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Peri-intraventricular hemorrhage: Study of the inhibitory effect of auditory efferent pathway

Hemorragia peri-intraventricular: Estudo do efeito inibitório da via auditiva eferente

Keywords

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ABSTRACT

Purpose: to determine the functioning of the efferent auditory system in premature newborns with intraventricular hemorrhage. **Method:** the sample consisted of 44 newborns, divided into two groups. The study group was composed of 22 premature newborns with intraventricular hemorrhage/and the control group was composed of 22 newborns without intraventricular hemorrhage, matched to the study group for gestational age, correct gestational age and sex. The groups were submitted to the evaluation of the inhibitory effect of auditory efferent in otoacoustic emissions (equipment ILOv6-Otodynamics Ltda[®]) and auditory evoked potential with and without contralateral noise (equipment SmartEP-Intelligent Hearing Systems[®]). **Results:** newborns with intraventricular hemorrhage exhibited a higher occurrence of central hearing alteration as well as a lesser occurrence of the inhibitory effect of auditory efferent in otoacoustic emissions and auditory evoked potential compared to the newborns without this condition. An association was found between central hearing alteration and a lower occurrence of inhibitory effect. Agreement was found between the inhibitory effect test on otoacoustic emissions and latency of the auditory evoked potential. **Conclusion:** premature newborns with intraventricular hemorrhage have a greater occurrence of functional abnormality of the afferent auditory system, which can be effectively identified through an evaluation of the inhibitory effect of auditory efferent in otoacoustic emissions evoked by a transient stimulus and latency parameter in the brainstem auditory evoked potential.

RESUMO

Objetivo: verificar o funcionamento do sistema auditivo eferente em recém-nascidos pré-termo com hemorragia peri-intraventricular. **Método:** a amostra foi constituída por 44 recém-nascidos, distribuídos em dois grupos. O grupo estudo foi composto por 22 recém-nascidos pré-termo com hemorragia peri-intraventricular, e o grupo controle por 22 sem hemorragia peri-intraventricular, pareados por idade gestacional, idade gestacional corrigida e sexo. Os grupos foram submetidos à avaliação do efeito inibitório da via auditiva eferente nas emissões otoacústicas (equipamento ILOv6-Otodynamics Ltda[®]) e no potencial evocado auditivo de tronco encefálico, sem e com ruído contralateral (equipamento Smart-EP-Intelligent Hearing Systems[®]). **Resultados:** recém-nascidos com hemorragia peri-intraventricular apresentaram maior ocorrência de alteração central, além de menor ocorrência do efeito inibitório da via auditiva eferente nas emissões otoacústicas e no potencial evocado auditivo. Houve associação entre alteração auditiva central e menor ocorrência do efeito inibitório. Observou-se, também, concordância entre o efeito inibitório da via auditiva eferente nas emissões otoacústicas e nas latências do potencial evocado auditivo. **Conclusão:** recém-nascidos pré-termo com hemorragia peri-intraventricular apresentaram maior ocorrência de alteração funcional do sistema auditivo eferente, que pôde ser identificada de forma efetiva por meio da avaliação do efeito inibitório da via eferente nas emissões otoacústicas evocadas por estímulo transiente e no parâmetro latência do potencial evocado auditivo de tronco encefálico.

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INTRODUCTION

Peri-intraventricular hemorrhage (PIVH) is an important neurological complication that affects preterm newborns (PTNB). It occurs initially in the subependymal germinal matrix, located in the caudothalamic groove⁽¹⁾. This embryonic structure is a site for proliferation of neuroblasts and glioblasts, and it involutes at approximately 34 weeks of pregnancy⁽²⁾. It has a complex etiopathogenesis and is attributed to the intrinsic fragility of the vascularization of the germinal matrix, to the fluctuation of cerebral blood flow, as well as to changes in platelet and coagulation function. It can be restricted to the germinal matrix region or extend to the ventricular system⁽³⁾.

Newborns (NB) affected by this disease may have abnormal neurological development and grow up with motor and cognitive deficits⁽²⁾. In addition, they are more likely to present hearing disorders, among other health problems. A recent study showed that 33.4% of these NBs have central auditory disorders, and the occurrence of central disorders remains high in auditory monitoring⁽⁴⁾.

Auditory system integrity is essential for proper development. In other words, central auditory disorders interfere with the ability to process acoustic stimuli and impairs the development of speech and language⁽⁵⁾. Therefore, retrocochlear disorders must be detected to enable early intervention in developmental disorders.

Non-invasive investigation of such disorders can be performed through the evaluation of the medial olivocochlear efferent system (MOCES), which originates in the medial nucleus of the superior olivary complex (located in the brainstem) and protrudes over the auditory nerve fibers and the outer hair cells, adjusting the response in the presence of a simultaneous stimulus. Thus, the MOCES can be activated by an inhibitory noise, thereby reducing the contractions of the outer hair cells and, consequently, OAE amplitude levels⁽⁶⁾.

This phenomenon is known as the inhibitory effect of the efferent auditory pathway (IHEAP) and allows better detection, recognition and auditory discrimination in the presence of noise, in addition to assisting in the localization of sound. Consequently, it is assumed that IHEAP assessment can be used as a complementary test to assess auditory processing in newborns, since the MOCES is closely related to auditory skills.

A previous study showed that IHEAP can also be evidenced in brainstem auditory evoked potentials (BAEP), since the presentation of contralateral white noise affects auditory evoked potentials (with possible increase in absolute latencies and decrease in wave amplitudes), suggesting the influence of the MOCES on the modulation of responses⁽⁷⁾. Thus, the development of new electrophysiological measures seems promising for consecutive, complementary and more thorough assessment of the central auditory pathway in newborns who are at risk for auditory disorders and have already undergone BAEP assessment.

The assumed hypothesis is that newborns with IHEAP may present greater occurrence of disorders in the central auditory system, which can be evidenced both in the assessment of IHEAP

in otoacoustic emissions and in BAEP, with the presentation of contralateral white noise.

Therefore, the objective of this study was to investigate the function of the efferent auditory system in preterm newborns with peri-intraventricular hemorrhage.

METHOD

This study was conducted in the neonatal ICU of Hospital São Paulo, Federal University of São Paulo, from January 2015 to May 2018, after approval by the institution's Research Ethics Committee, according to opinion number 32857014.2.0000.5505. The study was observational, cross-sectional and analytical, with comparison between groups. Data were collected by a single evaluator in a non-blind manner. The participants' parents or guardians were informed about the methodological procedures and signed a Free and Informed Consent Form before any procedure was performed.

The sample included 44 NBs with gestational age less than 37 weeks, post-conceptual age between 24 hours of life and 6 months of age, and a minimum of 35 weeks of corrected gestational age. In addition, all newborns should have TEOAE present bilaterally and responses at 20 dBnHL for BAEP-click, in both ears. TEOAE testing was performed with an *Otodynamics Ltda*[®].ILOV6 device. The test used an analysis window of 4 to 20 ms, that is, the standard analysis protocol. Non-linear clicks between 75 and 85 dBpeSPL were presented. Responses were considered to be present when they had a signal-to-noise ratio above 6 dB in the 2, 3 and 4 KHz frequency bands, reproducibility over 70% and probestability greater than 50%. Responses at 20 dBnHL in BAEP were measured with an *Intelligent Hearing Systems*[®] Smart-EP device. A total of 2,000 rarefaction clicks were presented through ER 3A earphones, with a duration of 100 μ s, repetition rate of 27.7/s, 100,000 amplification, analysis window of 12 ms and filters of 100-1500 Hz.

NBs with neurodegenerative disorders, malformations and/or genetic syndromes, as well as other risks for central auditory disorders (such as asphyxia, seizures, drug use during pregnancy, hyperbilirubinemia, viral meningitis, congenital HIV infection, cytomegalovirus, syphilis and toxoplasmosis) were excluded from the sample.

The Study Group (SG) consisted of 22 PTNBs whose diagnosis of PIVH was performed and reported by a radiologist using transfontanelar ultrasound. The Control Group (CG) was composed of 22 PTNBs without a diagnosis of PIVH, evidenced after transfontanelar ultrasound examination. These NBs were paired to those of the SG by gestational age, corrected gestational age, and sex.

The whole audiological assessment was carried out for all newborns under the same conditions and at the time of hospital discharge, in an electrically and acoustically insulated room, with the newborns in natural, postprandial sleep in a common cradle. Testing of IHEAP on emissions was performed using an ILOV6 device. For this assessment, two probes were positioned in the external acoustic meatus of the NB. One probe presented linear clicks between 60

and 65 peSPL while the other presented broadband noise at 60 dB SPL. Collections without and with contralateral noise were performed alternately and automatically in alternating 10-second blocks of clicks without noise and 10-second blocks of clicks with contralateral noise, until completing 260 scans in silence. IHEAP was considered to be present in TEOAE when there was a decrease greater than or equal to 0.2 dB SPL in the general response, as previously determined⁽⁸⁾.

BAEP were registered using an *Intelligent Hearing Systems*[®] Smart-EP device. After the skin was cleansed with an antiseptic scrub solution, the permanent electrodes were attached with the EEG conductive paste and microporous tape on the forehead (Fpz) and on the right and left mastoids (M2 and M1), in compliance with IES 10-20 (International Electrode System). Electrode impedance was kept below 3 kilohms.

The functional integrity of the auditory pathway - from the auditory nerve to the brainstem (neurological protocol) - was assessed by analyzing absolute latencies and interpeak intervals. For BAEP recordings, the following parameters were used: rarefaction polarity clicks at 80 dBnHL with ER 3A earphones; duration of 100 μ s; repetition rate of 27.7/s; 100,000 amplification; 12 ms analysis window; 100-1500 Hz filters and a minimum of 2,000 stimuli. The tracings were duplicated to ensure wave reproducibility. Absolute latencies and interpeak intervals were classified as normal or abnormal, considering the corrected age of the NB at the time of the examination and taking into account previously determined patterns⁽⁹⁾. Central auditory disorder was considered to occur in the event of delay in absolute latencies of waves III and/or V, increase in interpeak intervals I-III, III-V and IV or interaural time difference greater than 0.3 ms in the absolute latency of wave V and/or in the interpeak interval IV⁽⁹⁾. Abnormality in the lower brainstem was characterized by delayed latencies of waves III and V and increased interpeak intervals I-III and IV. Abnormality in the upper brainstem was signaled by delayed wave V latency and increased interpeak intervals III-V and IV. Diffuse abnormality was considered to be impairment of the upper and the lower halves of the brainstem⁽¹⁰⁾.

For the evaluation of IHEAP in BAEP, the same parameters of the neurological protocol were used, with an increase in contralateral white noise at 60dB SPL. The absolute latencies and amplitudes of waves I, III and V were analyzed in reproducible tracings. The results found in the absence and presence of contralateral noise were compared. Any increase in the absolute latency value or decrease in the wave amplitude value, owing to noise presentation, was considered as indicative of the presence of an inhibitory effect^(7,11). IHEAP-latency is the extension in latency, and IHEAP-amplitude is the decrease in wave amplitude, owing to the presentation of contralateral noise. The latencies and amplitudes, for each wave, were analyzed separately, and the absence of IHEAP in one or more waves indicated the absence of the inhibitory effect.

For the statistical analysis, the Wilcoxon, Friedman, Mann-Whitney, Wald and Fisher's Exact tests were used. A significance level of 0.05 (5%) was established. All confidence intervals were constructed with 95% statistical confidence.

RESULTS

The SG was composed of 22 newborns diagnosed with PIVH, with an average gestational age of 29.14 weeks (SD = 3.26 weeks) and an average corrected gestational age of 40.68 weeks (SD = 7.12 weeks). Five newborns with PIVH (22.7%) weighed above 1,500g at birth, while 17 (77.2%) weighed below 1,500g. Thus, PIVH was more frequent in infants with very low birth weight.

During the collection period of this study, 2,202 newborns were discharged from the hospital and underwent neonatal hearing screening. Frequency of PIVH was 1.81% in the total population, 4.82% in the population treated in a neonatal ICU and 37% among all NB weighing less than 1,500g. Of the 22 newborns with PIVH, 16 had PIVH grade I (72.7%); two, PIVH grade II (9%); three, PIVH grade III (13.6%), and one, PIVH grade IV (4.5%).

Table 1. Comparison between groups regarding the occurrence of central auditory disorders in the neurological protocol

Variable	Neurological protocol			P-value	Odds Ratio (1.65 - 128.4)
	Central	Normal	Total		
Study Group	9 (40.9%)	13 (59.1%)	22	0.009*	
Control group	1 (4.5%)	21 (95.5%)	22		
Total	10	34	44		

Wald test.

Caption: statistically significant value ($p < 0.05$).

The newborns with PIVH showed higher occurrence of central auditory disorder in BAEP (Table 1), with 75% of abnormality in the upper brainstem. Owing to the small size of the sample, no statistical analysis could be made of the association between degree of PIVH and occurrence of central auditory disorder. However, for descriptive purposes, central auditory disorder occurred in: 37.5% of newborns with PIVH grade I; 100% of newborns with PIVH grade II; 33.3% of newborns with PIVH grade III. Only one case of PIVH grade IV was evaluated, and normal BAEP were found.

Table 2. Comparison between groups regarding the occurrence of the inhibitory effect of the efferent pathway on TEOAE

Variable	EIVE in TEOAE		Total	P-value
	Present	Absent		
Study Group	9 (40.9%)	13 (59.0%)	22	0.001*
Control group	21 (95.4%)	1 (4.5%)	22	
Total	30	14	44	

Fisher's exact test.

Caption: statistically significant value ($p \leq < 0.05$); IHEAP: inhibitory effect of the efferent auditory pathway; TEOAE: transient-evoked otoacoustic emissions.

There was less occurrence of IHEAP in TEOAE for the SG, with no difference between ears, both for the CG and for the SG (Table 2). As for BAEP, there was also less occurrence of

IHEAP-latency in newborns with PIVH. However, the groups did not differ for IHEAP-amplitude (Table 3). There was no

difference between the ears for IHEAP-latency ($p = 0.735$) and for IHEAP-amplitude ($p = 0.469$).

Table 3. Comparison between groups regarding the occurrence of IHEAP-latency and IHEAP-amplitude

Variable	Conclusion IHEAP-latency			Conclusion IHEAP-amplitude		
	Absent	Present	Total	Absent	Present	Total
Study Group	18 (81.8%)	4 (18.8%)	22	22 (100%)	0 (0%)	22
Control group	1 (4.3%)	21 (95.7%)	22	18 (81.8%)	4 (18.8%)	22
Total	19	25	44	40	4	44
P-value	< 0.001*		0.139			

Fisher's exact test.

Caption: statistically significant value ($p < 0.05$); IHEAP: inhibitory effect of the efferent auditory pathway.

The result of the neurological protocol was associated with the result for IHEAP in TEOAE and in BAEP latency (Table 4), regardless of group. There was also an association between the

results for IHEAP tests in TEOAE and BAEP latency (Table 5). IHEAP-amplitude was not associated with IHEAP-latency in BAEP ($p = 0.225$) and with IHEAP in TEOAE ($p = 0.384$).

Table 4. Association between the results of the neurological protocol and the inhibitory effect of the efferent pathway for TEOAE and BAEP

Variable	TEOAE IHEAP			BAEP IHEAP-latency			BAEP IHEAP-amplitude		
	Present	Absent	Total	Present	Absent	Total	Present	Absent	Total
Central	4 (40%)	6 (60%)	10	1 (10%)	9 (90%)	10	0 (0%)	10 (100%)	10
Normal	26 (76.5%)	8 (23.5%)	34	25 (73.5%)	9 (26.5%)	34	4 (11.8%)	30 (88.2%)	34
Total	30	14	44	26	18	44	4	10	44
P-value	0.003*		< 0.001*	0.255					

Fisher's exact test.

Caption: statistically significant value ($p < 0.05$); IHEAP: inhibitory effect of the efferent auditory pathway; TEOAE: transient-evoked otoacoustic emissions; BAEP: brainstem auditory evoked potential.

Table 5. Association between IHEAP-latency results and the inhibitory effect of the efferent pathway on TEOAE

Variable	EIVE in TEOAE			Odds Ratio
	Present	Absent	Total	
BAEP IHEAP-latency	Present	23 (88,5%)	3 (11,5%)	12,04 (12,60-55,72)
	Absent	7 (38,9%)	11 (61,1%)	
Total	30	14	44	
P-value	0,002*			

Fisher's exact test.

Caption: statistically significant value ($p < 0.05$); IHEAP: inhibitory effect of the efferent auditory pathway; TEOAE: transient-evoked otoacoustic emissions; BAEP: brainstem auditory evoked potential

DISCUSSION

The average gestational age of newborns with PIVH was 29.14 weeks. Prematurity effectively represents the greatest risk factor for occurrence of this disease⁽¹³⁾. This is due to the presence of the germinal matrix, which has very vulnerable, immature vessels, in various stages of involution, which occurs at approximately 34 weeks of pregnancy^(2,3).

The occurrence of PIVH in NB admitted to a neonatal ICU (4.82%) was similar to the results of a study which reported 6.4% of impairment in a similar population⁽⁴⁾. The frequency of

PIVH, among the entire population born with less than 1,500 g (37%), was higher than the value found in a study carried out with 84,242 newborns with very low birth weight, admitted to neonatal ICUs coordinated by the *Pediatrics Medical Group* (United States), from 1997 to 2002, which reported 16% of PIVH⁽¹⁴⁾. In the present study, most of the NB in the SG had very low birth weight. In fact, the literature shows higher occurrence of the disease in NB weighing below 1,500 g at birth, because they are premature with a lower gestational age⁽³⁾. Between the 26th and 34th weeks, the vascular wall of the germinal matrix does not have smooth muscle and elastin. As pregnancy progresses, the germinal matrix involutes and the vascular tissue becomes intact, with less propensity for bleeding⁽²⁾.

The newborns with PIVH had 40.9% of central auditory disorder, with greater impairment in the upper brainstem, regardless of the degree of the disease. In addition, they were 14.54 times more likely to have central auditory disorder (Table 1). This occurrence was similar to the one found in previous research, which identified 33.4% of central auditory disorder⁽⁴⁾. This result was expected, since PIVH causes neurological sequelae⁽¹³⁾. The lesion in the upper brain stem reflects the impairment of the lateral lemniscus⁽¹⁰⁾, which is located closer to the place of origin of the hemorrhagic process, making it more susceptible to functional disorders.

Central disorder was identified in all grades of PIVH. This finding corroborates the literature, which proves that mild PIVH

can also have a negative impact on development⁽¹³⁾. Indeed, it was found that the NB with more severe central disorder (characterized by the absence of waves I and III) had PIVH grade II. Therefore, health workers must be cautious when evaluating patients with PIVH grades I and II.

The high occurrence of central disorder in newborns with PIVH confirms the need to assess the neurological protocol, associated with TEOAE, for early diagnosis in this population⁽¹⁵⁾.

There is widespread use of automatic BAEP (BAEP-a) by neonatal hearing screening services, but it appears that this may not be the best procedure of choice for assessment of risk for central auditory disorder in newborns. Such an examination has low specificity in identifying central auditory disorders, because although it is a brainstem analysis procedure, it presents only “pass” or “failure” responses, but it does not allow the examiner to see the waves⁽¹⁶⁾.

In addition, the occurrence of central disorder demonstrates the need for auditory monitoring with BAEP. The serial records of this exam provide data on the evolution of brainstem lesions and their response to stimulation⁽¹⁷⁾. For this reason, it demonstrates a useful clinical tool in the identification of newborns at risk for deficits in development, particularly in those with significant neurological disorders.

The newborns with PIVH had lower occurrence of IHEAP in TEOAE (Table 2). This abnormal result is probably associated with the sequelae of PIVH in the developing nervous system, owing to a decrease in the number of axons, dendrites, neurons, myelin and synapses⁽¹⁹⁾, since IHEAP in TEOAE is mediated by the synapse of the neurons of the MOCES with the outer hair cells. Therefore, the data point to the fact that newborns with PIVH have a high risk of functional impairment of the MOCES and reiterate the statement that IHEAP in emissions is a useful tool in assessing the performance of the efferent system on the cochlea of these patients⁽¹⁹⁾.

Abnormal results of IHEAP in TEOAE have been considered to signal risks for auditory processing disorders, including difficulties in sound localization, auditory recognition and discrimination, and difficulties in understanding speech in the presence of competitive noise⁽²⁰⁾. Thus, patients with PIVH have an additional risk of developing central auditory disorders and, therefore, deserve special attention in monitoring for assessment of these auditory skills. The inhibitory effect of the efferent pathway in TEOAE did not vary between the ears, regardless of group. In fact, this symmetry could reflect a risk for changes in auditory processing, since the brain needs interaural differences in time, frequency and intensity to understand information properly⁽²¹⁾.

The CG presented 95.7% of IHEAP-latency (Table 3), which demonstrates the performance of the MOCES in BAEP, also for PTNB. Such changes caused by contralateral noise suggest the influence of the efferent auditory nervous system on response modulation⁽¹¹⁾. Latency effects could reflect binaural processing in the brainstem. The cochlear nuclei receive projections from the ear contralateral to the sound, with the superior olivary complex being the first place of convergence of binaural information. Binaural mechanisms allow the central nervous system to calculate minimal differences in phase, frequency, intensity and time of a sound in each ear; thus, individuals are able to

locate the sound source, even in situations where the signal-to-noise ratio is not favorable, e.g., in noisy environments⁽²²⁾. Despite the high occurrence of IHEAP-latency in the CG, the occurrence of IHEAP-amplitude was low in both groups. This finding corroborates the data found in the literature⁽¹¹⁾ and indicates that amplitude is not a good parameter for evaluating the efferent system.

The SG presented a lower occurrence of IHEAP-latency (Table 3), with 81.8% of absence. The only study carried out with newborns at high risk for hearing loss found IHEAP-latency absent in 44% of newborns⁽⁷⁾. Thus, HPIV proved, again, to pose a risk for disorders in the MOCES. As with IHEAP in TEOAE, there was no difference in responses between ears in IHEAP in BAEP. A previous study also found no difference for efferent inhibition between the right and left sides⁽⁷⁾. Asymmetry between the ears is essential for the central auditory pathways. Segregation and location are an important means of separating the signal from noise and competing sources. Consequently, symmetry of the IHEAP in BAEP could reflect changes in auditory processing⁽²¹⁾.

In the current study, there was no association between neurological protocol and IHEAP-amplitude (Table 4). These data demonstrate, once again, that amplitude is not a good parameter for assessing MOCES. However, the neurological protocol was associated with IHEAP in TEOAE and in BAEP latency, i.e., newborns with central disorder had a lower occurrence of IHEAP in these tests. In addition, NB with central disorder had absent IHEAP-latency more often (90%) than IHEAP in absent TEOAE (60%). According to the literature, TEOAE present greater amplitude variability, while BAEP presents greater stability in test and retest situations. Thus, IHEAP-latency in BAEP detects a greater number of NB with disorders, because their responses are more stable⁽⁷⁾.

There was an association between IHEAP in TEOAE and IHEAP-latency, i.e., NB with IHEAP in absent TEOAE were 12.04 % more likely to present absent IHEAP-latency as well. The estimate of IHEAP-latency is 88.5% if the individual has IHEAP in TEOAE. There was no agreement between IHEAP-amplitude and the other tests. Therefore, once again, it was shown not to be a good test for assessment of the MOCES.

Based on the present results, IHEAP in TEOAE and in BAEP, confirmed to be a good clinical instrument, in addition to being objective and non-invasive for the evaluation of the MOCES. When taking into account the functionality of this system, the evaluation of IHEAP could be performed early on NBs at risk for central disorder with the aim of promoting early intervention, because abnormal processing causes an extremely negative impact on speech and language development.

Thus, future longitudinal studies should monitor the auditory skills of newborns with abnormal MOCES to prove that the absence of IHEAP is a predictor of auditory processing disorders.

CONCLUSION

Preterm newborns with peri-intraventricular hemorrhage showed high occurrence of functional disorder of the auditory efferent system, which could be effectively detected through the

inhibitory effect of the efferent auditory pathway on transient-evoked otoacoustic emissions and in the latency parameter in brainstem auditory evoked potentials.

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Authors' contributions

ECMS: study design, collection and analysis of data, writing of the manuscript;
MFA: advice on all stages of the manuscript.