THE PREDISPOSITION OF HEARING THRESHOLDS DAMAGE IN ELDERLY UNDERGOING CANCER TREATMENT WITH CISPLATIN

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ABSTRACT

Purpose: To study the hearing thresholds of elderly patients exposed to cancer treatment with cisplatin. Methods: 74 elderly people took part of the study in two groups (control and study). The study group is composed by elderly individuals with a concluded anatomapathological diagnosis of neoplasia and undergoing cancer treatment with exclusive use of cisplatin (approximate dose of 250 mg/m²). Both groups performed anamnesis, meatoscopy, tonal and vocal audiometry.

Results: When comparing the evaluated groups, the presence of hearing loss with presbyacusis characteristics was observed. There was a statistically significant difference for the frequencies of 1 and 6 kHz (p=0,003 and p=0,001) for audiograms with hearing loss and for the frequency of 6 kHz for normal audiograms of the study group compared to the control group.

Conclusion: It is believed that the use of cisplatin, a toxic drug to the hearing organ, predisposed the worsening of frequencies of 1 kHz and 6 kHz.

Keywords: Elderly; Neoplasia; Presbycusis; Hearing Loss

INTRODUCTION

Presbycusis, hearing loss in the elderly, is considered a sensory disorder that affects a large portion of the population. Among its negative impacts, there is a reduction in the quality of life due to difficulties in communication, dependence, frustration, isolation, and even depression. There is also a close link between the presence of hearing loss with repercussions on cognition that may be associated with the dementia process [1-3]

Cancer treatment is another factor that triggers or aggravates a predisposition to hearing loss in the elderly. It is known that the incidence of cancer development in this population is high since many tumors are related to older ages. Neoplasms occupy the 3rd place in multimorbidity rates and have an incidence of 84.6% in the elderly, losing only to diabetes mellitus (97.4%) and cardiovascular diseases (89.7%). Among the most prevalent cancer types in the elderly are breast, lung, and prostate [4,5]

In cancer treatment, chemicals that are toxic to the hearing organ are utilized, and cisplatin is widely used in chemotherapy. It is known that this drug can permanently injure the organ of Corti, however, the damage is directly related to the period and the dose administered. Doses between 200 to 800 mg/m^2 are harmful and hearing damage is irreversible. Hearing loss, in these cases, is usually bilateral and symmetrical, initially affecting high frequencies, then low frequencies, and can cause difficulties in oral communication with a negative influence on the quality of life [6,7]

In addition to hearing impairment, cancer treatment, especially in the elderly population, can trigger neurological manifestations, which are associated with vertigo, lethargy, and sensory deficit. Thus, it is common to worsen hearing symptoms such as auditory complaints and tinnitus. Such factors can also interfere in the life of the patient [5,8,9].

Studies related to the theme are advocated by the literature, since they allow the adoption of rehabilitation measures to actualize oral communication, to improve the social participation of the elderly in society. A multidisciplinary team in geriatrics and oncology is essential to improve the quality of life of this population.

Thus, the objective of the present research is to study the hearing thresholds of elderly people undergoing cancer treatment using cisplatin.

METHODS

The research was carried out between the years 2018/2020 and it is a nested case-control study with cross-section. It was submitted and approved by the research ethics committee (CEP) through the ordinance number 2,801,792.

All subjects who participated in the research signed the informed consent form. Secrecy, anonymity, and the exclusion of participants were guaranteed and respected in all of the stages of this study when requested.

The study included 74 elderly individuals, who were divided into two groups:

Control group (G1): Composed of 37 elderly people and, as an inclusion criterion, the participant had to be older than 60 years. The subjects were seen at the audiology outpatient clinic of the Hospital Universitário de Sergipe, upon demand, or as referred by the doctors of the hospital team.

Cancer group (G2): 37 elderly people participated in this group and were included according to the criteria: age greater than or equal to 60 years old, complete anatomopathological diagnosis of neoplasia, undergoing cancer treatment with exclusive use of cisplatin with an approximate dose of 250 mg/m^2. The subjects were seen in the oncology sector of a public hospital, and the audiological examination was performed in the hospital environment.

The exclusion criteria for both groups were: metabolic changes (diabetes mellitus and arterial hypertension), exposure to noise/acoustic trauma, ear surgery, and ear changes. It is worth mentioning that chemotherapy/radiotherapy, at some point in life, was listed as an exclusion criterion for the control group (G1). Besides, subjects who had undergone radiotherapy and who had an anatomopathological diagnosis of head and neck cancer were excluded from the cancer group (G2).

The convenience sample was chosen based on free demand and the referral of the multidisciplinary team. It is worth mentioning that, to obtain the sample, a time longer than usual was necessary for data collection (approximately two years) since one of the exclusion criteria was the presence of metabolic diseases, common in the elderly population.

The research was composed of the following procedures

Anamnesis: G1 and G2 performed all audiological procedures, but a different anamnesis was applied for each group.

The anamnesis of G1 was devised by professionals from the audiology outpatient clinic of the University Hospital, and this is a procedure performed on all patients who are treated there. It consists of seven parts, namely: identification; main complaint and history of the complaint; hearing health; signs and symptoms; past and current conditions (metabolic and cognitive diseases, medications used, surgeries performed, and history of deafness); professional and leisure activity; as well as the use of hearing aids.

The G2 anamnesis was designed by the researcher responsible for the research. It is divided into three parts: Identification, previous cancer history (time of discovery, symptoms, type of neoplasia, time of treatment start), and aspects related to hearing health (presence or absence of hearing complaint and otological history), as well as metabolic and cognitive changes.

Meatoscopy: An otoscope (Pocket Junior, model 22840, WelchAllyn-USA) was used to detect obstructions of the external auditory canal, and patients with alterations were referred to the otorhinolaryngologist for evaluation and management.

Pure tone audiometry: The examinations were carried out in an acoustic booth, in which they presented a technical report for noise measurement (ISSO 8253-1: 2010). For the testing of the two groups, the same equipment was used, an audiometer from the Interacoustics (Ad 229 B, Denmark, USA) brand with the use of TDH 39 headphones, properly calibrated (ISO 8253). The auditory thresholds were investigated in the inter-octave frequencies from 0.25 kHz to 8 kHz, air-conducted, and from 0.5 kHz to 4 kHz, bone-conducted.

Hearing loss was considered when the hearing thresholds were greater than 25 dBHL at any frequency. As for the type, hearing loss could be classified as: sensorineural (bone-conduction thresholds greater than 15 dBHL and airway thresholds greater than 25 dBHL, with an air-bone gap of up to 10 dB.); conductive (bone-conduction thresholds less than or equal to 15 dBHL and

airway thresholds greater than 25 dBHL, with an air-bone gap greater than or equal to 15 dBHL) and mixed (bone-conduction thresholds greater than 15 dBHL and thresholds of airways greater than 25 dBHL with an air-bone gap greater than or equal to 15 dB [10].

Logoaudiometry: Composed of the Speech Recognition Threshold (SRT) which aimed to assess the minimum intensity level at which the listener identifies 50% of the signal presented. This testing was performed only to confirm tonal thresholds.

Statistical Analysis

AAfter obtaining the data, the results were expressed as values of mean and standard deviation. For the comparison between two groups, under the influence of a single variation factor, the t-test was performed. For the results classified as non-parametric, when comparing two groups, under the influence of a single variation factor, the Mann Whitney test was performed.

In the research analyzes, cancer treatment was considered a fixed factor, with independent factors being hearing thresholds, age, and presence of tinnitus.

All statistical tests were processed using the Statistical Package for Social Sciences version 20 (SPSS, Chicago, USA). The critical level was set at 5% (P<0.05) to admit a difference in means as statistically significant. The graphs were made using GraphPad Prism software version 5.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

The audiometric configuration of the participants was compatible with sensorineural hearing loss with a decrease in high frequencies, affecting a total of 71.6% of the elderly assessed.

As the object of the study is cancer patients, the data described during the research will reference the comparison of G2 and G1.

In the analysis of the study groups, it was found that the G2 had a mean age of 67.72 years old, as described in Table 1.

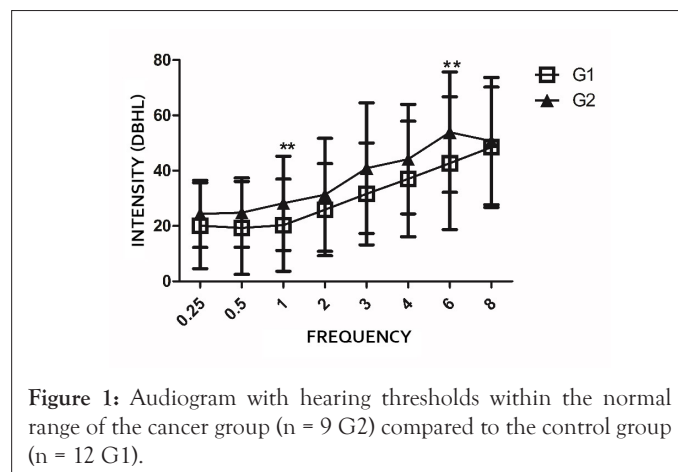| Characteristics	G1 (Control Group)	G2 (Cancer Group)
Age	60 to 85 years old	60 to 84 years old
	(66.95 years old ±6.98)	(67.72 years old ±7.65)
Gender	86.5% female	48.6% female
	13.5% male	51.4% male
Cancer Diagnosis	-----	35.1% prostate
		32.4% breast
		33.5% (uterus, cervix, bone, bladder, stomach, leukemia, liver, and pancreas)
Audiological Report	32.4% normal hearing thresholds	24.3% normal hearing thresholds
	67.6% sensorineural hearing loss	75.7% sensorineural hearing loss

Table 1: Characterization of the Research Subjects Regarding Age, Gender, Cancer Diagnosis, and the Audiological Report (n=37 G1, n=37 G2).

Regarding the age of the study groups, no statistically significant difference was observed (Student's T, p=0.52). There was a greater number of participants in the age group of 60 and 69 years old (70%), followed by 70 to 79 years old (20%) and 80 to 85 years old (10%).

Still in the age-related study, however in the presence of hearing loss, it was found that the older the age, the greater the probability of the presence of hearing loss for both groups. Thus, there is a positive interaction between the age factor in the elderly over 80 years of age and the presence of hearing loss (ANOVA test, p=0.00).

For the analysis of the audiological findings' data, the ears were analyzed in pairs since it was found in the Mann Whitney test an absence of significant differences between the right and left ears (RE and LE) (p ≥ 0.05).

In the analysis of audiometric configuration within the normal range, it was found that the G2 presented a significant worsening of the hearing thresholds for the frequency of 6 kHz when compared to G1 (Figure 1).

Figure 1: Audiogram with hearing thresholds within the normal range of the cancer group (n = 9 G2) compared to the control group (n = 12 G1).

When comparing the audiogram of subjects with hearing loss, from 3 kHz on, there was a significant increase in the hearing thresholds at frequencies of 1 kHz and 6 kHz in G2 when compared to G1 (Figure 2).
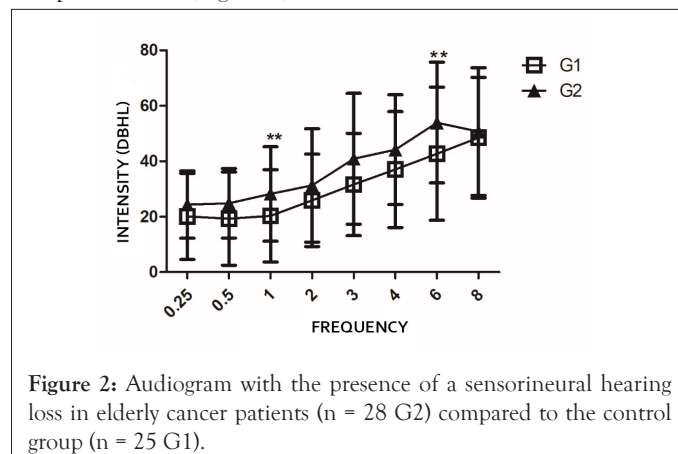

Figure 2: Audiogram with the presence of a sensorineural hearing loss in elderly cancer patients (n = 28 G2) compared to the control group (n = 25 G1).

DISCUSSION

TThe audiological diagnosis in the present study was characterized by an alteration of the sensorineural type with a decrease in the high frequencies in both groups. It is observed that the audiometric findings are compatible with the configuration of presbycusis, age-related hearing loss due to significant changes in the cochlea. It is known that degeneration of the stria vascularis with decreased vascularization is common in the elderly, which leads to a change in the formation of the endocochlear potential. Furthermore, there is still a significant reduction in the endolymphatic potential, with an attenuation of the action potential. Such changes significantly affect the functioning of the cochlear amplifier and cause hearing loss in the elderly [2]. It is also observed that the hearing impairment affected 71.6% of the patients, which is similar to the findings in the literature since about 63% of the elderly population has presbycusis [8,9,11].

The age of the participants ranged from 60 to 85 years, but most were between 60 and 69 years old (70%). Statistical data from the present study revealed a positive interaction between hearing loss and age in the elderly over 80 years old. These data corroborate the literature. After every ten years, the elderly present worse hearing thresholds, with this relationship present in 80% of the elderly over 80 years old [12].

A smaller percentage (28.4%) of elderly people with normal hearing thresholds was observed. However, the majority, in both groups, was diagnosed with sensorineural hearing loss. When comparing the hearing thresholds between the study groups, there was a significant decrease in the frequency of 6 kHz for audiograms within normal limits and in the frequencies of 1 kHz and 6 kHz for audiograms compatible with G2 sensorineural hearing loss. It is believed that the hearing impairment of the cancer group may occur due to the use of cisplatin since the participants did not have metabolic diseases (diabetes/hypertension) and did not use ototoxic drugs either. Also, there is a consensus in the literature about the toxic potential of cisplatin to the hearing organ. Cisplatin can be detected in the human body an hour after its administration and is eliminated by the body in weeks, but it remains active in the cochlea for months or years. It is known that cisplatin has a high-risk potential for damage to the auditory system, and the change in thresholds can occur even after the end of the treatment [13]. The drug affects the stria vascularis, changes the endolymphatic potentials, increases the formation of free radicals and oxidative stress, which generates a cochlear dysfunction triggering sensorineural hearing loss [14-16]. Recent studies report that, besides oxidative stress, there is an inflammatory process caused by cisplatin, which leads to the production of Reactive Oxygen Species (ROS), which are responsible for the cellular damage of DNA and proteins. To recover homeostasis, cochlear hair cells seek to activate mechanisms for DNA repair, but there is a failure in the defense of the system to reverse the inflammatory process and it thus induces the death of the endoplasmic reticulum of hair cells (autophagy, necroptosis, and apoptosis) [17].

It is also observed that the higher the dose of cisplatin, the worse the toxic effect of the drug on the hearing organ. In the present study, the cumulative dose of cisplatin was approximately 250 mg/m^2, and this dose may trigger hearing loss. Frisina et al [7] confirm these findings since doses ≤ 300 mg/m^2 caused moderately severe to profound hearing loss in approximately 30% of the evaluated subjects. The literature also reports that from 100 mg/m^2 it is possible to observe changes in hearing thresholds, however cumulative doses greater than 400 mg/m^2 increase the toxic potential of cisplatin and are more noxious to the hearing organ [18,19].

The hearing loss of G2 in the present research started in the high frequencies, and the data is significant for the frequency of 6 kHz. A study elucidates the significant difference before and after the use of cisplatin at the frequency of 6 kHz [20], which confirms the findings of the present research.

Hearing loss was characterized by a change from 3 kHz, however, the literature reports that the high frequencies are affected from 4 kHz due to the toxic effect of cisplatin [7,14]. It is worth mentioning that the damage to the frequencies is proportionally dependent on the dose administered, that is, the higher it is, the worse the hearing damage, with a higher number of affected frequencies [21].

On the other hand, there is no evidence in the literature regarding the significant worsening of the frequency of 1 kHz in G2, since studies show that hearing loss is rarely detected in the frequency range from 0.25 kHz to 1 kHz [20]. It is worth mentioning that the auditory thresholds of the frequency of 1 kHz were within the normal range, but there was a significant difference regarding G1, which is not reported in the literature.

Regarding the oncological findings of the study group, it is known that the types of neoplasms that most affect the population are: non-melanoma skin (177 thousand), breast and prostate (66 thousand), and colon and rectum (41 thousand), while there is an 11-fold increase in the chances of incidence and mortality for individuals over the age of 65. The present research corroborates the findings since the types of cancer that showed greater prominence were prostate cancer, followed by breast cancer [22,23]

Besides, the average age of the participants in this research was 67.72 years. It is observed that there is a greater susceptibility to the acquisition of neoplasia in individuals over 65 years old, which is considered one of the risk factors for the development of malignant tumors [24].

The present research is limited by the performance of the auditory reference exam in the elderly population. In the oncology service of the hospital where the research was carried out, the elderly, despite being referred for audiological evaluation, most of the time started the antineoplastic treatment before undergoing testing. One of the factors that may have created difficulties in audiometry is the emotional condition of the elderly, more likely to have anxiety and affective disorders such as depression

[25]. Besides, when cancer is diagnosed, there is an association of worsening the quality of life in the elderly, who now need more care [26,27] . The negative impact on the quality of life given by the oncological diagnosis and emotional disorders may explain the difficulty in accessing the audiological exams before starting the treatment. Another fact that reinforces the absence of the elderly in the reference exam is the difficulty in accepting the hearing problem if the person already has difficulty in oral communication [3].

Audiometric monitoring in this population is extremely important since presbycusis associated with cancer treatment can harm the lives of the elderly, worsening their quality of life. There is a change in the transduction of acoustic information by neural impulses, which results in the loss of sound information and leads to difficulties in understanding speech. This factor favors a decline in social activities that can lead the elderly to isolation [3,28]. The diagnosis of hearing loss and the intervention with the use of electronic devices has a positive effect on aspects related to the quality of life [29] and it can minimize the effects of hearing loss due to age and even cancer treatment.

CONCLUSION

The audiometric configuration is compatible with sensorineural hearing loss in high frequencies, common findings in presbycusis.

The elderly undergoing cancer treatment showed high hearing thresholds at the frequency of 6 kHz in normal audiograms and in the frequencies of 1 kHz and 6 kHz and in audiograms with hearing loss when compared to the control group. It is believed that the use of cisplatin, a drug that is toxic to the hearing organ, induced the worsening of these frequencies.

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