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Audiological follow-up in transplant patients treated with calcineurin immunosuppressants "Calcineurin inhibitors and Ototoxicity"

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Background: *Ototoxicity is a side effect of drugs and medications that usually leads to bilateral and symmetric sensorineural hearing loss that commonly affects the high-frequency range initially, with or preceded by tinnitus. Possible ototoxic side effects of calcineurin inhibitor immunosuppressants have been suggested, but this remains unclear. Therefore, this study aims to evaluate audiological changes in patients undergoing transplantation receiving immunosuppressive treatment with calcineurin inhibitors.* ***Methods:*** *Prospective cohort study. Adult patients undergoing liver or kidney transplantation treated with calcineurin inhibitors were included. Pure-tone audiometry, distortion product otoacoustic emissions, and the Tinnitus Handicap Inventory questionnaire were completed at baseline, one, three, and six months after transplantation. Hearing thresholds were compared and correlated with plasma concentrations of calcineurin inhibitors.* ***Results:*** *Seventeen patients were included, 59% males, with a median age of 54.7 years (29–68 years). Twelve patients underwent liver transplantation, four underwent kidney transplantation, and one patient underwent both. The median follow-up was 5.8 months (4–8 months). Significant pure-tone average shifts were observed in two patients. Both cases presented fluctuations in their hearing levels, which were not bilateral or symmetrical and affected the higher frequencies. All patients received tacrolimus within the therapeutic range during the follow-up period. Three different patients exceeded the expected range once; however, they were rapidly corrected and did not correlate with any changes in hearing.* ***Conclusions:*** *It appears that tacrolimus does not cause hearing loss when levels are within the therapeutic range for a follow-up period of six months post-transplantation.*

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Key words: *Ototoxicity; Hearing Loss; Tacrolimus; Calcineurin Inhibitors; Transplantation.*

Seguimiento audiológico en pacientes trasplantados en tratamiento con inmunosupresores inhibidores de calcineurina

Introducción: *La ototoxicidad corresponde a un efecto secundario a agentes terapéuticos que se manifiesta como hipoacusia sensorioneural bilateral simétrica de frecuencias agudas. Se postulan posibles efectos ototóxicos de los inmunosupresores inhibidores de la calcineurina, pero hasta la fecha es aún incierto. El objetivo de este estudio fue evaluar los cambios audiológicos en pacientes trasplantados en tratamien-*

to inmunosupresor con inhibidores de calcineurina. ***Material y Método:*** *Cohorte prospectiva. Se incluyeron pacientes adultos sometidos a trasplante hepático o renal tratados con inhibidores de calcineurina. Se realizó una evaluación otorrinolaringológica pre-trasplante con audiometría tonal, emisiones otoacústicas por producto de distorsión y cuestionario Tinnitus Handicap Inventory. Se realizó una evaluación audiológica de seguimiento uno, tres y seis meses después del trasplante. Se compararon los umbrales auditivos antes y después del inicio del tratamiento inmunosupresor y se correlacionaron con las concentraciones plasmáticas de IC.* ***Resultados:*** *Se incluyeron 17 pacientes, 59% hombres, con una mediana de edad de 54,7 años. La mediana de seguimiento fue 5,8 meses. Se observaron cambios en el promedio tonal puro en dos pacientes, los cuales no seguían un patrón audiométrico sugerente de ototoxicidad. Todos los pacientes recibieron Tacrolimus dentro del rango terapéutico durante el seguimiento. Tres pacientes diferentes excedieron el rango esperado una vez sin embargo, se corrigieron rápidamente y no se correlacionaron con cambios auditivos, puntaje de tinnitus o emisiones otoacústicas.* ***Discusión:*** *Impresiona que Tacrolimus no se asocia a hipoacusia cuando los niveles están en rango terapéutico durante un período de seguimiento de seis meses post trasplante.*

Palabras clave: *Ototoxicidad; Pérdida Auditiva; Tacrolimus; Inhibidores de Calcineurina; Trasplante.*

Calcineurin inhibitor immunosuppressants such as cyclosporin and tacrolimus are effective treatments for solid organ transplantation. Numerous adverse reactions are associated with these drugs, including nephrotoxicity, hypertension, neurotoxicity, and hepatotoxicity[1-3]. Ototoxicity has been proposed concerning immunosuppression with calcineurin inhibitors (CI), but the current evidence is insufficient and controversial[4].

Ototoxicity is a side effect of drugs that leads to the functional deterioration of the inner ear structures, which may be reversible or irreversible. Cochlear damage manifests as sensorineural hearing loss (SNHL), which commonly affects the high-frequency hearing range initially and is generally bilateral and symmetric[5]. It is often accompanied or preceded by tinnitus[6]. Audiological evaluation with pure-tone audiometry is the most commonly used hearing test worldwide for diagnosing ototoxicity[5].

Multiple case reports[7-12] of pediatric and adult patients with sudden or progressive SNHL associated with calcineurin inhibitors, are reported. In all these cases, hearing loss was associated with a high plasma concentration of cyclosporin or tacrolimus and ceased or even reversed after treatment dose adjustment. It appears that neurotoxicity[13], microangiopathy[14], inhibition of potassium secretion in the inner ear[15,16] and hypomagnesemia[17], among others, may play a role in CI-induced hearing loss. The quality of evidence available to date is insufficient to confirm whether CI are ototoxic, and there are no audiological monitoring recommendations for these patients.

This pilot study aims to evaluate audiological changes in patients undergoing transplantation receiving immunosuppressive treatment with CI to determine the potential ototoxic effects of these drugs.

Material and Method

Patient Population

A prospective cohort study was performed, including all adult patients who were candidates for kidney or liver transplantation at the UC-Christus Health Network in Santiago, Chile, in 2021. Patients who underwent transplant surgery during the follow-up period were included in this analysis. Patients not treated with CI, re-transplant patients, and patients who died during follow-up were excluded. In addition, demographics, medical history, drugs used, and history of prior hearing loss or tinnitus were recorded. Ethical approval for this study was obtained from the Pontificia Universidad Católica de Chile Health Sciences Scientific Ethics Committee (protocol number 210104005). Informed consent was obtained from all the patients.

Hearing evaluations

All patients underwent a complete head and neck examination before transplant surgery, including otoscopy, to exclude any apparent causes of conductive hearing loss. Baseline tympanometry (GSI TympStar Pro™), pure-tone audiometry, and distortion product otoacoustic emissions (DPOAEs) were performed. Follow-up audiological assessment was performed at one, three, and six months after transplantation using a pure-tone audiogram, DPOAEs, and the Tinnitus Handicap Inventory (THI) questionnaire. DPOAEs were not assessed at the six months follow-up.

Pure-tone audiometry (GSI AudioStar Pro™ or GSI Pello™ audiometers) included air conduction thresholds obtained for frequencies of 125, 250, 500, 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz, and bone conduction thresholds of 250, 500, 1,000, 2,000, 3,000, and 4,000 Hz. We used bone conduction thresholds to compare audiograms, except for 125, 6,000, and 8,000 Hz, where air conduction thresholds were used. The following criteria were established to determine significant hearing loss: 1. By pure-tone average (PTA): 10 dB difference between tests; 2. By testing independent frequencies: ≥ 15 dB threshold shift at any tested frequency, ≥ 10 dB threshold shift at ≥ 2 adjacent frequencies, and 3. By Word Recognition Score (WRS) ≥ 12%. The degree of hearing loss was classified as mild (21-40 dB HL), moderate (41-70 dB HL), severe (71-90 dB HL), or profound (> 90 dB HL)[18].

DPOAEs were also performed as they provide information on outer hair cell status, cells commonly affected at initial stages of ototoxicity, and could provide information regarding incipient ototoxicity[19]. DPOAEs were obtained with the Interacoustics Eclipse EP25 platform for frequencies 3,000 to 8,000 Hz; 21 different frequencies were tested. A signal-to-noise ratio of 7 dB and a reliability setting value of 99.9% were established to consider the presence of DPOAEs. We classified the results into one of three outcome categories: (a) DPOAE present and normal, which meant that 70% or greater of the tested frequencies were present; (b) DPOAE present but abnormal, which meant present, but in less than 70% of the tested frequencies; and (c) DPOAE absent: not present at any tested frequency[20].

For all these evaluations, patients served as their own controls to detect changes in hearing levels.

Tinnitus questionnaire

Patients completed a validated Spanish version of the THI[21] consisting of 25 easy-to-understand questions for the patient, with three response options for each question: yes (4 points), sometimes (2 points), and no (0 points); the sum of the total score can range from 0 to 100. Disability caused by tinnitus is classified into five levels: Grade 1, slight or no handicap (0 to 16); grade 2 or mild handicap (18 to 36); grade 3 or moderate handicap (38 to 56); grade 4 or severe handicap (58 to 76), and grade 5 or catastrophic handicap (78 to 100).

Plasma concentrations of CI

Plasma concentrations of immunosuppressants were monitored for all patients. Tacrolimus concentrations in blood were quantified using an automated microparticulate chemiluminescence immunoassay (CMIA Architect® i1000, Abbott). Cyclosporin A levels were obtained by Electro-Chemiluminescent Immunoassay (ECLIA, Cobas/Roche).

The therapeutic range of immunosuppressants was established according to the recommendations from the Chilean Public Health Institute[22] and was 5-20 ng/mL for tacrolimus.

Statistical Analysis

Exploratory data analysis was carried out to check for atypical values and determine the distribution of continuous quantitative variables. Descriptive statistics are reported as the mean and standard deviation. Differences between the baseline and post-transplantation measurements were calculated with the Wilcoxon Signed- Rank test. A P-value of < 0.05 was considered statistically significant.

Results

Patient demographics

Thirty-nine patients were recruited in this study. Twenty patients met the inclusion criteria. However, one patient was deceased, one patient discontinued participation, and one was already under CI immunosuppressive treatment. As a result, 17 patients were included in the study, 59% (10/17) were males (Table 1). The median age was 54.7 years (range 29-68 years). Twelve patients

underwent liver transplants, four underwent kidney transplants, and one underwent both liver and kidney transplants. Four patients reported hearing loss at baseline, and, six reported tinnitus grade 1 (slight or no handicap). Baseline audiograms showed two patients with moderate SNHL, one with mild SNHL, one with mild asymmetric SNHL, and one with mixed hearing loss associated with chronic otitis media. The median follow-up was 5.8 months (range 4-8 months).

Distortion product otoacoustic emissions

Most patients had present but abnormal DPOAEs at baseline and 1- and 3-month follow-ups. At baseline, 24.1% of the patients had no DPOAEs (seven ears). Of these ears, five ears were from patients with pre-existing hearing loss (average: 35.8 ± 9.2 dB); hence, these results were expected (Table 2). For most patients, DPOAEs did not change and were present but abnormal. We did not observe a pattern of decreasing data points for the tested ears during the follow-up period.

Hearing thresholds

Because there was variability in the criteria used to determine a significant hearing threshold change, we evaluated our data using three different criteria. When assessing hearing levels by PTA, the mean baseline measurement was 17.2 ± 10.9 dB, with a median of 14 dB. No patients had a 10 dB difference between baseline and follow-up audiometry testing at 1, 3, and 6-month follow-ups. Therefore, there were no significant

Table 1. Baseline patient characteristics

Patient	Gender	Age (years)	Etiology	Transplant	Prior hearing loss	Hearing status	THI score
1	F	68	NASH Cirrhosis	Liver	yes	Moderate SNHL	0
2	M	32	Cryptogenic cirrhosis	Liver	no	Normal	0
3	M	62	NASH Cirrhosis	Liver	no	Normal	0
4	M	57	Polycystic kidney disease	Kidney	no	Normal	0
5	M	49	IgA nephropathy	Kidney	no	Normal	0
6	F	60	Polycystic liver disease	Liver	no	Normal	4
7	M	60	Cryptogenic cirrhosis	Liver	no	Normal	2
8	F	51	NASH cirrhosis	Liver	no	Unilateral mild SNHL	0
9	M	55	MAFLD	Liver	no	Normal	0
10	F	57	MAFLD	Liver	yes	Normal	0
11	M	67	MAFLD	Liver	yes	Mild SNHL	0
12	M	67	Polycystic kidney disease	Kidney	no	Normal	0
13	F	54	Autoimmune hepatitis	Liver	no	Unilateral mixed hearing loss	2
14	M	68	Alcoholic liver disease	Liver	yes	Moderate SNHL	0
15	M	53	NASH Cirrhosis	Liver	no	Normal	0
16	F	41	Fanconi syndrome Cholestatic syndrome	Liver and Kidney	no	Normal	0
17	F	29	Unknown	Kidney	no	Normal	8

THI: Tinnitus handicap inventory, SNHL: Sensorineural hearing loss, NASH: Nonalcoholic Steatohepatitis, MAFLD: Metabolic (dysfunction) associated fatty liver disease.

Table 2. Distortion Product Otoacoustic Emissions

DPOAE	Data points present*	Present and normal (%)	Present but abnormal (%)	Absent (%)
Baseline (ears tested: 29)	6.8 ± 6.3	13.8	62.1	24.1
One month follow-up (ears tested: 18)	10.2 ± 7.6	27.8	61.1	16.7
Three-month follow-up (ears tested: 15)	10.4 ± 6.9	33.3	66.7	0

*Maximum: 21 data points, mean ± SD, DPOAE: Distortion Product Otoacoustic Emissions.

Table 3. Hearing thresholds

	Baseline	Follow-up: 1 month	Follow-up: 3 months	Follow-up: 6 months	Threshold shift (1 month)	Threshold shift (3 months)	Threshold shift (6 months)
PTA (dB): average ± SD	17.2 ± 10.9	17.7 ± 14.5	12.4 ± 10.6	17.8 ± 16.4	-1.8 ± 3.6	-2.2 ± 3.9	-1.7 ± 5.0
PTA (dB): Median	14	14	10.5	10	-	-	-
WRS (%): average ± SD	98.7 ± 2.7	99.5 ± 1.9	99.8 ± 0.8	98.8 ± 1.9	0.9 ± 2.4	0.5 ± 1.4	0.4 ± 3.6
WRS (%): Median	100	100	100	100	-	-	-

PTA: Pure-tone average, dB: decibel, WRS: Word recognition score, SD: Standard Deviation.

Table 4. Tinnitus Handicap Inventory Score

%	Baseline	Follow-up: 1 month	Follow-up: 3 months	Follow-up: 6 months
Grade 1	100	91	82	88.9
Grade 2	0	9	9	0
Grade 3	0	0	0	11.1
Grade 4	0	0	0	0
Grade 5	0	0	9	0

hearing threshold shifts at 1-month (P = 0.9838), 3-month (P = 0.9898), and 6-month (P = 0.9346) follow-up evaluations (Table 3).

When assessing individual frequency threshold shifts, we observed two patients had ≥15 dB threshold shifts at any tested frequency and ≥10 dB shifts at ≥ two adjacent frequencies. One patient (liver transplant) had a threshold shift of 15 dB at 125 Hz and 3, 4, and 6 kHz, but only at the 6-month follow-up. This patient also exhibited 10 dB threshold shifts at ≥ 2 adjacent frequencies at 125, 250, 500, and at 3 and 4 kHz (Figure 1). However, the patient also experienced an improvement in hearing at 8 kHz in the right ear starting at the first follow-up period. The other patient (renal transplant) had ≥15 dB threshold shifts at 6 and 8 kHz, but only in one ear at the 6-month follow-up; however, his hearing improved in the low-frequency range (Figure 2). Therefore, both cases were not bilateral, symmetrical, and affected at higher frequencies, as is commonly seen in systemic ototoxicity. In addition, they showed improvement in hearing at specific frequencies, which varied between the cases.

Regarding WRS, no patients had a change of ≥ 12% in their scores at any follow-up period, and the median baseline measurement was 100% (Table 3).

When assessing the post-transplantation history of both patients that exhibited non-specific changes in hearing, we observed that one of the patients (renal transplant) had cytomegalovirus (CMV) reactivation during follow-up and was treated with ganciclovir followed by valganciclovir.

Calcineurin inhibitors plasmatic concentrations

All the patients received tacrolimus as an immunosuppressive agent. Two patients changed their treatment to everolimus due to chronic rejection.

Most patients presented with plasma con-

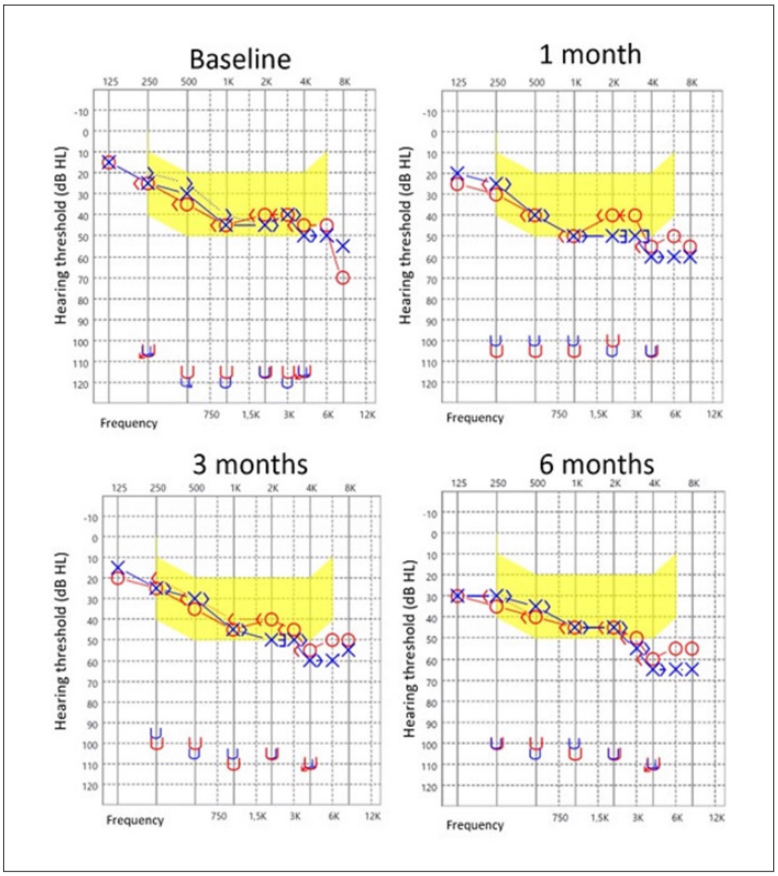

Figure 1. Hearing thresholds by pure-tone audiometry for patient #1 (liver transplant). Hearing level fluctuations can be seen at different frequencies for both ears (red: right ear, blue: left ear).

centrations of immunosuppressants within the therapeutic range during the follow-up period. Only three patients presented with isolated high blood levels (> 20 ng/mL) of tacrolimus during the follow-up; however, they were rapidly corrected (Figure 3). Concerning these three points over the expected range, we did not observe any changes in hearing thresholds, THI scores, or DPOAEs. Only one of these (23 ng/mL) was detected in one patient with a unilateral change in hearing with no temporal association.

Tinnitus

Most patients had slight or no tinnitus handicap at all the time points evaluated (Table 4). At the 6-month follow-up, three patients had new-onset tinnitus, two had slight or no handicap, and one had a moderate handicap. Interestingly, one patient reported a catastrophic handicap at the 3-month follow-up but no handicap at the 6-month follow-up; this patient had no hearing loss at any point. The patient who reported a grade 3 handicap at six months did not report any tinnitus prior to that evaluation. This patient had hearing loss prior to transplantation and had slightly fluctuating levels of hearing loss bilaterally throughout the 6-month follow-up.

Discussion

Only isolated case reports and a few case series regarding hearing loss in patients undergoing transplantation and receiving immunosuppression have been published. To our knowledge, Fortes et al[23]. published the first study that objectively evaluated adult patients undergoing liver transplantation who received cyclosporin or tacrolimus as immunosuppressants using pre-and post-transplantation audiometry. There were no significant changes in hearing in the cyclosporin group. However, they reported high-frequency

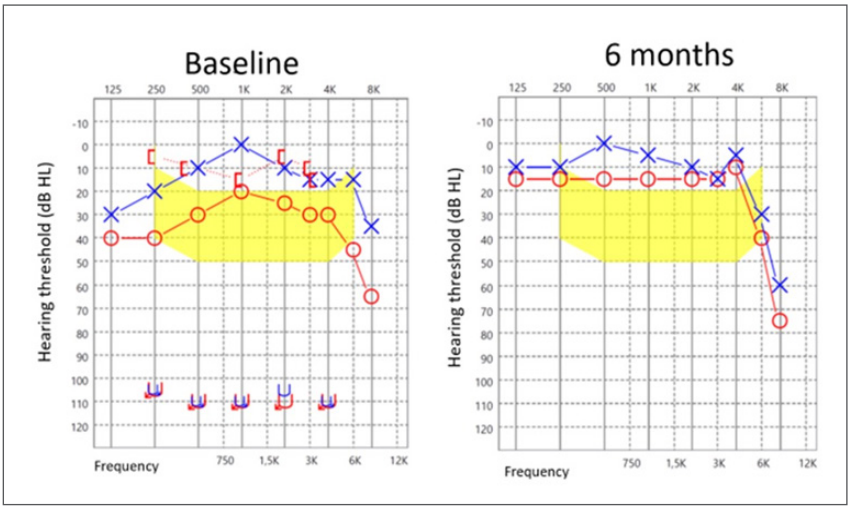

Figure 2. Hearing thresholds by pure-tone audiometry for patient #4 (renal transplant). A decrease in hearing can be observed at 6 and 8 kHz unilaterally (blue: left ear) at the 6-month follow-up but hearing improved in the low-frequency range.

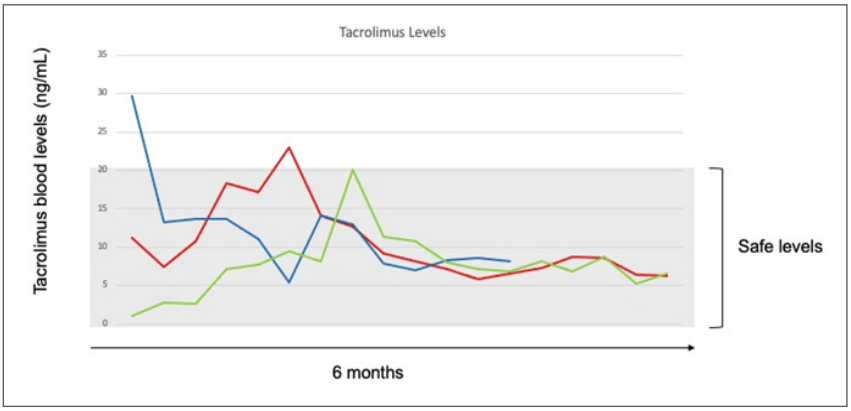

Figure 3. Tacrolimus levels. Three points (three different patients) were over the expected range once; however, they were rapidly corrected. Only one of these (23 ng/mL) was detected in one patient with a unilateral change in hearing. All the other tacrolimus blood levels were within range and considered safe.

changes in patients receiving tacrolimus, which were followed up for 513 days (range 31-947). Nevertheless, the authors did not mention criteria for determining hearing loss and chose to evaluate air conduction thresholds. Simsir et al.[24] performed pure-tone and high-frequency audiometry for renal transplant patients and compared two groups of patients, one receiving tacrolimus and the other receiving an mTOR inhibitor. Unfortunately, they do not have a baseline hearing measurement. Although they mention that the mid-frequencies were statistically different with tacrolimus vs mTOR inhibitor, both groups had hearing levels below 20 dB for the 500 to 2,000 Hz range; hence normal hearing for those frequencies, and the difference was approximately 5 dB, which is not considered significant with regards to audiometry testing.

Gulleroglu et al[25] evaluated the prevalence of hearing loss in pediatric patients undergoing renal transplantation and found that 63% of SNHL cases were associated with high levels of cyclosporin, suggesting dose-dependent cyclosporin toxicity. In addition, the mean follow-up time after the transplant was 29.8 ± 22.5 months, and mean assessment time of hearing impairment was 21.3 ± 12.2 months.

A recent systematic review[26] evaluating immunosuppressant drugs and hearing loss concluded that calcineurin inhibitors (cyclosporine or tacrolimus) were the most frequently involved in ototoxic manifestations and were often related to drugs' high serum levels. The only experimental study to date reports that tacrolimus had no ototoxic effect in the inner ear of rats, as measured by DPOAEs when applied at doses of 1 mg/kg and 0.1 mg/kg[27].

In our cohort, none of the patients presented

with bilateral symmetrical SNHL, which is commonly described for ototoxicity. In addition, only two patients had significant hearing threshold changes in one ear; however, they did not exhibit the classic audiometric pattern described for ototoxicity in both cases.

No significant differences were observed in the DPOAEs or THI scores which may be correlated with fluctuations in plasma CI levels. Immunosuppressant levels remained within the therapeutic range during the follow-up period, except at three-time points for three patients. These time points did not correlate with any changes in hearing.

We acknowledge the limitations of our study. Our follow-up period was six months following transplantation, and our sample size was small. We cannot exclude the possibility that CI ototoxicity is time-dependent, and that hearing impairment can be detected with a longer follow-up. In addition, patients undergoing transplantation can easily be lost to follow-up because they have multiple consultations, hospitalizations, and complications related to their underlying condition. We also recognize other factors to consider, such as concomitant ototoxic medications that may be administered during hospitalization.

Nevertheless, we obtained audiometric data and used various criteria to determine whether ototoxicity occurred. We also included multiple follow-up periods and evaluated CI levels associated with hearing levels.

Whether CI are ototoxic remains unclear, but our results show that tacrolimus does not cause SNHL when levels are within the therapeutic range and for a follow-up period of six months post-transplantation. The changes observed in two ears (two different patients) were at different frequencies and did not correlate with elevated tacrolimus levels, and the patients did not exhibit the usual ototoxicity audiometric patterns. Also, tacrolimus did not affect outer hair cell activity, as DPOAEs were present and abnormal pre-and post-transplantation without any significant differences. When assessing tinnitus, we did not recognize any particular pattern or worsening of THI scores that were significant. These results must be evaluated contextually, as tinnitus is multifactorial and can be enhanced under stress, and the THI questionnaire assesses distress associated with tinnitus.

One of the patients who exhibited hearing changes had a CMV reactivation during follow-up. This event is essential and relevant since it is known that congenital CMV infection causes SNHL, both fluctuating and progressive[28]. However, the association between acquired CMV and SNHL has not been clearly established. Nonetheless, most studies regarding acquired CMV and hearing loss include immunocompetent patients and CMV reactivation in an immunocompromised host can lead to uncontrolled viral replication and clinical disease[29]. We cannot exclude the possibility that CMV reactivation in a solid-organ transplant recipient could have had a deleterious effect on hearing for this patient.

Long-term prospective studies of better quality are needed to objectively assess hearing in patients undergoing transplantation and receiving CI immunosuppressants. This issue has become a relevant topic when considering the greater survival rates for transplant recipients and the impact of immunosuppression's possible adverse effects on their quality of life.

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Abbreviations

-dB, Decibels
-dB HL, Decibels Hearing Level
-CI, Calcineurin Inhibitors
-CMV, Cytomegalovirus
-DPOAEs, Distortion Product Otoacoustic Emissions
-Hz, Hertz
-kHz, Kilohertz
-PTA, Pure Tone Average
-SNHL, Sensorineural Hearing Loss
-THI, Tinnitus Handicap Inventory
-WRS, Word Recognition Score

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