

The influence of body proportionality on children born small for gestational age: a study of auditory pathway maturation

A influência da proporcionalidade corporal em crianças nascidas pequenas para a idade gestacional: estudo da maturação da via auditiva

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ABSTRACT

Purpose: To monitor the auditory pathway maturation of infants born small for gestational age (SGA), according to body proportionality, in the first six months of life. **Methods:** Brainstem auditory-evoked potential (BAEP) was performed during the neonatal period and at six months of life in 59 infants born small for gestational age; among them, 35 were born asymmetrical (SGA-A), and 24 were born symmetrical (SGA-S). The results were compared to those of 59 infants considered appropriate for gestational age (AGA). **Results:** The term and pre-term SGA-A and SGA-S infants showed a significant auditory maturation process (progressive decrease of BAEP latencies) from the neonatal period to six months of life. A similar result was observed with the AGA infants. The term and pre-term AGA infants and the SGA-S and SGA-A infants did not differ from each other from an auditory perspective during the six-month period. **Conclusion:** The SGA infants with symmetrical and asymmetrical patterns showed auditory maturation, suggesting that the duration of intrauterine injury did not represent a greater risk to hearing.

Keywords: Evoked potentials, Auditory, Brain stem; Hearing; Hearing disorders; Infant, Newborn; Child development

RESUMO

Objetivo: Acompanhar a maturação da via auditiva de lactentes nascidos pequenos para a idade gestacional (PIG), de acordo com a proporcionalidade corporal, nos primeiros seis meses de vida. **Métodos:** Potencial Evocado Auditivo de Tronco Encefálico (PEATE) realizado no período neonatal e aos seis meses de vida, em 59 lactentes, sendo 35 nascidos pequenos para a idade gestacional e assimétricos (PIG-A) e 24 simétricos (PIG-S), comparados a 59 lactentes nascidos com peso adequado (AIG), considerando a idade gestacional. **Resultados:** Os lactentes PIG-A e PIG-S a termo e pré-termo evidenciaram processo maturacional auditivo (diminuição progressiva das latências do PEATE) significativo, do período neonatal aos seis meses de vida, o mesmo ocorrendo em relação aos AIG. Os grupos AIG a termo e pré-termo, bem como os grupos PIG-S e PIG-A não se diferenciaram do ponto de vista auditivo durante os seis meses, quando comparados entre si. **Conclusão:** Os lactentes PIG com padrão simétrico e assimétrico evidenciaram maturação auditiva, sugerindo que o tempo de permanência no agravo intrauterino não representou risco auditivo maior.

Descritores: Potenciais evocados auditivos do tronco encefálico; Audição; Transtornos da audição; Recém-nascido; Desenvolvimento Infantil

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INTRODUCTION

Adequate fetal growth classification is based on the comparison of anthropometric data of the newborn (NB) with reference curves that relate weight to gestational age. A child classified as small for gestational age (SGA) is one whose weight is below the 10th percentile (Alexander et al., 1996)⁽¹⁾.

The birth of a SGA child may indicate that he/she suffered from intrauterine growth restriction (IUGR), a pathological process that does not allow the fetus to reach its genetically determined potential intrauterine growth. IUGR may occur at different stages of gestation, with different intensities and duration and, therefore, results in different growth and development prognoses. This phenomenon may be due to a chromosomal disorder, intrauterine infection, placental dysfunction, multiple pregnancy, low maternal height, or smoking⁽²⁾.

Infants considered SGA can be classified as having an asymmetrical or disproportionate pattern, in which case the weight is reduced while the height and head circumference remain normal. Injury in this circumstance is likely to have occurred in late pregnancy due to placental insufficiency. In contrast, symmetrical or proportional SGA infants are those whose weight, head circumference and height are all reduced, indicating injury at the beginning of pregnancy and extending throughout the prenatal period, which may lead to greater harm to the fetus^(3,4).

The classification of body proportionality of SGA NBs can be obtained using Rohrer's ponderal index (PI), the parameters of which are determined by the weight (in grams) divided by the cubic height (cm³), multiplied by 100. When the PI is greater than or equal to 2.49, the SGA is classified as having a symmetrical or proportional pattern, whereas when the PI is less than 2.49, the SGA is classified as having an asymmetrical or disproportionate pattern⁽⁵⁾.

There is consensus in the literature that increased risk of neurological morbidity may be associated with inadequate birth weight in relation to gestational age, resulting in a range of effects, from subtle forms of developmental delay to permanent brain damage. In this context, newborns with low birth weight and/or SGA are considered at risk for global or specific changes in language, hearing and learning^(4,6,7), as they represent an example of malnutrition at an early age and are possibly subjected to sequelae later in life caused by their in utero experience^(4,8).

Auditory monitoring, therefore, becomes critical because the first two years and, in particular the first six months of life, are critical for the development of oral language⁽⁹⁾.

Brainstem auditory-evoked potential (BAEP) has been the test of choice for the evaluation and monitoring of auditory pathway integrity in at-risk neonatal populations because it allows monitoring of the maturation of the central auditory system using changes in response latency and amplitude⁽¹⁰⁾.

The present study aimed to compare the results of BAEP in

SGA infants with symmetrical and asymmetrical patterns at the neonatal period and at six months of life to determine whether one condition represents more auditory risk than the other.

We hypothesize that SGA infants with a symmetrical pattern have different auditory behavior compared to that of SGA infants with an asymmetrical pattern, reaching, nonetheless, the same parameters established as normal after six months of life.

METHODS

This multicenter study was initiated after approval by the Research Ethics Committees of the *Universidade de São Paulo* (USP) (CAPPesq HCFMUSP), under protocol No. 372/10, of the University Hospital of the *Universidade de São Paulo*, under registration CEP-HU/USP No. 1009-10-SISNEP CAEE 0037.0.198.000-10, and of the Federal University of São Paulo, under protocol No. 1235/11. The mothers and/or legal guardians freely signed the informed consent form, agreeing to the participation of the NB in the study.

The study population was composed of NBs from two university hospitals, the University Hospital associated with the University of São Paulo and the São Paulo Hospital associated with the Federal University of São Paulo. The participants were chosen at random from their medical records, which contained anthropometric measurements (head circumference, weight and height at birth) for later application of the PI.

All of the infants were evaluated between December 2010 and June 2012.

The sample was one of convenience with a confidence interval of 95% and significance level of 5%. The population was divided into six groups: three groups of infants born at term; 16 SGA infants with an asymmetrical pattern (T/SGA-A), 19 symmetrical SGA infants (T/SGA-S) and 35 T/AGA infants; and three groups of infants born pre-term; 19 SGA infants with an asymmetrical pattern (PT/SGA-A), five symmetrical SGA infants (PT/SGA-S) and 24 PT/AGA infants.

The age range in the neonatal period of full-term NBs varied from 37 to 41 weeks of gestation. The age range of the pre-term NBs varied from 27 weeks and six days to 36 weeks and six days. The corrected age at the time of examination varied from 33 weeks and two days to 40 weeks and three days.

The eligibility criteria were as follows:

1. Presence of the indicator "small for gestational age" in the study groups for term and pre-term children, and "adequate for gestational age" in the control groups, both according to the reference curve for fetal growth adopted by both institutions⁽¹⁾. Birth weight adequacy data were extracted from the NB's medical records.
2. Bilateral presence of transient evoked otoacoustic emission (TEOAE) and type A tympanometric curve, according to the model by Margolis (1975)⁽¹¹⁾, for all the evaluated groups. Children at infectious risk for TORCHS (toxoplasmosis, rubella, cytomegalovirus, herpes and syphilis), encephalopathy,

craniofacial malformations and conductive and/or cochlear alterations were excluded from the study.

The procedures adopted included the extraction of data on inclusion criteria, anthropometric measures and gestational age, confirmed by ultrasound, from the NB's medical records.

After selection, the NBs were invited for the tests, which were conducted in the following order: inspection of the external auditory canal for visualization of the tympanic membrane using a Welch Allyn otoscope; and TEOAE testing and acoustic immittance (tympanometry), to ensure the integrity of the cochlear function (outer hair cells) and absence of middle ear impairment, respectively. The same procedures were repeated in the subsequent evaluations (at six months of age).

At the University Hospital of USP, to assess the TEOAE, the ILO 92 Cochlear Emissions Analyzer (Otdynamics®, London) with two channels incorporating the features of the ILO88-Version 5.61 was used. The B-Type ILO OAE Probe (described by Kemp, Ryan and Bray, 1990), wrapped in a soft olive, was used to transmit the stimulus. The eliciting stimulus was a non-linear click type, with an intensity between 78 and 83 dB peSPL, in Quickscreen mode. The presence of responses was considered according to a signal-to-noise ratio of 3 dB at 1 or 1.5 KHz and 6 dB at 2, 3 and 4 KHz, with reproducibility greater than 50% and stability greater than 70%. When responses were present, the test was stopped after 80 accepted stimuli; in the case of an absence of response, the test continued until reaching 260 stimuli (according to the equipment's manufacturer), at which point the NB was excluded from the sample and sent to the otorhinolaryngologist for evaluation and subsequent outpatient audiological follow-up.

At the São Paulo Hospital, AccuscreenPRO automatic portable equipment (GN Otometrics®) was used. To obtain a "pass" in the TEOAE testing, the equipment was calibrated by the manufacturer for the automatic analysis of responses, according to the following parameters: evaluation method by binomial statistics; nonlinear click-type stimulus, in a sequence with a velocity of 60 Hz and intensity of 70-84 dB SPL (45-60 dBHL, with self-calibration depending on the volume in the ear canal); frequency spectrum from 1.4 kHz to 4 kHz; and artifact lower than 20%. When these parameters were met, the equipment recorded a "pass".

The acoustic impedance measures included tympanometry with a 1-kHz probe tone, conducted with the Interacoustics® AT 235-H middle ear analyzer, in both institutions participating in the study.

For the BAEP testing, the child remained in the crib or on the mother's lap in a natural sleep state.

Intelligent Hearing Systems® Smart-EP clinical equipment/diagnostic equipment was used at both institutions to capture the BAEP. The preparation of all NBs for BAEP testing was conducted as follows: prior cleaning of the skin with abrasive paste and fixation of Kendal® Meditrace-200 disposable pediatric electrodes on the forehead (Fpz) and the right and left

mastoids (M_2 and M_1), according to the International Electrode Systems standards (IES 10-20). The acoustic stimulus was presented by a pair of ER-3A insertion earphones, eliciting the responses. The electrode impedance was kept below 3 k Ω .

The acoustic stimulus used was a rarefied polarity click presented to one ear at 80 dBnHL to evaluate the integrity of the auditory pathway, with a presentation speed of 27.7 clicks per second, duration of 0.1 ms, high-pass filters of 100 Hz and low-pass filters of 1,500 Hz, with a total of 2,048 stimuli. The recording window used was 12 ms. The BAEP was captured twice in each ear to obtain wave reproducibility, thus ensuring the presence of a response.

For the analysis of the BAEP responses, the absolute latencies of waves I, III, V and the interpeak intervals I-III, III-V, I-V at 80 dBnHL were measured in both evaluations performed (neonatal period and six months post-conceptual age). A normal BAEP was considered to be one where the absolute latencies and interpeak intervals were within the parameters described in the standard table for the equipment, according to the age group. The BAEP results were considered to be altered when the absolute latencies and/or interpeak intervals showed an increase in relation to the equipment's normal range.

The statistical analysis was initially performed by data description using the means and standard deviations of each studied group. All measures of the individuals' right and left ears were then compared using a paired Student's t-test. Comparison of the means between groups was performed using an analysis of variance (ANOVA) test. All of the tests were two-tailed, and the entire analysis was calculated using STATA® statistical software, version 10.0.

RESULTS

It should be noted that in the reporting of the results, the discussion and the conclusion, the SGA population with a symmetrical pattern was named SGA-S and that with an asymmetrical pattern was named SGA-A.

The data obtained in the SGA-S, SGA-A and AGA for each BAEP parameter were preliminarily analyzed separately for each ear.

In the neonatal period, seven children (37%) in the T/SGA-S group had an altered BAEP, but only one (5.2%) response remained altered at six months (I-V interpeak interval increased in the right ear); in the T/SGA-A group, five children (31.2%) had altered BAEP in both ears, and only one (6.2%) remained altered at six months (increased wave V latency and I-V interpeak in the left ear). Only one child (2.9%) in the term AGA group had an altered BAEP in the neonatal period, and at six months, all tests were normal.

In the premature infant groups, it was observed that out of the 10 PT/SGA-A newborns (52.6%) showing changes in BAEP, only one child (5.26%) had test results that remained

altered at six months (the I-V interpeak interval increased in both ears); in the PT/SGA-S group, only one child (20%) had an altered BAEP at birth, and the results normalized by six months. In the PT/AGA group, 11 NBs (45.8%) had an altered BAEP at birth, and all of the infants had an adequate BAEP at six months. Comparative analysis of the results showed the absence of significant differences between the right and left ears in the SGA and AGA groups.

It was therefore decided to use the right ear values for the subsequent analyses, maintaining the comparison between the SGA-S and SGA-A groups and between them and the AGA group.

In the analysis of the maturational behavior of BAEP wave latencies during the neonatal period and at six months of age, it was observed that all of the evaluated groups showed significant differences from a statistical point of view. The results are summarized in Figure 1.

Subsequently, we examined whether the maturation process occurs differently in SGA NBs in relation to the duration of intrauterine injury (symmetrical X asymmetrical) compared to NBs born with a normal weight.

Analysis of the results of the preterm SGA-S, SGA-A and AGA groups at the neonatal period showed that except for wave I, which was statistically more precocious in the AGA group ($p=0.02$), there were no differences in the latencies of the other BAEP waves; the same phenomenon occurred in the T/SGA-S, T/SGA-A and T/AGA NBs (Tables 1 and 2).

The BAEP absolute latencies and interpeak intervals of the PT/SGA-S, PT/SGA-A and PT/AGA groups were also compared at six months, with no differences observed between the groups for any of the BAEP parameters (Table 3).

The same comparison was made at six months between the T/SGA-S, T/SGA-A and T/AGA groups; again, no differences were observed between the groups (Table 4).

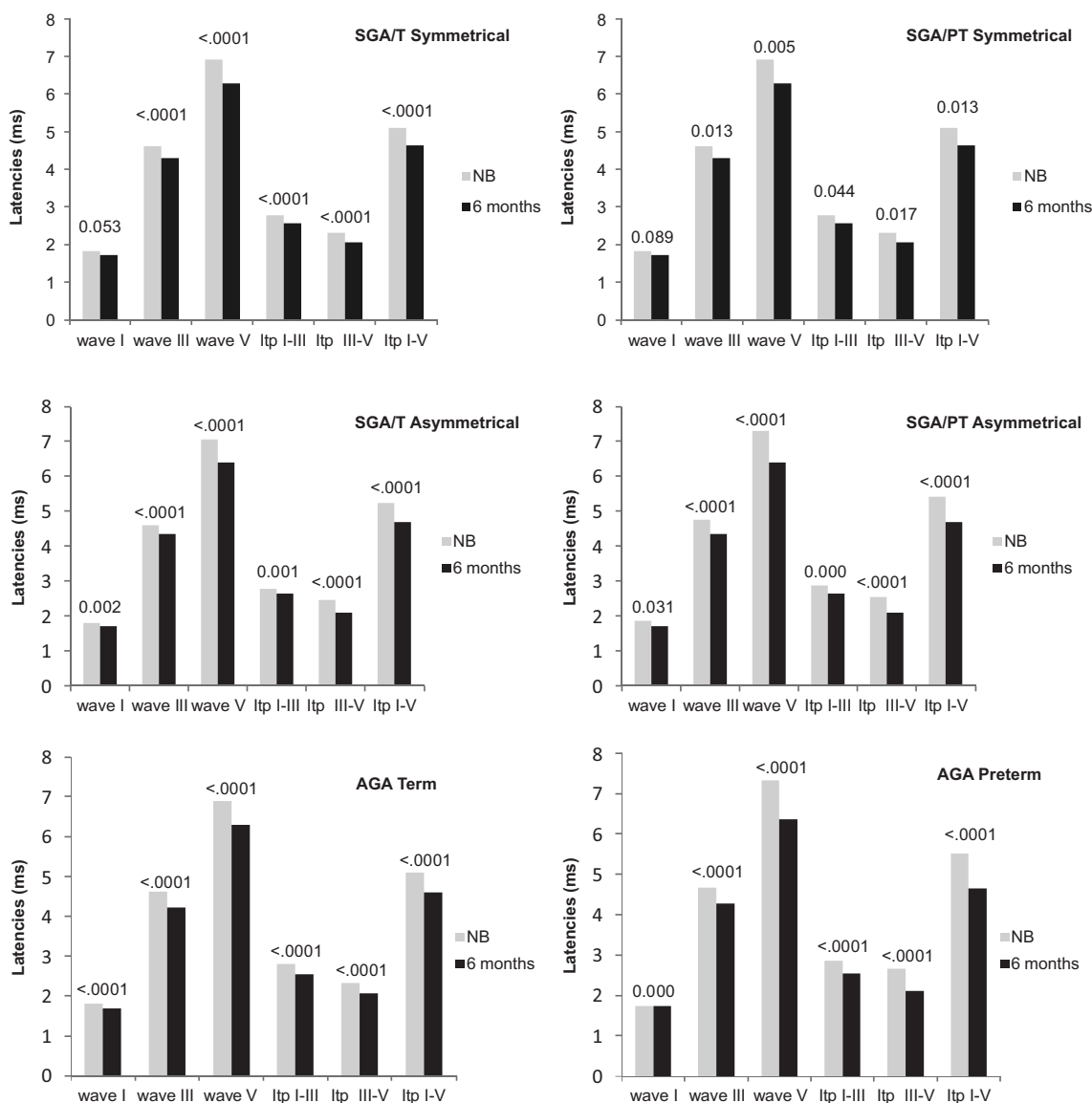


Figure 1. Comparative study of BAEP latencies during the neonatal period and at six months in the AGA and asymmetrical and symmetrical SGA groups born term and pre-term

Table 1. Comparative study of BAEP latencies during the neonatal period in the AGA and asymmetrical and symmetrical SGA groups born pre-term

NB	PT/SGA (n=19) Asymmetrical		PT/SGA (n=5) Symmetrical		PT/AGA (n=24)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Wave I	1.86	0.22	1.84	0.08	1.73	0.09	0.021
Wave III	4.81	0.27	4.68	0.25	4.67	0.23	0.164
Wave V	7.27	0.51	7.08	0.36	7.33	0.45	0.575
Itp I-III	2.93	0.26	2.99	0.35	2.86	0.25	0.478
Itp III-V	2.51	0.28	2.41	0.17	2.66	0.37	0.146
Itp I-V	5.46	0.50	5.25	0.28	5.51	0.52	0.575

ANOVA test (p<0.05)

Note: BAEP = Brainstem auditory-evoked potential; AGA = adequate for gestational age; SGA = small for gestational age; NB = newborn; SD = standard deviation; PT/SGA = pre-term and small for gestational age; PT/AGA = pre-term and adequate for gestational age; Itp = interpeak

Table 2. Comparative study of BAEP latencies in the neonatal period in the AGA and asymmetrical and symmetrical SGA groups born at term

NB	T/SGA (n=16) Asymmetrical		T/SGA (n=19) Symmetrical		T/AGA (n=35)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Wave I	1.80	0.13	1.83	0.23	1.81	0.15	0.914
Wave III	4.59	0.24	4.61	0.25	4.58	0.27	0.951
Wave V	7.04	0.39	6.92	0.33	6.95	0.34	0.574
Itp I-III	2.78	0.17	2.78	0.23	2.77	0.25	0.980
Itp III-V	2.45	0.26	2.31	0.31	2.34	0.28	0.285
Itp I-V	5.24	0.34	5.09	0.39	5.00	0.60	0.296

ANOVA test (p<0.05)

Note: BAEP = Brainstem auditory-evoked potential; AGA = appropriate for gestational age; SGA = small for gestational age; NB = newborn; T/SGA = term and small for gestational age; T/AGA = term and appropriate for gestational age; Itp = interpeak; SD = standard deviation

Table 3. Comparative study of BAEP latencies in pre-term newborns at six months in the AGA and asymmetrical and symmetrical SGA groups

Six months	PT/SGA (n=19) Asymmetrical		PT/SGA (n=5) Symmetrical		PT/AGA (n=24)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Wave I	1.72	0.11	1.7	0.13	1.73	0.09	0.861
Wave III	4.34	0.28	4.28	0.16	4.28	0.18	0.686
Wave V	6.40	0.30	6.19	0.21	6.36	0.28	0.335
Itp I-III	2.61	0.30	2.58	0.14	2.54	0.20	0.616
Itp III-V	2.06	0.14	1.96	0.16	2.10	0.20	0.277
Itp I-V	4.69	0.29	4.49	0.28	4.64	0.23	0.320

ANOVA test (p<0.05)

Note: BAEP = Brainstem auditory-evoked potential; AGA = appropriate for gestational age; SGA = small for gestational age; PT/SGA = pre-term and small for gestational age; PT/AGA = pre-term and appropriate for gestational age; Itp = interpeak; SD = standard deviation

DISCUSSION

Children born SGA comprise a heterogeneous population because they respond differently to injuries suffered during intrauterine life and, therefore, represent a public health challenge.

The lack of studies on the auditory pathway maturation process in the SGA population and, in particular, lack of studies that classify the same population according to the duration of intrauterine nutritional injury, which is the focus of this study,

hinders the discussion of this issue.

During the neonatal period, BAEP changes were observed in more than 30% of infants in both the SGA-S and SGA-A groups, suggesting possible transitional retrocochlear changes because this number was reduced significantly at six months. The findings of the present study corroborate the results of a previous study that evaluated 47 SGA and 39 AGA infants to verify whether the SGA condition represented a risk indicator for retrocochlear hearing loss. That study showed BAEP changes in 38% of the SGA group. The authors concluded that

Table 4. Comparative study of BAEP latencies of term newborns at six months in the AGA and asymmetrical and symmetrical SGA groups

Six meses	T/SGA (n=16) Asymmetrical		T/SGA (n=19) Symmetrical		T/AGA (n=35)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Wave I	1.71	0.15	1.72	0.11	1.68	0.11	0.440
Wave III	4.34	0.27	4.30	0.17	4.21	0.17	0.063
Wave V	6.39	0.35	6.29	0.36	6.29	0.26	0.525
Itp I-III	2.63	0.18	2.57	0.17	2.54	0.19	0.249
Itp III-V	1.09	0.21	2.06	0.20	2.06	0.15	0.787
Itp I-V	4.69	0.29	4.64	0.25	4.60	0.23	0.530

ANOVA test (p<0.05)

Note: BAEP = Brainstem auditory-evoked potential; AGA = appropriate for gestational age; SGA = small for gestational age; T/SGA = term and small for gestational age; T/AGA = term and appropriate for gestational age; Itp = interpeak; SD = standard deviation

full-term newborns, regardless of weight, could present either temporary or permanent retrocochlear hearing loss⁽¹²⁾.

Another study evaluated 72 preterm NBs (35 SGA and 37 AGA) of both genders to verify whether the SGA condition was a risk factor for retrocochlear hearing loss. The results showed changes in 32 children (44.4% of the total), with 15 SGA NBs (43%) and 17 AGA NBs (46%) and no difference between the groups. The authors concluded that the SGA condition was not a risk factor for retrocochlear change⁽¹³⁾.

In the present study, 3.39% of the total SGA population had maintained retrocochlear changes at six months of age, suggesting permanent nerve dysfunction. This may be due to improper brain development, as the lack of key nutritional elements caused by intrauterine restriction may result in damage to a number of synapses, changes in synaptic junction structure or may affect nerve fiber myelination⁽¹⁴⁾.

The results of the present study showed the lack of asymmetry between the ears in the evaluated groups, in contrast with a study that found higher wave V amplitude and lower BAEP wave latency in the right ear, suggesting that the right ear is favored in auditory processing along the auditory pathway⁽¹⁵⁾.

Our results are consistent with the current literature, concluding that the maturational process along the central auditory pathways occurs simultaneously in both ears⁽¹⁶⁻¹⁹⁾.

During the neonatal period, the comparison between the AGA and SGA groups (Table 1) showed no differences, except for wave I, which was significantly more precocious in the AGA group. Some authors have suggested the existence of a relationship between birth weight and cochlear maturation in the basal region and have attributed the extension of wave I to an immature cochlear basal region⁽²⁰⁾, a hypothesis that is shared by the present study.

The other BAEP parameters did not differ between the groups, leading to the conclusion that they behave the same way from an auditory point of view, a fact corroborated by another study that compared SGA and AGA infants without finding significant differences in the neonatal period⁽²¹⁾. A recent study observed the auditory behavior of SGA preterm

infants comparing them to AGA infants in the neonatal period. No significant differences were found in the BAEP responses. The authors concluded that the SGA condition was not a risk factor for retrocochlear change⁽¹³⁾.

At six months of age, the preterm AGA, SGA-S and SGA-A NBs (Table 3) did not differ with respect to the BAEP responses, with similar results observed with the term groups (Table 4). Thus, considering the developmental behavior in relation to hearing, the present study suggests that there is no influence of the duration of injury on the development of the central auditory pathways, up to six months of life.

These findings are contrary to the literature, which suggests that the degree of neurological impairment in SGA infants depends on the duration and severity of the injury and that the most vulnerable stages in terms of neurological injury occur between 15 and 20 weeks of gestation and between 30 weeks of gestation and 2 years of age, coinciding with nerve fiber myelination. It therefore seems logical to think that term and symmetrical SGA NBs could manifest greater losses compared to asymmetrical SGA NBs because they suffered the injury early in the gestation, just as preterm SGA manifest different characteristics because they were exposed to the injury over a shorter period of time^(4,5).

Considering that maturation of the brain stem is due to myelination and synaptic plasticity as a function of auditory experience, intrauterine restriction would imperatively lead to neurodevelopmental damage, and injury to the auditory pathways in this region could be responsible for speech difficulties^(4,5,22).

Several studies agree with the fact that malnutrition imposed during a critical period of brain development may lead to irreversible psychomotor effects, including those of the central auditory pathway, while others emphasize that the presence of brain dysfunction in the malnourished population may lead to cognitive dysfunction^(4,5,23,24).

Research on long latency auditory-evoked potentials (LLAEP) in children is a recent theme in the literature. Some studies have considered LLAEP to be a measure of cognitive

development, especially in children at risk for auditory processing disorders. In addition, a recent study concluded that malnourished children present changes in LLAEP, especially in components N1, P1 and P300, suggesting a deficit in the central auditory pathway and change in acoustic information processing.

This evidence lead to the consideration that the present study evaluated auditory behavior according to body proportionality in infants up to six months of age, at the level of the brainstem, the initial portion of the central auditory pathway. Perhaps the largest differences due to the degree and duration of intrauterine injury manifest itself in more central areas of the pathway because their maturation process continues to the cortical and subcortical structures, which are responsible for developing listening skills essential to language acquisition. Thus, it is believed that LLEAP would be a good evaluation tool in such conditions^(25,26).

It is, therefore, important to further investigate this process over a longer period of time to verify whether the duration of intrauterine restriction influences the acquisition and development of language.

CONCLUSION

Infants born with SGA with symmetrical and asymmetrical patterns showed auditory maturation, suggesting that longer duration and greater intensity of intrauterine injury did not represent a greater risk to hearing. These infants have similar hearing behavior when compared to the behavior of AGA infants, reaching the same parameters established normally after six months of life.

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