submitted to otorhinolaryngological examination and excluded from the study if they presented anatomical abnormalities of the outer, middle or inner ear, hearing loss, or if they failed to complete all three ABR evaluations.

Initially, the sample characteristic protocol was filled out, after which all the children were evaluated by the Otorhinolaryngology Service of HCPA. Those that presented normal otoscopy findings underwent audiological evaluation, including measurement of acoustic immittance, distortion product otoacoustic emissions and ABRs (Fig. 1). ABR analyses were conducted for three different age groups (4, 12 and 20 months old). Children who were unable to complete all the evaluations in the three phases studied (due to nonattendance or alterations of the middle or inner ear) were excluded from the study.

The three ENT and audiological evaluations were performed in order to guarantee that the children had no hearing changes, i.e. to exclude the possibility of outer, middle or inner ear problems.

The acoustic immittance measurements were carried out using an Interacoustics middle ear analyzer, model AZ26 (Interacoustics A/S, Assens, Denmark). Contralateral and ipsilateral acoustic reflexes were tested at 500, 1000, 2000 and 4000 Hz in both ears and tympanometric curves plotted. Frequency of 1000 Hz was used for tympanometric. All of the children included in the study presented acoustic reflexes at all of the frequencies tested and type A tympanometric curves, according to the Jerger [11] classification and descriptions by Rufino et al. [12].

The distortion product otoacoustic emissions were performed in an acoustic chamber with background noise less than 30 dB and ILO 292 equipment (OAE System Otodynamics) connected to a laptop computer with DPGRAM software and a microphone which was introduced in the external acoustic meatus and sealed with a flexible rubber mold. During the test, the child was held in his or her parent or guardian's lap, preferably while asleep. An intensity of 65 dBHL was used for the 500 Hz frequency ($F1$), with 55 dBHL for $F2$ (1000 Hz), 70% band reproducibility and signal-to-noise ratio $\geq$ 10 dB. The tests were considered normal according to standards proposed by Azevedo [13] Sleifer et al. [14] and Garcia et al. [15].

ABR analysis was conducted on children of both sexes, divided in two groups: pre-term and full-term children, according to the classification suggested by the World Health Organization in 1974 [16], which recommends use of the expression pre-term to refer to infants born up to 37 weeks of gestation (259 days from the first day of the last menstrual period).

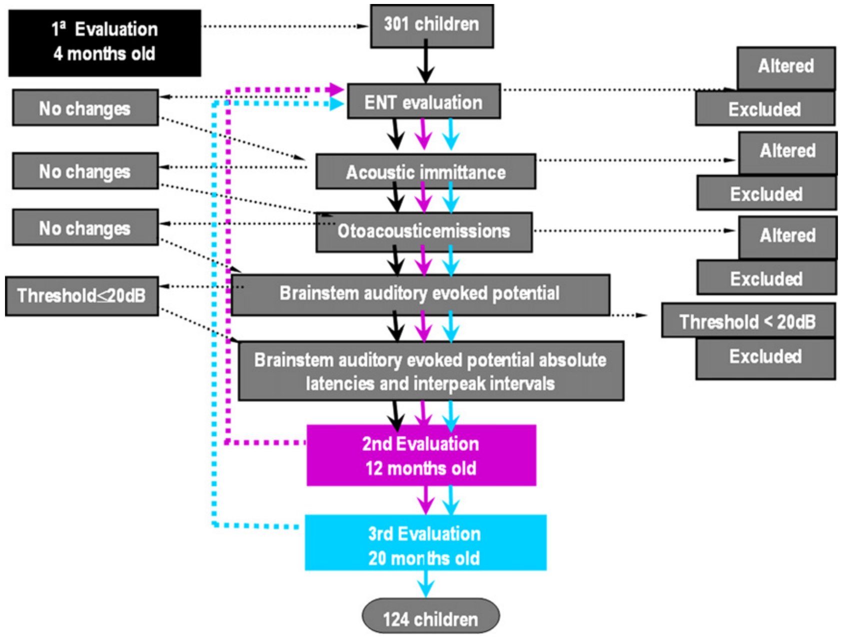

Fig. 1 Flowchart of the procedures carried out.

ABR analysis was performed in three periods of chronological age: at 16 weeks (4 months), 46 weeks (12 months) and 80 weeks (20 months). The three exams were performed in a room with acoustic and electrical isolation, low light and temperature of approximately 25 °C. Thresholds for each click in each ear were initially identified at hearing level (HL). The intensity of the stimuli used for the absolute and interpeak latency analyses between the two groups was 80 dBHL. The contralateral ear was masked with white noise at 40 dBHL less than the intensity of the stimulus used (80 dBHL). Computerized BERA Module equipment was used (Hortmann Neuro-Otometrie) with TDH 49 earphones (GN Otometrics GmbH & Co. KG-Hortmann Neuro-Otometrie, Neckartenzlingen, Germany). Calibration was performed at the beginning of the evaluation and monitored throughout.

The children were placed face-up on a gurney in a comfortable position. The test was conducted in natural sleep or, if necessary, under sedation with chloral hydrate—14% 0.5 ml/3 kg of body weight. According to Hood [3], Figueiredo and Castro Junior [4], the use of this sedative does not significantly affect amplitude, latency or detectability of ABRs. Surface electrodes were placed after cleansing the skin and applying conductive gel. One active (positive) electrode was placed on the forehead, a negative electrode was placed on the mastoid ipsilateral to the stimulus and a ground electrode (neutral) on the contralateral mastoid.

The parameters used were low pass 1500 Hz, high pass 100 Hz, rarefaction click stimulus, with click rate 2000 stimuli at the beginning of the evaluation and a window of analysis of 10 ms. Each record was duplicated to assure reproducibility and reliability of the peaks obtained.

The presence and absolute latency of peaks I, III and V, the interpeak latency for I—V, I—III and III—V, and the inter-ear difference for the absolute and interpeak latencies were analyzed according to the parameters suggested by Jewett et al. [17], Hecox and Galambos [18], Jacobson and Hall [19], Hood [3], Figueiredo and Castro Junior [4], Anias et al. [20] and Sousa et al. [21].

Based on the protocols used, a database was created in Excel and analyzed using SPSS for Windows, version 11.0. Categorical data are presented as relative frequencies and quantitative data as standard deviation. Inter-ear comparisons were made using Student's *t*-test for paired samples. To compare the absolute and interpeak ABR latencies between premature and full-term children, Student's *t*-test for independent samples was used. Pearson's coefficient was used to verify correlation among quantitative variables. *P* values less than 0.05 were considered significant.

3. Results

3.1. Sample description

Of the 301 children investigated, 124 were enrolled in the study and participated in all of the proposed procedures (ENT exam, tympanometria,

Table 1 Sample characteristics (n = 124)

	Total n = 124	Pre-term n = 73	Full-term n = 51
Gestational age (weeks)			
Average	35 ± 3.7	32.4 ± 2.53	38.6 ± 1.20
Minimum	28	28	37
Maximum	41	36	41
Sex			
Female	51.6%	50.7%	52.9%
Male	48.4%	49.3%	47.1%

Qualitative variables are described as percentages and quantitative variables as averages ± standard deviation with minimum and maximum values.

measurement of acoustic reflexes, distortion product otoacoustic emissions and ABR) in the three age groups studied (4, 12 and 20 months old) and presented results within normal limits, as previously described.

Data from 73 pre-term children (146 ears) and 51 full-term children (102 ears) were analyzed. Table 1 presents global and stratified characteristics of the sample in terms of gestational age and sex.

There was no significant difference found when the absolute latencies of peaks I, III and V and the interpeak intervals I—III, I—V and III—V were compared (using the t-test for independent samples) between sexes for both the pre-term and full-term children. There was also no significant difference found when the absolute latencies of peaks I, III and V and the interpeak intervals I—III and I—V were compared (using the t-test for paired samples) between right and left ears for both the pre-term and full-term children. As a result, the statistical unit used was the ear, rather than the individual.

Comparison between the groups of premature and full-term children at 4 and 12 months (first and second evaluations) showed significant differences for the absolute latencies of peaks I, III and V (Table 2) and interpeak latencies I—III, I—V and III—V (Table 3). At the third evaluation, (20 months), only the absolute latency of peak I was not significantly different between the groups.

Inverse correlation was found by applying Pearson's coefficient with gestational age in weeks and the absolute latencies of peaks I, III and V, as well as the interpeak intervals I—III, I—V and III—V (Figs. 2 and 3).

4. Discussion

4.1. Role of sex

We found no statistically significant difference when comparing the absolute latencies between children

Table 2 Comparison between the absolute latencies of peak I, III and V at the first, second and third evaluations (4, 12 and 20 months, respectively) in premature and full-term children

	Latency (ms)								
	Wave I			Wave III			Wave V		
	1[a]	2[a]	3[a]	1[a]	2[a]	3[a]	1[a]	2[a]	3[a]
Pre-term n = 146	2.31 ± 0.16	2.18 ± 0.12	2.08 ± 0.08	5.48 ± 0.22	4.85 ± 0.2	4.25 ± 0.17	8.20 ± 0.24	7.73 ± 0.18	7.18 ± 0.16
Full-term n = 102	2.18 ± 0.13	2.11 ± 0.12	2.06 ± 0.12	4.94 ± 0.33	4.60 ± 0.2	4.13 ± 0.11	6.90 ± 0.36	6.60 ± 0.27	6.11 ± 0.16
P value	<0.0001	=0.002	=0.392	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 3 Comparison of average interpeak latencies I—III, I—V and III—V at the 1st, 2nd and 3rd evaluations (4, 12 and 20 months of age, respectively) in pre-term and full-term children

	Interpeak latency (ms)								
	Interval I—III			Interval I—V			Interval III—V		
	1[a]	2[a]	3[a]	1[a]	2[a]	3[a]	1[a]	2[a]	3[a]
Pre-term $n = 146$	2.99 ± 0.29	2.60 ± 0.22	2.12 ± 0.13	5.40 ± 0.62	5.12 ± 0.56	4.67 ± 0.54	2.59 ± 0.42	2.53 ± 0.45	2.49 ± 0.64
Full-term $n = 102$	2.76 ± 0.30	2.49 ± 0.26	2.07 ± 0.10	4.71 ± 0.33	4.49 ± 0.26	4.05 ± 0.17	2.11 ± 0.08	2.06 ± 0.06	2.01 ± 0.13
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

of different sexes. This finding is similar to that of Gorga et al. [22] and Bento et al. [23], who studied ABRs in children. However our results differed from those of Beagley and Sheldrake [24], who reported that ABR latencies tended to be greater in males, especially peak III and V absolute latencies. These authors attributed this finding to differences in the maturation of auditory pathways.

4.2. Comparison of inter-ear analyses

When we examined the absolute and interpeak latencies between paired right and left ears for both premature and full-term children, we found no significant difference in the results. This finding is consistent with that of other authors who report normal auditory thresholds in pre-term and full-term children [2,9,24,25].

4.3. Correlation of ABR absolute latencies for peaks I, III and V with gestational age

By applying Pearson's coefficient, we found strong inverse correlations between gestational age and the ABR absolute latencies of peaks I, III and V for the three age groups studied (4, 12 and 20 month-olds). This fact demonstrates that the absolute latency of peaks I, III and V diminishes as gestational age increases. Peak I only decreased between the first and second evaluations of the premature children, with no change between the second and the third, while in the full-term children the absolute latency of peak I had already completed its maturation process at the first evaluation.

A very strong correlation was found for peak V absolute latency, suggesting that the degree of nerve myelination and the immaturity of the auditory pathways affect peak latencies. We observed that gestational age is an important variable in the analysis of the absolute latencies of peaks I, III and V in children, especially peak V. These findings confirm those reported by Cox [1], Castro Junior [2], Anias et al. [20], Chiang et al. [25], Costa [26], Despland and Galambos [27] and Fuess [28].

4.4. Correlation of the ABR interpeak latencies I—III, I—V and III—V with gestational age

Applying Pearson's coefficient between gestational age and the ABR interpeak intervals I—III, I—V and III—V for the three age groups studied (4, 12 and 20 month-olds), we found inverse correlations. For the interval I—III, the correlation was weak (values less than 0.5), while for intervals I—V and III—V the correlation was very strong (values greater than

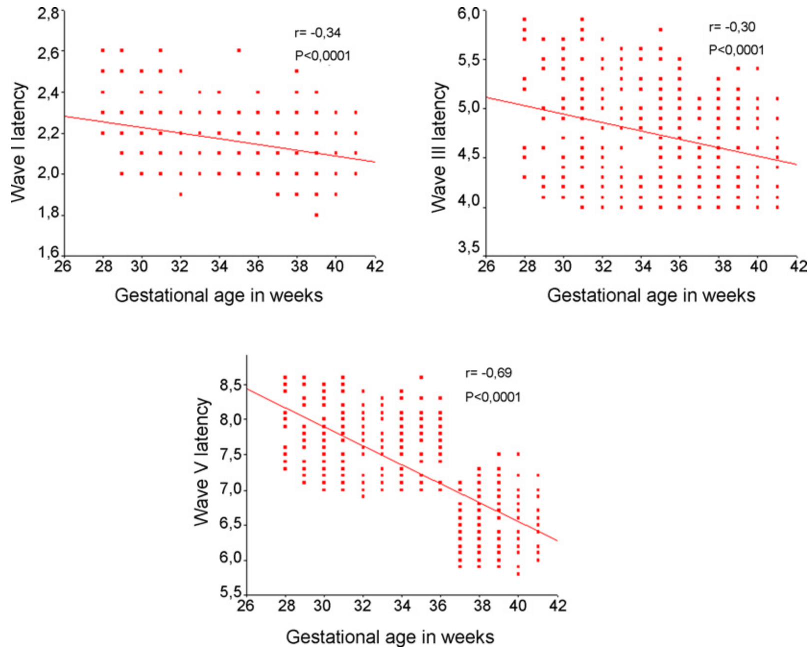

Fig. 2 Linear correlation graphs between gestational age in weeks and wave I, III and V latency.

0.7). This fact demonstrates that the interpeak intervals I—V and III—V diminish as gestational age increases. The strongest correlation was for the interval III—V, suggesting that the interpeak intervals are influenced by the process of auditory maturation, i.e. corresponding to a delay in electrical conduction due to the still developing myelination process, which is in turn dependent on gestational age at birth. Again, this implies that gestational age is an important variable in the analysis of the interpeak intervals I—V, III—V and especially III—V in children. We believe these results reflect the developmental maturation of the cochlear nuclei (origin of wave III), as well as of the inferior colliculus and the lateral lemniscus (origins of waves IV and V). In addition, this seems to influence the latencies of the interpeak intervals, as the interval grows shorter as gestational age at

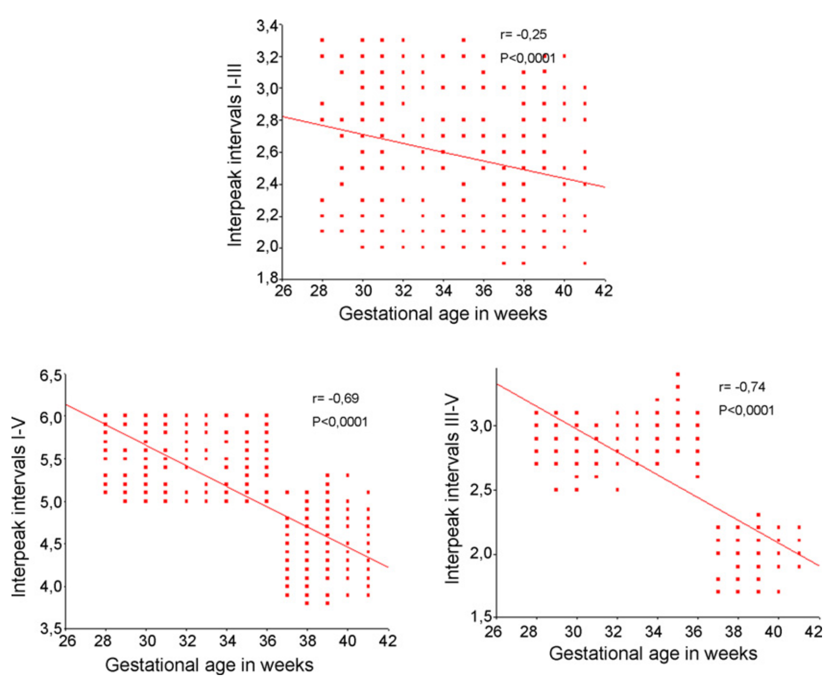

Fig. 3 Linear correlation graph between gestational age in weeks and interpeak intervals I—III, I—V and III—V.

birth increases. Our findings are consistent with those of Cox [1], Castro Junior [2], Gupta and Anand [7], Tibusseck and Meister [8], Hecox and Galambos [18], Anias et al. [20], Chiang et al. [25], Costa [26], Despland and Galambos [27] and Fuess [28].

The most significant ABR result found was the increase in the absolute latency of peak V in premature children, as well as the interpeak interval III—V. We believe this relates to the delay in electrical conduction due to incomplete myelination. These findings suggest a caudal—rostral maturity model, such as that described by Eggermont [29]. Acoustic information processing is similar to that of an adult by about 2 years of age, since peak V is still in the process of maturing until this time. Our results corroborate those of Cox [1], Hood [3], Gupta and Anand [7], Tibusseck and Meister [8] and Costa [26].

Maturation of the auditory system, as evaluated by the absolute and interpeak ABR latencies, occurs differently between premature and full-term children. When brainstem auditory-evoked potentials are used as a diagnostic test for auditory alterations in premature children up to 20 months old, they should be analyzed very critically; unless the test is repeated it may lead to inappropriate conclusions regarding the integrity of the auditory system. As these children grow older, their absolute and interpeak latencies tend to normalize.

Based on the findings of this study, we recommend that gestational age be taken into consideration when applying brainstem auditory-evoked potential as a tool for audiological evaluation in children less than 20 months old.

5. Conclusion

In this sample:

- we found no statistically significant difference when comparing right and left ears for absolute and interpeak latencies in both pre-term and full-term children;
- there was a significant difference in the absolute latencies for peaks III and V in pre-term and full-term children evaluated in three age groups (4, 12 and 20 months old). We found the greatest difference between the two groups at the first evaluation, at 4 months of age;
- there was a significant difference between peak I absolute latency in pre-term and full-term children at 4 and 12 months old;
- there was strong inverse correlation between gestational age and interpeak intevals I—V and III—V, especially at the first evaluation (4 months), suggesting that the interpeak intervals are influenced by the auditory maturation process;
- based on the findings of this study, we recommend that gestational age be taken into consideration when applying auditory brainstem response as a tool for audiological evaluation in children less than 20 months old.

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