Original Article

Silent Hearing Loss in Kidney Transplant Patients Receiving Tacrolimus: A Fact or a Myth?

Abstract

Background: It has been claimed that tacrolimus may have harmful effects on the auditory system, where it has been linked to ototoxicity and sensorineural hearing loss (SNHL). We evaluated silent SNHL in kidney transplant recipients (KTRs) receiving tacrolimus and the different factors affecting it compared to healthy controls. **Materials and Methods:** In this case control study, hearing functions were studied in 42 KTRs receiving tacrolimus as maintenance immunosuppressive therapy for more than 3 months in comparison to 27 age- and gender-matched healthy subjects using tympanometry, pure-tone audiometry (PTA), extended high frequency audiometry (EHFA), and transient evoked oto-acoustic emissions (TEOAEs). Also, different factors were studied in relation to SNHL. **Results**: PTA showed that 23.8%, 21.4%, and 4.8% had mild, moderate, and severe SNHL, respectively. One-fifth of KTRs had severe SNHL, according to EHFA. According to TEOAEs, 28.6% of KTRs had abnormal hearing. There was a significant positive correlation between the tacrolimus trough levels and the results of both the PTA ($P = 0.002$) and EHFA ($P = 0.035$) tests. **Conclusion:** SNHL was detected in about half of the studied KTRs. Silent SNHL in KTRs might be associated with higher tacrolimus trough levels.

Keywords: *Hearing loss, Renal transplant, Tacrolimus, Immunosuppression, Ototoxicity*

Ahmed ElSaeed Abdulgalil[1], Ola H. Elnagdy[2], Noha H. Elnagdy[3] Eman Nagy[1]

[1]Mansoura Nephrology and Dialysis Unit, Department of Internal Medicine, [2]Audiology Unit, Department of ENT, [3]Department of Rheumatology, Rehabilitation and Physical Medicine, Mansoura University, Mansoura, Egypt

***Corresponding author**: Eman Nagy, Mansoura Nephrology and Dialysis Unit, Department of Internal Medicine, Mansoura University, Mansoura, Egypt.*
E-mail: emannagy@mans.edu.eg

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Introduction

Kidney transplantation is the preferred treatment for patients with end-stage kidney disease (ESKD).[1] The number of transplants performed over the past three decades has continuously increased. The Egyptian experience exceeded 20,000 transplants up to the year 2020. The 10-year graft and patient survival rates in Mansoura Urology and Nephrology Center (one of the largest transplant centers in Egypt) were 65.5% and 77.8%, respectively.[2]

The mainstay of solid organ transplant immunosuppression is calcineurin inhibitors (CNIs). Tacrolimus remains the first-line treatment option, and this mandates an updated assessment of its safety profile. It has a narrow therapeutic window and might result in different adverse events such as nephrotoxicity, neurotoxicity, and new-onset diabetes. These adverse events are mostly related to either the long-term usage of tacrolimus or its increased trough level.[3]

It has been claimed that tacrolimus has harmful effects on the auditory system in some studies,[4-7] where it has been linked to ototoxicity and sensorineural hearing loss (SNHL). The cause of SNHL is usually the combined result of many factors. These neurotoxic side effects could be involved in the development of hearing impairment after transplant.[4] This work aimed to study silent hearing loss in transplant recipients (KTRs) receiving tacrolimus and the different factors affecting it in comparison to age- and gender-matched healthy controls.

Materials and Methods

This case control study was conducted between May 2022 and November 2022 in the Mansoura University Nephrology Unit and Audiology Department, Faculty of Medicine, Mansoura University, Egypt. The study was approved by the Institutional Review Board. An informed written consent was obtained from all patients included in the study or their caring relatives prior to the study.

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Forty-two KTRs, aged between 18 and 60 years and treated with tacrolimus continuously as maintenance immunosuppressive therapy for more than 3 months and attending the kidney transplant follow-up clinic during the duration of the study, were included in the transplant group. All KTRs included in this study had grafts from living, related donors. Most KTRs were maintained on prednisolone, mycophenolate mofetil (MMF), and tacrolimus. The doses of these drugs after one year of kidney transplantation as adopted by our center are as follows: prednisolone 5 mg/day. MMF 1500 mg/day and tacrolimus dose that kept its trough level between 5 and 6 ng/mL. The control group included 27 healthy subjects who were matched for age and gender with the transplant patients.

Complicated diabetic cases, patients with any other middle ear disease as otitis media or perforated drums in otoscopic examination, have used other ototoxic drugs within the last 3 months (antibiotics as aminoglycoside, erythromycin, vancomycin, or furosemide, etc.), had a history of hereditary or acquired hearing loss problems due to other reason (genetic syndromes with hearing loss as Alport, acoustic trauma, those with recurrent upper respiratory tract infection, neurological psychiatric problems, Meniere's disease, have intracranial pathology that may cause hearing loss, malignancy and have been receiving chemotherapy, have had ear trauma or surgery were excluded from the study.

Group sample sizes of 41 in group 1 (transplant group) and 21 in group 2 (control group) achieve 85.186% power to detect a difference between the group proportions of −0.3500. The proportion in group 1 (the transplant group) is assumed to be 0.5000 under the null hypothesis and 0.1500 under the alternative hypothesis. The proportion in group 2 (the control group) is 0.5000. The test statistic used is the two-sided Z-Test with unpooled variance. The significance level of the test is 0.0700.

All patients in both the groups were subjected to detailed clinical examination, including history of subjective hearing loss, purulent discharge from ear, tinnitus, or ototoxic drug exposure); investigations (including complete blood count (CBC), serum albumin, creatinine, magnesium, fasting blood sugar, and tacrolimus trough level [FK level]). Tacrolimus level was used as an average reading over the last 3 months. In addition, tympanometry, pure-tone audiometry (PTA), extended high frequency audiometry (EHFA), and transient evoked oto-acoustic emissions (TEOAEs) were done for all patients.

PTA was performed in a sound-treated room to minimize background noise according to the law of the European Economic Community. Madsen Itera 2 Clinical Audiometer (Natus, Denmark) was used to conduct the PTA examination. Thresholds of air conduction were estimated for 250–8000 Hertz (Hz).

EHFA was performed in a sound-proof room using Interacoustics AC 40, (Interacoustic, Assens, Denmark) at 10,000, 12,000, 16,000 and 20,000 Hz. Tympanometry was carried out by interacoustics AT 235 impedance audiometer (Interacoustic, Assens, Denmark). Type A tympanogram was found in all cases.

Acoustic reflex (AR): interacoustics AT 235 impedance audiometer (Interacoustic, Assens, Denmark) was used to measure ipsilateral AR at 500, 1000, 2000 and 4000 Hz. Scout (Bio-logic, United Kingdom) TEOAES was utilized to conduct oto-acoustic emissions (OAEs). Normal hair cell function was indicated by PASS indicated while abnormal hair cell function with an enhanced risk of hearing loss in the future was indicated by REFER.

The collected data were analyzed using SPSS 25 for personal computers. The Shapiro–Wilk test was used to test the normality of numeric variables. For parametric and non-parametric variables, quantitative data was expressed as mean±SD, or median (minimum-maximum), while qualitative data was expressed as number and percentages. Independent samples t-test was used to compare parametric variables, while the Mann-Whitney U test was used to compare non-parametric variables between two groups. The Chi-square test was used to compare qualitative variables with each other. Spearman correlation was used to correlate different variables with audiometric data. P values less than 0.05 were considered to be significant.

Results

The current study included 42 KTRs with a mean age of 36 years. The majority of them were males (71.4%) and hypertensives (64.3%). The median duration of the transplant was 43 months. All the patients were maintained on prednisolone, tacrolimus, and mycophenolate mofetil. The median serum creatinine of the patients was 1.2 mg/dL, while the mean serum magnesium level was 1.66 mg/dL. The median FK level was 5.89 ng/mL. Twenty-seven controls, matched for age and gender with KTRs, were studied [Table 1].

Audiometry of KTRs showed that half of the patients had normal hearing according to PTA, while 23.8%, 21.4%, and 4.8% of them had mild, moderate, and severe SNHL, respectively. One-fifth of KTRs had severe SNHL when tested by EHFA. According to TEOAE, 28.6% had abnormal hair cell function, with an enhanced risk of hearing loss in the future [Table 2]. The comparison of different Hz between KTRs and the control group showed that there were statistically significant differences in hearing thresholds between them with regard to 250, 500, 4000, and 8000 Hz [Figure 1]. Mean FK level was significantly higher in KTRs with SNHL as diagnosed by PTA ($P = 0.019$) [Figure 2].

Table 1: Demographic, clinical, and laboratory data of both groups

	Transplant patients (n = 42)	Control group (n = 27)	P value
Age, years	36.14 ± 10.53	35.22 ± 8.50	0.704*
	33.5 (20-58)		
Gender			
Male	30 (71.4%)	17 (63%)	0.461***
Female	12 (28.6%)	10 (37%)	
Original kidney disease		No	
Hypertension	4 (9.5%)		
Diabetes	1 (2.4%)		
Glomerulonephritis	8 (19%)		
Pregnancy related	7 (16.7%)		
Autosomal dominant polycystic kidney disease	2 (4.8%)		
Neurogenic bladder with reflux nephropathy	2 (4.8%)		
Stone kidney disease	2 (4.8%)		
Bilateral urinary tract obstruction	1 (2.4%)		
Unknown	15 (35.7%)		
Pre-transplantation dialysis	35 (83.3%)		
Duration of pre-transplantation dialysis (months)	24 (1–216)		
Duration of transplantation (months)	43 (3–96)		
Diabetes	3 (7.1%)	No	
Duration of diabetes (years)	12 (4–14)		
Hypertension	27 (64.3%)	No	
Duration of hypertension (years)	10 (2–20)		
Steroid dose (mg/day)	5 (5–30)		
Tacrolimus dose (mg/day)	3.5 (1.75–8)		
Serum creatinine (mg/dL)	1.2 (0.7–5.4)	0.8 (0.7–1.1)	**<0.001****
White blood cells (109/L)	8.25 (3.2–13.9)	5.4 (4.4–7.5)	**<0.001****
Neutrophil to lymphocyte ratio	1.73 (0.96–10.32)		
Hemoglobin (gm/dL)	13.02 ± 2.31	13.22 ± 0.89	0.663*
Platelets (10^9/L)	221.67 ± 66.05	251.85 ± 31.26	**0.030***
Serum calcium (mg/dL)	9.34 ± 0.87	9.39 ± 0.43	0.800*
Serum phosphorus (mg/dL)	3.57 ± 1.21	4.19 ± 0.32	**0.030***
Serum albumin (gm/dL)	4.20 ± 0.52	4.5 ± 0.23	0.023*
Serum magnesium (mg/dL)	1.66 ± 0.21	1.9 ± 0.08	**<0.001***
Tacrolimus trough level (ng/mL)	5.89 (2–11)		

Data were expressed by N (%), mean ± SD, median (minimum-maximum). *P value was computed by independent samples t-test. **P value was computed by Mann-Whitney U test. ***P value was computed by Chi-square test. The bold values denote that these values are statistically significant.

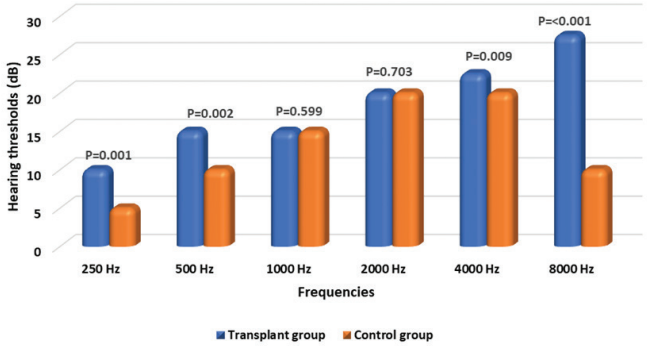

Figure 1: Comparison of median hearing threshold in dB between transplant group and control as regards different HZ using pure-tone audiometry. P value was computed by Mann-Whitney U test.

There was a significant positive correlation between tacrolimus trough levels and the results of both the PTA (rho = 0.469, P = 0.002) and EHFA (rho = 0.326, P = 0.035) tests, while there was no significant correlation with the TEOAE results [Table 3]. In addition, Spearman correlation between the different Hz and different variables showed that tacrolimus level was positively correlated with 4000 and 8000 Hz (rho = 0.342 and 0.424, p = 0.027 and 0.005, respectively). However, there was no significant correlation between the serum magnesium and tacrolimus levels (rho = −0.096, P = 0.680) [Table 4, Figure 3].

Table 2: Audiometric data of the transplant patients

	Transplant patients (N = 42)
PTA	
Normal	21 (50%)
Mild	10 (23.8%)
Moderate	9 (21.4%)
Severe	2 (4.8%)
EHFA	
Normal	19 (45.2%)
Mild	3 (7.1%)
Moderate	8 (19%)
Moderate to severe	3 (7.1%)
Severe	9 (21.4%)
TEOAE	
Refer	12 (28.6%)
Partially pass	7 (16.7%)
Pass	23 (54.8%)

PTA: Pure-tone audiometry; EHFA: Extended high frequency audiometry; TEOAE: Transient evoked oto-acoustic emissions. The data were expressed as N (%).

Discussion

Hearing impairment is a disorder that may affect KTRs' quality of life. Numerous adverse events of CNIs are well known, though few studies on their effect on hearing have been published. The results of the current study showed that half of KTRs had non-subjective SNHL according to the findings of the PTA test, where 21% and 4% had moderate and severe SNHL, respectively. These findings are consistent with those of Rifai *et al.*,[5] who investigated hearing disorders in 695 liver transplant patients receiving immunosuppressive drugs using a questionnaire. They discovered that 141 patients had hearing loss and/or tinnitus, with a significant positive correlation to tacrolimus

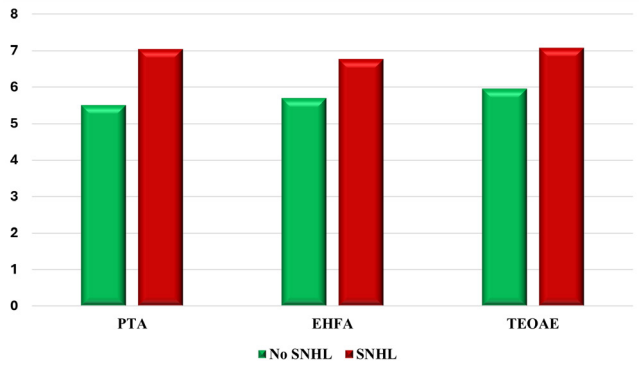

Figure 2: Comparison between with and without sensorineural hearing loss as regard mean tacrolimus trough level. PTA: Pure-tone audiometry, EHFA: Extended high frequency audiometry, SNHL: sensorineural hearing loss, TEOAE: Transient evoked oto-acoustic emissions. P value was computed using independent sample student t-test.

Table 3: Spearman correlation of audiometric tests with different variables in kidney transplant recipients

		PTA	EHFA	TEOAE
Age	Rho	0.080	0.207	-0.168
	P value	0.615	0.188	0.286
Duration of pre-transplantation dialysis	Rho	0.003	−0.185	0.077
	P value	0.987	0.288	0.660
Duration of transplantation	Rho	−0.208	−0.176	0.086
	P value	0.186	0.264	0.586
Duration of hypertension	Rho	0.144	−0.042	−0.228
	P value	0.493	0.841	0.272
Serum creatinine	Rho	−0.161	−0.210	0.145
	P value	0.310	0.182	0.360
Serum calcium	Rho	0.179	−0.132	−0.008
	P value	0.426	0.559	0.971
Serum phosphorus	Rho	−0.098	−0.173	−0.034
	P value	0.673	0.454	0.883
Serum magnesium	Rho	0.015	0.021	0.129
	P value	0.949	0.927	0.578
Tacrolimus trough level	Rho	0.469	0.326	−0.281
	P value	**0.002**	**0.035**	0.072
Steroid dose	Rho	0.023	−0.203	0.051
	P value	0.883	0.197	0.750
Tacrolimus dose	Rho	0.262	0.253	−0.129
	P value	0.094	0.107	0.415

PTA: Pure-tone audiometry; EHFA: Extended high frequency audiometry; TEOAE: Transient evoked oto-acoustic emissions. The bold values denote that these values are statistically significant.

in uni- and multi-variate analyses, where more than a third of the patients with hearing loss were on tacrolimus. Also, these results cope with the findings of Rifai *et al.*,[6] who studied 70 liver transplant cases (56% of them were on cyclosporine and 34% were on tacrolimus) using PTA and found that 50% of 18 patients without subjective hearing loss had moderate or severe SNHL, while those with subjective hearing loss had a significantly worse outcome as tested by PTA. Such results were consistent also with those of Fortes *et al.*,[7] who discovered profound hearing impairments in 24 liver transplant recipients given tacrolimus, when compared to those receiving cyclosporine by PTA.

On performing the EHFA test, 19%, 7%, and 21% of the KTRs in our study had moderate, moderate to severe, and severe SNHL, respectively. These findings are in agreement with the results of a recent study by Simsir *et al.*,[8] who evaluated hearing defects in 46 KTRs (30 of them were on tacrolimus) and found that a high percentage of their patients had hearing impairment, and this percentage increased as the frequency of sound increased, reaching up to 76% of their transplant patients.

The TEOAE results of KTRs in this study showed that nearly 29% of them had hearing abnormalities with an enhanced future risk of hearing loss, although these patients were

Table 4: Correlation of different Hz (250–500–1000–4000–8000 Hz) with different variables in kidney transplant recipients

Parameter		250 Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz	8000 Hz
Age	Rho	−0.015	−0.091	−0.136	−0.032	0.136	0.109
	P value	0.927	0.565	0.391	0.842	0.389	0.492
Duration of pre-transplantation dialysis	Rho	0.082	−0.046	−0.168	−0.029	−0.178	−0.066
	P value	0.638	0.795	0.334	0.870	0.305	0.705
Duration of transplantation	Rho	−0.118	−0.053	−0.152	−0.167	−0.140	−0.223
	P value	0.456	0.740	0.338	0.290	0.376	0.155
Duration of hypertension	Rho	0.199	0.133	0.079	−0.089	0.145	0.082
	P value	0.341	0.525	0.707	0.673	0.488	0.696
Serum creatinine	Rho	−0.257	−0.207	−0.141	−0.159	0.011	−0.046
	P value	0.101	0.189	0.374	0.314	0.947	0.771
Serum calcium	Rho	0.093	−0.091	0.090	−0.156	0.271	0.238
	P value	0.680	0.687	0.690	0.488	0.223	0.287
Serum phosphorus	Rho	−0.126	−0.103	0.211	0.055	0.221	0.096
	P value	0.586	0.658	0.358	0.814	0.336	0.679
Serum magnesium	Rho	0.127	0.153	0.194	0.273	−0.037	0.068
	P value	0.583	0.507	0.400	0.231	0.873	0.768
Tacrolimus trough level	Rho	0.081	0.109	0.021	−0.001	0.342	0.424
	P value	0.609	0.491	0.893	0.995	**0.027**	**0.005**
Steroid dose	Rho	−0.200	−0.150	−0.021	−0.145	−0.047	−0.045
	P value	0.203	0.343	0.894	0.361	0.769	0.779
Tacrolimus dose	Rho	0.173	0.099	0.010	0.110	0.128	0.199
	P value	0.272	0.531	0.948	0.490	0.419	0.206

The bold values denote that these values are statistically significant.

asymptomatic at the time of the study. These findings agree with those reported by Fadel *et al.*,[9] who studied 40 pediatric transplant cases receiving tacrolimus and found that 25% of the cases had hearing impairment. They also reported that children with longer pre-transplant duration on dialysis or biopsy proven rejection had significantly higher hearing affection than those without. However, in our study, there was no correlation between the duration of pre-transplant dialysis and the results of the different audiometric tests used in the study.

Different factors were studied in correlation to the results of different audiometric tests in this study. The tacrolimus trough level was the only factor found to have a significant positive correlation with the results of both the PTA and EHFA tests. All factors did not have a significant correlation with the results of the TEOAE test. These results are in agreement with other studies and case reports that showed that a high tacrolimus level was associated with SNHL.[10-12] However, other studies could not find a correlation between tacrolimus blood levels and SNHL.[8,9]

A recent case report[12] presented the case of a 51-year-old KTR who developed sudden vestibular disorders and SNHL after receiving tacrolimus; this condition was associated with severe hypomagnesemia. The patient's clinical condition improved after the correction of hypomagnesemia. The authors claimed

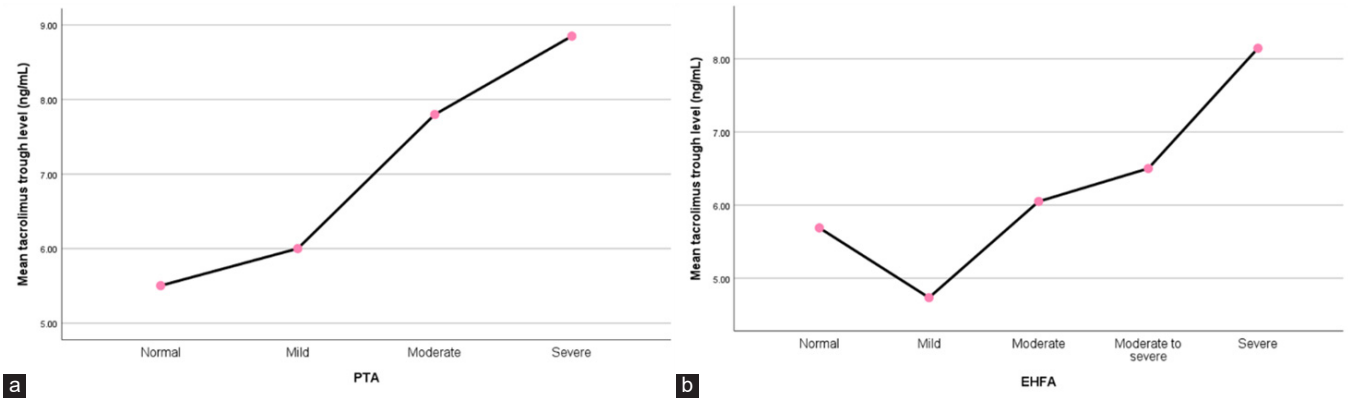

Figure 3: (a) Summary point plot mean of tacrolimus trough level by PTA and (b) summary point plot mean of tacrolimus trough level by EHFA. PTA: Pure-tone audiometry, EHFA: Extended high frequency audiometry.

that this condition was due to tacrolimus-induced hypomagnesemia. We studied the correlation of different factors, including magnesium, to SNHL and found that, although the mean serum magnesium level was below normal in the studied cases, it was not significantly correlated with either the results of different audiometric tests done for the patients or the tacrolimus level. This indicates that a low serum magnesium level is not the cause of SNHL related to tacrolimus. To our knowledge, we did not find any other studies that investigated the correlation of serum magnesium level with SNHL in KTRs receiving tacrolimus.

SNHL and other hearing disorders may be associated with the use of immunosuppressive drugs such as tacrolimus. A dose-dependent mechanism, like neurotoxicity, has been suggested to be the cause.[13] Different mechanisms have been suggested, including microscopic thromboembolic events, reduced molecular diffusion across the blood–inner ear barrier, and modification of the P-glycoprotein multidrug extrusion pump of the inner ear plasma membrane. The latter mechanism appears to cause the accumulation of considerable amounts of ototoxic substances within the inner ear.[14] Sudden SNHL was reported in several patients exposed to high blood levels of tacrolimus. There is evidence that vasculopathy and endothelial dysfunction, which disturb the blood-brain barrier, are the causes of CNI-related neurotoxicity. The vascular injury to the inner ear's capillary endothelial cells, causing disturbance of the blood-inner ear barrier, was believed to contribute to hearing loss.[15]

The clinical care for KTRs should include periodic audiometric evaluation for early detection of silent SNHL, which could be reversible by minimizing the dose of tacrolimus to the least effective dose to prevent graft loss and protect hearing. The impact of hearing loss on a KTR's quality of life should be kept in mind. Awareness of this potential of adverse event of tacrolimus may help with early detection and treatment.

SNHL was detected in about half of the studied KTRs. Silent SNHL might be associated with higher tacrolimus trough levels.

Conflicts of interest

There are no conflicts of interest.

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