

Effects of weight and gestational age on infants' auditory pathway

O efeito do peso e da idade gestacional na via auditiva de lactentes

El efecto del peso y la edad gestacional en la vía auditiva de los lactentes

Georgea Espindola Ribeiro* 

João César Lyra* 

Daniela Polo Camargo da Silva** 

Abstract

Introduction: Infants born with low birth weight in relation to their gestational age are more prone to neonatal and infant morbidity and mortality. Brainstem Auditory Evoked Potential (BAEP) is a useful tool to investigate the neuroelectric activity of the brainstem auditory pathway. **Objective:** To investigate the effects of birth weight and gestational age on infants' auditory pathway. **Methods:** cross-sectional study, conducted in a public hospital from January 2017 to December 2018 comprising small-for-gestational-age (SGA) infants in the study group and appropriate-for-gestational-age (AGA) infants in the control group. Both groups matched for gestational age, risk indicators for hearing loss, and age at audiological evaluation. All of them were submitted to transient otoacoustic emissions and BAEP examinations. **Results:** 172 infants participated, with an average age of 1.3 months for those born SGA and 1.5 months for AGA. In the evaluation using the BAEP, there was a significant increase only in the absolute latency values. However, the median values of both absolute and interpeak latencies were similar between them. **Conclusion:** The effects of birth weight and gestational age on infants born weighing less than the 10th percentile, did not demonstrate impairment of the auditory pathway in the first month of life.

Keywords: Infant; Newborn; Hearing; Electrophysiology; Birth weight; Hearing disorders.

* Universidade Estadual Paulista Júlio de Mesquita Filho. Faculdade de Medicina de Botucatu, Botucatu, SP, Brazil.

** Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina, Brazil.

Research conducted at the Hearing and Communication Disorder Rehabilitation Center (CERDAC), Clinics Hospital at the Botucatu Medical School – UNESP – Botucatu, São Paulo, Brazil.

Authors' contributions:

GER: study conceptualization, methodology, data collection, manuscript draft, and critical revision.

JCL: manuscript draft and critical revision.

DPCS: data collection, critical revision, and supervision.

Correspondence email address: Daniela Polo Camargo da Silva - daniela-polo@uol.com.br

Received: 09/08/2020

Accepted: 09/04/2021

Resumo

Introdução: Lactentes nascidos com baixo peso ao nascer em relação a sua idade gestacional são mais propensos à morbimortalidade neonatal e infantil. O Potencial Evocado Auditivo de Tronco Encefálico (PEATE) é uma ferramenta útil para averiguar a atividade neuroelétrica da via auditiva do tronco encefálico. **Objetivo:** Investigar o efeito do peso e da idade gestacional na via auditiva do tronco encefálico em lactentes. **Métodos:** Estudo transversal, realizado em um hospital público, no período de janeiro de 2017 a dezembro de 2018, composto por lactentes nascidos pequenos para idade gestacional (PIG), como grupo estudo e lactentes adequados para idade gestacional (AIG), como grupo comparação. Ambos foram semelhantes com relação à idade gestacional, indicadores de risco para deficiência auditiva e idade no momento da avaliação audiológica. Todos foram submetidos aos exames de emissões otoacústicas evocadas por estímulo transiente e PEATE. **Resultados:** Participaram 172 lactentes com idade média de 1,3 meses para os nascidos PIG e de 1,5 meses para os AIG. Na avaliação por meio do PEATE, houve aumento significativo apenas para os valores das latências absolutas, entretanto, os valores das medianas tanto das latências absolutas como das latências interpicos foram semelhantes entre os grupos. **Conclusão:** O efeito do peso ao nascimento e da idade gestacional, em lactentes nascidos com peso inferior ao percentil 10, não demonstrou comprometimento da via auditiva no primeiro mês de vida.

Palavras-chave: Recém-nascido; Audição; Eletrofisiologia; Peso ao nascer; Transtornos da audição.

Resumen

Introducción: Niños nacidos con bajo peso al nacer en relación con su edad gestacional son más propensos a la morbilidad y mortalidad neonatal e infantil. El Potencial Evocado Auditivo del Tronco Cerebral (PEATC) es una herramienta útil para investigar la actividad neuroeléctrica de la vía auditiva del tronco encefálico. **Objetivo:** Investigar el efecto del peso y la edad gestacional sobre la vía auditiva del tronco encefálico en los lactantes. **Métodos:** Estudio transversal, realizado en un hospital público, de enero de 2017 a diciembre de 2018, compuesto por lactantes nacidos pequeños para la edad gestacional (PEG), el grupo de estudio y lactantes aptos para la edad gestacional (AEG), como grupo de comparación. Ambos fueron similares con respecto a la edad gestacional, los indicadores de riesgo de hipoacusia y la edad en el momento de la evaluación audiológica. Todos fueron sometidos a pruebas de otoemisiones acústicas y PEATC. **Resultados:** Participaron 172 lactantes, con una edad promedio de 1,3 meses para los nacidos PEG y 1,5 meses para los AEG. En la evaluación con el BAEP, se observó un aumento significativo solo para los valores de las latencias absolutas sin embargo, los valores medianos de latencias absolutas e latencias entre picos fueron similares entre ellos. **Conclusión:** El efecto del peso e del edad gestacional en los lactantes con un peso inferior al percentil 10 no demostró deterioro de la vía auditiva en el primer mes de vida.

Palabras clave: Recién nacido; Audición; Electrofisiología; Peso al nacer; Transtornos de la audición.

Introduction

Birth weight is a cause of concern for health professionals because low-birth-weight infants are more prone to neonatal and child morbimortality, besides the higher risk of growth failure^{1,2}.

Being born small for gestational age (SGA) is usually associated with prematurity, restricted intrauterine growth, or a combination of both. As a consequence, they can damage the child's neuropsychomotor development and affect their auditory and language skills³⁻⁵.

Restricted intrauterine growth refers to children who have not reached their genetic intrauterine growth potential, which suggests a pathological process during fetal life. Recent studies show the tendency to use SGA as a term to refer to fetuses or newborns who failed to reach the established weight or anthropometric standard for a given gestational age^{5,6}.

Regarding anthropometry, the fetal growth curve is based on data such as sex, birth weight, and gestational age. Hence, infants whose birth weight is compatible with their sex and gestational age are classified between the 10th and 90th percen-

tiles, called appropriate for gestational age (AGA). When their birth weight is higher than expected, they are classified above the 90th percentile (90% of the general population have a lower weight), called large for gestational age (LGA). And, when the birth weight is lower than expected, they are classified below the 10th percentile (only 10% of the general population weighs less than the expected for sex and gestational age), called SGA⁷.

SGA birth may result from a series of gestational situations, such as congenital anomalies, infections, or inadequate use of drugs and substances. However, its main cause is placental insufficiency, in which a series of long-term unfavorable outcomes is expected^{5,8}.

In the last years, there has been an increasing interest in and concern with the prognosis of SGA newborns, motivated by the consequences on their overall development – which also affects the function of the central nervous system^{9,10}. At the cellular level, these newborns may suffer a loss of neurons and changes in myelination and maturation of the oligodendrocytes, with axonal damage and disorganization of the white matter⁸. Thus, these infants may have countless comorbidities, justifying the need for studies aimed at the effect this condition also has on hearing¹¹⁻¹³.

The brainstem auditory evoked potential (BAEP) is a useful tool to research the integrity of the neuroelectric activity in infants' auditory pathway, from the vestibulocochlear nerve to the brainstem, including the estimate of the sound detection threshold¹⁴⁻¹⁶.

Also, the literature shows that BAEP is influenced by auditory maturation, whose characteristics differ from preterm to full-term infants due to the myelination of the fibers of the auditory pathway, which take place in the caudal-rostral direction^{14,15}.

Research on this issue points out that SGA infants may have lower absolute and interpeak latency values in BAEP than AGA infants. This is explained by the smaller head circumference and shorter extension of the neural pathway^{17,18}.

However, other studies revealed higher BAEP latencies in SGA infants, which led to the supposition that there is an impairment in the maturational process of the auditory pathway in this population^{11,18}. Other investigations with a similar sample did not observe significant differences, revealing

the absence of abnormalities in the central auditory pathway at the beginning of the neonatal period^{13,18}.

Given these controversies, the main objective of this study was to investigate the effect of weight and gestational age on infants' brainstem auditory pathway.

Methods

This study was approved by the institution's Research Ethics Committee (process no. 402/08). The parents or guardians who agreed to participate in the research signed the informed consent form.

This is a cross-sectional study, conducted at a public hospital between January 2017 and December 2018.

Subjects

The sample comprised SGA infants (who formed the study group) and AGA infants (who formed the comparison group). The classification of birth weight in relation to gestational age was based on the growth curve proposed by Fenton and Kim (2013)¹⁹.

Both groups were matched for neonatal characteristics, such as gestational age, risk indicators for hearing loss according to the Joint Committee on Infant Hearing (JCIH)²⁰, and age at audiological assessment. The only difference, then, was their weight – that is, having or not appropriate birth weight for gestational age.

Thus, the sample was divided as follows:

- SGA infants: birth weight below the 10th percentile¹⁹.
- AGA infants: birth weight between the 10th and 90th percentile¹⁹.

The sample included infants born at the study site, which presented responses in the transient evoked otoacoustic emissions in both ears and underwent all the auditory tests in a single session. Infants with changes in the outer and/or middle ear detected by an otorhinolaryngologist, a history of congenital infections, hypoxia-ischemia, bacterial meningitis, peri-intraventricular hemorrhage, genetic syndromes, craniofacial malformation, and hyperbilirubinemia with exchange transfusion were excluded.

Technical specifications of the transient evoked otoacoustic emissions

The examination registered the responses in both ears, elicited while the infant was naturally sleeping in a quiet room. The equipment used in all the assessments was the OtoRead/Interacoustics. The examination was performed by introducing a probe with an attached microphone into the external acoustic meatus. The analysis criteria were based on the PASS/FAIL parameter, described in the protocol of the equipment, with click-stimulus at 83 dB SPL, assessing six frequency bands (between 1.5 kHz and 4 kHz). The PASS values were as follows: present emissions, with 6 or higher dB response amplitude in at least three consecutive frequency bands, including 4 kHz²¹.

Technical specifications of the click-BAEP

The equipment used in the examination was the EP15 – Eclipse, Interacoustics®/Denmark. It was conducted in a quiet room while the infant was comfortably and naturally sleeping on the parent's/guardian's lap. After cleaning the skin with abrasive substance (Nuprep®), the active and ground surface electrodes manufactured by Neuroline® were positioned on the forehead (Fz, Fpz), while the reference ones were positioned in the mastoid regions (M1 and M2). The stimulus was monaurally presented via insert earphone ER 3A with filtered clicks (high-pass filter at 100 Hz and low-pass at 3000 Hz), lasting 100 µs, rarefaction polarity and intensity of 80 dBnHL. Altogether, 2,048 clicks were given, with 20 ms analysis time, repeated to confirm wave reproducibility. The impedance of

the electrodes was kept always below 3 kOhms. The stimuli were presented at the rate of 27.7 clicks per second.

The main parameters assessed were the absolute latency values of waves I, III, and V, and latency values of interpeak intervals I-III, III-V, and I-V, in both ears.

Statistics

Both sample groups had risk indicators for hearing loss associated with the condition being studied. Therefore, the influence of these indicators on the outcome was investigated with the Mann-Whitney test, and the possibility of the age at examination and sex having influenced the outcome was investigated with the chi-square test.

After preliminary analysis of the confounding effects, the absolute and interpeak latencies in click-BAEP of both groups were compared with multiple linear regression to fit the latencies in relation to birth weight (AGA and SGA). The associations were considered statistically significant when $p < 0.05$. The SPSS v21.0 was used to apply the statistical methods.

Results

Of the 182 infants recruited for the study, 10 were excluded due to the absence of responses in the transient evoked otoacoustic emissions in either ear or some risk indicator present in only one of the groups. Hence, 172 met the inclusion criteria. The SGA subjects' mean age was 1.3 months, and the AGA infants', 1.5 months. The other characteristics of the sample are shown in Table 1.

Table 1. Sample characterization

Groups/Variables	AGA (n=86)	SGA (n=86)
Females	35 (40.7%)	30 (34.9%)
Males	51 (59.3%)	56 (65.1%)
Gestational age (weeks)*	34 (27-41)	35 (27-42)
Birth weight (grams)*	2467(1030-3815)	1665 (680-3315)

* Gestational age and birth weight median (minimum and maximum) values.

A total of 121 infants recruited to the study had risk indicators for hearing loss according to JCIH²⁰ (Table 2). These indicators can interfere with the interpretation of the BAEP findings, as confound-

ing effects. Nevertheless, there was no significant difference between the SGA and AGA infants in the sample regarding the total risk indicators ($p = 0.128$, Mann-Whitney test).

Table 2. Risk indicators for hearing loss

Variable	n	%
ICU stay*	66	54.5
Birth weight < 1500g	29	23.9
Low Apgar*	34	28.0
Ototoxic drug usage	13	10.7
Use of mechanical ventilation	33	27.2
Hearing loss in the family	7	5.7

* ICU = Intensive Care Unit

* Low Apgar = One-minute Apgar lower than 4 and five-minute Apgar lower than 6.

Likewise, the age at examination and sex were not identified as confounding effects ($p = 0.082$ and $p = 1.00$, respectively, chi-square test).

Comparing the groups in terms of the BAEP parameters, the absolute latencies of waves I, III, and V were higher in the SGA group, with a statisti-

cally significant difference only for waves I and III in the left ear. The latencies of interpeak intervals I-III and I-V in both ears were also higher in the SGA group, although with no statistical significance (Table 3).

Table 3. Comparison of BAEP absolute and interpeak latencies between the SGA and AGA groups.

Outcome	AGA			SGA			p	
	Md	Min	Max	Md	Min	Max		
Right ear	I	1.43	1.27	1.78	1.46	1.30	1.99	0.218
	III	4.07	3.80	4.0	4.20	3.70	4.93	0.065
	V	6.33	5.77	7.69	6.40	2.76	7.69	0.818
	I-III	2.67	2.20	3.28	2.71	2.33	3.38	0.089
	III-V	2.26	1.87	3.10	2.24	1.70	3.02	0.123
	I-V	4.90	4.03	6.23	4.96	4.43	5.91	0.891
Left ear	I	1.43	1.27	1.88	1.50	1.30	1.91	0.045*
	III	4.07	3.67	4.85	4.20	3.80	4.93	0.026*
	V	6.39	4.73	7.84	6.49	5.83	7.84	0.310
	I-III	2.63	2.07	3.20	2.73	2.30	3.31	0.134
	III-V	2.23	1.93	3.20	2.23	1.73	3.04	0.283
	I-V	4.92	4.27	6.33	5.02	4.40	5.96	0.895

Md = median, Min = minimum, max = maximum (in milliseconds).

AGA = Appropriate for gestational age

SGA = Small for gestational age.

Despite this statistically significant difference in the SGA infants, the median values of both the

absolute and interpeak latencies were similar in the two groups (Table 3).

Discussion

The main interest of this study was to verify whether the relationship between birth weight and gestational age interferes with the neural conduction of sounds at the brainstem level. Verifying the functioning of this pathway at an early age is essential to develop more complex auditory skills and adequate oral language. Hence, electrophysiological techniques, such as BAEP, make it possible to verify the consequences of intrauterine malnutrition to hearing by analyzing the onset and amplitude of time of response after the acoustic stimulation²².

Moreover, the central structures are more vulnerable to nutritional insults and suffer adverse effects during the critical period of brain growth and maturation. Therefore, these infants may suffer loss in their synaptic connection formation and/or efficiency, regardless of other factors that make up their clinical history, even only a few months after birth^{13, 17}.

Detecting possible audiological, cochlear, and/or retrocochlear changes in the first month of life allows better therapy management and family guidance. Therefore, it is also necessary to know whether the SGA infants' brainstem auditory pathway has been impaired, based on the classification that relates birth weight to gestational age, in agreement with the standards established by the World Health Organization²³.

Given the above, the auditory function at the brainstem level was examined with BAEP in SGA and AGA infants. There was a delay in the response onset time for waves I, III, and V and interpeak intervals I-III and I-V in both ears of the SGA group. The difference was statistically significant only for waves I and III in the left ear of this group. However, the analysis of the medians showed a similar response behavior between the groups. Also, despite the differences described, they had no clinical significance to the population and age group studied (Table 3).

The statistical difference found in wave I, which was 1.50 ms for the SGA group, is close to the expected in the literature for normally hearing adults²⁴. Despite the statistical difference in wave III latency in the left ear, there was dispersion between the groups – i.e., there was a quite small variability between them, and the results with statistical significance occurred at random.

Therefore, the significantly higher absolute latencies in waves I and III found in the SGA infants' left ears reveal a purely physiological finding.

Furthermore, both groups showed the integrity of the auditory structure at the peripheral level. The cochlear outer hair cells were functioning properly, which was proved by the responses in the transient evoked otoacoustic emissions in both ears. The difference was observed in BAEP, excluding the consequences of possible cochlear changes.

The human brainstem auditory pathway is myelinated between the 26th and 29th fetal weeks from the proximal end of the cochlear nerve to the inferior colliculus^{17,22,25}. The beginning of the myelination process coincides with the beginning of the acoustic motor reflexes and the brainstem evoked responses, which depend on fast and synchronous conduction of auditory impulses in the vestibulocochlear nerve and brainstem^{17,22,25}. Also, the greater myelin density is a key factor in the constant decrease in BAEP responses. Hence, complications during pregnancy, such as nutritional restriction, may interfere with these processes, though discretely²⁵ – as evidenced in this study, with slight differences in the SGA group.

As in this research, Angrisani et al. (2013)¹⁸, who conducted a comparative analysis of BAEP responses in the study (SGA) and control (AGA) groups, did not find statistical significances between the groups. Hence, they concluded that there are no differences in the BAEP responses between small premature infants and those appropriate for gestational age – i.e., being small did not prove to be a condition of risk of retrocochlear change.

Differences in the development of SGA and AGA infants' brainstem auditory pathway can be also verified with a cohort design. Hence, Angrisani et al. (2014)²⁶ assessed longitudinally the auditory maturation of 23 SGA infants and found their BAEP responses were symmetric with those of AGA infants. They further highlighted that only prematurity influenced the results, without a relationship between birth weight and gestational age.

A study conducted by Jiang and Li (2015)²⁷ compared the BAEP latency values in a population of SGA and AGA infants and observed slightly higher latency values in the SGA group, especially for waves III and V and interpeak interval I-V. However, the click-stimulus was presented at a faster rate than in this research. The authors suggested an auditory impairment at the brainstem

level in this population due to myelination impairment and synaptic dysfunction.

Divergences can still be found in the citations regarding the BAEP findings in SGA infants. These can be explained by the different inclusion criteria, parameters, equipment, and SGA classification each one used.

The first year of life is when the brainstem neurons mature, the neural connections are established, and the brainstem and thalamus are beginning to connect with the auditory cortex. Therefore, any impact on the auditory system entry point, particularly during the first months of life, can drastically impair the morphofunctional properties of the neurons in the central auditory system, causing irreparable damage to the auditory processing at the central level and to language development²⁸.

Lastly, the results of this study suggest a discrete response delay in SGA infants' brainstem auditory pathway. Such a result may be due to the sample size of the groups assessed. Longitudinal studies with more participants in the same condition will help demonstrate the actual impact of birth weight associated with gestational age on the central auditory structures.

Conclusion

The birth weight and gestational age of infants whose birth weight was lower than the 10th percentile did not reveal an impairing effect on the auditory pathway in the first month of life.

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