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Original Article
Artigo Original

Cortical auditory evoked potentials in full-term and preterm neonates

Potenciais evocados auditivos corticais em neonatos nascidos a termo e pré-termo

Ândrea de Melo[1,2]
Eliara Pinto Vieira Biaggio[2]
Inaê Costa Rechia[2]
Pricila Sleifer[1]

Keywords

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ABSTRACT

Purpose: To measure the exogenous components of the cortical auditory evoked potential (CAEP) in term and preterm newborns and compare them considering the variables latency and amplitude. **Methods:** This is a cross-sectional, prospective, comparative, contemporary study. One hundred twenty-seven newborns were evaluated; 96 of these were included in the study after analysis of the exams by three referees. Participants were divided into two groups: Term Group: 66 infants and Preterm Group: 30 neonates. The recordings of CAEP were performed using surface electrodes with newborns comfortably positioned in the lap of their mothers and/or guardians in natural sleep. To this end, binaural verbal stimuli were presented with /ba/ as the frequent stimulation and /ga/ the rare stimulus, at an intensity of 70 dB HL, through insert earphones. The presence or absence of exogenous components and the latency and amplitude of P1 and N1 were analyzed in both groups. Pertinent tests were used in the statistical analysis of data. **Results:** The latency of the waves P1 and N1 was smaller in participants in the Term Group. However, there were no statistically significant differences in the amplitude of P1 and N1 between the groups. No difference between the groups was found when comparing the presence and absence of the components P2 and N2. **Conclusion:** It is possible to measure the CAEP in term and preterm neonates. There was influence of the maturational process only on the measure of latency of the components P1, binaurally, and N1, in the left ear, which were smaller in participants in the Term Group.

Descritores

Potenciais Evocados
Potenciais Evocados Auditivos
Recém-nascido
Eletrofisiologia
Prematuridade

RESUMO

Objetivo: Mensurar os potenciais exógenos do potencial evocado auditivo cortical (PEAC) em neonatos nascidos a termo e pré-termo, além de compará-los considerando as variáveis latência e amplitude dos componentes. **Método:** Estudo transversal, prospectivo, contemporâneo e comparativo. Foram avaliados 127 neonatos; destes, foram considerados 96, após análise dos exames por três juízes, distribuídos em dois grupos: Grupo Termo: 66 neonatos e Grupo Pré-termo: 30 neonatos. Os registros do PEAC foram feitos com os neonatos posicionados no colo da mãe e/ou responsável, em sono natural, por meio de eletrodos de superfície. Foram apresentados estímulos verbais binauralmente, sendo /ba/ o estímulo frequente e /ga/ o estímulo raro, na intensidade de 70 dBNA, por meio de fones de inserção. Foi analisada a presença ou ausência dos componentes exógenos em ambos os grupos, bem como, latência e amplitude de P1 e N1. Para análise dos dados, utilizaram-se os testes pertinentes. **Resultados:** A latência da onda P1 bilateralmente e N1 na orelha esquerda foi menor no Grupo Termo. No entanto, não houve diferença estatisticamente significante quanto à amplitude de P1 e N1 entre os grupos. Na comparação entre presença e ausência dos componentes P2 e N2, também não foi observada diferença entre os grupos. **Conclusão:** É possível mensurar os PEAC, em neonatos nascidos a termo e pré-termo. Verificou-se influência do processo maturacional apenas na medida da latência dos componentes P1 bilateralmente e N1 na orelha esquerda, sendo estas menores no Grupo Termo.

Correspondence address:
Ândrea de Melo
Universidade Federal do Rio Grande do Sul – UFRGS
Rua Cassilda Genro, 1540, Bairro Maria Alice Gomes, Santiago (RS), Brazil, CEP: 97700-000.
E-mail: andrea.de.melo@hotmail.com

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Study carried out at Universidade Federal de Santa Maria – UFSM - Santa Maria (RS), Brazil.
[1] Universidade Federal do Rio Grande do Sul – UFRGS - Porto Alegre (RS), Brazil.
[2] Universidade Federal de Santa Maria – UFSM - Santa Maria (RS), Brazil.
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INTRODUCTION

Objective electrophysiologic testing allows measurement or observation of the function of peripheral and central auditory pathways. These tests are of paramount importance for complementary assessment, aiming at an accurate diagnosis and/or understanding of the auditory status, especially when conducted with populations that present difficulties to respond satisfactorily to behavioral evaluations, such as neonates, infants, and young children.

Electrophysiologic and electroacoustic methods of assessment are used as routine tests in newborn hearing screening (NHS) by means of transient evoked otoacoustic emissions (TEOAE) and/or brainstem auditory evoked potentials - automated (BAEP-A)[1,2]. Nevertheless, there are other electrophysiologic procedures that can be included in the audiology process to enhance the diagnostics, e.g., brainstem auditory evoked potential (BAEP) and auditory steady state response (ASSR), which can measure the auditory electrophysiologic hearing thresholds, as well as visualize the audiometric configuration.

With technological and scientific development, other tests such as long latency auditory evoked potential (LLAEP) and cortical auditory evoked potential (CAEP) are currently in use, allowing a variety of clinical applications[3]. An example of the possibilities of these procedures is the monitoring of auditory maturation in neonates, considering that these assessments allow us to observe auditory pathway responses until the cerebral cortex, through the auditory stimulus. In addition, if this maturation is observed longitudinally, it will allow us to infer on how the auditory system is organized with respect to sound reception at cortical level over time. It is worth mentioning that LLAEP measures bioelectric responses of the cortical and thalamic activities at a time interval ranging from 80 to 600 ms[3,4].

In adults and older children with normal hearing, it is possible to observe the presence of all components, both positive (P1, P2 and P3) and negative (N1 and N2). Components P1, N1, P2 and N2 are characterized as exogenous potentials, which are influenced by the physical characteristics present in the acoustic stimulus, such as intensity, frequency, and duration; whereas component P3 is an endogenous potential, which is predominantly related to cognitive skills such as attention to the acoustic stimulus[5]. This endogenous potential, P3, appears when the individual consciously realizes a change in the sound stimulus presented[5]. Moreover, the wave N2 presents greater negativity in children under five years old, becoming stable only after this age. Exogenous potentials are known as cortical auditory evoked potentials, whereas the endogenous potential is known as the cognitive potential[6].

From birth, responses in the CAEP, whether by stimulation of pure tones and/or by complex stimuli (syllables), show the organization of cortical generators and the development of the central auditory system[7]. In neonates/infants, it is possible to notice only the presence of the components P1, N1, P2, and N2, whose observation do not depend on individual attention to the acoustic stimulus presented during the assessment; they are thus a representation of the cortical ability to detect them[3,8]. Maturation depends on the myelination of the nerve fibers that will send impulses to the corresponding cortical centers. Because of this, infants' responses are reflex until approximately the age of three months; they become inhibited as maturation of the Central Nervous System progresses, when the cortex begins to command children's responses[9].

Therefore, normal functioning of the central auditory structures is of great importance to the acquisition of perceptual skills by individuals[10], considering that the integrity of such structures enables the proper development of oral language, as well as its acquisition[11].

Studies have reported differences between the responses of term and preterm newborns in the BAEP, showing that the responses generated between the peripheral and central auditory pathways are influenced by the maturation process and gestational age, allowing visibility of the maturational effect on preterm neonates due to the difference in latency between responses when compared to those of neonates born at term[9,12-14].

However, few studies the literature consulted[8,15] have addressed the applicability of CAEP in neonates, which indicates the need for research aiming to describe electrophysiologic findings, especially cortical evoked potentials, in this population. In addition, to investigate the use of measuring the exogenous components of LLAEP in monitoring the auditory maturation, and to study parameters related to latency and amplitude, such as normative values, in the analysis and morphology of waves in neonates, it is important to provide early intervention and minimize the negative effects of any disturbance in the central auditory pathway.

In this context, the objective of the present study is to measure the exogenous components of the cortical auditory evoked potential (CAEP) in term and preterm newborns and compare them considering the variables ear, latency, and amplitude.

METHODS

This is a cross-sectional, prospective, comparative, contemporary study which aims to clinically observe and analyze the electrophysiologic results obtained at the cortical auditory evoked potential (CAEP). This research was part of an existing project from the Federal University of Santa Maria - UFSM approved by the Research Ethics Committee of the aforementioned institution under no. 14804714.2.0000.5346. It is worth mentioning that Resolution no. 466/12, which deals with research involving human beings, was fully respected. In this context, only neonates whose parents and/or guardians signed the Informed Consent Form (ICF) participated in the study. The ICF stated the objective, methodology, risks and discomforts of the proposed study, and established a nondisclosure agreement.

The following exclusion criteria were observed: neonates with clear neurological impairment; neonates with failing results at the newborn hearing screening (NHS), with absence of brainstem auditory evoked potential (BAEP) or auditory steady state response (ASSR) in the first screening; newborns with presence of apparent organic alterations; neonates under drug treatment; and infants older than one month (considering the corrected age in the Preterm Group).

Participants in the initial sample were 127 (86 term and 41 preterm) neonates treated at the NHS program of the university hospital. Initially, aiming to verify the eligibility criteria, anamnesis addressing the following information was conducted: mother's name; newborn's name, birth date, weight, Apgar score, pregnancy time (in weeks), presence of risk indicators for hearing loss (RIHL)[1], and clinical history.

After being submitted to the NHS, participants underwent electrophysiologic assessment using CAEP, that is, measurement of the exogenous components of cortical potentials. CAEP was performed in a two-channel, SmartEP module, Intelligent Hearing Systems (IHS). Parents were expressively oriented with regard to the fact that neonates should be well fed and in natural sleep in their mother/guardian's lap, because any movement during the vigil state could interfere in the assessment responses, such as the waves of the components.

Assessment was conducted using insertion phones and electrodes placed on the skin (after cleaning with abrasive paste) with conductive electrolytic paste and adhesive plaster. The active (Fz) and ground (Fpz) electrodes were positioned on the forehead and the reference electrodes were placed on the left (M1) and right (M2) mastoids. The individual impedance value of the electrodes was ≤ 3 (kΩ). Speech stimulation using frequent /ba/ and rare /ga/ was presented binaurally at the intensity of 70dBNA. A minimum of 150 stimuli were presented: approximately 80% (120 stimuli) of frequent stimulation and 20% (30 stimuli) of rare stimulation (Oddball paradigm). Alternate polarity was used with 1 – 30 Hz band-pass filter and 1020 ms window. After that, the computer emitted a wave with the morphology of the potential generated at 300 ms (P300), after each rare stimulus, which was not considered for not being evaluated in neonates owing to dependence on individuals' attention. The wave was then identified with the measurement of latency and amplitude of the components P1, N1, P2 and N2 were printed for further analysis.

Eventually, the tests were analyzed by three speech-therapy referees with expertise on CAEP. Thirty-one neonates were excluded from the survey owing to the high frequency of artifacts, which invalidated the trustworthiness of the results obtained; therefore, the final sample was composed of 96 neonates. Artifact level was established at 10%.

In this context, the sample was as follows: 96 newborns divided into two groups: Term Group: 66 neonates (34 females and 32 males) and Preterm Group: 30 neonates (11 females and 19 males). With respect to mean gestational age, participants in the Term Group were born at 39 weeks (37 to 41 weeks and three days), whereas individuals in the Preterm Group were born at 34 weeks and four days (26 weeks and two days to 36 weeks and five days). Subsequently, data were organized on Microsoft Excel worksheets and analyzed using Statistical Analysis System (SAS) for Windows, 9.2. Categorical variables were expressed in relative frequency and quantitative data were presented by the mean and standard deviation. The Wilcoxon test was used for the samples related to comparison between the ears; the Mann-Whitney test was employed for comparison of variables between the groups; the Chi-square test was applied in the analysis of presence and absence of the waves between the groups. Significance level of 5% (p<0.05) was used for all statistical analyses.

RESULTS

Most of the newborns surveyed presented the components P1 and N1: only 4.5% (n=3) of term neonates and 13% (n=4) of preterm neonates did not present these components.

Analysis of the mean latency response values related to these components showed statistically significant difference in the comparison between groups for the components P1, binaurally, and N1, in the left ear. However, no statistically significant difference was found between the ears, as shown in Table 1.

No statistically significant difference was observed between the groups and between the ears (Table 2) with respect to the amplitude values of the components P1 and N1.

Analysis between the presence and absence of the components P2 and N2 showed no statistically significant difference between the groups (Table 3).

Table 1. Analysis of latency values for the P1 and N1 components/waves, in milliseconds, by ear, in the Term and Preterm Groups

LATENCY Mean ± SD [min – max]	Term Group (n=63)	Preterm Group (n=26)	p^a
	Mean ± SD [min – max]		
P1 WAVE (ms)			
RE	214.10 ± 44.22	247.93 ± 51.14	0.002*
LE	213.78 ± 45.73	251.23 ± 51.99	0.010*
p^b	0.715	0.427	
N1 WAVE (ms)			
RE	367.93 ± 67.11	395.39 ± 73.58	0.071
LE	371.26 ± 70.32	403.77 ± 86.04	0.044*
p^b	0.585	0.319	

[a] Mann-Whitney test for comparison of variables between the groups. 5% significance level (p<0.05); [b] Wilcoxon test for samples related to comparison between the ears; * Statistically significant value
Caption: RE = right ear; LE = left ear; SD = standard deviation; ms = milliseconds; n = number of individuals

Table 2. Analysis of amplitude values for the P1 and N1 components/waves, in milliseconds, by ear, in the Term and Preterm Groups

AMPLITUDE	Term Group (n=63) Mean ± SD [min – max]	Preterm Group (n=26) Mean ± SD [min – max]	p[a]
P1-N1 WAVES (ms)			
RE	7.02 ± 4.03	5.74 ± 2.12	0.174
LE	6.84 ± 3.90	5.80 ± 1.94	0.368
p[b]	0.408	0.892	
N1-P2 WAVES (ms)			
RE	7.02 ± 4.03	3.70 ± 2.00	0.759
LE	6.84 ± 3.90	3.76 ± 2.22	0.567
p[b]	0.408	0.516	

[a] Mann-Whitney test for comparison of variables between the groups. 5% significance level (p<0.05); [b] Wilcoxon test for samples related to comparison between the ears
Caption: RE = right ear; LE = left ear; SD = standard deviation; ms = milliseconds; n = number of individuals

Table 3. Analysis of presence or absence of the P2 and N2 components/waves in the Term and Preterm Groups

EAR	P2 WAVE		p[a]	N2 WAVE		p[a]
	Term Group (n=66)	Preterm Group (n=30)		Term Group (n=66)	Preterm Group (n=30)	
RE						
Presence	68.18% (n=45)	83.33% (n=25)	0.122	59.09%(n=39)	70.00% (n=21)	0.306
Absence	31.82% (n=21)	16.67% (n=05)		40.91%(n=27)	30.00% (n=09)	
LE						
Presence	68.18% (n=45)	80.00% (n=24)	0.233	56.06%(n=37)	60.00% (n=18)	0.718
Absence	31.82% (n=21)	20.00% (n=06)		43.94%(n=29)	40.00% (n=12)	

[a] Chi-square test at 5% significance level (p<0.05)
Caption: RE = right ear; LE = left ear; n = number of individuals

DISCUSSION

Absence of the components P1 and N1 was observed in 13% (n=4) of the neonates in the Preterm Group and in 4.5% (n=3) of those in the Term Group. Such a finding, referring to the absence of the wave P1, had already been reported in a previous study in which the authors cautioned that the absence of waves in the CAEP in preterm infants may be a predictor for cognitive changes[16] or immaturity of cortical structures in this population.

Latency values of the exogenous components are increased in this study (Table 1), corroborating the results found in previous studies which report that newborns present latency values higher than those expected in older children, considering that these values decrease rapidly and gradually in the first and second decades of life, respectively[17].

A recent study conducted with 15 newborns indicated that such increased latency values of the components P1 and N1 are justified by the immaturity of cortical structures in this population, regardless of gestational age[8]. As previously mentioned, the latency of the components of cortical potentials can be influenced by maturation[18]. This fact has been confirmed in the present research, which shows that there was a significant difference between the latency values of the components P1 and N1. Most likely, it is because of the difference in gestational age between the sample groups, demonstrating that the maturation process influences the cortical responses in newborns before 29 days of life, which is mainly observed in the latency values of these components (the first ones to be formed).

The development of synaptic efficiency during the first two years of a child's life shows an activity of slower waves. Waves/components with well-defined peaks are expected in adults with normal hearing; however, for the infant population, such morphology begins to emerge as of the age of four[19]. As referenced, this potential, combined with other measures, are important in the cognitive neuroscience in this population[20]. Recently, a study seeking to verify the association of the CAEP with language categories in children showed that the potentials enable the generation of a similar sequence of categorization processes in the child's brain through the rapid and continuous stimulation of this test[21].

Cortical potentials can also be used to show the effects of the use of individual hearing aids in children, especially for those with moderate to severe hearing loss[22]. The CAEP can also be used in neonates with cochlear implant (CI) to verify the maturation process. Researchers investigated the relationship between the findings on the wave P1 and vocalizations produced by two implanted infants at different times after CI activation. These authors concluded that communicative development is positively influenced, and observed changes in the Central Nervous System by means of progressive decrease in the latency of the P1 wave, which normalized after three months of the CI activation[19]. A similar study was conducted with five older children, mean age of two years and three months, at the time of CI activation. These children were compared with their peers of same age with normal hearing to verify whether there was proper development of the auditory pathway in individuals in the study group. The authors concluded that the latency values of the wave P1 in implanted children after three months of CI activation is higher than that of normal-hearing children, with reduction occurring at four years of age[23].

Still with regard to the analysis of the results presented in Table 1, data from the Preterm Group are similar to those observed in another study[14] on the use of other electrophysiologic measure, BAEP, in neonates considered small for gestational age. Progressive reduction of the latency values of waves was observed in both preterm and term newborns, with no difference between body proportion and auditory maturation[14]. A previous study showed an increasing trend of the latency values in all individual components and of the interpeak intervals in preterm neonates for BAEP, as well as marked difference in cortical potentials in the comparison between full-term and premature newborns[24]. Along the same lines, the authors stated that the gestational age at the time of evaluation should be considered, because there are differences in the maturation of the central auditory system, observed in the BAEP, in premature infants aged 20 months or less[9].

In the present study, although higher values were observed for participants in the Term Group (Table 2), no statistically significant difference was found between the ears regarding the amplitude of the components P1 and N1 between the groups. With respect to this measure, researchers have observed the effects of aging in the CAEP in different age groups: neonates younger than seven days, infants aged 13-41 months, children aged 4-6 years, and adults between 18 and 45 years old. As a result, they found no important difference between amplitude values for neonates and children up to six years of age; however, the components are influenced by time, because the amplitude values decreased for P1 and N2 and increased for N1 and P2 with increasing age[25]. That research corroborates another previous study conducted with 15 neonates aged two to four days, who were assessed after birth and subsequently at every three months until they were one year old, in which the authors emphasize that the amplitude of the components of cortical potentials increases according to the maturation process, consequently improving the morphology[18]. Some authors have underscored that the amplitude of response is directly related to the amount of neural structure involved in the response[3], being proportional to the magnitude of synaptic activation[26]. Other researchers have observed influence of age in the amplitude and latency responses in humans[27].

Using the BAEP, some authors concluded that there is no difference in hearing development between the right and left ears, which occurs simultaneously[9,28-30]. Such findings are similar to those of the present study, considering that no statistically significant difference was found between the ears for the latency values of the components P1 and N1, as well as there were no significant results when comparing the presence and absence of the components P2 and N2 between the ears and the groups surveyed.

Analysis of the presence or absence of the components P2 and N2 (Table 3) shows that the component P2 was present in 68.18% in both ears in the Term Group and in 83.33% in the right ear and 80% in the left ear in the Preterm Group, whereas the component N2 was present in 59.09% in the right ear and 56.06% in the left ear in the Term Group and in 70% in the right ear and 60% in the left ear in the Preterm Group. These findings are in disagreement with those of a recent study conducted with 25 neonates that reported the presence of the P2 component in only 6.7% (n=1) of full-term neonates and in 20% (n=2) of premature neonates[8]. This fact may be related to the difference between sample sizes between the studies, considering that presence of the components P2 and N2 was observed in most neonates regardless of the group surveyed in the present study, which was conducted with a larger sample. The literature consulted shows no agreement with the present findings, which opens a precedent for further research.

CONCLUSION

The study results show that it is possible to measure the cortical auditory evoked potentials in term and preterm neonates. Analyses of the comparisons show influence of the maturation process only on the measure of latency of the components P1, binaurally, and N1, in the left ear, which were smaller in the Term Group. However, no significant correlation was found between the groups regarding the values of amplitude.

It is worth noting that there was no statistical difference between the presence and absence of the components P2 and N2 between the sample groups.

The need for normative values for this population should be emphasized, considering that previous studies were conducted with small samples and, therefore, were not able to infer on such normality.

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Author contributions

AM participated in the data collection, interpretation of results and writing of the manuscript; EPVB performed the analysis and interpretation of results and critical review of the manuscript on the important intellectual content; ICR participated in the data collection and analysis of results; PS participated in the interpretation of results and critical review of the manuscript on the important intellectual content.