AUDIOLOGICAL EVALUATION IN INFANTS WITH AGENESIS OF THE CORPUS CALLOSUM

Avaliação audiológica em lactentes com agenesia de corpo caloso

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ABSTRACT

Purpose: to assess the occurrence of hearing loss in infants with corpus callosum agenesis comparing them to children without such malformation. **Methods:** a cohort study in two parts: a retrospective from 2008 to 2011, and prospective from 2011 to 2012. The study group consisted of 12 infants diagnosed with agenesis of the corpus callosum and the control group of 12 infants, matched for sex and post conceptional age. All patients underwent otoacoustic emissions transient stimulus, Auditory Evoked Potential (analysis of the average latencies of waves I, III and V and interpeak I-III, III-V and IV 80dBnNA) and behavioral auditory tests. **Results:** the analysis of the occurrence of hearing impairment evaluationotoacoustic emissions transient stimulusand Auditory Evoked Potential showed differences in both groups, withhighest percentage of normal results in the control group. There was significant difference between the ears, the latencies of wave III and I-III interpeak interval, and lower right in the control group. In behavioral assessment, there was significant difference between the groups in relation to normal and abnormal results, with higher prevalence of central alteration in the study group. Also in this group, the second assessment showed a statistically significant higher rate of abnormal results when compared to the first assessment. **Conclusion:** hearing disorders in infants with corpus callosum agenesis were not identified at birth, but within the first six months of life. Most of the changes occurred in the central auditory pathway in the brainstem.

KEYWORDS: Corpus Callosum; Hearing; Evoked Potentials, Auditory; Infant

INTRODUCTION

The corpus callosum is the main route connecting the cerebral hemispheres. Its function is to allow the transfer of information from one hemisphere and another causing them to act harmonically[1]. Its formation starts at approximately the 12th week of intrauterine life and is fully developed between the 18th and 20th week of gestation[2,3].

Agenesis of the corpus callosum, as well as dysgenesis, refers to a source of malformation of the embryogenesis of the telencephalon and is applied to various degrees of abnormality from the total absence of its commissures (agenesis) to its minimum deficiency development[4,5]. Agenesis or dysgenesis occurs in 1-3:1000 births[4].

Clinical manifestations of agenesis of the corpus callosum are extremely variable. Isolated agenesis of the corpus callosum may be asymptomatic or present central nervous system disorders including epilepsy, sensorineural hearing loss among hydrocephaly and others[6-8].

Studies show a relationship between the absence of the corpus callosum and dichotic listening with the right ear advantage reflecting the dominance of the left hemisphere for speech. The role of the corpus callosum in dichotic listening has been studied due to the fact that it would be the bridge for the transfer of auditory information from one hemisphere to the other[9].

To check the peripheral and central auditory functions in children, it has been recommended to use the otoacoustic emissions test (OAE), auditory

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brainstem response(ABR) and the Behavioral Assessment of auditory[10].

OAEs have to evaluate the functionality of the cochlea, specifically external hair cells[11]. Auditory brainstem response (ABR) is the most widely used in clinical practice because it can be applied to newborns to evaluate the integrity of the central auditory pathway[12]. Other methods to assess the peripheral and central auditory function include auditory observations and behavioral and visual reinforcement audiometry. By six months of age the behavioral assessment observation of some auditory skills (attention, location) and visual reinforcement audiometry evaluates the peripheral auditory function to obtain the hearing thresholds.

Based on these, and considering that the hearing loss (peripheral or central) impair language development, the aim of this study was to verify the occurrence of hearing loss in infants with abnormal corpus callosum, comparing them to children without such malformations.

METHODS

The study was initiated after approval by the Ethics and Research Committee of the Federal University of São Paulo under number 02840412.1.0000.5505.

This was a cohort study divided into two parts: retrospective analysis of the records from 2008 to 2011 with the results of the assessments already carried out in infants with agenesis of the corpus callosum, and prospective from 2011 to 2012 with conducting evaluations at birth, and between 6 and 16 months of age.

To perform the prospective part of this study, the legal guardian have read and signed the consent form, according to Resolution 196/96, thus agreeing with the participation of infants in this study.

The sample was divided into two groups: Study Group (SG) consisted of 12 infants (eight males and four females) with a mean gestational age of 35.95 weeks, and corrected age at the time of OAE and ABR of 41.26 weeks, born in the maternity of the Hospital of São Paulo, Federal University of São Paulo (HSP / UNIFESP) between 2008-2011 with diagnostic neuroimaging of agenesis of the corpus callosum. The control group (CG) consisted of 12 infants born in the same period, without neurological damage, including eight males and four females, with a mean gestational age of 35.51 weeks, and corrected age at the time of OAE and ABR was 39.27 weeks.

Returned for audiology follow up for Behavioral Assessment, 12 patients (50%), six from the Study group (four males and two females) and six of GC (four males and two females), and mean corrected age of 8.8 months for SG, and 8.5 for the GC.

Sample was performed by reading medical records of infants in the GC and SG, it was surveyed: gestational age, gender, results of neuroimaging, the presence or absence of risk factors for hearing loss, the search results of examinations of otoacoustic emissions (OAE), Auditory Brainstem Response (ABR), constant of the protocol for Newborn Hearing Screening of the same hospital.

Inclusion criteria were established to determine the groups: the study group (SG) was formed by infants with change on callosum confirmed by imaging performed during the prenatal and / or postnatal (first months of life). The control group (CG) consisted of infants with no change in the corpus callosum and / or central nervous system, such as syndromes, encephalopathy (hydrocephalus, microcephaly, seizures, cerebral palsy). The infants were matched for gender and approximate age at the time of the examination of the infants of the SG.

All infants were evaluated at birth with transient evoked otoacoustic emissions (TEOAE)and Auditory Brainstem Response.

The ABR and transient evoked otoacoustic emissions (TEOAE) were carried out in the sector of the Newborn Hearing Screening HSP / UNIFESP and Behavioral Assessment Clinic in the Department of Hearing Disorders, Federal University of Sao Paulo.

The preparation of all infants for the testing occurred after the inspection of the external auditory canal through otoscope WelchAllyn brand to visualize the tympanic membrane.

The TEOAE was performed after positioning the probe ear of the automatic portable *AccuscreenPRO* in the ear canal of infants, for assure the acoustic stimulus.

The *AccuscreenPRO* was calibrated by the manufacturer for automatic analysis by statistical binomial responses, allowing obtaining record of "PASS" or "FAIL" in EOAT[13].

The ABR was performed with the equipment model Smart-EP, *IntelligentHearing Systems* brand, in intensity of 80dBnNA (for the research of the integrity of the auditory pathway), using the acoustic stimulus of rarefaction polarity type, presentation speed of 27.7 / sec with replication of traces.

For the analysis of ABR responses, it was measured the absolute latencies of waves I, III, V and interpeaks I-III, III-V, IV. The normal criteria considered was the one indicated in the Smart-EP Intelligent Hearing device[14].

The classification of the changes found in ABR follow the criteria below: raise on changesof conductive behavior are shown when the absolute

latencies of waves I, III and V, take place, with normal interpeaks; changes of moderate cochlear type characterized by absolute latencies of waves I, III and V and interpeak with normal electrophysiological threshold and increased presence of wave V only in cases of cochlear loss being severe or profound, without TEOAE in both cases; retrocochlear alterations, characterized in various ways as interpeak latency increased, absence of waves III and V and the presence of only wave I, absence of all waves, lack of reproducibility, interaural difference of of interpeak latency on I-V waves, or the absolute latency of wave V greater than 0.3ms[15].

The follow up was conducted between six and 16 months with the Behavioral Assessment which comprised: behavioral observation, visual reinforcementaudiometry, recognition and voice recognition commands.

In behavioral observation, sound stimulus was delivered through the musical instrument rattle (77dBNPS) presented at 20 cm from the pinna of the child in a lateral plane. It was expected as a response,the lateral location, down and up, being directly or indirectly, according to age by the time of the examination[16].

A study of the cochleo-eyelid (eyelid movement in response to a sudden stimulus of high intensity) was performed by the percussion of the great bell musical instrument – *Agogô*(100dBNPS) – according to the evaluation parameters of Azevedo[16]. For this research, the infant was seated next to the legal guardian of the child, and the stimulus played at 20 cm from the infant'sear[11].

The visual reinforcement audiometry was performed with the pediatric audiometer Interacoustics PA-2, which produces pure tones modulated (warble) in the frequencies of 500Hz, 1000Hz, 2000Hz and 4000Hz, the 80dBNA, 60dBNA, 40dBHL and 20dB HL. The modulated pure tones were presented at 20 cm from the infant's ear, right and left, in the frequencies of 1000, 2000, 4000 and 500 Hz, in that order. The light stimulus as reinforcement was triggered when the answer was of no sound localization to turn his/her head toward the sound. It was consideredas minimum level of response,the lesser intensity occurred in that location, for each sound frequency[16].

In testing for voice suggested by Norhern and Downs[17] the verbal stimulus was the natural speech of the familyat 50 cm, in a lateral direction towards the ear of the child without amplification and without providing visual cues. To investigate the recognition of orders we used the procedures proposed by Azevedo (1991) for children aged between 12 and 15 months. Responses were classified according to the references of normality for the age[18].

It was considered as suggestive of alteration in central Behavior Assessment Hearing, children who had the following responses: exaggerated responses, increased response latency, difficulty with sound localization with normal acuity, absence of habituation to repeated stimuli and cochleo-eyelid absent to those of normal hearing acuity[19].

The test results of TEOAE, ABR and auditory behavior were analyzed in two groups, taking into account the responses for each age and compared for possible differences in the development of auditory skills.

RESULTS

It was applied the *ANOVA* statistical test forthe quantitative analysis of the latencies of ABR, and Testing Equality of Two Proportions for qualitative analysis of the study. It was defined a significance level of 0.12 (12%), considering the small sample size and the fact that the data are qualitative and less sensitive to changes.

The analyses used for this software were: SPSS V17, Minitab 16 and Office Excel 2010.

The distribution of the sample with respect to gender is shown in Table 1.

Table 1 - Distribution of the sample in relation to gender

Gender	Female		Male		p-value
	n	%	n	%	
Study	4	33,3%	8	66,7%	0,102
Control	4	33,3%	8	66,7%	0,102
P-valor	1,000		1,000		

n: number of the sample; equality test of two proportions, p-value - 0.12

In the distribution of gender subjects, it was noticeable that there were differences between the percentages of male and female for both groups, in which there was a higher percentage of male.

The occurrence of hearing loss in the first audiological evaluation conducted with ABR and TEOAE is described on Table 2.

Table 2 - Occurrence of changes in groups during the first hearing evaluation (ABR + TEOAE)

Neonatal	Normal		Changed		p-value
	n	%	n	%	
Study	10	83,3%	2	16,7%	0,001
Control	12	100,0%	0	0,0%	<0,001
P-valor	0,140		0,140		

n: number of the sample; equality test of two proportions, p-value - 0.12

In intragroup statistical analysis, it was concluded that there were differences in both groups with the highest percentage of normal results. There was no statistical significant difference in the comparative analysis between the groups.

The values of latencies of waves I, III and V and interpeaks I-III, III-V and IV obtained in the control group comparing the right and left ears are shown in Table 3.

Table 3 - Descriptive measures of average (mean) and standard deviation of the latencies of waves I, III and V, and interpeak I-III, III-V and IV of the Control Group

CG	Right Ear		Left Ear		p-value
	Mean	SD	Mean	SD	
I	1.80	0.11	1.80	0.07	0.818
III	4.61	0.13	4.71	0.16	0.005
V	7.07	0.22	7.10	0.22	0.367
I-III	2.81	0.16	2.91	0.16	0.005
III-V	2.46	0.19	2.39	0.18	0.146
I-V	5.27	0.25	5.30	0.23	0.389

SD: standard deviation, GC: control group, p-value - 0.12.

In the control group there was a statistically significant difference on the ears, the latencies of wave III and interpeak interval I-III, with lower latency and interpeak for the right ear.

The occurrence of hearing alterations in the Audiological test performed between six and 16 months is presented in Table 4.

Table 4 - Occurrence of hearing loss in Audiological follow up (6-16 months) compared to groups

	Normal		Changed		p-value
	n	**%**	**n**	**%**	
Study	2	33,3%	4	66,7%	0,248
Control	6	100%	0	0%	<0,001
P-valor	0,014		0,014		

n: number of the sample; equality test of two proportions, p-value - 0.12

There was a higher incidence of normal results in the control group. When comparing both groups, there was a statistically significant difference in relation to normal findings as well as regarding the changed ones.

The distribution of auditory type obtained in behavioral evaluation of six and 16 months in SG are shown in Table 5 and illustrated in Figure 1.

Table 5 - Distribution of change type during behavioral assessment in the Study group

Behavioral assessment (SG)	n	%	p-value
Central Alteration	3	75%	0,157
PeripheralAlteration	1	25%	

n: number of the sample; behavioral assessment, equality test of two proportions, p-value - 0.12

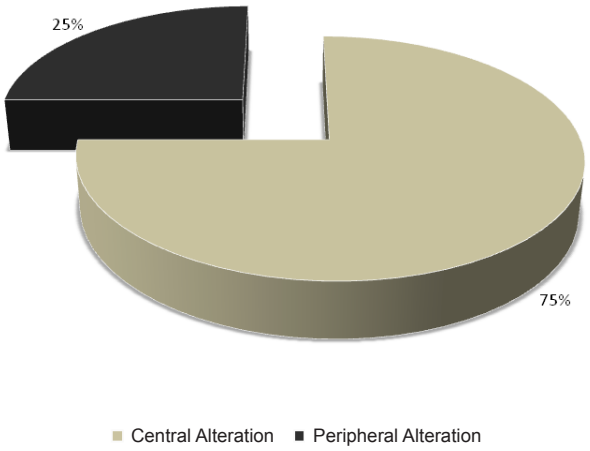

Figure 1 - Distribution of the type of change in behavioral assessment in the SG

It was concluded that there was no statistical difference between central and peripheral changes in SG. However, there was a tendency for differences, with increased central alteration.

The occurrence of hearing loss in SG comparing the first and second evaluation is presented in Table 6.

There was statistical significant difference between the first and second evaluation performed in the SG.

Table 6 - Occurrence of change in both periods in the Study group

Study Group	Neonatal		Behavioral assessment		p-value
	N	%	n	%	
Normal	10	83,3%	2	33,3%	0,034
Changed	2	16,7%	4	66,7%	0,034

n: number of the sample; behavioral assessment, equality test of two proportions, p-value - 0.12

DISCUSSION

In this study, the objective was to verify the possible hearing alterations in infants with agenesis of the corpus callosum in both the neonatal period and after six months of age. It is worth mentioning the difficulty encountered in patients return for audiological follow-up, in both groups. Only half of the subjects returned, even after phone contact, stating the importance of the follow up. This may be due to low socio economic and cultural background of the population treated at Hospital of Sao Paulo, which often hinders the return to appointments. Moreover, such children need other medical specialties treatment as well, especially pediatric and neurology. Therefore, the ideal scenario would be of multidisciplinary care involving other health professionals, avoiding excessive returns to hospital.

Studies relate the difficulty in monitoring patients with risk factors for hearing loss[20,21].

The agenesis of the corpus callosum (ACC) is one of the most common birth problems in humans; however it is difficult to define an exact incidence because the literature is varied[22].

In the present study it was possible to note a greater number of males with agenesis of the corpus callosum (66.6%) compared to female (33.3%). This finding is in accordance to the literature, in which there is a higher prevalence of ACC in males[22-24].

Also in this study, children were assessed at two points in the neonatal period and between six and 16 months of age. The development of hearing has its critical period in the first year of life during the maturation of the nervous system central[19]. Thus the speech therapy is extremely important.

During the first evaluation the TEOAE and ABR were performed. These tests are recommended by the Joint Committee onInfantHearing to identification of hearing losses to assess both the peripheral portion of the hearing, such as the cochlea, and the auditory brainstem nerve.

In the study group, the 12 who underwent Audiological assessment at HSP / UNIFESP, ten (83.3%) had normal results on ABR and TEOAE, and two (16.7%) had abnormal results. In the control group, 12 (100%) the patients selected had adequate results for age (Table 2), thus, the majority of children in both groups showed no changes or alterations.

These results are similar to those obtained in Newborn Hearing Screening performed with OAE and ABR in infants with and without risk, in which more than 90% of newborns without risk and more than 80% of those under risk presented normal OAEs and AABR[25].

In the evaluation of ABR in SG and CG, the mean values of latencies of waves I, V IIIand interpeaks I-III, III-V and IV were higher than those obtained in studies of infants at term and pre-term[26-28]. Such differences could be attributed to differences in equipment used, parameters such as velocity and polarity of the stimulus or age differences in the day of evaluation.

In the evaluation of the ABR, the control group showed a statistically significant difference between the ears, the latencies of wave III and interpeak interval I-III, with lower latency and interpeak for the right ear. This finding is similar to that obtained by Casali and Santos[26] that evaluating neonates, lower latency was observed and interpeak I-III in the right ear.

The study in neonates with ABR (click) identified asymmetry of auditory function with small but significant ear advantage for the right ear [29].

However, other studies found no statistical differences between the ears to the absolute latencies and interpeaks[25,26,30].

The behavioral assessment is used to monitor auditory development, reflecting maturation of the central nervous system. Skills that require intact auditory pathway are required. Audiological assessment conducted between six and 16 months, enabled to check statistically significant occurrence of hearing between the groups, in which SG had a higher occurrence of changes (67.7%) compared to 100% normality of CG.

In theSG, comparing the occurrence of changes in evaluations performed in the neonatal period and after six months of age, the difference was statistically significant, with a reduction of normal, from 83.3% to 33.3% and increased occurrence of hearing loss, from 16.7% to 66.7%. This finding demonstrates the importance of an audiological follow up of infants who have agenesis of the corpus callosum, whereas the groups did not differ in the neonatal period. However, groups differed in the assessment between six and 16 months. This result was expected, since central changes tend to interfere with the development of auditory skills.

As children who have changes in hearing, tend to have a higher incidence of language disorders, children with agenesis of the corpus callosum could be considered at risk for language delay.

Regarding the type of change evident in SG, there was a trend toward higher incidence of central alteration in SG. In the SG behavior assessment, it was found that four infants showed changes, three with central alteration and a patient examination with suggestive cochlear hearing loss on the left ear and normal hearing in the right ear.

The central changes identified in the evaluation were characterized by infants who have not responded or showed increased thresholds in visual reinforcement audiometry. In fact, the inconsistency of response to pure tones with better responses to sounds as broad spectrum broadband noise and narrowband is considered as a sign of neurological change[31]. The child with inconsistent response to pure tones between six and 12 months, have 4.7 times higher chance of presenting neurological alteration at the age of three[32]. Also, infants with agenesis of the corpus callosum showed delay in the recognition of commands which is also considered a sign central change[31]. Study states that children who do not recognize orders between 12 and 18 months have 12.5 times higher chance of having language delay between four and six years old[33]. Children on the SG also presented change in ability to locate sounds, during the follow up. The difficulty of sound localization with normal hearing has been regarded

as a sign of change in the auditorycentral nervous system[31]. Study revealed that children who do not properly localize sound from six to nine months have 1.69 higher chance of having language impairment between four and six years of age[33].

For the processing of auditory information,it is required integrity of structuresof the brainstem to the cortex. Auditory processing skills include attention, detection and identification of a sound stimulus. The corpus callosum serves as a bridge for the transmission of information from one hemisphere to the other, which could hinder the transfer of auditory information, undermining the central auditory processing. Difficulties in dichotic listening in patients with abnormal corpus callosum are described in literature[9]. Studies show a relation between the absence of the corpus callosum and the ability to change dichotic listening, with the use of verbal stimuli; there is right ear advantage reflecting left-hemisphere dominance for speech[9]. It would be important to recommend the evaluation of processing hearing for children with agenesis of the corpus callosum.

It is noteworthy that an infant, who had normal hearing at birth, came to present cochlear hearing loss on the left during monitoring. In this case, there would be the possibility of the occurrence of Mondini dysplasia, in which the child is born with normal hearing and presents progressive hearing loss during the first year. In fact, due to the return of this patient in other specialties, it was identified that was suspected genetic syndrome with developmental delay. The agenesis of the corpus callosum has been found in association with neurosensorial hearing loss[7,8]. Smith et al.[34] reported a case of association between agenesis of the corpus callosum and Mondini dysplasia.

According to the literature, it is most common malformation of the corpus callosum alone, it can be found in association with nearly twenty-five genetic syndromes, inborn errors of metabolism, and excessive maternal use of alcohol and cocaine[35-37]. Another study in which the author evaluated 41 patients with agenesis and dysgenesis of the corpus callosum,it was identified in 32% a genetic prevalence[38].

Thus, the study suggests that hearing loss in infants with abnormal corpus callosum cannot be identified at birth with the TEOAE and ABR probably due to the location of the structures. The identification of changes was greater in the behavioral assessment performed between six and 16 months, which require listening skills and more complex interaction between the hemispheres. Thus, it is extremely important the speech therapy early in life, as these children who have central alteration between six and 16 months are considered at risk for language delay and learning difficulties at school.

Further studies including evaluation of central auditory processing in children with agenesis of the corpus callosum are needed.

CONCLUSION

There was a higher incidence of agenesis of the corpus callosum in males.

In the first evaluation performed in the neonatal period there was no difference between the control and study groups.

In the control group there was a statistically significant difference between the ears with latencies of wave III and interpeak interval I-III, and lower latency and interpeak for the right ear.

Evaluation during the second semester of life showed differences between the groups, with the presence of higher occurrence of changes in the group with agenesis of the corpus callosum.

There was one case of progressive cochlear loss, and most of the alterations were of the central auditory nervous system type.

RESUMO

Objetivo: verificar a ocorrência de alterações auditivas em lactentes com alteração do corpo caloso, comparando-os a crianças sem tal malformação. **Métodos:** estudo de coorte dividido em duas partes: retrospectivo de 2008 a 2011 e prospectivo de 2011 a 2012. O grupo estudo foi constituído por 12 lactentes com diagnóstico de agenesia de corpo caloso e o grupo controlepor12 lactentes, pareados por idade pós concepcional e sexo. Todos realizaram Emissões Otoacústicas Evocadas por Estimulo Transiente, Potencial Evocado Auditivo de Tronco Encefálico (análise da média das latências das ondas I, III e V e interpicos I-III, III-V e I-V a 80dBnNA) e Avaliação do Comportamento Auditivo. **Resultados:** na análise da ocorrência de alteração auditiva na avaliação com Emissões Otoacústicas Transientes e Potencial Evocado Auditivo de Tronco Encefálico, houve diferença em ambos os grupos com maior percentual de resultados normais no grupo controle. Houve diferença significante entre as orelhas, nas latências da onda III e intervalo interpico I-III, menor à direita, nogrupo controle. Naavaliação comportamental, houve diferença significante entre os grupos em relação aos resultados normais e alterados, com maior ocorrência de alteração central no grupo estudo.Ainda neste grupo, a segunda avaliação mostrou maior índice de resultados alterados quando comparados à primeira avaliação, sendo estaticamente significante. **Conclusão:** as alterações auditivas nos lactentes com alteração do corpo caloso não foram identificadas ao nascimento, tendo sido apenas a partir de seis meses de vida. A maioria das alterações ocorreram na via auditiva central, no tronco encefálico.

DESCRITORES: Corpo Caloso; Audição; Potenciais Evocados Auditivo; Lactente

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