Analysis of Hearing Thresholds of the Onco-Pediatric Population Submitted to Chemotherapy Treatment

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Análise dos Limiares Auditivos da População Oncopediátrica Submetida a Tratamento Quimioterápico

Análisis de los Niveles de Audición en la Población Oncopediátrica Sometida a Tratamiento de Quimioterapia

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ABSTRACT

Introduction: Fast and effective treatments are essential for pediatric patients with cancer due to its high risk of mortality. However, the treatment can cause severe side effects, including ototoxicity. **Objective:** To investigate the effect of chemotherapy on hearing thresholds of pediatric patients with cancer and to identify the presence of hearing complaints, psychoacoustic thresholds by frequency and the relations between hearing diagnosis and the variables age, sex and ear (left or right). **Method:** Cross-sectional, observational and contemporary study. Hearing thresholds of 42 children diagnosed with cancer of both sexes, 17 females and 25 males, aged between seven and 11 years old and 11 months were investigated. All children underwent pure tone audiometry for peripheral audiological assessment. **Results:** The sample's mean age was 8.7 years (SD = 1.08). Six children were diagnosed with sensorineural hearing loss (14.3%) and one with conductive hearing loss (2.4%). Borderline hearing thresholds were identified in 31 children (73.8%). **Conclusion:** Changes of hearing thresholds of the sample investigated were associated with chemotherapy exposure. There was a higher prevalence of borderline thresholds and left-ear hearing loss in males, predominantly in the age range of eight years old.

Key words: Hearing/drug effects; Child; Antineoplastic Agents/adverse effects; Ototoxicity.

RESUMO

Introdução: Na infância, o câncer representa um risco elevado de mortalidade, por isso a preocupação em realizar tratamentos rápidos e eficazes. Contudo, o tratamento pode resultar em efeitos colaterais graves, entre eles a ototoxicidade. **Objetivo:** Investigar a associação entre a quimioterapia e os limiares auditivos da população oncológica pediátrica. Além disso, verificar a presença de queixa auditiva, os limiares psicoacústicos por frequência, a relação entre o diagnóstico auditivo e as variáveis: idade, sexo e orelha (esquerda ou direita). **Método:** Estudo transversal, observacional e contemporâneo. Foram avaliadas 42 crianças com diagnóstico oncológico de ambos os sexos, sendo 17 do sexo feminino e 25 do sexo masculino, entre 7 e 11 anos e 11 meses de idade. Todas realizaram audiometria tonal liminar para avaliação audiológica periférica. **Resultados:** A média de idade da amostra foi de 8,7 anos (DP = 1,08). Foram diagnosticadas seis perdas auditivas sensorioneurais (14,3%) e uma perda auditiva condutiva (2,4%). Identificaram-se limiares auditivos limítrofes em 31 crianças (73,8%). **Conclusão:** Verificou-se na amostra que alterações nos limiares auditivos estão associadas à exposição à quimioterapia. Constatou-se maior prevalência de limiares limítrofes e perda auditiva na orelha esquerda, no sexo masculino, predominando na faixa etária dos 8 anos de idade.

Palavras-chave: Audição/efeitos dos fármacos; Criança; Antineoplásicos/efeitos adversos; Ototoxicidade.

RESUMEN

Introducción: En la infancia, el cáncer representa un alto riesgo de mortalidad, por lo que existe una preocupación por llevar a cabo tratamientos rápidos y eficaces. Sin embargo, el tratamiento puede dar lugar a efectos secundarios graves, entre ellos la ototoxicidad. **Objetivo:** Investigar el efecto de la quimioterapia sobre los niveles de audición en niños con cáncer. Además, comprobar la presencia de quejas auditivas, los umbrales psicoacústicos por frecuencia, la relación entre el diagnóstico auditivo y las variables: edad, sexo y oído (izquierdo o derecho). **Método:** Estudio transversal, observacional y contemporáneo. Se evaluaron 42 niños con diagnóstico oncológico de ambos sexos, 17 niñas y 25 niños, con edades comprendidas entre los 7 y los 11 años y 11 meses. A todos se les realizó una audiometría para la evaluación audiológica periférica. **Resultados:** La edad media de la muestra fue de 8,7 años (DE = 1,08). Se diagnosticaron seis hipoacusias neurosensoriales (14,3%) y una hipoacusia conductiva (2,4%). Se identificaron niveles de audición limítrofes en 31 niños (73,8%). **Conclusión:** Los resultados de la muestra demostraron que la quimioterapia afecta a los niveles de audición de estos pacientes. Hubo una mayor prevalencia de niveles de audición limítrofes y pérdida de audición en el oído izquierdo, en los varones, predominantemente en el grupo de edad de 8 años.

Palabras clave: Audición/efectos de los fármacos; Niño; Antineoplásicos/efectos adversos; Ototoxicidad.

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INTRODUCTION

Cancer is the term used to designate over a hundred different types of malignant diseases characterized by the disorderly growth of cells that can invade adjacent tissues or distant organs. Due to its rapid cell division process, these cells multiply uncontrollably, forming aggregates that grow, damage neighboring tissues, and change their physiology[1,2]. In childhood, carcinogenesis is believed to happen due to cells that undergo genetic mutation not maturing as expected, keeping characteristics similar to their embryonic period, making the proliferation of tumors faster in this population. Thus, it is possible to affirm that cancer types identified in children differ from those identified in adults, especially regarding histological type, clinical behavior, and original location, with leukemias, lymphomas, and tumors of the central nervous system being more prevalent[2,3].

The prevalence of neoplasm diagnoses in children corresponds to 1-4% of oncological diagnoses reported worldwide. In Brazil, the reported prevalence ranges from 2% to 3% of the total recorded cancer cases[4]. Cancer represents an elevated risk of mortality, being characterized in the country as the primary cause of death for children aged 1 to 19 years old, representing around 8% of mortality causes in this age group[5]. However, when diagnosed early, it has a great healing potential, estimated at around 70%[6], and treatment can involve chemotherapy, radiotherapy, and/or oncological surgery for tumor removal. The healing probability is higher when combined with more than one treatment modality, but it can also result in severe side effects to the body[7].

Chemotherapeutic drugs universally used in the treatment of neoplasms, especially in children, are effective against cancer. On the other hand, one of their most known side effects is ototoxicity, damaging hearing cells that may cause hearing losses[8]. It must be highlighted that such hearing losses are typically classified as bilateral and irreversible, targeting high frequencies, at first, and can be triggered soon after the first dose of chemotherapy[9,10].

The prevalence of hearing losses due to childhood cancer treatment varies, with reports percentages ranging from 4% to 90% of assessed samples. This heterogeneity is attributed to diverse factors, such as the time of hearing assessment in relation to exposure, type of treatment adopted (chemotherapy, radiotherapy, surgical intervention, or association of methods), and test used in the assessment, among others[11]. However, exposure to ototoxic drugs is known to initially affect the basal portion of the cochlea, compromising high frequencies, and later, can evolve to the apical portion, reaching medium and low frequencies, compromising more frequencies, and impairing the understanding of speech.

From the examined scientific literature, it was possible to verify that most studies analyze the findings of otoacoustic emissions (OAEs) as the hearing assessment method in children[12,13]. Despite being a recommended method for early identification of changes in external ciliated cells, OAEs also have limitations, as they do not provide information on the hearing threshold in each frequency like Pure tone audiometry (PTA), which is the gold standard test for hearing assessment and whose results are necessary to determine hearing rehabilitation strategies[14,15].

Regarding studies analyzing hearing thresholds in the population exposed to chemotherapy in childhood, few studies[16-18] assessed the patients while in treatment. Other studies assessed adults who survived childhood cancer and did not present data from patients before and during treatment as a method for hearing loss screening[19,20]. The fact that those children did not undergo audiometry early may be a consequence of the lack of routine hearing screening actions in oncological treatment centers. A study mentions that 50% of team members routinely performed hearing assessments[21]. In comparison, another study claims that 20% of professionals regularly assessed hearing and 80% of oncologists were unaware of how and when to refer their patients to hearing assessment[22].

In this context, the objective of the present study was to investigate the effect of chemotherapeutic treatment on the hearing thresholds of oncopediatric population during childhood, in periods closer to the exposure to chemotherapeutic drugs. Moreover, to verify the prevalence of hearing impairments, the presence of hearing complaints, psychoacoustic thresholds by frequency, and the relations between hearing diagnosis and the variables age, sex, and ear (left or right).

METHOD

Cross-sectional, observational, and contemporary study. The sample comprised 42 children with cancer diagnoses, both sexes, aged 7 to 11 years and 11 months, referred by partner hospitals of the Rio Grande do Sul Childhood Cancer Institute (*Instituto do Câncer Infantil do Rio Grande do Sul*, ICI). The sample was non-probabilistic and by convenience. All the children followed up by the ICI speech-language pathologists who were in line with the inclusion criteria were assessed.

The inclusion criteria were children with a cancer diagnosis, exposed to chemotherapy, both sexes, aged between 7 and 11 years and 11 months, no risk indicators

for hearing loss before the cancer diagnosis (genetic syndromes, craniofacial anomalies, hyperbilirubinemia, prematurity, low weight at birth, permanence in neonatal ICU longer than 5 days, cytomegalovirus infections, rubella, herpes, toxoplasmosis or human immunodeficiency virus, family history of deafness), with no hearing loss diagnosis before chemotherapy, confirmed by the family during anamnesis and by analyzing ICI medical records, with meatoscopy showing no presence of earwax and aptitude to undergo air and bone-conduction hearing threshold tests and vocal audiometry on the day of assessment. Children from other age groups and who did not understand, or for any reason, could not perform the procedures stipulated in the protocol were excluded.

The cancer diagnosis was consulted in the ICI electronic medical record, which is provided by the children's hospital medical team at the time of referral to the institution, using codes from the 10th Classification of Diseases and Related Health Problems (ICD-10)[23]. Later, these were categorized for analysis according to the International Classification of Childhood Cancer (ICCC)[24].

First, anamnesis was conducted, followed by an inspection of the external acoustic meatus to verify their condition. Next, in the acoustic cabin, PTA was performed, by air conduction, in the 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 6000 Hz, and 8000 Hz frequencies, and by bone conduction, in the 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, and 4000 Hz frequencies.

The World Health Organization classification was used to rate the children's hearing loss[25]. Thus, the mean of the thresholds at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz was calculated. With the mean result, the following hearing thresholds were considered: ≤15 dB normal hearing, 16<30 dB slight hearing loss, 31<60 dB moderate hearing loss, 61<80 dB severe hearing loss, and >81 dB profound hearing loss. Although the adopted impairment classification considers the result of the mean of the four frequencies mentioned above, it was decided to assess the hearing thresholds individually at each frequency. When these were equal to 15 dB, they were considered borderline.

Next, a speech audiometry was conducted using the Speech Discrimination Score (SDS) and Speech Reception Threshold (SRT). To perform SDS, 25 monosyllable words were presented in a fixed and comfortable intensity (ranging from 25 dBNA to 40 dBNA above the mean of 500 Hz, 1000 Hz, and 2000 Hz frequencies in air conduction), in each ear, and the child was oriented to repeat what they heard. For SRT, the initial intensity was 40 dBNA above the mean in the air conduction, being reduced to reach an intensity level in which the patient understood and repeated 50% of the trisyllable words presented. For children with speech or language disorders, simple commands[26] or image identification were used. The audiometer used in the PTA and speech audiometry was by Inventis, Harp model, previously calibrated. It is worth highlighting that speech audiometry was conducted with the aim of confirming results obtained in the PTA.

The data collected were arranged in a Microsoft Excel and Google Sheets spreadsheet and were analyzed in *R Studio*[27] (version 2020.12.0+353) program in R[28] (version 4.2.2). For the statistical analysis, U Mann-Whitney test was used to compare medians, Fisher exact test to compare categorical variables with two levels, and chi-square test for categories with three or more levels. The significance level adopted was 5% (p<0.05).

The present study is part of a research project that has been approved by the Research Ethics Committee, report number 7272930 (CAAE (submission for ethical review): 78453924.5.0000.5334), in compliance with Resolution 466/2012[29] of the National Health Council.

RESULTS

Of the 42 children with a cancer diagnosis, 25 (59.5%) were male and 17 (40.5%) were female, with a mean age of 8.7 years (standard deviation – SD ±1.08). The most frequent oncological diagnoses were leukemias, myeloproliferative and myelodysplastic diseases (47.4%). In addition to those, the sample also comprised children with diagnosis of aplastic anemia (4.8%), marrow aplasia (2.4%), bone marrow aplasia (2.4%), lymphomas and reticuloendothelial neoplasms (4.8%), retinoblastoma (2.4%), tumors of the central nervous system and diverse intracranial and intraspinal neoplasms (16.7%), soft tissue tumors and other extraosseous sarcomas (4.8%), liver tumors (4.8%), and kidney tumors (9.5%). The sample characterization data regarding hearing thresholds by age, treatment, and presence of hearing complaints are described in Table 1.

Seven children were diagnosed with hearing loss (16.6%), with six (14.2%) presenting sensorineural hearing loss and one (4.2%) presenting conductive hearing loss. The analysis considered responses of each ear separately to identify the percentage of unilateral or bilateral hearing loss. Of the 12 ears with impairment, seven were left, and five were right, meaning a greater percentage of bilateral hearing loss in the sample. However, it was observed that, in cases where only the left ear (LE) was affected, the right ear (RE) presented borderline thresholds in the 6000 and 8000 Hz frequencies. In addition, predominant hearing loss was characterized by lowering thresholds starting

at 3000 Hz, namely hearing loss in high frequencies. Table 2 shows the results obtained from the sample audiological diagnosis, according to the classification defined for children. Table 3 shows borderline threshold percentages in the ears with and without associated hearing loss.

Concerned about the possibility of future hearing loss due to chemotherapy treatment exposure, this study opted to analyze the borderline hearing thresholds (15 dB for the pediatric population). Twenty-four children (77.4%) presented borderline thresholds in the LE and 26 (83.9%) in the RE. Regarding the analysis of compromised

Table 1. Characterization of the sample

Characteristic		Audiological diagnosis		Total	*p*
		Normality N (%)	Borderline or hearing loss N (%)		
Total		11 (26.2)	31 (73.8)	42	
Age	7	0 (0.0)	4 (12.9)	4 (9.5)	0.020
	8	3 (27.3)	14 (45.2)	17 (40.5)	
	9	6 (54.5)	3 (9.7)	9 (21.4)	
	10	1 (9.1)	9 (29.0)	10 (23.8)	
	11	1 (9.1)	1 (3.2)	2 (4.8)	
Active chemotherapy	No	9 (81.8)	20 (64.5)	29 (69.0)	0.492
	Yes	2 (18.2)	11 (35.5)	13 (31.0)	
Hearing complaint	No	9 (81.8)	25 (80.6)	34 (81.0)	1.000
	Yes	2 (18.2)	6 (19.4)	8 (19.0)	

Captions: CNS = Central nervous system; *p* refers to *t* test for comparison between means, Fisher's exact test for comparison between categorical variables with 2 levels and chi-square test for categorical variables with 3 or more levels.

Table 2. Audiological diagnosis per ear

Audiological diagnosis	Right ear n (%)	Left ear n (%)	Total n (%)
Normality	37 (44.0)	35 (41.6)	72 (85.6)
Slight sensorineural hearing loss	1 (1.2)	2 (2.4)	3 (3.6)
Moderate sensorineural hearing loss	1 (1.2)	1 (1.2)	2 (2.4)
Sensorineural hearing loss – Hearing thresholds lowered starting at 3000 Hz	1 (1.2)	1 (1.2)	2 (2.4)
Sensorineural hearing loss – Hearing thresholds lowered at 6000 Hz	1 (1.2)	1 (1.2)	2 (2.4)
Sensorineural hearing loss – Hearing thresholds lowered at 8000 Hz	1 (1.2)	1 (1.2)	2 (2.4)
Conductive hearing loss	0 (0.0)	1 (1.2)	1 (1.2)

Table 3. Borderline thresholds per ear, with or without associated hearing loss

	Borderline thresholds - Right ear			Borderline thresholds - Left ear		
	Yes	No	Total	Yes	No	Total
Normal	0 (0.0)	11 (100.0)	11 (26.2)	0 (0.0)	11 (100.0)	11 (26.2)
With loss	26 (83.9)	5 (16.1)	31 (73.8)	28 (90.3)	3 (9.7)	31 (73.8)
Total	26 (61.9)	16 (38.1)	42 (100.0)	28 (66.7)	14 (33.3)	42 (100.0)
p		<0.01			<0.01	

Captions: *p* refers to Fisher's exact test for comparison between categorical variables with 2 levels and chi-square test for categorical variables with 3 or more levels.

frequencies in the borderline hearing thresholds, 15 children (51.7%) presented changes in the RE and 16 (55.2%) in the LE, at the 8000 Hz frequency. At 4000 Hz, 13 children (41.9%) presented changes in the LE, and at 6000 Hz, 11 children (37.9%) also presented changes in the LE.

DISCUSSION

The sample of this study mainly comprised male patients. This data reflects what has been demonstrated by worldwide epidemiological studies on the prevalence of cancer diagnoses in boys and girls[30,31]. Although there is no consensus about the biological differences between sexes that justify a greater prevalence in boys, a data review on childhood cancer incidence[31] mentioned greater susceptibility in the male sex worldwide for the most common childhood cancer types, such as leukemias, lymphomas, neoplasms of the central nervous system, neuroblastoma, retinoblastoma, and liver tumors. Additionally, the characterization findings of the current sample show leukemia as one of the most prevalent diagnoses, confirming the information compiled in the review.

Regarding audiological diagnosis, hearing loss was observed in 16.6% of the sample, characterized by sensorineural losses with more damage in higher frequencies. Moreover, of the children who presented sensorineural hearing loss, five (83.3%) had bilateral, and three (50%) had symmetrical losses. This finding is in line with researchers[9,10] who demonstrated that the audiological profile of the oncopediatric population is often represented by sensorineural, bilateral, and symmetrical hearing loss, due to the high risk of ototoxicity in the frequently used antineoplastic drugs, especially platinum-based, such as vincristine and vinblastine. This is due to the physiological mechanism of these drugs that damage the cochlea, initially affecting the ciliated cells located in the basal portion, the region where high frequencies are detected[12,13].

It is worth noting that the other two cases of sensorineural hearing loss were asymmetrical, one bilateral with different grades and audiometric settings and the other, unilateral. This data shows that, despite being less frequent in ototoxicity reports, asymmetrical losses can also affect this population, reinforcing the importance of screening and early diagnosis, as they affect central hearing abilities, possibly affecting children's learning and social experiences. Studies show that children with unilateral or asymmetrical hearing loss have more difficulty locating sound sources, and differentiating sounds in noisy environments[32,33], and present more auditory fatigue, i.e., feeling tired when exposed to prolonged periods of continuous audio stimuli, like in a classroom. Furthermore, studies demonstrate that in cases of asymmetry in detecting auditory information, the cognitive load increases, because the child needs to make an effort to compensate for the lack of sensibility in the affected side, which hinders their educational performance[34,35].

The study verified that one child in the sample was diagnosed with unilateral conductive hearing loss. Some studies mention that immunosuppressed children may be more susceptible to viral respiratory conditions that lead to them developing acute otitis media[36,37]. In addition, the auditory deprivation caused by the compromised middle ear may also make it more difficult to understand auditory information, impacting the child's social interaction.

In addition to hearing losses, a significant percentage of the sample obtained borderline hearing thresholds in their assessment, especially starting at 4000 Hz. It must be noted that this was more prevalent in the 8-year-old age group (45.2% of the sample). Additionally, the data was identified more frequently in children who had completed chemotherapy protocols, which means, they were not actively undergoing chemotherapy. These results reinforce the importance of frequent and continuous auditory screening in these children, regardless of the treatment to which they were exposed, because in addition to the delay in the development of oral and written language, and deficits in the auditory ability of figure-ground segregation[38], these thresholds may indicate early changes that may evolve into hearing loss in the future. A study showed that adults who survived childhood cancer presented a greater risk of needing individual hearing amplifiers within 30 years of finishing treatment, suggesting a progressive worsening of the hearing function at a faster rate than adults who were not exposed to chemotherapy drugs. The authors suggest hearing thresholds should be periodically assessed until adulthood so that rehabilitation can improve the quality of life of these individuals[39].

Although there are surveillance actions for patients exposed to platinum-derived components and radiotherapy, a study[40] showed a prevalence of 23% of failures in the auditory screening of patients who underwent treatments considered of low-ototoxicity risk, with the greatest incidence of failures occurring in patients tested 7 years after the treatment, suggesting that other drugs may also affect hearing, with damages observed in the long-term. The study also made associations between demographic variables and the screening result, though no variable influenced the results, reinforcing the hypothesis that auditory change resulted from exposure to ototoxic drugs.

Another relevant data refers to the hearing complaints reported by the patients or their guardians. Thirty-four children (81%) did not report any hearing complaints, however, 25 (80.6%) of them presented borderline thresholds or hearing loss. This data shows the importance of periodical assessment even without complaints because the guardians are not always aware of the child's hearing complaints, as demonstrated in a study[41], which may delay referral to evaluation and early diagnosis.

Among the reported complaints, the most prevalent was tinnitus. There was a significant predominance of complaints from males (90.5%). Tinnitus is one of the most frequent symptoms in patients who received antineoplastic treatment, more specifically chemotherapy, with an estimated prevalence of 40% in this population, and may be due to sudden lesions in cochlear cells[42,43]. However, it remains an underestimated clinical sign, especially in children. Despite that, current recommendations for ototoxicity surveillance suggest that patients exposed to platinum-derived drugs have an increased risk of tinnitus and, in case they perceive the symptom, should be referred to audiological evaluation[43,44].

The present research has some limitations, like the reduced sample size and heterogeneity in diagnoses and treatments to which the children were exposed, which impaired more specific associations. Thus, further studies in this population are suggested to fill in those gaps, show the importance of hearing screening, and identify the possible repercussions in the quality of life associated with hearing symptoms of children exposed to chemotherapy treatment.

CONCLUSION

An association between changes in hearing thresholds and exposure to chemotherapy treatment was verified in the studied sample, in addition to tinnitus complaints by the children and/or their guardians, and increased prevalence of borderline thresholds and hearing loss in the male sex, most occurring in the 8-year-old age group and the LE. Moreover, the study highlights that any kind of hearing deprivation affects child development, therefore, it is essential that hearing evaluations are performed in childhood for early diagnosis and rehabilitation.

CONTRIBUTIONS

Camila Franciozi has contributed to the study design, planning, data acquisition, analysis, and interpretation, as well as the wording. Viviann Magalhães Silva Borges has contributed to data analysis and interpretation, and wording. Letícia Gregory has contributed to the study design, planning, data analysis and interpretation, and wording. Paulo Ricardo Gazzola Zen and Pricila Sleifer have contributed to the study design, planning, data analysis and interpretation, wording, and critical review. Lauro José Gregianin has contributed to data acquisition, wording and critical review. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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