Original Article

Children with phenylketonuria: basic audiological evaluation and suppression of otoacoustic emissions

Crianças com fenilcetonúria: avaliação audiológica básica e supressão das otoemissões

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ABSTRACT

Purpose: To evaluate the auditory pathways of children with early-treated phenylketonuria through audiometry, immitance tests, and suppression of transient otoacoustic emissions. **Methods:** Prospective cross-sectional study with sample composed by 28 children: 12 with phenylketonuria and 16 without the disease. Participants underwent auditory evaluations composed of air- and bone-conduction pure-tone audiometry, speech audiometry, immittance tests and suppression of transient otoacoustic emissions. **Results:** All participants presented normal results in pure-tone and speech audiometry; however, speech discrimination scores were lower on the phenylketonuria group. Immitance tests revealed normal tympanograms for all children, but stapedial reflex thresholds demonstrated higher thresholds in 2 and 4 kHz for children with phenylketonuria. The suppresion of transient otoacoustic emissions did not show difference in the comparison between groups. **Conclusion:** The basic audiologic assessment do not identify hearing disorders in children with phenylketonuria; however, speech discrimination scores were lower and stapedial reflexes were higher in these children, which may indicate auditory processing disorders. The study of the suppression of transient otoacoustic emissions demonstrated integrity of the olivocochlear efferent system in children with phenylketonuria.

Keywords: Hearing; Phenylketonurias; Hair cells, auditory; Hearing disorders; Otoacoustic emissions, spontaneous

INTRODUCTION

Phenylketonuria (PKU) is a metabolic disease that is genetically transmitted in an autosomal recessive form, caused by a mutation in the gene that codes the phenylalanine hydroxylase enzyme, which is responsible for transforming the amino acid phenylalanine into tyrosine[1,2]. Elevated levels of phenylalanine in the blood facilitates the passage of this enzyme in excessive amounts into the central nervous system, where its accumulation results in a toxic effect with mental retardation being the most significant manifestation of this disease[3-5]. Thus, failure to treat PKU is associated with a high risk of damage to cognitive development[6].

In infants with PKU, no apparent abnormalities are observed at birth, because the mother's liver protects the fetus[3]. Undiagnosed children who do not receive early treatment may not achieve the necessary initial brain development and may present progressive impairment in brain function. When the disease is not treated at the right time, symptoms such as irritability, learning difficulty, lack of attention, behavioral disturbances, hyperactivity, and seizures may occur between the ages of 6 and 18 months[3].

Excess levels of phenylalanine and its catabolites in the blood has a toxic effect on the somatic functions and central nervous system, interferes in cerebral protein synthesis and myelination, reduces the formation of serotonin, and alters the concentration of amino acids in the spinal fluid. These impairments lead to a loss of intellectual functions, locomotion and speech in the carrier, together with hyperactivity, tremors, microcephaly, growth impairment, and principally, irreversible mental retardation of a varying degree and intensity[3].

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Conflict of interests: None

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PKU is diagnosed using the *Teste do Pezinho* (Guthrie Test), which is mandatory throughout Brazil, as stipulated in the Statute on Children and Adolescents)[7]. In Minas Gerais, this test is performed at the Center for Research in Diagnostic Support of the Faculty of Medicine at the Universidade Federal de Minas Gerais (UFMG). Patients with diagnostic suspicion are directed to the Special Genetics Department of the Hospital das Clínicas (UFMG), where they are evaluated by an interdisciplinary team[5].

Treatment for PKU is essentially by maintaining proper diet; when initiated at an early stage, which is usually within the first 30 days after birth (ideally within the first 21 days), this treatment method can even prevent impairments from a biochemical as well as clinical point of view. The dietary treatment involves the exclusion or substitution of all foods containing phenylalanine[8]. The treatment has to be maintained throughout the patient's life, because even after complete neurological development of the individual, presence of high levels of phenylalanine can impair cognitive functions. The amount of phenylalanine that can be ingested depends on the existing plasma levels of phenylalanine, activity of hepatic phenylalanine hydroxylase enzyme, and tolerance to phenylalanine, which can vary among individuals[3]. Although early intervention can prevent clinical manifestations of PKU, some children are known to show global development delay and hearing and language deficiencies[9].

Because PKU is a disease that compromises the myelination process even in children who are treated early, the evaluation of peripheral and central hearing must be performed in these children to identify possible hearing impairments. Recent studies show the need for further research related to the identification of possible deficits involving lesions in other areas of the central nervous system, toward more in-depth knowledge of the genetics and biochemistry of PKU, need for other treatment options, and development of new therapeutic strategies for these patients[10-12].

Otoacoustic emissions (OAE) are defined as release of sound energy produced in the cochlea that is propagated through the middle ear until it reaches the external acoustic meatus[13]. In normal individuals, these sounds are generated spontaneously or in response to an acoustic stimulus by the external ciliated cells (ECC) and is captured in the external acoustic meatus by amplification, because these sounds are of low intensity. The ECC facilitates an increase in the intensity of a stimulus to up to 50 dB[13]. The ECC amplifies the sounds created by movements of the basilar membrane, by quick and slow contractions, which are controlled by the efferent auditory system, to aid in frequency selection. The OAE supply information on the functioning of the organ of Corti and the efferent system[13].

OAE have great importance and is used in the following situations: differential diagnosis of peripheral and central hearing impairments in children with other disabilities, such as autism and encephalopathies, during neonatal and school hearing screenings; monitoring cochlear function in individuals exposed to extreme noise or medication with ototoxic drugs; analysis and diagnosis of sudden and progressive hearing loss; cochlear dysfunction due to endolymphatic hydrops and metabolic impairments; and evaluation of the medial olivocochlear efferent system[14-16].

Suppression of OAE is characterized by reduction in the amplitude of the responses obtained by application of a stimulus ipsilaterally to or against the ear during evaluation in individuals with healthy auditory pathways[14]. This is because of the action of the medial olivocochlear efferent system, which functions as a modulator and adjusts the active process of the cochlea by slow contractions of the ECC and attenuating the quick contractions. The effect of suppression of the OAE is approximately 0.5 to 1 dBNPS[14]. Noise as well as the stimulus must be presented in low intensities, between 60 and 65 dBNPS, to avoid the effects of activation of the middle ear protection system. A brief stimulus (click) must be used, with blank noise as the attenuating noise, which activates the olivocochlear system, resulting in suppression[14,15].

The suppression of the OAE provides important information about the functioning of the efferent system and the interaction between the afferent and efferent pathways, which aids in showing the difference between peripheral and central hearing losses. No suppression is observed in retrocochlear hearing loss in patients who have undergone vestibular neurectomy[16], and in cases of with acoustic neuroma, multiple sclerosis[17], and neuropathy[16].

Only few studies have investigated the auditory pathway in PKU individuals. In a recent study[18], compared to the control group, the PKU group showed impairments during basic audiological evaluation, as shown by the poor air-conducted and speech reception thresholds and low speech recognition indices, in addition to an increase in the stapedial reflex thresholds.

Studies evaluating brainstem auditory evoked potentials (BAEPs) have shown some differences after comparing the results obtained from individuals with PKU and from those of the control group. In a study, which BAEPs were studied in pediatric patients with different neurological disturbances, an increase was observed in the I-V interpeak latency of these potentials in a child with untreated PKU at 14 months of age[19].

A prospective longitudinal study analyzed the development of BAEPs during the first year of life in eight children with early-treated PKU and 58 children without PKU. Thus, it was concluded that the average I-V interpeak latency was significantly greater in the group of children with PKU than in children from the control group. The three principal components of the BAEPs (i.e., I, III, and V waves) were present in all children with PKU throughout the first year of their life. Compared to the control group, the early-treated PKU group showed no differences between the neurophysiological auditory parameters and biochemical or clinical signs[20].

In a systematic review, the presence of hearing impairments was considered related to PKU disease, with only few studies investigating this relationship, with controversial results. While some studies found impairments in the neurophysiological auditory parameters in PKU patients with early or late treatment, others presented results within the normal limits. Hence, the authors concluded that the relationship between PKU and hearing impairments deserves further study to clarify possible peripheral and central hearing impairments in individuals with early-treated PKU[21].

The proposal for this study emerged after monitoring research and reviewing the literature, which showed a scarcity in studies evaluating OAE in children with PKU. Because this genetic disease causes impairments in myelination, and even individuals who have received early treatment present hearing impairments, as established in some studies by using BAEPs, it is necessary to evaluate the efferent auditory pathway in these individuals by OAE suppression.

The objective of this study was to evaluate the peripheral and central auditory pathway by basic audiological evaluation and suppression of transient otoacoustic emissions in children with early-diagnosed and treated PKU.

METHODS

A transversal study was conducted based on the comparison between independent groups, which was approved by the Research Ethics Committee of UFMG (No. 062/07). The sample included 12 children with classic PKU (study group; age between 6 and 13 years) and 16 children without PKU (control group; age between 6 and 14 years). In the study group, we included only those children without any impairment associated with PKU, such as prematurity, evidence or history of delays in neuropsychomotor development, and evident sensory, neuromotor, or psychocognitive impairment. Children with PKU were screened by NUPAD-MG and treatment was initiated to up to 80 days after birth. The control group comprised children recruited from the Pediatric Outpatient Clinic of the home institution to ensure equivalence in the socio-economical level of the two groups. The following inclusion criteria were considered for the control group: type A, tympanometric curve with the presence of contralateral stapedial reflexes on immittance testing; absence of prior history of recurrent otitis; absence of cerumen in the external acoustic meatus; absence of developmental delays or other sensory, neuromotor, or psychocognitive impairment; children born at term with appropriate weight for their gestational age; and children whose guardians have agreed to participate in the study and have signed the informed consent form.

The data were collected at the Audiology Service of the Hospital das Clínicas of UFMG. The audiological evaluation began with meatoscopy, followed by immittance testing, involving the determination of the tympanometric curve and study of contralateral stapedial reflexes at frequencies of 500 Hz, 1, 2, and 4 kHz. The tympanometric tests were conducted using Interacoustics® AZ7 impedance audiometer, and the results were used for classifying the patients on the basis of the criteria proposed by Jerger[22].

After this, a study of audibility thresholds through air and bone conduction was conducted using the Interacoustics® AD229-b audiometer, and the results were used for classifying the patients on the basis of the criteria by Davis, Silverman[23]. The speech audiometry involved determination of the speech discrimination scores (SDS) and speech recognition thresholds (SRT) bilaterally. The OAE study was conducted following this in an acoustically insulated room by using the Bio-logic® AuDx system for recording. White noise of 60 dB intensity was applied to the contralateral ear through a TDH-39 headphone.

After data collection, those of interest to this study were analyzed and compared to investigate possible hearing impairments of children from different groups. The database was structured using Excel, and the statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 15.0. Descriptive statistics, including measures of the central tendency (average) and dispersion (standard deviation), and frequency, were used to characterize children from both the groups in relation to demographic variables; further, these were used to describe the responses obtained in each group. For the analysis of dependent variables, a comparison was first made between the ears of the study patients by using the paired *t* test. In case no differences were detected, then the variables were compared between groups by using the *t* test for independent groups or Mann-Whitney *U* test, when deemed more appropriate (non-Gaussian distribution). For qualitative dependent variables, the comparison between groups was conducted using Chi-squared test. In all analyses, the level of significance was considered as α=0.05.

RESULTS

The intergroup distribution of children in relation to age, gender, and start of treatment was equal (Table 1). The average age of the control group was 10 years and that of the study group was 10 years and 4 months, with no intergroup difference (p=0.160).

Table 1. Distribution of children in relation to age, gender and start of treatment

Variables	Control Group (n=16)	Study Grup (n=12)
Mean age in years (SD)	10.0 (2.2)	10.4 (2.1)
Start of treatment in days of life (SD)	-	34.6 (23.4)
Gender (n)		
Male	9	6
Female	7	6

Note: SD = standard deviation

The analysis of the results from all the evaluations was initiated by comparisons between that of each ear, with difference only for the variable related to the air-conducted thresholds (p=0.028). For all other variables, the average of the values obtained in both the ears was considered for intergroup comparisons.

In relation to the basic audiological evaluation, the air and bone-conduction audibility thresholds were within the standard patterns, and no intergroup difference for the thresholds was obtained (p=0.870 and p=0.652, respectively). In the speech audiometry, the SRT was within normal limits in both the groups (p=0.416). However, an intergroup difference was observed for SDS (p=0.049) (Table 2).

In immittance testing, a type A tympanometric curve was observed in all study participants. In relation to contralateral stapedial reflexes, children from the study group presented an

Table 2. Pure-tone and speech audiometry, and contralateral stapedial reflexes thresholds in all groups

Variable		Control Group (n=16)		Study Group (n=12)		p-value
		RE Mean (SD)	LE Mean (SD)	RE Mean (SD)	LE Mean (SD)	
Pure-tone thresholds (in dBHL)		6.8 (3.8)	5.1 (4.6)	7.8 (5.8)	6.9 (4.6)	0.870
SRT (in dBHL)		13.4 (7.9)	11.6 (7.5)	15.8 (9.0)	15.4 (6.6)	0.416
SDS (in %)		97.5 (3.5)	98.0 (3.3)	94.7 (3.9)	96.7 (3.7)	0.049*
SR thresholds (in dB)	500 Hz	97.2 (6.6)	97.8 (7.9)	100.8 (7.6)	101.2 (9.3)	0.427
	1 kHz	94.7 (6.4)	95.3 (6.2)	99.2 (6.7)	100.4 (7.5)	0.204
	2 kHz	92.8 (7.1)	92.2 (9.5)	100.4 (8.6)	97.5 (6.6)	0.032*
	4 kHz	95.3 (10.4)	96.6 (11.5)	100.4 (13.7)	102.1 (11.8)	0.047*

* Significant values (p≤0.05) – t test

Note: SD = standard deviation; SRT = speech reception threshold; SDS = speech discrimination score; SR = stapedial reflexes; RE = right ear; LE = left ear

increase in their thresholds at frequencies of 2 kHz (p=0.032) and 4 kHz (p=0.047).

The study of transient OAE did not show any intergroup difference for average OAE with noise (p=0.052), without noise (p=0.160), and suppression (p=0.530). Further, no difference was obtained after comparing OAE between the right and left ears without noise (p=0.932), with noise (p=0.733), or suppression (p=0.468) (Table 3).

Tabela 3. Resultados obtidos para as EOA

OAE (in dBSPL)		Control Group (n=16)	Study Group (n=12)
Without noise	Mean (SD)	14.9 (4.1)	13.7 (5.3)
	Minimum	7.4	1.7
	Maximum	21.7	21.2
	p-value	0.052	
With noise	Mean (SD)	13.8 (4.0)	13.3 (5.7)
	Minimum	7.6	-1.8
	Maximum	20.8	21.3
	p-value	0.160	
Suppresion	Mean (SD)	-1.1 (1.2)	-0.4 (1.8)
	Minimum	-3.5	-5.0
	Maximum	1.2	2.9
	p-value	0.530	

t-test (p≤0.05)

Note: OAE = otoacoustic emissions; SD = standard deviation

DISCUSSION

In relation to the time between birth and start of PKU treatment, the average was 34 days (Table 1). In this study, the criterion for inclusion in the study group was diagnosis and start of treatment by the 80th day after birth. Although from the literature, it is recommended that treatment be started by 21 days after birth[1,8], some authors specify that the start of treatment by up to 90 days is desirable[3].

The air-conduction and bone-conduction thresholds were within the normal limits for both the groups. This result was expected because tonal audiometry threshold evaluates peripheral hearing; further, serum accumulation of phenylalanine, which leads to biochemical impairments in the central nervous system, affects the myelination process and does not interfere with the functioning of the middle and/or inner ear. In case demyelination has occurred in the auditory nerve or in the brainstem auditory pathways, the normality of the auditory thresholds is not be observed, because in cases of retrocochlear hearing loss, the audiometric results generally show bilateral symmetric or asymmetric hearing loss of a mild to acute degree[24]. In cases of lesions in the more central areas of the auditory pathway, which manifests in auditory processing disorders, individuals may present normal tonal thresholds[25], as observed in the PKU group.

Type A tympanometric curve was observed for all participants, which showed normality in the functioning of the middle ear. This result was expected, because the symptoms associated with PKU do not include interferences in the functioning of the middle ear, as mentioned earlier. Further, the type A curve was expected with respect to impairments in the retrocochlear auditory pathways of children with PKU.

Regarding contralateral stapedial reflexes, there was a difference in comparison between the groups for frequencies of 2 and 4 kHz, with the PKU group showing high thresholds. This increase in the acoustic reflex thresholds was also observed in another study on children with PKU[18]. A normal tympanogram and stapedial reflexes are strong indicators of the integrity of the middle ear and absence of hearing loss at a severe or acute level. It is known that individuals with auditory processing disorder may present impairments in acoustic reflexes that are evidenced as absence or increase in their reflex thresholds[25], without impairments in the tonal audiometry. Therefore, these patients may present pathological manifestations of the central auditory nervous system[26], and they should be referred for evaluation of auditory processing.

In speech audiometry, the SRTs for both the ears were within normal limits, with no intergroup differences. It must be stressed that these results confirm the air-conduction audibility thresholds[27], which were also within normal ranges for all participants.

Intergroup differences were observed for SDS with the PKU group showing poor averages. This poor performance of children with PKU may also indicate deficits in the processing of auditory information. Another recent study showed higher

SRT and poorer SRT performance in the PKU group than in the control group[18]. Because excess levels of PKU causes deficiency in the production of neurotransmitters, an investigation of the more central auditory areas is necessary to discard the possibility of lesions in the auditory pathway of these patients.

The analysis of OAE suppression did not show any intergroup difference, showing the integrity of the medial olivocochlear efferent system in children with PKU. No studies were found in the literature that showed OAE results in individuals with PKU that could be compared with the findings of this study. Based on this finding and considering the results obtained in studies performed with BAEPs in individuals with PKU, it can be speculated that the auditory pathway of these children showed impairments originating from the brainstem. This is why no impairments were observed during transient OAE suppression, which clarified the functioning of the efferent system and the interaction between the afferent and efferent pathways. As a limitation of the study, the sample was relatively small, which might have interfered with the findings in this study.

CONCLUSION

Basic audiological evaluation by audiometry could not identify hearing impairments in children with PKU. The speech audiometry analysis showed poorer results for SDS in the PKU group, and evaluation of the stapedial reflexes showed that children with PKU show high thresholds at 2 and 4 kHz, which may indicate the deficits in the processing of auditory information.

The evaluation conducted by OAE suppression did not show the differences between children with and without the disease, indicating that children with early-diagnosed and treated PKU do not show damages to the efferent auditory pathways.

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RESUMO

Objetivo: Avaliar a via auditiva de crianças com fenilcetonúria tratadas precocemente, por meio de audiometria, imitanciometria e supressão das emissões otoacústicas transientes. **Métodos:** Estudo prospectivo transversal comparativo com amostra composta por 28 crianças, sendo 12 com fenilcetonúria e 16 sem a doença. Foi realizada a pesquisa dos limiares de audibilidade por via aérea e óssea, logoaudiometria, imitanciometria e supressão das emissões otoacústicas transientes. **Resultados:** A audiometria e a logoaudiometria estiveram normais em todos os participantes. Foram encontrados piores resultados para o índice de reconhecimento de fala (IRF) no grupo com fenilcetonúria. A imitanciometria revelou curva normal para todas as crianças, mas a pesquisa dos reflexos estapedianos demonstrou que as crianças do grupo com fenilcetonúria apresentaram aumento nos seus limiares nas frequências de 2 e 4 kHz. A supressão das emissões otoacústicas transientes não revelou diferença na comparação entre os grupos. **Conclusão:** A avaliação audiológica básica não identifica alterações na audição das crianças com fenilcetonúria, mas há pior discriminação ao IRF e aumento nos limiares de reflexos estapedianos nessas crianças, podendo indicar distúrbios do processamento auditivo. O estudo da supressão das otoemissões demonstra integridade do sistema eferente olivococlear medial nas crianças com fenilcetonúria.

Descritores: Audição; Fenilcetonúrias; Células ciliadas auditivas; Transtornos da audição; Emissões otoacústicas espontâneas

REFERENCES

1. Starling AL, Aguiar MJ. Fenilcetonúria. In: Leão E, Corrêa EJ, Mota JA, Viana MB. Pediatria ambulatorial. 4a ed. Belo Horizonte: COOPMED; 2005. p. 69-70.
2. Monteiro LT, Cândido LM. Fenilcetonúria no Brasil: evolução e casos. Rev Nutr. 2006;19(3):381-7.
3. Scriver CR, Beaudet AL, Sly WS, Valle D. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw-Hill Inc; 2001. p. 1667-724.
4. Mira NV, Marquez UM. Importância do diagnóstico e tratamento da fenilcetonúria. Rev Saúde Pública. 2000;34(1):86-96.
5. Kanufre VC, Santos JS, Soares RD, Starling AL, Aguiar MJ. Abordagem dietética para fenilcetonúria. Rev Med Minas Gerais. 2001;11(3):129-34.
6. Sarkissian CN, Gámez A. Phenylalanine ammonia lyase, enzyme substitution therapy for phenylketonuria, where are we now? Mol Gen Metab. 2005;86(Suppl.1):S22-6.
7. Brasil. Lei Federal 8.069 de 13 de julho de 1990 – Estatuto da Criança e do Adolescente, 7a ed. [Internet]. Brasília: Edições Câmara, 2010. Disponível em: http://bd.camara.gov.br/bd/bitstream/handle/bdcamara/785/estatuto_crianca_adolescente_7ed.pdf?sequence=10
8. Report of Medical Research Council Working Party on Phenylketonuria. Recommendations on the dietary management of phenylketonuria. Arch Dis Child. 1993;68(3):426-7.
9. Melnick CR, Michals KK, Matalon R. Linguistic development of children with phenylketonuria and normal intelligence. J Pediatr. 1981;98(2):269-72.

10. Santos LL, Magalhães MC, Januário JN, Aguiar MJ, Carvalho MR. The time has come: a new scene for PKU treatment. Genet Mol Res. 2006;5(1):33-44.
11. DeRoche K, Welsh M. Twenty-five years of research on neurocognitive outcomes in early-treated phenylketonuria: intelligence and executive function. Dev Neuropsychol. 2008;33(4):474-504.
12. Sarkissian CN, Gámez A, Scriver CR. What we know that could influence future treatment of phenylketonuria. J Inherit Metab Dis. 2009;32(1):3-9.
13. Kemp DT. Stimulated acoustic emissions from within the human auditory system. J Acoust Soc Am. 1978;64(5):1386-91.
14. Collet L, Veuillet E, Bene J, Morgon A. Effects of contralateral white noise on click-evoked emissions in normal and sensorioneural ears: towards and exploration of the medial olivocochlear system. Audiology. 1992;31(1):1-7.
15. Berlin CI, Hood LJ, Hurley A, Wen H. The First Jerger Lecture. Contralateral suppression of otoacoustic emissions: an index of the function of the medial olivocochlear system. Otolaryngol Head Neck Surg. 1994;110(1):3-21.
16. Pialarissi PR. Emissões otoacústicas: estudo dos seus registros com estimulação contralateral em indivíduos com audição normal e sua aplicação no diagnóstico de doenças retrococleares [dissertação]. São Paulo: Universidade de São Paulo - Faculdade de Medicina; 1999.
17. Rabinovich K. Estudos do efeito de supressão nas emissões otoacústicas evocadas transientes em indivíduos com audição normal e em portadores de esclerose múltipla [dissertação]. São Paulo: Universidade Federal de São Paulo; 1999.
18. Mancini PC, Starling AL, Penna LM, Ramos CA, Ferreira MI, Iório MC. Achados audiológicos em crianças com fenilcetonúria. Rev Soc Bras Fonoaudiol. 2010;15(3):383-9.
19. Hecox KE, Cone B, Blaw ME. Brainstem auditory evoked response in the diagnosis of pediatric neurologic diseases. Neurology. 1981;31(7):832-40.
20. Cardona F, Leuzzi V, Antonozzi I, Benedetti P, Loizzo A. The development of auditory and visual evoked potentials in early treated phenylketonuric children. Electroencephalogr Clin Neurophysiol. 1991;80(1):8-15.
21. Mancini PC, Starling AL, Alves CF, Martins TM, Iório MC. Alterações auditivas e fenilcetonúria: uma revisão sistemática. Rev CEFAC. 2010;12(1):140-5.
22. Jerger J. Clinical experience with impedance audiometry. Arch Otolaryngol. 1970;92(4):311-24.
23. Davis H, Silverman SR. Auditory test hearing aids. In: Davis H, Silverman SR. Hearing and deafness. Holt: Rinehart and Winston; 1970.
24. Horacio CP, Goffi-Gomez MV. A contribuição da leitura orofacial na comunicação do neuropata auditivo. Rev CEFAC. 2007;9(3):411-6.
25. Carvallo RM. Fonoaudiologia, informação para a formação - Procedimentos em audiologia. Rio de Janeiro: Guanabara Koogan; 2003. Medidas eletroacústicas da audição: imitância acústica; p. 1-22.
26. Meneguello J, Domenico ML, Costa MC, Leonhardt FD, Barbosa LH, Pereira LD. Ocorrência de reflexo acústico alterado em desordens do processamento auditivo. Rev Bras Otorrinolaringol, 2001;67(6):830-5.
27. Russo IC, Santos TM. A prática da audiologia clínica. 4a. ed. São Paulo: Cortez; 1994. Logoaudiometria. p. 81-122.