Original Article

https://doi.org/10.1590/2317-6431-2019-2251

Audiology Communication Research
ISSN 2317-6431

Electrophysiological follow-up of the central auditory system in children born small for gestational age

Monitoramento eletrofisiológico do sistema auditivo central em crianças nascidas pequenas para a idade gestacional

Rosanna Giaffredo Angrisani[1], *Carla Gentile Matas*[2], *Edna Maria Albuquerque Diniz*[2], *Ruth Guinsburg*[1], *Marisa Frasson de Azevedo*[1]

ABSTRACT

Purpose: To follow up the central auditory system of children born small for gestational age, through electrophysiological evaluation of hearing, in order to verify the occurrence of possible neural dysfunctions in this system. **Methods:** A longitudinal study was carried out with 23 children divided into four groups: Term-born group, subdivided into small for gestational age (four children) and four children born with appropriate weight for gestational age, whose age at the end of the research was three years old. Preterm group subdivided into small for gestational age (seven children), and appropriate for gestational age (eight children), whose corrected age, at the end of the research was three years old. All children were subjected to assessment of auditory brainstem auditory evoked potentials at birth, at six months and at three years of age, and Long-Latency Auditory Evoked Potential at three years. **Results:** children born at term and small for gestational age had a higher occurrence of hearing alterations in relation to the other groups, with increased latency of waves III and V and interpeaks I-III and I-V. All children presented normal evaluation in the Long-Latency Auditory Evoked Potential. **Conclusion:** Children born term and small for gestational age present dysfunctions in neural conduction in the brainstem and should be considered at risk for alterations in the development of the auditory skills that are necessary to guarantee quality of acoustic information processing.

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

RESUMO

Objetivo: Monitorar o sistema auditivo central de crianças nascidas pequenas para a idade gestacional, por meio da avaliação eletrofisiológica da audição, para verificar a ocorrência de eventuais disfunções neurais nesse sistema. **Métodos:** Estudo longitudinal, cuja casuística foi composta por 23 crianças distribuídas em quatro grupos: 1) grupo de quatro crianças nascidas pequenas para a idade gestacional e a termo; 2) grupo de sete crianças nascidas pequenas para a idade gestacional e pré-termo; 3) grupo de quatro crianças nascidas com peso adequado para a idade gestacional e a termo; 4) grupo de oito crianças nascidas adequadas para a idade gestacional e pré-termo, cuja idade ao final da pesquisa foi de 3 anos (variação entre 34 e 39 meses). O critério de inclusão foi presença bilateral de emissões otoacústicas transientes. Todas as crianças foram submetidas ao potencial evocado auditivo de tronco encefálico ao nascimento, aos 6 meses e aos 3 anos de idade e à pesquisa do potencial evocado auditivo de longa latência aos 3 anos. **Resultados:** crianças nascidas pequenas para a idade gestacional e a termo tiveram maior ocorrência de alterações, em relação aos demais grupos, com aumento da latência das ondas III e V e interpicos I-III e I-V. Todas apresentaram resultados normais no potencial evocado auditivo de longa latência. **Conclusão:** Crianças nascidas pequenas para a idade gestacional e a termo apresentam disfunções na condução neural no tronco encefálico e devem ser consideradas de risco para alterações do desenvolvimento das habilidades auditivas necessárias para garantir qualidade de processamento da informação acústica.

Palavras-chave: Potenciais evocados auditivos do tronco encefálico; Audição; Transtornos da audição; Recém-nascido; Desenvolvimento infantil

Study carried out at Programa de Pós-graduação, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP), Brasil.
[1]Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP), Brasil.
[2]Faculdade de Medicina, Universidade de São Paulo – USP – São Paulo (SP), Brasil.
Conflict of interests: No.
Authors' contribution: RGA participated in the study conception and design, data collection, analysis and interpretation, and in the writing of the manuscript; CGM, EMAD, RG and MFA were responsible for the supervision and approval of the final version of the manuscript to be published; CGM participated as co-advisor of the research, and in the study conception and design, data analysis and interpretation; MFA participated as postdoctoral advisor, and in the study conception and design, data analysis and interpretation, and in the revision of the manuscript.
Funding: None.
Corresponding author: Rosanna Giaffredo Angrisani. E-mail: roangrisani@gmail.com
Received: September 19, 2019; **Accepted:** May 20, 2020.

INTRODUCTION

Intrauterine nutritional restrictions cause deficits of fundamental elements such as oxygen, iron, fatty acids, and proteins. Such deficits may lead to a loss in the formation and number of synapses, alter the synaptic junction or affect myelination of brain nervous fibers[1,2].

The damages suffered during the intrauterine period may lead to the birth of a child small for gestational age (SGA), defined as the one whose weight-to-gestational-age ratio was less than the 10th percentile on the evaluation scale[3]. Such injuries may have occurred at different times, intensity and duration. In this regard, SGA infants have different prognoses regarding the degree of neurological, growth and development impairments.

The literature reports that such children may have a higher occurrence of minimal neurological dysfunctions such as attention deficit, hyperactivity and poor school performance due to malabsorption of essential nutrients, which can be manifested immediately or later. It is thus clear that these children need hearing and speech monitoring during the critical period for neurodevelopment[4,5].

Monitoring the integrity of the peripheral and central auditory system is crucial for the development of speech, as the child must be able to pay attention, detect, discriminate, locate sounds, memorize and integrate auditory experiences, in order to be able to recognize and understand speech[6].

Studies have reported that electrophysiological assessment, combined with behavioral evaluation, can provide important data on the maturation of the auditory system and the development of processing skills of acoustic information. This joint evaluation allows for adequate intervention during the critical period of maturation of the central nervous system and neural plasticity[7].

The Brainstem Auditory Evoked Potential (BAEP) is a recommended procedure for the audiological assessment of children as it allows checking the anatomical and functional integrity of the auditory pathway structures from its peripheral portion to the central portion in the brainstem, as well as a follow-up of its maturation[6].

Currently, in addition to BAEP, Cortical or Long-Latency Auditory Evoked Potentials (LLAEP) have drawn much interest within the scientific community for allowing an objective cognitive evaluation of attention, integration, memory and sound discrimination skills. Thus, determining the integrity and functionality of central structures through LLAEP in children, during the critical period of language development, will enable a more accurate diagnosis of any auditory processing disorders[8] and, therefore, the implementation of early prevention and/or intervention programs, this being the justification for the study[8].

The hypothesis of the present study is that children born small for gestational age may have minimal neural dysfunctions identified by the cortical and brainstem auditory evoked potentials, signaling possible delays in language acquisition, when compared to children born with appropriate weight for gestational age.

The aim of the present study was to monitor the central auditory system of children born SGA through electrophysiological assessment of hearing, in order to verify the occurrence of any neural dysfunctions in this system.

METHOD

This is a longitudinal research study which started after being approved by the Research Ethics Committee of the Federal University of São Paulo, process no. 922.580/14 and CAEE 38101714.5.0000.5505.

In compliance with the ethical principles of research involving human beings, the mothers and/or guardians of the children were asked to read and sign the Informed Consent Form, which describes all the procedures to be performed, also agreeing with the release of the results, according to the National Health Council's resolution No. 466 of December 12, 2012.

The initial proposal was to evaluate 119 children born in a public hospital in São Paulo (SP), who also participated in a previous longitudinal study conducted by the same researcher[9], who evaluated them in the neonatal period, at 3 and 6 months of age. However, there was loss of contact with 53 children, 32 refused to return for reevaluation, eight confirmed presence but did not came for the tests, and three children had no transient-evoked otoacoustic emissions, and were referred to the Otorhinolaryngology Clinic, returning with a diagnosis of otitis media and were therefore excluded from the study.

The final sample population of the present study thus comprised 23 children: 11 born small for gestational age (SGA) and 12 born appropriate for gestational age (AGA), who were subdivided into four groups: (1) T/SGA group, made up of four children born at term (T) and SGA; (2) PT/SGA group, formed by seven preterm-born children (PT) and SGA; (3) T/AGA group made up of four children born at term and AGA, and a PT/AGA group formed by children born preterm and AGA.

It was decided to subdivide the groups into term- and preterm-born children considering the neuromaturation process of the central auditory pathway.

It should be noted that the classification "term and preterm" birth followed the criteria defined by the World Health Organization, which considers term-born infant the one whose gestational age was between 37 and 41 weeks; preterm-born infant refers to the child born with gestational age between 24 to 36 6/7 weeks[10].

All children were assessed at three different moments, as follows: at birth (moment 1 = M1), at six months of age (moment 2 = M2) and when they were three years old (moment 3 = M3).

The age at the end of the study ranged from 34 to 38 months (mean age 36 months = 3 years) for term infants. For preterm infants, the corrected age at the end of the survey ranged from 34 to 39 months (mean age 36.5 months = 3 years). Eligibility criteria for inclusion in the study were: a) having attended all proposed evaluations; b) bilateral presence of transient-evoked otoacoustic emissions (TEOAE), captured in a portable automated screening device (AccuscreenPRO; GN Otometrics trademark); c) presence of the weight-to-gestational-age indicator below the 10th percentile of the growth curve, which characterizes a child born small for gestational age - SGA; d) presence of the weight-to-gestational-age indicator between the 10th and 90th percentile of the growth curve, which characterizes a child born appropriate for gestational age - AGA[3]

As exclusion criteria were children considered at risk for TORCHS infection (toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis), conductive and/or cochlear hearing disorders, craniofacial malformations, genetic syndromes and major neurological diseases, as clinical evidence of neonatal

encephalopathy, and peri-intraventricular hemorrhage confirmed by transfontanelle ultrasonography.

All children had a BAEP assessment performed at birth (M1), when aged six months (M2) and three years (M3). At M1 and M2, the children were in natural sleep on the mother's lap, or comfortably accommodated in the crib. At M3, when the BAEP and the LLAEP were performed, the children remained on their mother's lap, or comfortably accommodated in an armchair, watching a DVD for kids, devoid of sound. LLAEP was performed only for children aged 3 years (M3).

For the electrophysiological assessment of the brainstem and long-latency auditory evoked potentials, the clinical diagnosis model Smart-EP of the Intelligent Hearing Systems® brand was used, with a stimulation channel. After previous cleaning of the skin with abrasive paste, disposable pediatric electrodes (Meditrace-200 - Kendal®) were placed on the frontal region (Fpz) and on the right and left mastoids (M_2 and M_1), following the 10-20 method of the International Electrode System[11].

The acoustic stimuli used to capture the BAEPs were rarefied polarity clicks presented monaurally by a pair of insertion headphones, model ER-3A, at 80 dBnNA, to assess the integrity of the auditory pathway, at a speed of 27.7 clicks per second, duration of 0.1 millisecond (msec), high-pass filters of 100 Hz and low-pass filters of 1500 Hz, using a total of 2048 stimuli recorded in a 12-msec time window. The impedance of the electrodes was kept below 3 kΩ.

The absolute latencies of waves I, III, V and the I-III, III-V, I-V interpeak intervals were analyzed and rated as normal and altered, according to the reference values proposed in the Evoked Potential Software Manual of the Smart-EP equipment used, considering the age at the time of the test[12].

Then, the long-latency auditory evoked potentials (LLAEPs) were recorded, identifying the components P1, N1, P2. The reference electrodes were positioned on the right or left mastoids (M2 and M1), depending on the side to be examined, the active electrode was placed on the vertex (Cz), and the ground electrode was that of the mastoid of the contralateral ear. The acoustic stimulus used was the syllable complex / Ba / at 70 dBnNA, in monoaural condition, promediation of 300 stimuli randomly elicited by the computer, in a 512-msec recording window, at a rate of 1.9 stimulus per second, trapezoidal stimulus intensity envelope. The evaluation parameters were: bandpass filter from 1 to 30 Hz, gain of 100,000, the window of analysis of response from -100 msec pre-stimulus to 500 msec post-stimulus, and the electroencephalogram (EEG) window with 100% level (open). The presence and absence of these potentials were verified, and their latencies were determined.

The LLAEP components, as well as their latency value, were marked, considering the maximum amplitude point, which was determined as the difference between the baseline and the maximum positive or negative point, according to the component examined. For identification of the LLAEP components, the values proposed by McPherson[13] were used.

The BAEP and LLAEP plotted graphs were examined visually by two judges with experience in the field of hearing electrophysiology and, when in doubt, a third qualified judge was invited to perform the analysis.

It should be emphasized that the components of BAEP and LLAEP were recorded at least twice to verify the reproducibility of auditory responses, ensuring that they are electrical activities responding to auditory stimulus along the central auditory pathway.

Statistical analysis

The analysis of the results was carried out by an expert in statistics in two stages: descriptive and inferential, considering the results in the neonatal period, at six months and at three years of age.

In the descriptive analysis, tables were built showing the percent values of normal and altered results for the four groups at the three moments of assessment and for both ears. In the inferential analysis, for waves III and V and interpeak I-III and I-V, on each side, Fisher's Exact test was used to compare two groups at each time of assessment (M1 - newborn, M2 - six months old, and M3 - 3 years old), to determine occurrence of changes in the population studied[14].

For each wave and interpeak, the variable "rating" was created, defined as normal or altered, being normal when at the three moments of assessment the wave or interpeak value was within the parameters of normality defined in the equipment. It was rated as altered when the wave or interpeak value was outside the normal parameters at least in one moment of evaluation. The means of LLAEP latency were obtained using the maximum and minimum latency values obtained for each potential, in each group[14].

The level of significance adopted for all hypothesis tests carried out was 0.05 (5%). In cases of sample restriction, when the p-value obtained in a hypothesis test was higher than 5%, but less than 10%, it was concluded that there was an indication of statistical significance. The entire analysis was calculated using the statistical software STATA®, version 10.0.

RESULTS

The statistical analysis of BEAP resulted in the comparison of percentages of normal and altered results for absolute latencies and interpeak intervals between the assessments made at the moment of birth (M1), at six months (M2), and three years (M3) of age.

The latency values of wave I and interpeak III-V were within normal limits in both ears, at the three moments of assessment, for all four groups of children, with no difference between them.

The T/SGA-born children had a greater occurrence of alterations in the absolute latency of wave III compared to the other groups of children, in both ears, at the three moments of assessment, being significant at M2 in the right ear and at M3 in the left year (Figure 1). At M2, the group of PT/AGA and T/SGA children differed from the other two groups (Table 1).

In the T/SGA group of children there was also a greater occurrence of alterations in the latency of wave V compared to the other groups, in both ears at the three moments assessed (Table 2).

In the neonatal period, occurrence of alterations in the interpeak I-III interval was higher for the T/SGA group in the right ear, compared to the other groups, with no differences between them at all moments assessed (Figure 2, Table 3).

At birth (M1), there was a significant difference for the I-V interpeak interval in the right ear of the T/SGA group when compared with the other groups; at the moments M1 and M3 there was also an increase of the interpeak I-V interval in the left ear of the T/SGA group when compared to the other groups(Table 4).

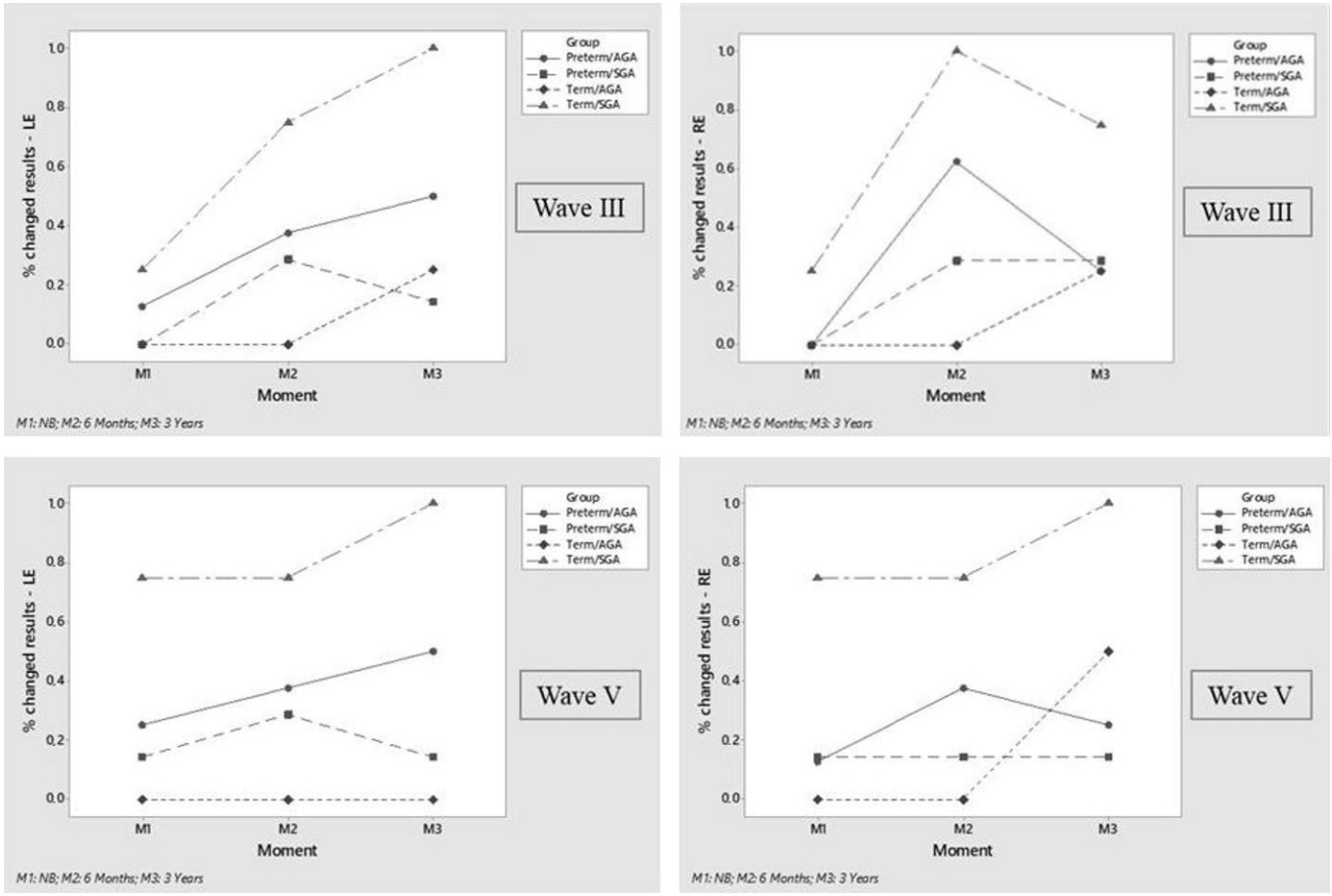

Figure 1. Profiles of percentages of altered results of waves III and V at each, per group of children and time of assessment

Table 1. Descriptive analysis and comparison of percentages of wave III alterations between the groups of children at each moment of assessment

Moment Group	WAVE III											
	M1				M2				M3			
	RE		LE		RE		LE		RE		LE	
	n	%	n	%	n	%	n	%	n	%	n	%
PT/AGA	0	(0%)	1	(12.5%)	5	(62.5%)	3	(37.5%)	2	(25%)	4	(50%)
PT/SGA	0	(0%)	0	(0%)	2	(28.6%)	2	(28.6%)	2	(28.6%)	1	(14.3%)
T/AGA	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(25%)	1	(25%)
T/SGA	1	(25)	1	(25%)	4	(100%)	3	(75%)	3	(75%)	4	(100%)

	M1	p- Value		M2	p -Value		M3	p -Value
RE	PT/AGA + PT/SGA +T/AGA – T/SGA	0.174	RE	PT/SGA - T/AGA	0.491	RE	PT /AGA +T/AGA – PT/SGA	>0.999
LE	PT/SGA +T/AGA – PT/AGA	0.421	LE	PT/SGA - T/AGA	0.491	LE	PT/SGA - T/AGA	>0.999
LE	PT/SGA +T/AGA + PT/AGA – T/SGA	0.324	RE	PT/SGA + T/AGA – PT/AGA	0.074	LE	PT/SGA +T/AGA- PT/AGA	0.319
			LE	PT/SGA + T/AGA – PT/AGA	0.603	RE	PT /AGA +T/AGA + PT/SGA – T/SGA	0.103
			RE	PT/SGA + T/AGA – T/SGA	0.011*	LE	PT /AGA +T/AGA + PT/SGA – T/SGA	0.024*
			LE	PT/SGA + T/AGA + PT/AGA - T/SGA	0.103			
			RE	PT/AGA - T/SGA	0.491			
			RE	PT/SGA + T/AGA – (PT/AGA +T/SGA)	0.012			

Fisher's test p- values; *significant statistical differences

Subtitle: n = number of alterations in each group; T/AGA: at term/appropriate for gestational age; T/SGA: at term/small for gestational age; PT/AGA: preterm/appropriate for gestational age; PT/SGA: preterm/small for gestational age; RE: right ear; LE: left ear; M1: Moment 1 (newborn); M2: Moment 2 (6 months old); M3: Moment 3 (3 years old)

Table 2. Descriptive analysis and comparison of percentages of wave V alterations between the groups of children at three different moments of assessment

Moment	WAVE V											
	M1				M2				M3			
Group	RE		LE		RE		LE		RE		LE	
	n	%	n	%	n	%	n	%	n	%	n	%
PT/AGA	1	(12.5%)	2	(25%)	3	(37.5%)	3	(37.5%)	2	(25%)	4	(50%)
PT/SGA	1	(14.3%)	1	(14.3%)	1	(14.3%)	2	(28.6%)	1	(14.3%)	1	(14.3%)
T/AGA	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(50%)	0	(0%)
T/SGA	3	(75%)	3	(75%)	3	(75%)	3	(75%)	4	(100%)	4	(100%)

	M1	p-value		M2	p-value		M3	p-value
RE	PT/AGA – T/AGA	>0.999	RE	PT /SGA - T/AGA	>0.999	RE	PT/AGA – PT/SGA	>0.999
LE	PT/AGA – T/AGA	>0.999	LE	PT/SGA - T/AGA	0.491	LE	PT/SGA - T/AGA	>0.999
RE	PT/AGA +T/AGA - PT/SGA	>0.999	RE	PT/SGA + T/AGA - PT/AGA	0.262	RE	PT/AGA + PT/SGA - T/AGA	0.272
LE	PT/SGA +T/AGA - PT/AGA	0.546	LE	PT/SGA +T/AGA - PT/AGA	0.603	RE	PT/AGA +PT/SGA + T/AGA - T/SGA	0.014*
RE	PT/AGA +T/AGA + PT/SGA – T/SGA	0.021*	RE	PT/SGA + T/AGA + PT/AGA - T/SGA	0.067	LE	PT/SGA + T/AGA + PT/AGA - T/SGA	0.014*
LE	PT/SGA +T/AGA + PT/AGA – T/SGA		LE	PT/SGA +T/AGA + PT/AGA – T/SGA	0.103	LE	PT/SGA + T/AGA – PT/AGA	0.111
			RE	PT/SGA + T/AGA – PT/AGA	0.603			
			RE	PT/SGA + T/AGA – T/SGA	0.011*			
			RE	PT/AGA - T/SGA	0.491			
			RE	PT/SGA + T/AGA – (PT/AGA +T/SGA)	0.012*			

Fisher's test p- values; *significant statistical differences

Subtitle: n = number of alterations in each group; T/AGA: at term/appropriate for gestational age; T/SGA: at term/small for gestational age; PT/AGA: preterm/appropriate for gestational age; PT/SGA: preterm/small for gestational age; RE: right ear; LE: left ear; M1: Moment 1 (newborn); M2: Moment 2 (6 months); M3: Moment 3 (3 years)

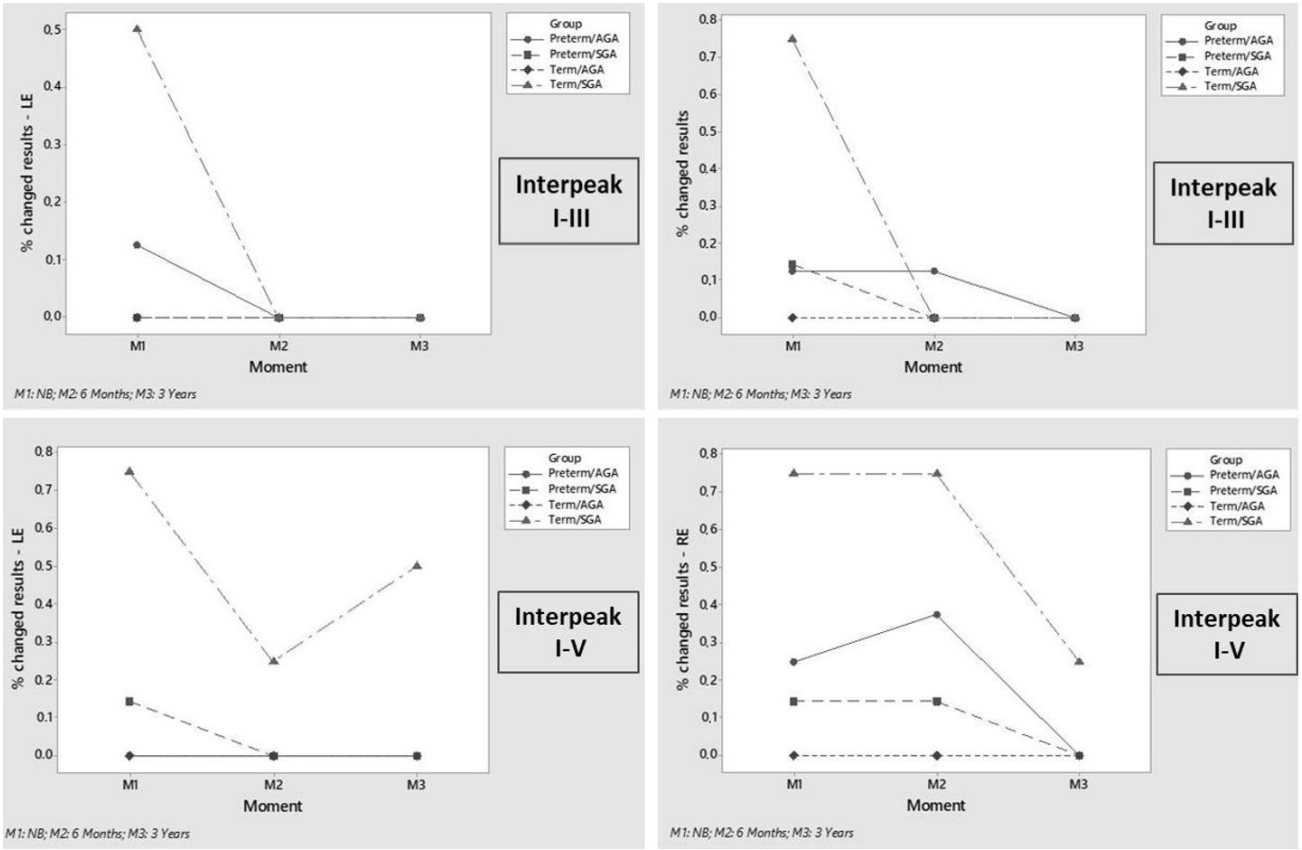

Figure 2. Profiles of percentages of altered results of Interpeak I-III and I-V, per group of children and time of assessment

Table 3. Descriptive analysis and comparison of percentages of alterations in interpeak I-III intervals between groups of children at three different moments of assessment

Moment Group	INTERPEAK I-III											
	M1				M2				M3			
	RE		LE		RE		LE		RE		LE	
	n	%	n	%	n	%	n	%	n	%	n	%
PT/AGA	1	(12.5%)	1	(12.5%)	1	(12.5%)	0	(0%)	0	(0%)	0	(0%)
PT/SGA	1	(14.3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
T/AGA	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
T/SGA	3	(75%)	2	(50%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)

	M1	p -value		M2	p -value		M3	p -value
RE	PT/AGA -T/AGA	>0.999	RE	PT/SGA + T/AGA + T/SGA - PT/AGA	0.348			
RE	PT/AGA +T/AGA – PT/SGA	>0.999						
RE	PT/SGA +T/AGA + PT/AGA – T/SGA	0.021*						
LE	PT/SGA + T/AGA - PT/AGA	0.421						
LE	PT/SGA + T/AGA + PT/AGA - T/SGA	0.067						

Fisher's test p- values; *significant statistical differences
Subtitle: n = number of alterations in each group; T/AGA: at term/appropriate for gestational age; T/SGA: at term/small for gestational age; PT/AGA: preterm/appropriate for gestational age; PT/SGA: preterm/small for gestational age; RE: right ear; LE: left ear; M1: Moment 1 (newborn); M2: Moment 2 (6 months); M3: Moment 3 (3 years)

Table 4. Descriptive analysis and comparison of percentages of alterations in the interpeak I-V interval between groups of children at three different moments of assessment

Moment Group	INTERPEAK I – V											
	M1				M2				M3			
	RE		LE		RE		LE		RE		LE	
	n	%	n	%	n	%	n	%	n	%	n	%
PT/AGA	2	(25%)	0		3	(37.5%)	0		0	(0%)	0	(0%)
PT/SGA	1	(14.3%)	1		1	(14.3%)	0		0	(0%)	0	(0%)
T/AGA	0	(0%)	0		0	(0%)	0		0	(0%)	0	(0%)
T/SGA	3	(75%)	3		3	(75%)	1		1	(25%)	2	(50%)

	M1	Value-p		M2	Value-p		M3	Value-p
RE	PT/SGA - T/AGA	>0.999	LE	PT/AGA +PT/SGA + T/AGA - T/SGA	0.174	RE	PT/SGA +T/AGA + PT/AGA – T/SGA	0.174
RE	PT/SGA +T/AGA - PT/AGA	0.546	RE	PT/SGA + T/AGA - PT/AGA	0.262	LE	PT/AGA + PT/SGA + T/AGA - T/SGA	0.024*
RE	PT/SGA +T/AGA + PT/AGA – T/SGA	0.040*	RE	PT/SGA +T/AGA + PT/AGA – T/SGA	0.067			
LE	PT/AGA + T/AGA - PT/SGA	0.368						
LE	PT/AGA +T/AGA + PT/SGA – T/SGA	0.009*						

Fisher's test p- values; *significant statistical differences
Subtitle: n = number of alterations in each group; T/AGA: at term/appropriate for gestational age; T/SGA: at term/small for gestational age; PT/AGA: preterm/appropriate for gestational age; PT/SGA: preterm/small for gestational age; RE: right ear; LE: left ear; M1: Moment 1 (newborn); M2: Moment 2 (6 months); M3: Moment 3 (3 years)

With respect to the LLAEP analysis, the comparison between the four groups did not show differences between them for the component P1 (p=0.851), which also was found in the analysis of N1 (p= 0.309) and P2 (p=0.451). In the comparison between the ears, there was no significant difference for P1 (p=0.400), N1 (p=0.475) and P2 (p=0.292 msec).

The mean values of P1 wave latencies were of 141 to151 msec in the right ear and 127 to 149 msec in the left ear, with no difference between ears and groups of children.

The latencies of the component N1 ranged from 166 to 300 msec in the right ear and from112 to 282 msec in the left ear, with mean values of N1 between 212 and 243 msec. The latencies of the component P1 ranged from 267 to 388 msec in the right ear and from 311 to 423 msec in the left ear, with no differences. The P2 values were not recorded in a T/SGA born infant.

DISCUSSION

The present study enabled an effective follow-up of the neurological/auditory development of SGA-born children, from birth to three years of age.

In the literature search, few references were found, which used a methodology similar to the present study.

The results showed that, except for wave I and Interpeak III-V, the percentage of altered results in BAEP was higher in the T/SGA group, at the three moments assessed, affecting both ears significantly (Figures 1 and 2).

The brainstem maturation process occurs in the caudorostral direction during the first 18 to 24 months of life. The literature agrees on the fact that during intrauterine period, insufficient intake of essential nutrients for this process to occur may affect the formation and quantity of synapses, which may cause failures in neuronal myelination[1,2]. Such failure, in turn, would cause a delay in neural transmission, thus affecting the quality of transmission, with probable impacts on language development as much as the auditory system is challenged to carry an increasing volume of acoustic information along the brainstem.

It is also known that the myelination of the auditory system goes on slowly during the last trimester of the intrauterine life and rapidly at the immediate postnatal period until approximately two years of age, with an increased number of neurons and synapses. Therefore, if the system suffered nutritional deprivation, it is clear that this process will be impaired from the very beginning. Added to this is the fact that in the processing required for speech perception, there is an essentially automatic basis that occurs mostly in the brainstem[15,16]. Thus, an impairment of the auditory pathway in this region could be accountable for numerous difficulties in the understanding and expression of speech.

Other factor that confirms the likelihood of greater alterations in infants born at term and small for gestational age would be the brain vulnerability due to the impact caused by intrauterine nutritional restriction; therefore, the degree of neurological impairment of a SGA child will depend on the time, severity and duration of the insult[1]. In addition, T/SGA infants, when compared to T/AGA infants, are three times more likely to develop morbidities, possibly because they have a different maturation rhythm of the auditory pathway when compared to AGA children[1,17,18].

The present study corroborates a previous study which showed that immature perception of speech in children may be associated with delayed development of the brainstem neural, which is responsible for an accurate acoustic coding of speech[17]. Thus, it seems reasonable that T/SGA-born children should be monitored at least until the end of the period of language development to prevent possible morbidities.

However, it seems that the same risk of morbidities does not occur with PT/SGA individuals possibly because they remained in the insult for a shorter time; the results showed that the neurodevelopment of PT-SGA children was similar to the T/AGA and PT/AGA groups, agreeing with previous study, which concluded that in preterm-born children, the small-for-gestational-age condition is not a risk for retrocochlear alteration[19].

One limitation of the present study was that BAEP was not captured with speech stimulus, in order to confirm or not a previous study, which found that brainstem neurons react differently to codify clicks in relation to speech sounds. The same study concluded that the course of development takes more than two years for codifying speech stimulus properties in brainstem[20].

LLAEP research is a recent and promising topic in the assessment of cognitive development of infants and children, especially those who have risks for auditory processing disorders[21].

The component P1 of LLAEOs was established as a biological marker to assess maturation of the central auditory system in children for being a robust positive response easily identifiable, which occurs between 100-300 msec after stimulus, depending on the child's age[22-24].

The results of this study (Table 5) showed that the latency means of the component P1 were within the normality range (between 127 and 151 msec), in agreement with the results of studies conducted earlier[22-24], although slightly higher than in other studies, which found, for the same age group, P1 responses between 87 and 126 msec[24,25]. The mean values found for N1 in the present study (between 212 and 243 msec) were also higher than in a previous study with children in the same age group, where the values ranged from 131 to 158 msec[25].

Such discrepancies in the study results could be explained by variations in the methodologies used, e.g., positioning of electrodes, intensity used, and presentation rate, among others, and probably not due to the maturational process, considering that the findings were similar in the four groups.

The P1 - N1 - P2 complex indicates the neural processing of the acoustic signal in the auditory cortex. Thus, its presence indicates that coding of the acoustic stimulus in the auditory cortex was achieved, while its absence would suggest noncoding of this stimulus[25]. So, although small-for-gestational-age infants have higher occurrence of alterations in the brainstem auditory evoked potential, the sound stimuli are reaching the auditory cortex.

A recent study reported that the component P2 was found in 90% of hearing children, though the P1 and N1 components were observed in 100% of the pediatric population[26]. Thus, the fact that the component P2 was not visualized in a term/AGA-born child seems to have no clinical relevance and more relationship with neuromaturation of the auditory system, which occurs gradually, and the appearance of the components P1, N1, P2 and N2 as well as their latency values vary in childhood[27].

The present study also found variations in the morphology of LLAEP recordings. The major morphological variation found was the presence of a protrusion in the component P1,

Table 5. Mean values of latencies of long-latency auditory evoked potentials

Group	RE		LE		RE		LE		RE		LE	
	Min. max. P1 (msec)	Mean P1	Min. max. P1 (msec)	Mean P1	Min. max. N1 (msec)	Mean N1	Min. max. N1 (msec)	Mean N1	Min. max. P2 (msec)	Mean P2	Min. max. P2 (msec)	Mean P2
T/AGA	119-195	151	116-188	149	166-249	212	205-282	241	-	-	-	-
T/SGA	120-171	136	107-163	142	211-282	241	190-280	243	267-354	311	375-423	399
PT/AGA	131-181	141	112-160	127	212-300	226	112-160	208	291-388	340	311-360	336
PT/SGA	115-183	146	121-159	142	182-260	231	181-235	220	276-286	279	265-316	287

Subtitle: T/AGA: at term/appropriate for gestational age; T/SGA: at term/small for gestational age; PT/AGA: preterm/appropriate for gestational age; PT/SGA: preterm/small for gestational age; RE: right ear; LE: left ear; msec: milliseconds; –not viewed; Min.max.: minimum. maximum; P1, N1, P2: components of long-lattency auditory evoked potentials

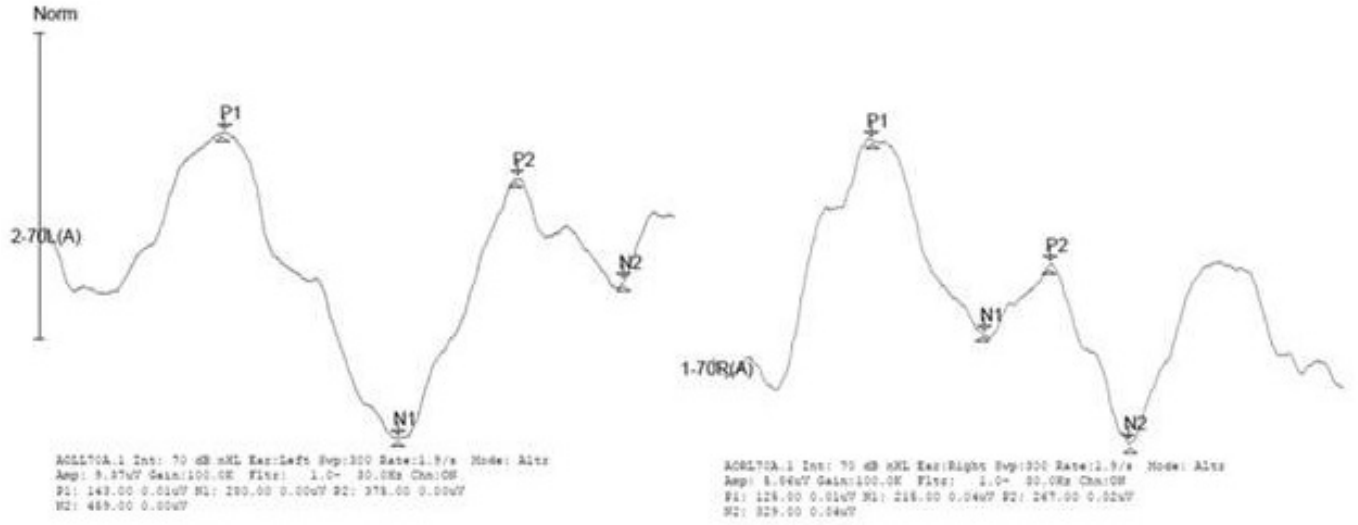

Figure 3. Plotted line with the presence of components of long-latency auditory evoked potentials of a child born at term and small for age at three years of age

preceding N1, which coincides with findings reported in the literature studied[25,28] (Figure 3). This characteristic could result from cortical neuronal immaturity, because, according to the literature, as age advances there is a better definition of the components, which results from an increased synchronization of the neuronal activity and the establishment of effective structural networks[25].

The present study was based on the hypothesis that SGA children could have minimal neural disorders identified by BAEP and LLAEP, indicating possible delays in language acquisition, when compared to AGA children. However, for the age groups studied, only the BAEP results indicated possible dysfunctions. Such dysfunctions probably occur at lower levels of the central auditory pathway in the brainstem, causing a less than expected neural transmission. Despite that, such dysfunctions reach the cortex, considering that they indicate the presence of long-latency potentials, which does not ensure that the processing of speech sounds is achieved in the same way in the four groups.

Active hearing exposure in early childhood to nonverbal stimuli, containing linguistically relevant acoustic tracks seems to confer an advantage in acoustic processing when compared to passive exposure or maturation itself only. This experience seems to facilitate neural plasticity and sensory processing during the period of development[29]. So, it seems clear that if there is some problem (such as neural dysfunction) at the beginning of the path to be travelled by these stimuli (brainstem), the acoustic information will reach the cortex, but deprived of some relevant tracks. In fact, other study with malnourished children also considered that if the lower levels of the central hearing system are impaired by dysfunctions, like a "domino effect" (or chain reaction), such dysfunctions will add up along the diverse sites that generate auditory potentials[30].

Finally, considering that delays in the development of SGA children often occur in the central and psychomotor nervous systems, it is recommended an overall monitoring of their neurobehavioral competencies at least during the first three years of age, period that is considered sensitive for appropriate acquisition of language. Such monitoring could provide tools to pediatricians and caregivers to identify children with alterations in development during early childhood, so that they can be referred to rehabilitation services before starting school, thus increasing their chances for a successful academic, social, and professional life.

CONCLUSION

SGA children born at term have a higher percentage of alterations in BAEP compared to AGA children born at term and SGA and AGA preterm children. SGA- born children are considered at risk for auditory alterations/dysfunctions relating to the development of hearing skills that are necessary to ensure quality of processing of acoustic information.

REFERENCES

1. Dobbing J, Sands J. Head circumference, biparietal diameter and brain growth in fetal and postnatal life. Early Hum Dev. 1978;2(1):81-7. http://dx.doi.org/10.1016/0378-3782(78)90054-3. PMid:569046.

2. Pryor J. The identification and long term effects of fetal growth restriction. Br J Obstet Gynaecol. 1997;104(10):1116-22. http://dx.doi.org/10.1111/j.1471-0528.1997.tb10933.x. PMid:9332987.

3. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States National Reference for Fetal Growth. Obstet Gynecol. 1996;87(2):163-8. http://dx.doi.org/10.1016/0029-7844(95)00386-X. PMid:8559516.

4. Strauss RS. Adult functional outcome of those born small for gestational age: twenty-six-year follow-up of the 1970 British birth cohort. JAMA. 2000;283(5):625-32. http://dx.doi.org/10.1001/jama.283.5.625. PMid:10665702.

5. Goto MMF, Gonçalves VMG, Netto AA, Morcillo AM, Moura-Ribeiro MVL. Neurodesenvolvimento de lactentes nascidos a termo pequenos para a idade gestacional no segundo mês de vida. Arq Neuropsiquiatr. 2005;63(1):75-82. http://dx.doi.org/10.1590/S0004-282X2005000100014. PMid:15830069.

6. Azevedo MF, Angrisani RG. Fonoaudiologia: desenvolvimento da audição. In: Takaoka L, Coutinho L, Weiler R, editores. Odontopediatria: a transdisciplinaridade na saúde integral da criança. Barueri: Manole; 2016. p. 243-52.

7. Gonçales AS. Avaliação do desenvolvimento das habilidades auditivas durante o primeiro ano de vida. In: Aquino AMCN, editor. Processamento auditivo: Eletrofisiologia e Psicoacústica. São Paulo: Lovise; 2002. p. 111-20.

8. Cóser MJS, Cóser PL, Pedroso FS, Rigon R, Cioqueta E. P300 auditory evoked potential latency in elderly. Rev Bras Otorrinolaringol. 2010;76(3):287-93. PMid:20658005.

9. Angrisani RMG. Estudo eletrofisiológico longitudinal da via auditiva em lactentes nascidos pequenos para a idade gestacional [tese]. São Paulo: Programa de Ciências da Reabilitação, Faculdade de Medicina, Universidade de São Paulo; 2013.

10. WHO: World Health Organization. Born too soon: the global action report on preterm birth. Geneva: WHO; 2012.

11. Jasper HH. The ten twenty electrode system of International Federation. Electroencephalogr Clin Neurophysiol. 1958;(10):917-75.

12. IHSYS: Intelligent Hearing Systems. Smart-EP software manual: evoked potential acquisition software manual version 5.00 [Internet]. Miami: IHSYS; 2012 [citado em 2019 Set 19]. Disponível em: http://www.ihsys.com/site

13. McPherson DL. Late potentials of the auditory system. Sa Diego: Singular; 1996.

14. Bussab WO, Morettin PA. (2013). Estatística básica. 8. edição. Sao Paulo: Saraiva.

15. Kraus N, Nicol T. Aggregate neural response to speech sounds in the central auditory system. Speech Commun. 2003;41(1):35-47. http://dx.doi.org/10.1016/S0167-6393(02)00091-2.

16. Johnson KL, Nicol T, Zecker SG, Kraus N. Developmental plasticity in the human auditory brainstem. J Neurosci. 2008 Abr 9;28(15):4000-7. http://dx.doi.org/10.1523/JNEUROSCI.0012-08.2008. PMid:18400899.

17. Doctor BA, O'Riordan MA, Kirchner HL, Shah D, Hack M. Perinatal correlates and neonatal outcomes of small for gestational age infants born at term gestation. Am J Obstet Gynecol. 2001;185(3):652-9. http://dx.doi.org/10.1067/mob.2001.116749. PMid:11568794.

18. Angrisani RG, Diniz EMA, Guinsburg R, Ferraro AA, Azevedo MF, Matas CG. Longitudinal electrophysiological study of auditory pathway in small for gestational age infants. CoDAS. 2014;26(4):294-301. http://dx.doi.org/10.1590/2317-1782/201420140042. PMid:25211688.

19. Angrisani RMG, Azevedo MF, Carvallo RMM, Diniz EMA, Ferraro AA, Guinsburg R, et al. Electrophysiological characterization of hearing in small for gestational age premature infants. CoDAS. 2013;25(1):22-8. http://dx.doi.org/10.1590/S2317-17822013000100005. PMid:24408166.

20. Rocha-Muniz CN, Filippini R, Neves-Lobo IF, Rabelo CM, Morais AA, Murphy CFB, et al. Can speech-evoked Auditory Brainstem Response become a useful tool in clinical practice? CoDAS. 2016;28(1):77-80. http://dx.doi.org/10.1590/2317-1782/20162014231. PMid:27074194.

21. Choudhury N, Benasich AA. Maturation of auditory evoked potentials from 6 to 48 months: prediction to 3 and 4 year language and cognitive abilities. Clin Neurophysiol. 2011;122(2):320-38. http://dx.doi.org/10.1016/j.clinph.2010.05.035. PMid:20685161.

22. Romero AC, Frizzo AC, Chagas EF, Isaac ML. Cortical auditory evoked potential in babies and children listeners. Rev Bras Otorrinolaringol. 2019. No prelo. http://dx.doi.org/10.1016/j.bjorl.2019.01.007. PMid:30926456.

23. Sharma A, Cardon G, Henion K, Roland P. Cortical maturation and behavioral outcomes in children with auditory neuropathy spectrum disorder. Int J Audiol. 2011 Fev;50(2):98-106. http://dx.doi.org/10.3109/14992027.2010.542492. PMid:21265637.

24. Silva LAF, Couto MIV, Tsuji RK, Bento RF, Matas CG, Carvalho ACM. Auditory pathways' maturation after cochlear implant via cortical auditory evoked potentials. Rev Bras Otorrinolaringol. 2014;80(2):131-7. http://dx.doi.org/10.5935/1808-8694.20140028. PMid:24830971.

25. Ventura LMP, Costa AO Fo, Alvarenga KF. Maturação do sistema auditivo central em crianças ouvintes normais. Pró-Fono. 2009 Abr-Jun;21(2):101-6. http://dx.doi.org/10.1590/S0104-56872009000200003. PMid:19629318.

26. Agostinho-Pesse R, Alvarenga KF. Potencial evocado auditivo de longa latência para estímulo de fala apresentado com diferentes transdutores em crianças ouvintes. Rev CEFAC. 2013;16(1):13-22. http://dx.doi.org/10.1590/S1516-18462013005000028.

27. Silva LAF, Magliaro FCL, Carvalho ACM, Matas CG. Maturation of long latency auditory evoked potentials in hearing children: systematic review. CoDAS. 2017;29(3):e20160107. http://dx.doi.org/10.1590/2317-1782/20172016107. PMid:28538829.

28. Gomes H, Dunn M, Ritter W, Kurtzberg D, Brattson A, Kreuzer JA, et al. Spatiotemporal maturation of the central and lateral N1 components to tones. Brain Res Dev Brain Res. 2001 Ago;129(2):147-55. http://dx.doi.org/10.1016/S0165-3806(01)00196-1. PMid:11506859.

29. Benasich AA, Choudhury NS, Realpe-Bonilla T, Roesler CP. Plasticity in developing brain: active auditory exposure impacts prelinguistic acoustic mapping. J Neurosci. 2014;34(40):13349-63. http://dx.doi.org/10.1523/JNEUROSCI.0972-14.2014. PMid:25274814.

30. Almeida RP, Matas CG. Long latency auditory evoked potentials in malnourished children. CoDAS. 2013;25(5):407-12. http://dx.doi.org/10.1590/S2317-1782201300050000. PMid:24408543.