Original Article

Artigo Original

Electrophysiological study of hearing in full-term small-for-gestational-age newborns

Estudo eletrofisiológico da audição em recém-nascidos a termo pequenos para a idade gestacional

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Keywords

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ABSTRACT

Purpose: To describe the Brainstem Auditory Evoked Potential (BAEP) results of full-term small-for-gestational-age newborns, comparing them to the results of full-term appropriate-for-gestational-age newborns, in order to verify whether the small-for-gestational-age condition is a risk indicator for retrocochlear hearing impairment. **Methods:** This multicentric prospective cross-sectional study assessed 86 full-term newborns – 47 small- (Study Group) and 39 appropriate-for-gestational-age (Control Group – of both genders, with ages between 2 and 12 days. Newborns with presence of transient evoked otoacoustic emissions and type A tympanometry were included in the study. Quantitative analysis was based on the mean and standard deviation of the absolute latencies of waves I, III and V and interpeak intervals I-III, III-V and I-V, for each group. For qualitative analysis, the BAEP results were classified as normal or altered by analyzing these data considering the age range of the newborn at the time of testing. **Results:** In the Study Group, nine of the 18 (38%) subjects with altered BAEP results had the condition of small-for-gestational-age as the only risk factor for hearing impairments. In the Control Group, seven (18%) had altered results. Female subjects from the Study Group tended to present more central alterations. In the Control Group, the male group tended to have more alterations. **Conclusion:** Full-term children born small or appropriate for gestational age might present transitory or permanent central hearing impairments, regardless of the presence of risk indicators.

Descritores

Potenciais evocados auditivos do tronco encefálico
Audição
Transtornos da audição
Recém-nascido
Recém-nascido pequeno para a idade gestacional

RESUMO

Objetivo: Caracterizar as respostas do Potencial Evocado Auditivo de Tronco Encefálico de recém-nascidos a termo pequenos para idade gestacional, comparando-as às de recém-nascidos a termo adequados para idade gestacional, verificando se a condição de pequeno para a idade gestacional é indicador de risco para alteração auditiva retrococlear. **Métodos:** Este estudo multicêntrico transversal prospectivo avaliou 86 recém-nascidos a termo, sendo 47 pequenos (Grupo Estudo) e 39 adequados para idade gestacional (Grupo Controle), de ambos os gêneros, com idades entre 2 e 12 dias de vida. Foram incluídos os recém-nascidos com presença de emissões otoacústicas evocadas por estímulo transiente e timpanometria tipo A. A análise quantitativa dos dados foi feita baseada na média e desvio-padrão das latências das ondas I, III, V e interpicos I-III, III-V, I-V para cada grupo. Para análise qualitativa, os resultados dos potenciais evocados auditivos foram classificados em alterados ou normais mediante essas análises, considerando-se a faixa etária do recém-nascido no momento do exame. **Resultados:** No Grupo Estudo, dos 18 (38%) que apresentaram potencial evocado auditivo alterado, nove tiveram como risco auditivo apenas o fato de ser pequeno para a idade gestacional. No Grupo Controle, sete (18%) tiveram alteração. Encontrou-se tendência a alterações centrais no Grupo Estudo do gênero feminino. No Grupo Controle, houve tendência a alterações no gênero masculino. **Conclusão:** Crianças a termo, nascidas com peso adequado ou pequenas para a idade gestacional, podem apresentar alterações auditivas de caráter central, transitórias ou permanentes, independente da presença de indicadores de risco auditivo.

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INTRODUCTION

The adequacy of birth weight is a predictive factor of morbidity and mortality in the first years of life. The newborn (NB) considered small for gestational age (SGA) is below the percentile 10 of a determined growth curve that relates birth weight and gestational age[1]; the SGA condition might be an indicator of intrauterine growth delay.

SGA newborns can also be classified into two subgroups, according to the time at which their intrauterine life was affected: asymmetric or disproportionate SGA NB, in which the weight is below the expected, but stature and cephalic perimeter are normal, and the likely injury occurred late in pregnancy, due to placental insufficiency; symmetric or proportionate SGA NB, in which weight, cephalic perimeter and stature are below the expected, suggesting that injuries occurred early in pregnancy, probably extending throughout the whole neonatal period, and causing greater impairments to the fetus[2]. There are several causes of intrauterine growth restriction, such as smoking, low maternal stature, congenital infections, among others. International literature data have reported that, when compared to infants born adequate for gestational age (AGA), SGA infants have neuropsychomotor and language development handicaps, among others[3-6].

Language and auditory abilities are developed in the first two years of life, especially in the first six months[2,7-10]. The Brainstem Auditory Evoked Potential (BAEP) is considered the "gold standard" test in the diagnosis of the integrity of auditory nerve and pathways of the central nervous system in neonates. Moreover, it allows the follow-up of the central nervous system maturation at brainstem level, which occurs from the first months of life until around 18 months, when responses become similar to the adults'[11].

The purpose of this study was to characterize the BAEP responses of small-for-gestational-age (SGA) newborns, comparing them to those of adequate-for-gestational-age (AGA) infants, in order to verify whether the SGA condition is a risk indicator for retrocochlear hearing impairments.

METHODS

This multicentric study was approved by the Committee for the Analysis of Research Protocols of the Universidade de São Paulo (CAPPesq HCFMUSP 372/10), the Research Ethics Committee of the University Hospital of the Universidade de São Paulo (CEP-HU/USP nº 1009-10 – SISNEP CAEE 0037.0.198.000-10), and the Research Ethics Committee of the Universidade Federal de São Paulo (UNIFESP 1235/11).

According to the ethical principles of research with human beings, mothers and/or legal guardians agreed with the participation of the newborns in this study, and signed the Free and Informed Consent Term, which described all the procedures that would be carried out, in accordance with Resolution 196/96.

The sample comprised 86 full-term newborns (FTNB), with gestational age varying from 37 weeks and one day (37 1/7) to 41 weeks, assessed in the immediate post-natal period (between two and 12 days of life). Forty seven infants were classified as SGA, and 39 as AGA, according to a study that normalized the percentiles for classification, considering weight and gestational age[12].

The Study Group (SG) comprised 47 SGA FTNB, 30 female and 17 male. The Control Group (CG) comprised 39 AGA FTNB, 20 female and 19 male.

It is worth emphasizing that the classification of proportionality for SGA FTNB can be obtained by Rohrer's ponderal index (PI), which is defined by weight (in grams) divided by stature cubed (cm^3), multiplied by 100. If PI≥2.49, the newborn is considered symmetric or proportionate SGA; if PI<2.49, the newborn is asymmetric or disproportionate SGA.

The first procedure adopted was carefully reading the NB's medical records, in order to collect data about the eligibility criteria of the sample (SGA and AGA FTNB), including the infant's anthropometric measures and gestational age (based on the date of the mother's last period, confirmed by ultrasonography). Bilateral presence of transient otoacoustic emissions (TOAE) and type A tympanometric curve were also adopted as eligibility criteria[10].

Newborns with history of encephalopathy, conductive and/or cochlear malformations and alterations were excluded from the sample. These were referred to otorhinolaryngological evaluation and management, and later audiological follow-up.

All NB were prepared for the tests according to the following procedure: an inspection of the external auditory canal was initially performed, using a Welch Allyn® otoscope to visualize the tympanic membrane. After that, infants were submitted to Transient Otoacoustic Emissions (TOAE) and acoustic immitance measures (tympanometry), in order to guarantee cochlea normality and absence of middle ear disorders.

To register the TOAE, we used either the ILO92 - Otodynamics® equipment with non-linear click stimulus, in an intensity level between 78 and 83 dB SPL (at the Research Center of the Department of Physical Therapy, Speech-Language Pathology and Audiology, and Occupational Therapy of the Universidade de São Paulo), or the portable automatic equipment AccuscreenPRO, from GN Otometrics® (at the São Paulo Hospital, Universidade Federal de São Paulo). In the last case, the equipment was calibrated by the manufacturer for automatic analysis of responses using the following parameters: evaluation method of binomial statistics; non-linear click stimuli in speed sequence of 60 Hz and intensity between 70 and 84 dB SPL (45-60 dB HL, with auto-calibration depending on the ear canal volume); frequency spectrum from 1.4 to 4 kHz; artifact lower than 20%. When these parameters were not obtained, the equipment registered "fail", and when they were obtained, the result shown was "pass".

Acoustic immitance measures included tympanometry with 1 kHz probe tone, carried out using the middle ear analyzer Interacoustics®, model AT 235.

For the BAEP, the infant was positioned in the crib or in the mother's arms, during natural sleep. The clinical/diagnostic equipment Intelligent Hearing Systems®, model Smart-EP, was used to register BAEP responses. All NB were prepared for the test according to the following procedure: pre-cleaning of the skin using abrasive paste, and placing of disposable pediatric

electrodes Meditrace-200, from Kendal®, over the frontal region (Fpz) and right and left mastoids (M_2 e M_1), according to the IES 10-20 rule (International Electrode System)[13]. Responses were elicited through acoustic stimuli presented using a pair of insert earphones, model 3A.

The acoustic stimulus used was the rarefaction polarity click, monoaurally presented at 80 dBnHL (for assessing auditory pathway integrity), 50 dBnHL, and 30 dBnHL, at presentation speed of 27.7 clicks per second, with 0.1 milliseconds (ms) duration, totalizing 2048 stimuli. The recording window used was of 12 ms. Absolute latencies of waves I, III and V and interpeak intervals I-III, III-V and I-V were analyzed. These parameters were used for being the assessment protocols used to register BAEP responses in NB at the institutions participating in this study.

BAEP responses were qualitatively analyzed, and the results obtained were classified as normal or altered, according to the values of absolute latencies of waves I, III and V, and interpeak intervals I-III, III-V and I-V, as proposed by Cox[14], considering the infant's age range at the time of assessment.

Statistical analysis applied the Chi-square test, the Paired t test, and the Independent t test[15], adopting a significance level of 5%, with confidence interval of 95%.

RESULTS

The Study Group, which comprised 47 FTNB, was divided into two subgroups for intra-subjects qualitative analysis of BAEP responses: 33 symmetric and 14 asymmetric SGA NB. There was no difference between groups (Table 1). Hence, further analyses of the SGA infants considered the group as a whole.

Table 1. BAEP responses obtained by symmetric and asymmetric SGA infants

SGA groups	Normal n (%)	Altered n (%)	Total n (%)
Symmetric	22 (66.7)	11 (33.3)	33 (100)
Asymmetric	7 (50)	7 (50)	14 (100)
Total	29 (62)	18 (38)	47 (100)

Chi-square test (p=0.455)
Note: SGA = small for gestational age

The comparative analysis of BAEP responses between Study (SGA) and Control (AGA) groups found alterations in 25 infants (29% of the sample) – 18 SGA NB (38%) and seven AGA NB (18%). No difference was found between groups (p=0.067), even though there was a higher tendency of alterations in the Study Group (Table 2).

In the comparison between male and female subjects in the SGA group regarding BAEP results (normal or altered), no difference was evidenced for the distribution of alterations (p=0.214). The same comparison in the AGA group also did not show difference regarding the distribution of alterations (p=0.081). Nevertheless, the results suggest that, in the AGA group, male NB presented higher tendency to central auditory alterations (31.6%), when compared to female NB (5%) (Table 3).

Table 2. Comparative study of BAEP responses

Groups	Normal (%)	Altered (%)	Total (%)
AGA	32 (82)	7 (18)	39 (100)
SGA	29 (62)	18 (38)	47 (100)
Total	61 (71)	25 (29)	86 (100)

Chi-square test (p=0.067)
Note: AGA = adequate for gestational age; SGA = small for gestational age

In the comparative analysis between Study and Control groups for the male gender, nine SGA NB (53%) presented BAEP alterations, which were characterized by increase of the absolute latencies of waves III and/or V and of interpeaks I-III and/or I-V. No differences were found between SGA and AGA groups for male infants (p=0.337) (Table 3).

In the comparative analysis of BAEP responses obtained by Study and Control groups for the female gender, nine SGA NB (30%) presented altered results, which were characterized by increase of the absolute latencies of waves III and/or V and of interpeaks I-III and/or I-V. In the AGA group, only one infant (5%) presented increase of the absolute latencies of waves III and V. These results did not evidence difference between SGA and AGA groups for female infants (p=0.071), although the SGA group showed tendency to present more alterations (Table 3).

Table 3. Comparison of BAEP responses between SGA and AGA infants, between male and female genders

Resultado	AGA		SGA	
	Female (1) n (%)	Male (2) n (%)	Female (3) n (%)	Male (4) n (%)
Normal	19 (95)	13 (68.4)	21 (70)	8 (47)
Altered	1 (5)	6 (31.6)	9 (30)	9 (53)
Total	20 (100)	19 (100)	30 (100)	17 (100)
Comparative		p-value		
AGA – Gender (1) x(2)		0.081		
SGA – Gender (3) x (4)		0.214		
Female – Group (1) x (3)		0.071		
Male – Group (2) x (4)		0.337		

Chi-square test (p≤0.05)
Note: AGA = adequate for gestational age; SGA = small for gestational age

Preliminarily, the results obtained by group (SGA and AGA) for each BAEP parameter (absolute latencies of waves I, III and V, and interpeaks I-III, III-V and I-V) were separately analyzed for each ear, using the Paired t test (Table 4). It is noticed that, in the Study Group (SGA), there was difference between right and left ears only in the interpeak I-III (p=0.048). Having in mind that a single parameter presented difference, that this result was very close to the significance level, and that the mean values of interpeaks I-III are very close between ears (2.80 ms in the right ear, and 2.84 in the left ear), the results obtained were considered clinically similar, allowing the values obtained in the right and left ears to be grouped. Hence, we analyzed

Table 4. Comparison of the absolute latencies of waves I, III, V and interpeak intervals I-III, III-V, I-V obtained in the BAEP between right and left ears

Waves/ interpeaks		SGA (n=47)		p-value	Result	AGA (n=39)		p-value	Result
		Right	Left			Right	Left		
I	Mean	1.83	1.81	0.518	R=L	1.80	1.82	0.256	R=L
	SD	0.18	0.17			0.15	0.17		
III	Mean	4.62	4.65	0.122	R=L	4.61	4.63	0.504	R=L
	SD	0.27	0.28			0.25	0.29		
V	Mean	7.02	6.97	0.25	R=L	6.97	6.93	0.452	R=L
	SD	0.36	0.41			0.32	0.32		
I-III	Mean	2.80	2.84	0.048*	R<L	2.95	2.79	0.261	R=L
	SD	0.23	0.26			0.90	0.25		
III-V	Mean	2.36	2.33	0.298	R=L	2.33	2.31	0.642	R=L
	SD	0.31	0.31			0.27	0.26		
I-V	Mean	5.16	5.16	0.944	R=L	5.05	5.12	0.342	R=L
	SD	0.38	0.40			0.57	0.33		

* Significant values (p≤0.05) – Paired t test

Note: SD = standard deviation; R = right ear; L = left ear; AGA = adequate for gestational age; SGA = small for gestational age

each BAEP parameter considering both ears together, while comparing Study (SGA) and Control (AGA) groups.

No differences were found between groups SGA and AGA regarding the absolute latencies of waves I, III and V. There were also no differences between groups in the comparative analysis of interpeaks I-II, III-V and I-V (Table 5).

Table 5. Comparison of the absolute latencies of waves I, III, V and interpeak intervals I-III, III-V, I-V in the BAEP between SGA and AGA groups

Waves/ Interpeaks		SGA (n=47)	AGA (n=39)	p-value
I	Mean	1.81	1.80	0.620
	SD	0.17	0.16	
III	Mean	4.64	4.62	0.699
	SD	0.273	0.268	
V	Mean	6.99	6.95	0.380
	SD	0.384	0.319	
I-III	Mean	2.81	2.87	0.459
	SD	0.244	0.663	
III-V	Mean	2.34	2.34	0.600
	SD	0.306	0.264	
I-V	Mean	5.15	5.08	0.267
	SD	0.389	0.463	

Independent t test (p≤0.05)

Note: SD = standard deviation; AGA = adequate for gestational age; SGA = small for gestational age

We also analyzed the influence of risk indicators for hearing alterations, described by the Joint Committee on Infant Hearing (JCIH)[12] and added by those of Azevedo[16]. From the 47 SGA NB, 29 had normal BAEP results (62%), and 18 presented central alterations (38%). From these 18 NB, 16 had the fact of being born SGA as the only risk factor. From the 39 AGA NB, 32 presented normal BAEP results (82%), and seven (18%) presented alterations that suggested central alterations (from these, five did not present any risk indicator for hearing alterations). There was no difference between SGA and AGA groups regarding central alterations with and without associated risks.

The characterization of risk indicators in both studied population (SGA and AGA) regarding normal and altered BAEP results is described in Chart 1.

Chart 1. Influence of risk indicators regarding BAEP responses in SGA and AGA groups

Indicators	SGA		AGA	
	Normal	Altered	Normal	Altered
No risk	26	16	24	5
Familiar history	0	0	4	1
Ototoxic	1	0	0	0
Toxoplasmosis	0	0	2	0
HIV +	2	0	2	0
Rubella	0	0	0	0
ICU > 5 days	0	1	0	0
Hyperbilirubinemia	0	0	0	1

Note: HIV= human immunodeficiency virus; HIV + = positive serology for acquired immunodeficiency syndrome; ICU = intensive care unit; AGA = adequate for gestational age; SGA = small for gestational age

DISCUSSION

There is consensus in international literature that SGA NB might present alterations in neuropsychomotor development, since they are an example of early malnutrition[3-6,17]. Another important aspect to be considered, according to literature, is the moment at which the child suffered restriction and for how long. In the present study, no significant differences were found between symmetric (restrictions in early pregnancy) and asymmetric (restrictions in late pregnancy) SGA NB regarding the BAEP results obtained.

A study that involved 47 normal full-term NB with adequate-for-gestational-age weight, who were submitted to BAEP assessment (alternate polarity stimulus and presentation speed of 10/s) at two days of life, considered the data obtained (mean absolute latencies of waves I, III and V, and mean interpeaks I-III, III-V and I-V) as the normality standard for this population[18]. Another recent study had the aim to establish

Chart 2. Characterization of absolute latencies of waves I, III, V and interpeak intervals I-III, III-V, I-V in the BAEP, in studies with full-term newborns

Study	BAEP parameters	n	I Mean (SD)	III Mean (SD)	V Mean (SD)	I-III Mean (SD)	III-V Mean (SD)	I-V Mean (SD)
Guilhoto et al.[18]	alternate click rate=10/s i: 80 dBNA f: 100 Hz – 3 kHz	47	1.79 (0.20)	4.54 (0.31)	6.75 (0.38)	2.75 (0.36)	2.22 (0.22)	4.97 (0.43)
Mahajan et al.[26]	click – polarity not mentioned rate – not mentioned i: 70 dBnNA f: 150 Hz – 3 kHz	SGA=25	1.92 (0.40)	4.26 (0.73)	6.44 (0.68)	2.37 (0.43)	2.20 (0.32)	4.55 (0.48)
		AGA=25	1.82 (0.20)	4.04 (0.55)	6.09 (0.56)	2.27 (0.41)	2.02 (0.39)	4.30 (0.47)
Amorim et al.[19]	rarefaction click rate=21,1/s i: 80 dBnNA f: 30 Hz – 3 kHz	46	1.67 (0.28)	4.49 (0.47)	6.77 (0.54)	2.80 (0.49)	2.25 (0.50)	5.05 (0.75)
Present study	rarefaction click rate=27,7/s i: 80 dBnNA f: 100 Hz – 1,5 kHz	SGA=47	1.81 (0.17)	4.64 (0.27)	6.99 (0.38)	2.81 (0.24)	2.34 (0.30)	5.15 (0.39)
		AGA=39	1.80 (0.16)	4.62 (0.26)	6.95 (0.32)	2.87 (0.66)	2.31 (0.26)	5.08 (0.46)

Note: rate = click acquisition speed; i = initial intensity; f = high-pass and low-pass filters; SD = standard deviation; AGA = adequate for gestacional age; SGA = small for gestacional age

normal values of absolute latencies of waves I, III and V, and interpeaks I-III, III-V and I-V on the BAEP assessment (rarefaction polarity stimulus and presentation speed of 21.1/s) of 86 full-term infants divided into several groups, according to their gestational age. In the NB group (0 to 29 days of life), the means obtained were slightly lower than in the present study[19].

In this study, slightly higher absolute latencies were evidenced for all the BAEP parameters analyzed, when compared to the studies mentioned above. In fact, this difference might be attributed to the different parameters used in obtaining the BAEP, agreeing with previous studies[18,20,21] that concluded that increasing the presentation speed of acoustic stimuli causes slight increase in absolute latencies and interpeak intervals.

The comparative results of mean absolute latencies of waves I, III, V, and mean interpeaks I-III, III-V and I-V between the present study and those previously mentioned are described in Chart 2.

There was also no difference between ears regarding BAEP measures, which suggests that auditory pathways maturation occurs simultaneously in both ears, corroborating other data from literature[18,19,22,23]. This fact also disagrees with studies that have investigated possible asymmetry mechanisms in newborns using the BAEP, with better results in the right ear[24,25].

A research conducted in India compared the BAEP responses of 25 FTNB SGA from undernourished mothers and 25 FTNB AGA from healthy mothers, paired by gender and gestational age. The study did not find significant differences between groups. According to the authors, the absolute latencies of wave V and interpeaks I-V were in the upper normal limit in the study group, when compared to the control group, and it was concluded that maternal malnutrition might have a small negative influence in the brainstem intrauterine development[26]. This research corroborates the findings of the present study.

We did not find literature data regarding the influence of risk indicators in the comparison between AGA and SGA FTNB. However, our findings indicate that, regardless the presence of these indicators, BAEP alterations suggestive of central impairment are more frequent (although without significant difference) in SGA FTNB, reinforcing literature data about the fact that these children are prone to greater risks for neurodevelopmental alterations, when compared to AGA FTNB[2,27,28].

Literature agrees that SGA children might suffer several impairments in neuropsychomotor development, which are carried on into adulthood[3-6,27-29]. The SGA NB are a very heterogeneous group, since they may have been affected at different moments of intrauterine life, with several possible causes. Their hearing behavior is also diversified, and, therefore, it is important to monitor their development until the end of the language acquisition and development process, since hearing and language are correlated interdependent functions[29]. Hence, when hearing impairments are evidenced through BAEP, it is indispensible to guide these children's parents and teachers regarding hearing stimulation, in order to solve or avoid future difficulties.

It is also worth emphasizing that the central impairments found might be transitory, resulting from immaturity of the auditory system, as concluded in a research[30] that corroborates this study. Thus, these children should be later reassessed in order to confirm the results.

CONCLUSION

Children born full-term adequate or small for gestational age might present central hearing impairments, transitory or permanent, regardless the presence or absence of risk indicators.

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