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Cortical auditory evoked potentials in full term and preterm neonates: gender and risk factors for hearing impairment

Potencial evocado auditivo cortical em neonatos a termo e pré-termo: gênero e indicadores de risco para deficiência auditiva

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ABSTRACT

Purpose: To investigate the exogenous potential in normal hearing neonates born at full term and preterm, correlating them to gender and to the presence of risk indicators for hearing impairment (IRDA). **Methods:** 96 of 127 newborns were considered after judges' analysis. Sixty six were born at term and 30 preterm in a public hospital. All neonates had result "pass" in neonatal hearing screening. The exam records were conducted with newborns, in natural sleep, through positioned electrodes: the active on the forehead (Fz), the ground (Fpz) on the forehead and the reference ones on the left (M1) and right (M2) mastoid. Verbal stimuli were presented binaurally. The frequent stimulus was /ba/ and /ga/ was the rare stimulus, in intensity of 70 dBHL, through insert earphones. The oddball paradigm was respected. The presence or absence of exogenous potential was analyzed. For data analysis, statistical tests were used. **Results:** There was a statistically significant difference in the values of female gender components related to N1-P2 amplitude in the left ear. There was no significant difference between the IRDAs presence and components absence. **Conclusion:** It was verified that the cortical auditory evoked potentials in neonates present higher amplitude values in the preterm group in females, and no statistically significant difference related to latency. However, regarding the presence of IRDAs and absence of components, it was not found significant connection.

Keywords: Evoked potentials; Evoked potentials, Auditory; Infant, Newborn; Electrophysiology; Infant, Premature

RESUMO

Objetivo: Pesquisar os potenciais exógenos em neonatos normo-ouvintes, nascidos a termo e pré-termo, correlacionando-os ao gênero e presença de Indicadores de Risco para Deficiência Auditiva (IRDA). **Métodos:** A amostra inicial foi composta por 127 neonatos e, após análise de juízes, foram considerados 96. Destes, 66 eram nascidos a termo e 30 nascidos pré-termo, em um hospital público. Todos os neonatos apresentaram resultado "passa" na triagem auditiva neonatal. Os registros do exame foram feitos com os neonatos em sono natural, por meio de eletrodos assim posicionados: o ativo na fronte (Fz), o terra (Fpz) na fronte e os de referência na mastoide esquerda (M1) e direita (M2). Foram apresentados estímulos verbais, binauralmente, sendo /ba/ o estímulo frequente e /ga/ o estímulo raro, em intensidade de 70 dBNA, por meio de fones de inserção. Respeitou-se o paradigma *oddball*. Foi analisada a presença ou ausência dos potenciais exógenos. Para análise dos dados foram utilizados os testes estatísticos. **Resultados:** Houve diferença significativa nos valores dos componentes para o gênero feminino, relacionados à amplitude de N1-P2, na orelha esquerda. Não houve diferença entre presença de IRDAs e ausência de componentes. **Conclusão:** Verificou-se que os Potenciais Evocados Auditivos Corticais em neonatos apresentaram valores maiores de amplitude no Grupo Pré-termo, no gênero feminino, e ausência de diferença quanto à latência. Quanto à presença de IRDAs e ausência de componentes, não foi encontrada relação.

Descritores: Potenciais evocados; Potenciais evocados auditivos; Recém-nascido; Eletrofisiologia; Prematuro

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INTRODUCTION

The objective evaluation techniques in the field of Audiology have been being utilized through electrophysiological tests, which are non invasive procedures and can be described according to the path traveled by the sound, during the evaluation. The following procedures can be listed: otoacoustic emissions (EOA), which evaluate the cochlear function and the outer hair cells; Brainstem Auditory Evoked Potential (BAEP), which Evaluates Auditory function up to brainstem[1]; Cortical Auditory Evoked Potentials (CAEP) or Long Latency Auditory Evoked Potential (LLAEP), which evaluate the Auditory Function in its more central portion, up to the auditory cortex[2]. The tests that assess the peripheral hearing have been already researched and validated, however, currently, the interest and need to study the central auditory changes in neonates and infants have been growing[3].

The LLAEP is an interesting method to measure capabilities related to central and cognitive auditory skills, allowing the display of delay in the maturation of the evaluated components in advance and, thus, facilitating the guiding to intervention. This procedure can be used to perform the maturational monitoring of the auditory pathway and/or to provide data on the arrival of sound information to the auditory cortex[2,4].

In neonates and infants, the trace obtained in the evaluation allows the observation of P1, N1, P2 and N2, exogenous components, called CAEP. It is important to say that these components are not influenced by the physical characteristics of stimuli, such as duration, intensity and frequency, and besides that do not depend on a cognitive response of the patient[2]. The responses generated in this assessment are bioelectric results of the cortical and thalamic activity, in a time interval between 80 ms and 600 ms[3,5]. Therefore, in neonates and infants, these components (P1, N1, P2 and N2) are highlighted, considering that do not depend on individual attention to the sound stimulus, they are an inherent representation to the subject and depend on cortical ability to detect them[3,4].

The main components of CAEP undergo substantial changes in the pattern of responses depending on the development stage from the birth to adolescence, which enables its use for monitoring of auditory function, as stated previously[2,4]. The CAEP has its use as a maturational biomarker of the auditory pathway, due to decrease of exogenous components latency over the first years of life[6]. Differences in latency and amplitude of components were studied in different age groups through the LLAEP[2,4,7,8,9,10,11] or BAEP[12,13,14,15,16,17,18].

In a study that analyzed the effects of age and gender, related to the response and latency mode of BAEP components[12], conducted with 123 subjects, the authors verified that there was a difference, probably because the cranial proportions differ between genders, presenting changes during its growth in the central nervous system. Also according to the authors, the male gender may show bigger conducting time related to anatomical and structural issues (bigger head diameter) and, therefore, present longer auditory pathways. A more current study[15] aimed to identify the influences of gender and the weight/gestational age in 176 newborns, 88 preterm and 88 term, confirming that these variables influence on responses on BAEP, in the term group. In relation to the CAEP, researchers refer that there is no difference between the latencies of components and genders[9], regardless of age[11].

Another important factor in the evaluation of neonates is the investigation of the presence of Risk Indicators for Hearing Impairment (IRDA), defined as complications that can maximize the possibility of the children having hearing deficiency. According to international and national committees, among the IRDA, are mentioned: use of drugs or maternal alcoholism during pregnancy[18], permanence in intensive care neonatal unit for longer than five days, use of ototoxic medication, family history of hearing deficiency, diagnose or suspected syndromes, use of alcohol, drugs and/or tobacco by the mother during pregnancy, gestational infection[1,19]. The audiologist and the pediatrician should question themselves about the presence of these indicators, due to possible cochlear alterations, or at the level of the auditory nerve, which can be caused by them.

In the consulted literature, no articles were found relating IRDA and LLAEP or CAEP, however, there are studies that investigates the relationship between IRDA and the responses on BAEP[16,20].

It is added that the clinical use of CAEP is something recent. Therefore, researches that seek to clarify the correlation between the latencies, of exogenous components of LLAEP and variables, such as gender and presence of IRDA are relevant, both for academic issues and to clinical practice. Nationwide, there was no reference located in the consulted literature, which makes this study unprecedented, since its purpose was to study the subject.

The purpose of this study, therefore, was to correlate the findings in Cortical Auditory Evoked Potentials among the term and preterm neonates, and analyze the presence of the components in relation to gender and IRDA.

METHODS

This is a cross-sectional, prospective, contemporary and comparative study, having as clinical outcome the observation and analysis of electrophysiological responses in the CAEP exam, in neonates.

This research was approved by the Research Ethics Committee of the *Universidade Federal de Santa Maria*, under the 14804714.2.0000.5346 number and met all the prerequisites required for research involving human beings (Resolution No. 466/12).

Regarding the eligibility criteria, only subjects whose parents or guardians signed the consent form were included. As exclusion criteria for participation in the survey, the following conditions were considered: more than a month of life (taking into consideration the corrected age in preterm group); suspected hearing impairment in newborn hearing screening (TAN), with no Otoacoustic Emissions Transients (EOAT) (protocol for newborns without IRDA) or Brainstem Auditory Evoked Potential – Automatic (BAEP-A) (protocol for newborns with IRDA) in the first screening; evident neurological or organic commitment; use of medication.

The initial sample consisted of 127 newborns treated at the TAN program of a public hospital. Initially, an anamnesis was made with the newborns responsible, covering data such as name of the mother and the newborn, date of birth, weight, Apgar score, gestational age, presence of IRDA and medical history, in order to verify the exclusion criteria. The survey of IRDA followed the recommendations of the Joint Committee on Infant Hearing[1] and the Multidisciplinary Committee on Hearing Health[19].

For the research of CAEP components, parents/guardians were oriented that the infant was fed and in natural sleep, comfortably positioned, because its movement in vigil could change the paths of the components and interfere with test results. The evaluation was performed in an outpatient setting, through Intelligent Hearing Systems (IHS) equipment, SmartEP module, two channels, with the use of insert earphones and electrodes positioned with electrolytic conductive paste and adhesive tape, after cleaning the skin with abrasive paste. The active electrode was placed on the forehead (Fz), the ground (Fpz) on the forehead and the reference ones on the left mastoid (M1) and right mastoid (M2). The value of the impedance of the electrodes was equal to or less than 3 kohms and frequently speech stimuli were used /ba/ and rare /g/, presented in binaural way, at an intensity of 70 dBNA. For each type of stimulus, it was used 150 stimuli (approximately 120 frequent and 30 rare - Oddball paradigm). The polarity used was the alternating, bandpass filter 1 to 30 Hz and 1020 ms window. It was considered, maximum, 10% of artifacts. This protocol was based on a national study that used the same equipment to measure the CAEP[4]. The identified tracing received the markings with measuring of the latency and amplitude of exogenous components (P1, N1, P2 and N2), on the stroke of the frequent stimuli, and then, it was printed for analysis.

At the end, the exams were analyzed independently by three speech therapists qualified judges (with knowledge about CAEP). The analysis occurred blindly. Two of the judges made the markings independently (one with no knowledge regarding the marking of components and analysis of the other) and a third judge held the final analysis by checking the markings of the first two judges and her own knowledge about the exam. Thirty-one exams were excluded because of disagreement over markings and high presence of artifacts, which invalidated the reliability of the result. Therefore, the final sample consisted of 96 neonates, divided into two groups, according to gestational age: 66 born at full term (Term Group), 32 male and 34 female, and 30 born at preterm (Preterm Group), 19 males and 11 females.

The average gestational age of the Term Group was 39 weeks, ranging between 37 and 41 weeks and three days. As for the Preterm Group, it was 34 weeks and four days, ranging between 26 weeks and two days and 36 weeks and five days.

For analysis of the results, the values of the components, amplitude and latency, were organized in Microsoft Excel, and analyzed using the Statistical Analysis System (SAS) software for Windows®, version 9.2. Categorical data were presented in relative frequency. Chi-square test or Fisher's exact test were used in smaller amounts than five, to verify the correlation between the findings of CAEP between the groups or in neonates with IRDA and Mann-Whitney test for correlation check between the averages of responses, considering significant values below 0.05. It was opted to analyze correlation between the presence or absence of the components and the presence of some IRDA to seek possible influence on the responses on CAEP.

RESULTS

It was possible to observe a relationship between presence and absence of CAEP components, by ears, in both groups (Table 1).

There was no significant difference between the presence and absence of the CAEP components on the right and left ear, neither for full term neonates, nor for preterm neonates.

The latency values of exogenous components in each group, considering the comparison between genders, can be seen in Table 2.

The amplitude values of exogenous components P1, N1 and P2, according to gender, in both groups, are shown in Table 3.

It is noteworthy that the gender variable showed no influence on the latency values of CAEP components in any of the groups studied. However, when considering the analysis of the amplitude of the N1-P2, in the preterm group, the female gender newborns presented higher amplitude.

Regarding the relationship between the absence of P1, N1, P2 and N2 components and the presence of IRDA in the evaluated population, the values found are related to the number of neonates that presented each indicator and absence of components in the CAEP research (Chart 1).

Regarding the relationship between the absence of CAEP components and presence of IRDA, it is important to highlight that there was no significant difference in any of the groups, between the absence of exogenous components and the following IRDA: family history of hearing impairment (p=0.541 term and p=0.565 preterm), stay in the intensive care unit (UTI) (p=0.631 preterm), use of ototoxic medication (p=0.611 term and p=0.772 preterm), mechanical ventilation (p=0.175 preterm), congenital infection (p=0.825 term), use of alcohol during pregnancy (p=0.753 term and p=0.565 preterm) and

Table 1. Analysis of the presence or absence of P1, N1, P2 and N2 components in Cortical Auditory Evoked Potential in term and preterm neonates

	Presence		Absence		p-value*
	Term Group (n=66)	Preterm Group (n=30)	Term Group (n=66)	Preterm Group (n=30)	
RE					
P1	92.42% (n=61)	93.33% (n=28)	7.58 (n=5)	6.67% (n=2)	1.000
N1	92.42% (n=61)	93.33% (n=28)	7.58 (n=5)	6.67% (n=2)	1.000
P2	68.18% (n=45)	83.33% (n=25)	31.82% (n=21)	16.67% (n=5)	0.122
N2	59.09% (n=39)	70% (n=21)	40.91% (n=27)	30% (n=9)	0.306
LE					
P1	95.45% (n=63)	86.67% (n=26)	4.55 (n=3)	13.33% (n=4)	0.200
N1	93.94% (n=62)	86.67% (n=26)	6.06 (n=4)	13.33% (n=4)	0.252
P2	68.18% (n=45)	80% (n=24)	31.82% (n=21)	20% (n=6)	0.233
N2	56.06% (n=37)	60% (n=18)	43.94% (n=29)	40% (n=12)	0.718

* Fisher's exact test for lower variable than five. Chi-square test for analysis of categorical variables (p<0.05)
Subtitle: RE = right ear; LE = left ear

Table 2. Comparative study of the average latencies of P1, N1, P2 and N2 components in Cortical Auditory Evoked Potentials in term and pre-term groups, in both genders

	Term Group				p-value*	Preterm Group				p-value*
	Female (n=34)		Male (n=32)			Female (n=11)		Male (n=19)		
	Average	SD	Average	SD		Average	SD	Average	SD	
RE										
P1	215.56	46.56	212.48	42.24	0.329	246.80	38.03	245.44	58.20	0.943
N1	359.38	71.02	377.38	62.38	0.236	401.80	49.08	391.83	85.36	0.631
P2	482.87	123.92	507.55	110.33	0.352	524.22	104.61	510.13	112.04	0.799
N2	568.95	120.61	596.30	132.53	0.518	622.57	167.38	608.00	97.39	0.654
LE										
P1	210.06	41.94	217.87	49.97	0.491	257.40	31.10	247.38	62.32	0.356
N1	365.88	74.63	377.38	65.84	0.558	401.40	55.14	405.25	102.50	0.654
P2	486.04	129.40	523.14	115.41	0.380	590.89	105.22	503.87	116.47	0.136
N2	574.22	133.26	609.21	139.19	0.447	665.00	161.93	594.67	109.41	0.708

*Mann-Whitney test for analysis of numerical variables between groups (p<0.05)
Subtitle: RE = right ear; LE = left ear; SD = standard deviation

use of tobacco during pregnancy (p=0.575 term and p=0.107 preterm).

DISCUSSION

The findings of this study, relating to the absence or presence of exogenous components (Table 1) indicate that the presence or absence of CAEP components would not be related to gestational time, term or preterm, disagreeing with studies that evaluated the effects of maturation between full term and preterm infants using BAEP as a means of evaluation, demonstrating differences in responses between the groups[21].

Another study verified the presence of the P1 component in infants from 20 to 22 weeks of age and from 10 to 13 weeks, in order to compare the responses obtained in the different age groups, not being observed the presence of the N450 component in older infants[22]. It can be inferred, therefore, that the maturational differences in the auditory pathway are highlighted when the child begins to develop cognitive skills, such as non voluntary attention. The attention ability control is one of the first executive functions to develop in the prefrontal cortex and it appears in early childhood[23].

Regarding the P2 component, a recent study observed the presence in only 6,7% (n=1) of full term neonates and in 20% (n=2) in preterm infants[4], unlike the results of this study (Table 1). It is believed that this divergence has occurred due to the difference in sample size between studies. The findings of the current study are in agreement with similar research that,

Table 3. Comparative study of the average amplitude of P1, N1 and P2 components of the Cortical Auditory Evoked Potentials in term and preterm groups, in both genders

	Term Group				Valor de p	Preterm Group				Valor de p
	Female (n=34)		Male (n=32)			Female (n=11)		Male (n=19)		
	Average	SD	Average	SD		Average	SD	Average	SD	
RE										
P1-N1	7.58	4.94	6.41	2.64	0.535	5.98	2.65	5.61	1.83	0.867
N1-P2	4.15	2.87	3.95	2.23	0.930	3.74	2.41	3.68	1.82	0.910
P2-N2	2.60	1.31	2.64	1.99	0.673	2.34	1.10	2.13	1.75	0.332
LE										
P1-N1	7.53	4.63	6.06	2.74	0.293	6.26	2.11	5.51	1.83	0.399
N1-P2	4.83	3.57	3.70	2.05	0.495	5.04	2.03	2.99	2.01	0.019*
P2-N2	2.46	1.53	2.92	2.12	0.770	1.21	1.22	2.19	1.24	0.055

* Significant value (p<0,05) - Mann-Whitney test for analysis of numerical variables between groups
Subtitle: RE = right ear; LE = left ear; SD = standard deviation

Chart 1. Influence of risk indicators for the absence of response in term and preterm neonates

Indicators	Group Term								Group Preterm							
	Right ear				Left ear				Right ear				Left ear			
	P1	N1	P2	N2	P1	N1	P2	N2	P1	N1	P2	N2	P1	N1	P2	N2
Family history of HI	1	1	3	3	0	0	1	1	0	0	0	0	0	0	0	0
Ototoxicity	0	0	1	1	0	0	1	1	2	2	4	5	2	2	3	4
Extremely low birth weight (>1500 g)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ICU > 5 days	0	0	0	0	0	0	0	0	2	2	5	6	3	3	5	7
Hyperbilirubinemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Use of alcohol/illicit drugs during pregnancy	0	0	1	1	0	0	1	1	0	0	0	0	0	0	0	1
Mother smokes	1	1	3	3	0	0	2	2	1	1	1	1	2	2	2	4
MV	0	0	0	0	0	0	0	0	2	2	3	4	2	2	2	3
TBI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Without risk	4	4	16	22	3	4	15	23	0	0	0	3	1	1	1	5
n Total	5	5	21	27	3	4	18	26	2	2	5	9	4	4	6	13

Subtitle: HI = hearing impairment; ICU = intensive care unit; MV = mechanical ventilation; TBI = Traumatic brain injury

despite not using the same evaluation procedure, verified the presence of responses in the Mismatch Negativity (MMN) in 85% of evaluated neonates[24]. As for the difference of the P2 component presence among full term and preterm infants, it was not possible to realize inference on this finding.

Regarding the average of latencies of P1, N1, P2 components and N2 in CAEP, (Table 2), there was no statistic difference in the analysis of values of the components in groups, possibly due to the neurological phenomenon called catch-up, characteristic in preterm born, on post-natal period, characterized by the increase of growth speed for the recovery of intrauterine growth retardation, regardless of gender[25].

In contrast, the use of BAEP, studies show differences in relation to gender. A study consisted of 111 preterm and 92 full term showed higher absolute latency of components I, III and V and their interpeaks in the male gender[17]. Another study with BAEP verified lower responses in females, when compared to males, for term newborns, except for the component I and higher latency values for females in preterm infants[15]. It should be noted that although this study did not observe significant differences in latency analysis of CAEP between genders, the findings were similar to the study of Angrisani and colleagues[15].

It is added that in surveys conducted with BAEP in the referred sample[15], no differences were observed between the values of absolute latencies of components I, III and V, in the comparison between the ears[3,14,15,16,26,27] and in relation to gender[13]. The lack of difference between the ears, or regarding to gender[9,11] was also observed in studies using the LLAEP as a mean of evaluation[4,9]. These findings show that maturation occurs simultaneously between the hemispheres (between the ears) and does not differ between genders, exceptionally before completing one month of life.

Authors found as latency values for the P2 component peak between 200 and 250 ms and for N2, between 300 and 550 ms[7,8]. Such values are not consistent with the findings of this study (Table 2), as they resemble to the values of P1 and N1. The findings of this study confirm recent survey, conducted in the same public service, in which the average values for P1 wave were 230 ms in the group term and 201 ms in the preterm group. For N1 wave, the average values were 341 ms in the term group and 301 ms in the preterm group[4]. According to the authors, there was no difference in the latencies of P1 and N1 components between ears, regardless of the group, full term or preterm[4].

A survey conducted with 4 months old infants and adults showed that the cortical response to verbal stimulation /da/, for both populations, is similar for the N1-P1-P2 complex regarding morphology, however, the infants showed higher latencies values[28]. Researchers conducted evaluation with CAEP in 6 months old infants and followed up to 4 years, showing that the values of amplitude and latency suffer Influence of maturation with increasing age[29]. Results described by other researchers using MMN, showed absolute values increased in infants[30]. Both studies confirmed the findings of the present research, that showed increased latencies in the evaluated neonates.

In the current research with infants, there was a significant result for N1-P2 amplitude in the left ear, between the genders, only in the preterm group, showing higher values in the females (Table 3). Researchers verified differences between the responses of amplitude in term and preterm neonates, with no complaints related to health, finding lower N2 amplitude in preterm, in the MMN research[30]. Considering the comparison of latency and amplitude values of CAEP/LLAEP among children (3-12 years) and young adults, the researchers reported no difference between the genders, regardless of age[11]. As for the BAEP, authors found significantly increased values for amplitude of III and V components in females, for both preterm and term group[17].

Because there is no standard of normality for values of latency and amplitude in the studied population, it was decided to seek correlation of IRDA in the presence or absence of the components. Considering that, in this study sample, there was no significant correlation between the IRDA presented by the neonates and the absence of exogenous components, in the CAEP research (Chart 1), it appears that the presence of some IRDA did not influence in the absence of CAEP components. Due to the lack of studies on the role of IRDA in newborns of different gestational ages and the CAEP, it is pointed out the need of new studies with potential IRDAs for central auditory disorders.

In the consulted literature, only one study has examined the relationship between IRDA (preterm newborn, small for gestational age) and BAEP in preterm neonates. The authors noted that this condition has not revealed risk for retrocochlear change when compared preterm infants considered small and appropriate for gestational age[16].

CONCLUSION

Before the proposed objective, it was not possible to observe difference between the presence and absence of the CAEP components between full term and preterm neonates. It was not found a difference either between genders or in the latency of CAEP components, in neither of the groups. Only the female newborns had higher N1-P2 amplitude in the left ear (preterm group). Regarding the presence of IRDAs and absence of CAEP components, there was no relationship found.

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