Original Article

Artigo Original

Genetic and audiologic study in elderly with sensorineural hearing loss

Estudo genético e audiológico em idosos com perda auditiva sensorioneural

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Keywords

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ABSTRACT

Purpose: This study aimed to correlate probable predisposing factors for sensorineural hearing loss in elderly by investigating the audiologic characteristics and frequency of mutations in genes considered responsible for non-syndromic hearing loss. **Methods:** Sixty elderly patients were separated into two groups: the Case Group, composed of 30 individuals, 21 females and nine males, all 60 years old or older and presenting diagnoses of sensorineural hearing loss, and the Control Group, composed of 30 elderly individuals matched to the experimental group by age and gender, presenting normal hearing. The patients underwent anamnesis and pure tone audiometry in frequencies of 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz. Blood samples were collected from each patient for analysis of mutations in nuclear and mitochondrial genes related to non-syndromic sensorineural hearing loss. **Results:** It was observed a greater tendency to noise exposure and consumption of alcohol in the Case Group. The statistically significant symptoms between the groups were tinnitus and hearing difficulty in several situations as: silent environment, telephone, television, sound location and in church. All the individuals of Case Group presented sensorineural and bilateral hearing loss. The symmetry and progression of the hearing impairment were also statistically significant between the groups. No genetic mutations were identified. **Conclusion:** The most reported symptoms were communication difficulties and tinnitus. The predominant auditory characteristics included sensorineural, bilateral, progressive and symmetrical hearing loss. It was not evidenced a relationship between sensorineural hearing loss in elderly and genes considered responsible for non-syndromic hearing loss as no genetic mutation was found in this study.

Descritores

Perda auditiva
Idoso
Presbiacusia
Surdez
Genética

RESUMO

Objetivo: Este estudo teve como objetivo correlacionar prováveis fatores predisponentes para a perda auditiva sensorioneural em idosos, investigando as características audiológicas e a frequência de mutações em genes considerados responsáveis por perda auditiva não-sindrômica. **Métodos:** Sessenta idosos foram separados em dois grupos: Grupo de Caso, composto por 30 indivíduos, 21 do gênero feminino e nove do gênero masculino, com 60 anos ou mais, apresentando diagnóstico de perda auditiva sensorioneural, e o Grupo Controle, composto por 30 idosos pareados com o grupo experimental por idade e gênero, apresentando audição normal. Os pacientes foram submetidos à anamnese e audiometria tonal liminar nas frequências de 250, 500, 1000, 2000, 3000, 4000 e 6000 Hz. Amostras de sangue foram coletadas de cada paciente para análise de mutações em genes nucleares e mitocondriais relacionados à perda auditiva sensorioneural não sindrômica. **Resultados:** Houve uma maior tendência à exposição a ruído e consumo de bebidas alcoólicas no Grupo de Caso. Os sintomas estatisticamente significativos entre os grupos foram zumbido e dificuldade para ouvir em diversas situações como: ambiente silencioso, telefone, televisão, localização sonora e na igreja. Todos os indivíduos do Grupo de Caso apresentaram perda auditiva sensorioneural bilateral. A simetria e progressão da deficiência auditiva também foram estatisticamente significativas entre os grupos. Não foram identificadas mutações genéticas. **Conclusão:** Os sintomas mais relatados foram zumbido e dificuldades de comunicação. As características audiológicas predominantes foram perda auditiva sensorioneural, bilateral, simétrica e progressiva. Não foi evidenciada relação entre perda auditiva sensorioneural em idosos e genes considerados responsáveis por perda auditiva não sindrômica, pois não foram encontradas mutações genéticas neste estudo.

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INTRODUCTION

Life expectancy has increased throughout the world over the past several decades. According to the World Health Organization-WHO[1], elderly people are those aged over 65 years; however, this reference age is valid for developed countries. In developing countries, such as Brazil, the age that defines elderly people is 60 years. In Brazil, elderly population has increased by 70%, from 1980 to 1999, an increase of six million people aged at least 60 years old and, in 2000, the elderly population reached 14,536,029, representing 8.6% of the total Brazilian population[2].

Throughout the natural aging process, many changes occur in several systems of the body, including the auditory system. Aging of the hearing system includes changes to the ear (outer, middle and inner), auditory pathways in the central nervous system and, especially, the degeneration of cochlear hair cells, which usually causes the hearing loss associated with aging[3]. According to the World Health Organization[1], in 2001, more than 15 million Brazilians had a hearing problem and only 40% of the affected individuals were aware of the disease. Elderly individuals compose an important subset of those affected with hearing problems, and they are the focus of this study.

Hearing loss associated with aging is called presbycusis and presents in a sensorineural manner, either as a progressive or bilateral form, that initially affects hearing of high frequencies[4]. Presbycusis generally occurs in individuals over 60 years old and the likelihood of development increases significantly with age. Additionally, presbycusis is more common in males than in females[5]. It can lead to serious difficulties in oral communication for elderly individuals because people with presbycusis exhibit decreased in hearing sensitivity and a decline in speech intelligibility, reducing their social contacts and greatly reducing quality of life[6].

Despite the high prevalence of presbycusis, it is difficult to prevent, the underlying cause is unknown, and there is no way to reverse the hearing deficit. Some authors have indicated that both endogenous factors, such as heredity or disease (for example: diabetes and hypertension) and exogenous factors, such as nutrition, stress, and exposure to noise, may influence non-syndromic hearing loss[7].

Some studies have also identified several new mutations in genes responsible for non-syndromic hearing loss, including GJB2, GJB6 and mitochondrial genes. Mutations in the GJB2 gene, which codifies the Conexin 26 protein (Cx26), are responsible for more than half of the cases of genetic hearing loss[8].

The relationship between mitochondrial disease and hearing loss was first established by Petty et al.[9], in 1986, from the study of a patient with mitochondrial myopathy and hearing loss. Diseases linked to mitochondrial DNA are passed to both sexes only by the mother and correspond to 0.5 to 1% of the genetic causes of sensorineural hearing loss[10].

Mitochondrial hearing loss can be classified as one of two types: syndromic, when hearing loss is related to a clinical multiple frame (often severe), and non-syndromic, which occurs when the hearing loss is the only symptom, as in aminoglycoside hypersensitivity and presbycusis[11].

Considering the previous information, this study aimed to correlate probable predisposing factors for sensorineural hearing loss in elderly by investigating the audiologic characteristics and frequency of mutations in genes considered responsible for non-syndromic hearing loss.

METHODS

This is a cross-sectional study conducted from August 2008 to June 2010 in the cities of Fortaleza (CE) and Campinas (SP). The research was approved by the Research Ethics Committee of Universidade de Fortaleza, by the Opinion nº 319/2005. The study followed the Resolution nº 196/96 of the National Health Council and the individuals agreed to participate by signing a Free and Informed Consent Term which described the stages of the study and its purpose.

The sample was consisted of 60 elderly patients randomly selected in the city of Fortaleza (CE). The average age of the individuals was 75.2 years, ranging between 61 and 85 years old, and 42 (70%) were female and 18 (30%) were male. The elderly were separated into two groups: the Case Group contained 30 individuals, 21 females and nine males, aged at least 60 years old and presenting diagnoses of sensorineural hearing loss, and the Control Group, which contained 30 elderly individuals matched to the experimental group by age and gender, presenting normal hearing.

The selected patients were referred to the Audiology Department at Universidade de Fortaleza and underwent pure tone audiometry, air and bone pathways, performed with a Grason Stadler-16 audiometer and TDH-29 headphones in an acoustically treated cab. The hearing thresholds of 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz frequencies were measured for all patients to classify them in the groups. The hearing impairment was defined according to the criteria of Bureau International d'Audiophonologie (BIAP)[12]. The audiometries were analyzed and classified according to type of hearing loss, laterality, symmetry and the progressive characteristic was evidenced considering the patients' report. Individuals with neurological diseases or neoplasms were excluded from the study.

According to the inclusion criteria of both groups, the patients were sorted, and answered an audiologic anamnesis containing information on audiologic history such as family history of hearing loss, noise exposure, cranial trauma and ototoxic drugs; situations and environments of hearing difficulty; otologic history as ear pain, dizziness, tinnitus, otorrhea, nauseas, swoons and ear, throat and/or nose surgery; and medical history containing information on general health of the patients.

A peripheral blood sample was collected from each patient by puncturing the fingertip and was sent to the Laboratory of Human Genetics at the Institution for analysis of mutations in nuclear genes, analysis of the 35delG mutation in the GJB2 gene, deletions D (GJB6-D13S1830) and D (GJB6-D13S1854), amplification and sequencing of the GJB2 gene,

study of polymorphisms in the CDH23 gene and study of single nucleotide polymorphisms (SNPs) in the KCNE1, KCNQ1 and KCNQ4 genes. The A1555G mitochondrial mutation and the deletion mtDNA4977 were also investigated.

The Two Proportions Equality Test, which compares if the proportion of responses of two specific variables and/or their levels are statistically significant, was used for statistical analysis. The significance level in this study was set at 0.05 (5%) and the result of each comparison is reported as p-value statistic. Statistically significant results were indicated with the symbol (*) and results tending to be significant were indicated with the symbol (#). The symbol (-x-) was used when it was not possible to apply the test.

RESULTS

The data gathered in this study are presented in Tables 1 to 3. The statistically significant results are properly evidenced in the tables.

DISCUSSION

The age related hearing loss is a complex disorder, influenced by genetic, lifestyle, environmental and stochastic factors[13]. According to the audiologic history obtained in our study (Table 1), there was a greater tendency to noise exposure in patients of Case Group. Previous studies have indicated that

Table 1. Data related to audiologic anamnesis

	Control		Case		p-value
	n	%	n	%	
Audiologic history					
Family history of hearing loss	4	13.3	8	26.7	0.197
Noise exposure	1	3.3	5	16.7	0.085#
Cranial trauma	2	6.7	2	6.7	1.000
Ototoxic drugs	0	0.0	1	3.3	0.313
No	22	73.3	16	53.3	0.108
Situations of hearing difficulty					
Noisy environment	17	56.7	23	76.7	0.100
Silent environment	1	3.3	7	23.3	0.023*
Telephone	5	16.7	19	63.3	<0.001*
Television	2	6.7	19	63.3	<0.001*
Sound location	3	10.0	11	36.7	0.015*
Difficulty with voices	3	10.0	8	26.7	0.095#
Church	1	3.3	11	36.7	0.001*
Parties	1	3.3	4	13.3	0.161
No	12	40.0	4	13.3	0.020*
Otologic history					
Ear pain	6	20.0	5	16.7	0.739
Dizziness	7	23.3	9	30.0	0.559
Tinnitus	8	26.7	19	63.3	0.004*
Otorrhea	1	3.3	4	13.3	0.161
Nauseas	1	3.3	2	6.7	0.554
Swoons	0	0.0	1	3.3	0.313
Ear, throat and/or nose surgery	3	10.0	2	6.7	0.640
No	14	46.7	7	23.3	0.058#
Medical history					
Hypertension	18	60.0	19	63.3	0.791
Allergies	7	23.3	9	30.0	0.559
Visual problems	22	73.3	26	86.7	0.197
Bone diseases	9	30.0	10	33.3	0.781
Diabetes	4	13.3	5	16.7	0.718
Smoke	2	6.7	4	13.3	0.389
Alcohol	1	3.3	5	16.7	0.085#
Tuberculosis	0	0.0	1	3.3	0.313
Malaria	1	3.3	0	0.0	0.313
Cardiac or vascular problems	6	20.0	5	16.7	0.739
Thyroid problems	1	3.3	3	10.0	0.301
Renal disease	1	3.3	3	10.0	0.301

*p-value statistically significant; #p-value next to acceptance limit, tending to be significant; Two Proportions Equality Test

Table 2. Data related to audiologic characteristics

	Control		Case		p-value
	n	%	n	%	
Type					
Sensorineural	0	0.0	30	100.0	<0.001*
Conductive	0	0.0	0	0.0	- x -
Mixed	0	0.0	0	0.0	- x -
Symmetry					
Yes	0	0.0	27	90.0	<0.001*
No	0	0.0	3	10.0	0.076#
Laterality					
Unilateral	0	0.0	0	0.0	- x -
Bilateral	0	0.0	30	100.0	<0.001*
Progression					
Yes	0	0.0	27	90.0	<0.001*
No	0	0.0	3	10.0	0.076#

*p-value statistically significant; #p-value next to acceptance limit, tending to be significant; Two Proportions Equality Test

Legend: - x - = impossible to apply Two Proportions Equality Test

Table 3. Data related to investigated mutations

Genetic mutations	Control		Case		p-value
	n	%	n	%	
35delG (GJB2)	0	0	0	0	- x -
Deletion D(GJB6-D13S1830)	0	0	0	0	- x -
Deletion D(GJB6-D13S1854)	0	0	0	0	- x -
Polymorphisms in gene CDH23	0	0	0	0	- x -
Mitochondrial mutation A1555G	0	0	0	0	- x -
Deletion MtDNA4977	0	0	0	0	- x -

Legend: - x - = impossible to apply Two Proportions Equality Test

factors responsible for sensorineural hearing loss in elderly include the physiological processes of aging, endogenous factors, and environmental causes (exogenous factors)[14,15]. Noise is the most studied and best documented environmental factor causing hearing loss. However, after a lifetime of noise exposure, it is difficult to distinguish between noise induced hearing loss and wage related hearing loss, audiometrically as well as anatomically[13].

Studies have demonstrated that hearing loss has a negative effect on the functional status, on quality of life, on cognitive function, and on the emotional, behavioral and social well-being of the elderly[16]. In the situations of hearing difficulty (Table 1), we identified a statistically significant difference between the groups in several variables: silent environment, telephone, television, sound location and in church. Difficulties in daily routine can be explained by studies that have revealed a decrease in hearing sensitivity and a reduction in speech intelligibility in individuals with presbycusis[6,15,17].

Tinnitus is the subjective perception of sound in the absence of external sound sources. It is defined as a disorder that produces extreme discomfort and it is difficult to characterize, treat and, according to its severity, can exclude affected individuals from their normal social life[18]. Some studies[19,20] have also reported that tinnitus is often followed by development of a hearing deficit. This finding was also observed in our study, as tinnitus showed a statistically significant difference between the two patient groups (Table 1).

Some studies previously identified a significant relationship between alcohol use and hearing loss[21-23]. According to the medical history provided (Table 1), it was observed a greater tendency to alcohol ingestion among the patients of Case Group. Although this relationship between alcoholism and hearing loss has been studied, it remains contradictory due to the fact that the hearing deficit is often associated with age.

Previously published literature indicates that hearing loss in elderly is characterized by sensorineural hearing loss[3,4,24] and presents in a bilateral and progressive form, worsening with age[5,25,26]. In this study (Table 2), all patients in the Case Group presented with sensorineural bilateral hearing loss and reported progressive characteristics, agreeing with published data. A symmetric audiometric characteristic has also been observed in some studies[4,26,27], in agreement with data from our study, in which 90% of the Case Group individuals presented symmetry in their audiometric curves.

It is estimated that over 100 genes are potentially involved in non-syndromic deafness[28]. Mutations in the GJB2 gene have been potentially linked to many cases of hearing loss[8,29]. This gene is involved in both recessive and dominant forms of non-syndromic hearing loss and the most frequent mutation found in this gene is the 35delG[28]. In cases lacking mutations in the GJB2 gene or in heterozygotes for 35delG, mutations in the GJB6 gene (Cx30) may be responsible for the development of hearing loss, as it exhibits a close relationship to GJB2 (about 76% of identical amino acids) and its proximity to the chromosomal location of the Cx26 gene, receiving the same designation of Cx26[30].

This high prevalence reveals the importance of genetic research on investigation of deafness, contributing substantially to determine an accurate diagnostic and an appropriate treatment to the hearing impairment. Nevertheless, it was not identified any genetic mutations related to non-syndromic hearing loss in this study (Table 3).

The sensorineural hearing loss is a multifactorial disorder; therefore, more studies are extremely important in order to investigate the real influence of those factors in the susceptibility of hearing loss in the elderly. Certainly, our small sample does not permit generalization of the findings in the study, however, provides important information to guide further researches on hearing impairment in the elderly.

CONCLUSION

In agreement to the findings, the most reported symptoms were communication difficulties and tinnitus. The predominant auditory characteristics included sensorineural, bilateral, symmetrical and progressive hearing loss. It was not evidenced a relationship between sensorineural hearing loss in elderly and genes considered responsible for non-syndromic hearing loss as no genetic mutation was found in this study.

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**KVCM performed the data collection; analysis of results and writing of scientific article; MFSC guided all the stages of the study; ELS performed the genetic analysis of the study.*

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