Original Article

Cyclosporine A effect on Hearing in Children with Steroid Dependent Nephrotic Syndrome and Steroid Resistant Nephrotic Syndrome.

Mohamed S. El-Farsy [1], Maged Ashraf A. Ibrahim [1], Fathy N. Fatouh [2], Ahmed T. Abdel Fattah [3]

1- Pediatrics Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
2- Audiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
3- Ministry of Health, Cairo, Egypt.

Abstract

Introduction: Cyclosporine A (CsA) plays a confounding role in the treatment of nephrotic syndrome (NS) in children. It is a widely used in pediatric nephrology practice for the treatment of patients with steroid dependent nephrotic syndrome (SDNS) and steroid resistant nephrotic syndrome (SRNS).

Aim of the study: To assess hearing defects in children with steroid dependent nephrotic syndrome (SDNS) and steroid resistant nephrotic syndrome (SRNS), before and after receiving CsA for 6 months.

Methods: Prospective observational study was conducted on 25 pediatric patients with SDNS and SRNS in pediatric nephrology clinic, Children's hospital, Ain Shams University, were trialed to evaluate hearing defects before and after receiving CsA for 6 months. Patients were subjected to history taking and basic audiological evaluation before and 6 months after initiation of CsA treatment.

Results: Valid cases showed that the average mean hearing threshold shows non-significant changes before and after six months of cyclosporine A treatment with (p= 0.954) at 250 Hz, (p= 0.868) at 500 Hz, (p= 0.473) at 1000 Hz, (p= 0.680) at 2000 Hz, (p= 0.535) at 4000 Hz and (p= 0.865) at 8000 Hz respectively. There was no correlation between age, weight, height, age at first clinical presentation, duration of corticosteroid intake, regarding average of hearing before and after six months of cyclosporine A treatment. Concerning speech and language evaluation, all patients had bilateral excellent speech discrimination before and after CsA treatment. Immitancemetry showed bilateral type A tympanogram reflecting normal middle ear pressure in all patients before and after CsA treatment.

Conclusion: CsA cause no hearing impairment effect on patients with SDNS and SRNS after 6 months of administration. We may suggest that there is no sufficient evidence to consider routine audiological assessment in children with SDNS and SRNS treated with CsA.

Keywords: Cyclosporine A, Steroid Dependent, Steroid Resistant, Nephrotic Syndrome
Running title: Cyclosporine A effect on Hearing in Children with Nephrotic Syndrome

Corresponding Author Mohamed S. El Farsy, MD
Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
Address: Ain Shams University Children's Hospital, Abbassyia, Cairo, Egypt.
PO Box: 11566
Email: moh_elfasry@yahoo.com
ORCID ID: 0000-0002-7454-2844

Introduction

Nephrotic syndrome (NS) is the most common glomerular disease in children. More than 70% of children experience a relapse with recurrent episodes of edema and proteinuria after corticosteroids therapy [1].

About 80 % of children with NS show remission of proteinuria following treatment with corticosteroids and are classified as 'steroid sensitive.' Most patients have multiple relapses [frequently relapsing nephrotic syndrome (FRNS) / steroid dependent nephrotic syndrome (SDNS)], placing them at risk for steroid toxicity, systemic infection, and other complications [2]. A small proportion of patients who do not respond to steroids are known to have steroid resistant nephrotic syndrome (SRNS) for which therapeutics other than steroids are used as a treatment [3].

Cyclosporine A (CsA) plays a confounding role in the treatment of NS in children [4]. It is a widely used in pediatric nephrology practice for the treatment of patients with (SDNS, FRNS and SRNS) or as part of a regimen in renal transplantation. CsA is a cyclic polypeptide, the effect of which is caused by inhibiting calcineurin activity. This process results in reversible inhibition of T-helper-cell proliferation, sparing T-suppressor lymphocytic, antibody-independent T-cell-mediated and phagocytic immunity [5].

In experimental studies, it was shown that CsA impairs the function of p-glycoprotein (P-gp), which serves as a pump located on the surface of the capillary endothelial cells in the inner ear [6]. In another case, slowly developing bilateral sensorineural hearing loss have been associated with CsA and audiological findings in that study pointed to a cochlear disorder [7]. In a study on children with FRNS, SDNS and SRNS, impairment in the hearing thresholds was observed especially in the relapse period and worse thresholds were determined in SRNS patients, which was associated with higher cumulative doses of furosemide and hypocalcaemia [8].

An association exists between renal and inner ear disorders. This association may be genetically determined and manifest as Alport's syndrome, branchio-oto-renal syndrome, and others. The organs of the inner ear and the kidney are physiologically similar in that both are concerned in maintaining the electrolyte concentration gradient. Children with acute kidney injury and chronic kidney disease are known to have hearing impairment. Children with NS have biochemical impairments which include hyponatremia, hypocalcemia, and hyperlipidemia. These biochemical abnormalities are known to cause hearing impairment. Many children with NS are treated with multiple courses of diuretics, which also cause ototoxicity. These factors increase the risk of hearing impairment in children with NS [9].

Aim of the study

To assess hearing defects in children with steroid dependent nephrotic syndrome (SDNS) and steroid resistant nephrotic syndrome (SRNS), before and after receiving CsA for 6 months.

Methods

A prospective observational study was conducted on twenty five children with

SDNS and SRNS. The study was approved by the ethics committee of our university and it conforms to standards currently applied in Egypt. All children are enrolled at the Pediatric Nephrology clinic, Children's hospital, at our University. The purpose of the study was explained in details to the children's guardians and informed written consent was obtained from the parents of each child before enrollment according to the Declaration of Helsinki. This study was carried from the first of July 2018 to the end of December 2018. This study children with SDNS and SRNS before and after receiving CsA for 6 months. Hearing test was done before and after receiving CsA for 6 months. ''Steroid resistance'' was defined as failure to respond to a 4-week course of daily prednisolone (60 mg/m^2) followed by 3 pulse methylprednisolone (PMP) courses.

All the following children are excluded from the study: Children with previous history of hearing defect, trauma or surgery for the inner ear, recurrent otitis media, otitis externa and ear wax. History of congenital hearing loss, birth asphyxia, hyperbilirubinemia, or head trauma. Family history of hearing problems. Children using hearing aid. Patients who refused participating in the study. Uncooperative children during the audiometric examination. Age <5 years (potential inability to cooperate with testing procedures).

The study included 15 patients with SDNS (5 patients of them with mesangioproliferative GN and 10 patients with MCNS) and 10 patients with SRNS (all of them with FSGS), none of the children in the study were prescribed any other cytotoxic drug.

Duration of the disease for SDNS was more than 1 year and for SRNS as defined before. Dose of CsA used was 3 mg/kg/day increasing to 5 mg/kg/day if CsA trough level was less than 65 ng/mL. CsA trough level all through the study was kept between 65-100 ng/mL.

Fortunately, no serious complications of CsA use were detected during the study, (e.g impaired kidney functions, hypertension (out of steroid induced), thrombocytopenia or bleeding). Only two patients developed mild gum hyperplesia without bleeding per gums, twenty patients developed hirsutism and fifteen patients suffered from GIT upset.

All patients included in the study were subjected to the following: Detailed History: Laying stress on age, sex, age at presentation, systemic diseases, ear problems, renal biopsies (if present) and exposure to ototoxic agents. General examination: Assessment of anthropometric measures including weight in kilograms (Kg) and height in centimeters (Cm). Hearing test: Otorhinolaryngological examination was performed in all children before hearing tests were to exclude otitis media, otitis externa and for ear wax. Those with ear wax were tested for hearing loss after wax removal.

A double walled sound treated room I.A.C model 1602, two channel audiometer Inter-acoustics, model AC40; calibrated according to ANSI S.3.6, 1996 and connected to headphones TDH 39, bone vibrator B71 and two loudspeakers for sound field testing, acoustic Immittance meter MAICO model MI 34. Otological examination: Basic audiological evaluation including: Pure Tone Audiometry (PTA). Speech Audiometry. Acoustic Immitancemetery.

Statistical Analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science (SPSS 15.0.1 for Windows; SPSS Inc., Chicago, IL, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

1- Descriptive statistics:
   a. Mean and Standard deviation for quantitative parametric data.
   b. Median and Interquartile range for quantitative non-parametric data.
   c. Frequency and percentage was used for presenting qualitative data**.**

2- Analytical statistics:
   a. Student T Test was used to assess the statistical significance of the difference between the study groups means.
   b. Chi-Square test was used to examine the relationship between two qualitative variables. P-value > 0.05 will be considered statistically significant.

Correlation analysis (using Pearson′s method)

To assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically ″r″ defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables.

- r = 0-0.19 is regarded as very weak correlation
- r = 0.2-0.39 as weak correlation
- r = 0.40-0.59 as moderate correlation
- r = 0.6-0.79 as strong correlation
- r = 0.8-1 as very strong correlation.

Results

The study included 25 children with SDNS and SRNS before and after receiving CsA for 6 months, 7 female and 18 male with mean age 10.36 year ± 3.18, with mean age at 1st clinical presentation 4.72 ± 3.02 year, mean weight 36.96 kg and mean height 139.04 **(Table 1).**

Table 2 shows non-significant difference between average hearing thresholds in right and left ears before starting cyclosporine A treatment for children. **Table 3** shows non-significant difference between average hearing thresholds in right and left ears after cyclosporine A treatment for 6 months. **Table 4** shows non-significant difference between hearing thresholds in right and left ears before and after six months of cyclosporine A treatment for children with SDNS and SRNS.

Table 5 shows non-significant difference between average mean hearing thresholds before and after six months of cyclosporine A treatment in patients with MCNS. **Table 6** shows non-significant difference between average mean hearing thresholds before and after six months of cyclosporine A treatment in patients with FSGS. **Table 7** shows non-significant correlation between age, weight, height and age at 1st clinical presentation (yrs), regarding average of hearing before and after six months of cyclosporine A treatment.

Estimated GFR and kidney functions were measured before and every 3 months during the study and fortunately, did not deteriorate all through the study. There is non-significant correlation between average hearing thresholds in right and left ears after cyclosporine A treatment for 6 months and cyclosporine A level ranging from 65-100 ng/mL

Table 1: Demographic data at the time of the study.

		No. = 25
Age (yrs)	Mean ± SD	10.36 ± 3.18
	Range	6 – 15
Sex	Females	7 (28.0%)
	Males	18 (72.0%)
Wt (kg)	Mean ± SD	36.96 ± 13.28
	Range	18 – 65
Ht (cm)	Mean ± SD	139.04 ± 16.85
	Range	114 – 166
Age at 1st clinical presentation (yrs)	Mean ± SD	4.72 ± 3.02
	Range	1 – 12

Table 1: Comparison between mean hearing thresholds in right & left ears before cyclosporine A treatment.

Frequency (Hz)	Right	Left	Paired t-test	p-value
250 Hz	18.00 ± 5.00	18.80 ± 5.06	-1.693	0.103
500 Hz	17.60 ± 3.85	18.00 ± 4.56	-0.527	0.603
1000 Hz	17.40 ± 3.85	17.60 ± 3.57	-0.327	0.746
2000 Hz	16.80 ± 4.97	17.00 ± 3.54	-0.272	0.788
4000 Hz	16.00 ± 3.82	17.60 ± 5.42	-2.317	0.029
8000 Hz	17.60 ± 5.23	17.60 ± 5.97	0.000	1.000
Average	17.23±3.66	17.77±3.57	1.801	0.084

Table 2 : Comparison between mean hearing thresholds in right and left ears after cyclosporine A treatment for six months.

Frequency (Hz)	Right	Left	Paired t-test	p-value
250 Hz	18.20 ± 5.75	18.80 ± 5.06	-0.901	0.376
500 Hz	17.80 ± 5.22	18.20 ± 4.76	-0.401	0.692
1000 Hz	17.80 ± 4.58	18.80 ± 5.26	-1.044	0.307
2000 Hz	15.80 ± 4.25	17.00 ± 4.79	-1.541	0.136
4000 Hz	15.40 ± 4.06	16.60 ± 4.73	-2.009	0.056
8000 Hz	17.80 ± 6.14	18.00 ± 6.12	-0.253	0.802
Average	17.13 ± 4.22	17.90±4.33	1.306	0.204

Table 3 : Comparison between mean hearing thresholds before and after six months of cyclosporine A treatment.

Frequency (Hz)	Pre	Post	Percentage of change	Test value•	P-value	Sig.
	Mean±SD	Mean±SD	Median(IQR)			
	Right		**Mean hearing thresholds (dB)**			
250 Hz	18.00 ± 5.00	18.20 ± 5.75	0 (-25 – 33.33)	-0.112	0.912	NS
500 Hz	17.60 ± 3.85	17.80 ± 5.22	0 (-20 – 33.33)	-0.143	0.888	NS
1000 Hz	17.40 ± 3.85	17.80 ± 4.58	0 (-20 – 0)	-0.347	0.731	NS
2000 Hz	16.80 ± 4.97	15.80 ± 4.25	0 (-25 – 0)	0.722	0.477	NS
4000 Hz	16.00 ± 3.82	15.40 ± 4.06	0 (-25 – 33.33)	0.486	0.632	NS
8000 Hz	17.60 ± 5.23	17.80 ± 6.14	0 (-25 – 33.33)	-0.110	0.913	NS
	Left		**Mean hearing thresholds (dB)**			
250 Hz	18.80 ± 5.06	18.80 ± 5.06	0 (-25 – 33.33)	0.000	1.000	NS
500 Hz	18.00 ± 4.56	18.20 ± 4.76	0 (-25 – 33.33)	-0.146	0.885	NS
1000 Hz	17.60 ± 3.57	18.80 ± 5.26	0 (0 – 33.33)	-0.947	0.353	NS
2000 Hz	17.00 ± 3.54	17.00 ± 4.79	0 (-25 – 33.33)	0.000	1.000	NS
4000 Hz	17.60 ± 5.42	16.60 ± 4.73	0 (-25 – 33.33)	0.679	0.503	NS
8000 Hz	17.60 ± 5.97	18.00 ± 6.12	0 (-33.33 – 33.33)	-0.212	0.834	NS
			Average			
250 Hz	18.40 ± 4.89	18.50 ± 5.15	0 (-22.22 – 33.33)	-0.059	0.954	NS
500 Hz	17.80 ± 3.77	18.00 ± 4.33	0 (-12.5 – 14.29)	-0.168	0.868	NS

1000 Hz	17.50 ± 3.39	18.30 ± 4.31	0 (0 – 14.29)	-0.730	0.473	NS
2000 Hz	16.90 ± 3.91	16.40 ± 4.09	0 (-25 – 16.67)	0.417	0.680	NS
4000 Hz	16.80 ± 4.36	16.00 ± 4.15	0 (-25 – 33.33)	0.629	0.535	NS
8000 Hz	17.60 ± 5.33	17.90 ± 5.80	0 (-22.22 – 42.86)	-0.172	0.865	NS

> 0.05 NS: Non significant; < 0.05 S: Significant; < 0.01 HS: Highly significant.

Table 4 : Comparison between mean hearing thresholds before and after six months of cyclosporine A treatment in patients with MCNS.

MCGN	Pre	Post	% of improvement	Test value	P-value	Sig.
Average						
250 Hz	20.94 ± 4.21	18.13 ± 2.91	-15.56 (-31.11 – 7.14)	1.317	0.229	NS
500 Hz	17.50 ± 3.27	18.13 ± 2.22	0.00 (-11.81 – 23.81)	-0.424	0.685	NS
1000 Hz	17.81 + 3.64	17.50 ± 4.01	0.00 (-5.00 – 7.14)	0.357	0.732	NS
2000 Hz	16.88 ± 4.17	15.94 ± 3.52	-6.25 (-19.64 – 7.14)	0.753	0.476	NS
4000 Hz	17.50 ± 3.54	15.31 ± 3.64	-12.50 (-29.17 – 7.14)	1.313	0.231	NS
8000 Hz	20.00 ± 6.55	17.50 ± 4.23	-17.14 (-22.22 – -6.25)	1.000	0.351	NS

Table 5 : Comparison between mean hearing thresholds before and after six months of cyclosporine A treatment in patients with FSGS.

Focal segmental GS	Pre	Post	% of improvement	Test value	P-value	Sig.
Average						
250	19.38 ± 3.15	17.50 ± 4.56	-8.33 (-20.83 – 0.00)	1.567	0.215	NS
500	18.13 ± 2.39	16.88 ± 4.73	7.14 (-25.00 – 15.48)	0.420	0.703	NS
1000	17.50 ± 2.04	17.50 ± 2.89	7.14 (-12.50 – 14.29)	0.000	1.000	NS
2000	17.50 ± 2.04	16.25 ± 4.33	7.14 (-25.00 – 15.48)	0.420	0.703	NS
4000	16.25 ± 1.44	18.13 ± 2.39	16.67 (-7.14 – 33.33)	-1.000	0.391	NS
8000	16.88 ± 2.39	17.50 ± 6.12	-0.89 (-23.81 – 31.25)	-0.225	0.836	NS

Table 6 : Correlation between age, weight, height & age at 1st clinical presentation (yrs), regarding average of hearing before & after six months of cyclosporine A treatment.

Average of hearing	Age (yrs)		Wt (kg)		Ht (cm)		Age at 1st clinical presentation (yrs)	
	r	P-value	r	P-value	r	P-value	r	P-value
Pre CsA treatment	0.335	0.102	0.249	0.231	0.322	0.117	0.081	0.701
Post CsA treatment	-0.052	0.803	-0.122	0.563	-0.047	0.824	-0.024	0.908

Discussion

An association exists between renal and inner ear disorders. This association may be genetically determined and manifest as Alport's syndrome and others. The organs of the inner ear and the kidney are physiologically similar in that both are concerned in maintaining the electrolyte concentration gradient. Children with NS have biochemical impairments which include hyponatremia, hypocalcemia, and hyperlipidemia. These biochemical abnormalities cause hearing impairment. Many children with NS are treated with multiple courses of diuretics, which also cause ototoxicity. These factors increase the risk of hearing impairment in children with NS [10].

In the present study, twenty five pediatric patients with SRNS were assessed by doing basic audiological evaluation prior to the study, as an initial record, and the same hearing tests were repeated after receiving CsA for 6 months. All hearing tests were done in the remission period in all patients. Any patient had hearing impairment in the initial hearing tests was excluded. Regarding the age of the patients enlisted in the study, the mean age was 10.36 ±

3.18 years. This was comparable to Kasap-Demir et al. (2017) [11] that stated that the mean age of the patients receiving CsA was 10.75 ± 5.27 years.

Concerning the sex of patients enrolled in this study, 72% were males and 28% were females. In comparison to Kasap-Demir et al. (2017) [11], 62.5% were males and 37.5% were females. The mean age at first presentation was 4.72 ± 3.02 years, which was more than that of Kasap-Demir et al. (2017) [11] (2.55 ± 1.175 years).

Renal biopsy was done in 64% of patients which revelaed MCGN in 50%, FSGS in 25%, Diffuse proliferative GN in 6.3%, Mesangio-proliferative GN type II in 6.3%, Mesangial GN in 6.3%, Minimal change with mesangial hypercellularity in 6.3% patients and no biopsy was performed in 36% of the patients. In comparison to Kasap-Demir et al. (2017) [11], 50% of patients receiving CsA their biopsies were FSGS.

In terms of hearing tests, the current study on valid cases showed that hearing thresholds in the right and left ears at (250, 500, 1000, 2000, 4000 and 8000 Hz) showed non-significant difference before and after six months of cyclosporine treatment in the studied patients. The present study showed that CsA treatment for 6 months does not cause any hearing defects in children with SRNS. To the best of our knowledge, this study was the second one to study the effects of CsA on hearing in children with NS.

The first clinical study investigating the effects of CsA on hearing in children with NS was by Kasap-Demir et al. (2017) [11] which was a cross-sectional study that included 29 patients with SDNS, FRNS and SRNS, receiving CsA for at least 6 months. Hearing tests showed that CsA treatment for at least 6 months does not cause any hearing defects in children with SDNS, FRNS or SRNS, which is in agreement with our study's findings.

In other studies, CsA was responsible for the inhibition of the B and T cell interaction by inhibiting T-lymphocyte synthesis of various cytokines (IL-4, IL-2) and inducing a reduction in the CD40 expression. This mechanism reduces antibody production, so it is effective in autoimmune sensorineural hearing loss [12]. In addition, protective effects of CsA on the integrity and function of Corti organ in acoustic injury of the cochlea were demonstrated in guinea pigs [13].

The other available studies were mainly on pediatric renal transplantation recipients, Gulleroglu et al. (2015) [14] stated that dose-dependent CsA toxicity in pediatric renal transplantation recipients is related with hearing impairment, particularly in the higher-frequency tones. After dosage correction, pure-tone audiometry showed improvement of hearing loss progression. The mechanism of CsA related ototoxicity is under debate. The most prominent initial manifestation of drug ototoxicity is elevated thresholds at higher frequencies progressing to median and low frequencies.

Another study by Marioni et al. (2004) [7] stated that CsA-associated hearing impairment was found in high frequencies, which was caused by long-term CsA treatment in renal transplantation recipients. A suggested explanation of this CsA ototoxicity is vascular damage caused by CsA localized in the capillary endothelial cells of the inner ear which form blood/inner ear barrier by tight junctions, leading to cochlear SNHL [6]. The action of CsA on the blood/inner ear barrier has been

demonstrated by Saito et al. (2001) [15] who concluded that inhibition of the plasma membrane extrusion pump p-glycoprotein, localized in the capillary endothelial cells of the inner ear, by a high dose of CsA was responsible for inner ear accumulation and vinblastine and doxorubicin related ototoxicity.

Another explanation of CsA ototoxicity is neurotoxicity which is a major adverse effect of calcineurin inhibitors. Numerous studies have reported diverse neurotoxic effects ranging from mild symptoms (e.g. tremor, headache and peripheral neuropathy) to more severe symptoms (e.g. psychoses, hallucinations, blindness, seizures, cerebellar ataxia, motor weakness and leukoencephalopathy). Calcineurin plays an important role in the rapid functioning of neurons. Neurotoxicity is likely due to the inhibition of calcineurin within nerve cells. These neurotoxic adverse effects could be involved in developing hearing impairment [16].

In addition, the current study noted that there is non-significant difference between average mean hearing thresholds before and after six months of cyclosporine treatment in the studied patients whose biopsies were MCNS and FSGS.

Clinical studies evaluating the hearing status in children with NS has contradictory results. Bayazit et al. (2005) [17] stated that there were no hearing defects either in remission or relapse periods in children with MCNS. Other study was by Saha et al. (2013) [8] showed that children with FRNS/SDNS had a statistically significant higher threshold for hearing (sensorineural hearing impairment) at frequencies of 250 and 500 Hz than normal children in about 15% of the group. However, children with SRNS had a higher threshold for hearing at frequencies of 250, 500, 1,000, and 2000 Hz than the controls in 50% of the group.

Orendorz et al. (2008) [18] realized that children with nephrotic syndrome had worse hearing outcome than the healthy children even after remission. El Mashad et al. (2017) [19] also evaluated hearing in children with INS. 40% had SNHL mostly mild degree hearing impairment that occurred at the lower frequencies (250, 500, and 1000). This was worse for the SRNS group than in other groups. The threshold of hearing at higher frequencies in different groups was statistically insignificant.

Moreover, the current study found no correlation between age, weight, height and age at first clinical presentation, regarding average of hearing before and after six months of cyclosporine treatment. The available studies were mainly studied the relationship between duration of CKD patients and hearing impairment, one of the available studies was by Renda et al. (2015) [20] that found no correlation between the duration of CKD and hearing loss.

Concerning speech discrimination, all patients had bilateral excellent speech discrimination before and after CsA treatment. However, Gulleroglu et al. (2015) [14] noted that 47% of patients with hearing impairment on audiological assessment had decreased speech understanding, which was not reversible after dose reduction in transplantation patients.

Finally, Immitancemetry showed bilateral type A tympanogram reflecting normal middle ear pressure in all patients before and after CsA treatment. However,

Bayazit et al. (2005) [17] noted that in the relapsing and remission periods, type A tympanogram was found in 86.4% and 92.3% of the ears, respectively. Type B tympanogram was found in 11.5% and 3.8% of the ears in the relapsing and remission periods, respectively. Type C tympanogram was found in 3.8% of the ears both in the relapsing and remission periods. Differences between the tympanometry results were insignificant.

There are some limitations to our study, such as the small sample size, short follow-up period. Nevertheless, the strength of our study was its prospective nature. It would be ideal to investigate the possible ototoxicity of CsA in the same group of patients with SRNS, whose initial hearing tests was normal, and compare it with hearing tests after receiving CsA for a period of 6 months. In addition, we could form homogenous group in terms of treatment modalities which was impossible in a previous retrospective study.

However, we recommend that a further study utilizing a duration more than six months, and a larger sample size (more than twenty five patients) to be done for confirmation of the present results.

Conclusion

CsA cause no hearing impairment in patients with SRNS after 6 months of administration. We may suggest that there is no sufficient evidence to consider routine audiological assessment in children with SRNS treated with CsA.

Abbreviations

CD	Clusters of Differentiation
CKD	Chronic kidney disease
CsA	Cyclosporine A
FRNS	Frequently relapsing nephrotic syndrome
FSGS	Focal segmental glomerulosclerosis
GN	Glumerulonephritis
IL	Interleukin
INS	Idiopathic Nephrotic syndrome
MCNS	Minimal change nephrotic syndrome
NS	Nephrotic syndrome
PMP	Pulse methylprednisolone
PTA	Pure Tone Audiometry
SDNS	Steroid dependent nephrotic syndrome
SRNS	Steroid resistant nephrotic syndrome

References:

1. Seikaly MG, Prashner H, Nolde-Hurlbert B and Browne R: Long-term clinical and pathological effects of cyclosporine in children with nephrosis. Pediatr Nephrol. 2000; 14: 214–217.
2. Indian Pediatrics Nephrology Group and Indian Academy of Pediatrics: Management of steroid sensitive nephrotic syndrome: Revised guidelines. Indian Pediatr. 2008; 45:203–214.
3. Bhimma R: Steroid resistant nephrotic syndrome in children. Pediatric Oncall Journal. 2005; 2(12).

4. Takeda A, Takimoto H, Mizusawa Y and Simoda M: Prediction of subsequent relapse in children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2001; 16: 888–893.

5. Dawson DG and Trobe JD: Blindness after liver transplant. Surv Ophthalmol. 2002; 47: 387–91.

6. ZhangZJ, Saito T, Kimura Y, Sugimot o C, Ohtsubo T, Saito H: Disruption of mdrla p-glycoprotein gene results in dysfunction of blood-inner ear barrier in mice. Brain Res 2000; 852: 116–26.

7. Marioni G, Perin N, Tregnaghi A, Bellemo B, Staffieri A and De Filippis C: Progressive bilateral sensorineural hearing loss probably induced by chronic cyclosporin A treatment after renal transplantation for focal glomerulosclerosis. Acta Otolaryngol. 2004; 124: 603–607.

8. Saha A, Gupta V, Kapoor K, Dubey NK, Lal P, Sidhu TS, Batra VV and Upadhyay AD: Hearing status in children with frequently relapsing and steroid resistant nephrotic syndrome. Pediatr Nephrol. 2013; 28: 439–445.

9. Thodi C, Thodis E, Danielides V, Pasadakis P and Vargemezis V: Hearing in renal failure. Nephrol Dial Transplant. 2006; 21:3023–3030.

10. Saha A, Gupta V, Kapoor K, Dubey NK, Lal P, Sidhu TS, Batra VV and Upadhyay AD: Hearing status in children with frequently relapsing and steroid resistant nephrotic syndrome. Pediatr Nephrol. 2013; 28: 439–445.

11. Kasap-Demir B, Ozmen D, Kirkim G, Dogan E, Soylu A, Serbetcioglu B and Kavukcu S: Cyclosporine causes no hearing defect in paediatric patients with nephrotic syndrome. Internat. J Audiol. 2017; 56(9):701-705.

12. Di Leo E, Coppola F, Nettis E, Vacca A and Quaranta N: Late recovery with cyclosporine-A of an auto-immune sudden sensorineural hearing loss. Acta Otorhinolaryngol Ital. 2011; 31; 399–401.

13. Gulleroglu K, Baskin E, Aydin E, Ozluoglu L, Moray G and Haberal M: Hearing status in pediatric renal transplant recipients. Exp Clin Transplant. 2015; 13, 324–328.

14. Saito T, Zhang ZJ, Tokuriki M, Shibamori Y, Yamamoto T and Ohtsubo T: Cyclosporin A inhibits the extrusion pump function of p-glycoproteinin the inner ear of mice treated with vinblastine and doxorubicin. Brain Res. 2001; 901: 265–270.

15. Tan TC and Robinson PJ: Mechanisms of calcineurin inhibitor-induced neurotoxicity. Transplantation Reviews. 2006; 20:49-60.

16. Bayazit YA, Balat A, Pakir HI, Güler E and Kanlikama M: Influence of relapse and remission periods on hearing status in children with minimal change nephrotic syndrome. Rev Laryngol Otol Rhinol. 2005; 126(3):171–173.

17. Orendorz-Frqczkowska K, Medynska A, Jablonka A and Gawron W: Hearing organ function in children with nephrotic syndrome in course of primary glomerulopathy, Otolaryngologia Polska. 2008; 12:182–187.

18. El-Mashad GM, Abo El Fotoh WM, Zein El Abedein AM and Abd El Sadek FA: Biochemical alteration in children with idiopathic nephrotic syndrome associated with an increased risk of sensorineural hearing loss; additional insights in cochlear renal

relationship. International Journal of Pediatric Otorhino-laryngology. 2017; 97:206–210.

19. Renda R, Renda L, Selcuk OT, Eyigor H, Yilmaz MD and Osma U: Cochlear sensitivity in children with chronic kidney disease and end-stage renal disease undergoing hemodialysis. International Journal of Pediatric Otorhinolaryngology. 2015; 79; 2378–2383.

Statements

Ethics approval and consent to participate:
This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Pediatric Department, Children Hospital, Ain Shams University and informed written consent was obtained in every case from their legal guardians.

Consents for publication
″Not applicable″
Availability of data and material
″Not applicable″
Conflict of interest
The authors declare no conflict of interest.
Funding
The authors declare that the research is self-funded by the authors.
Acknowledgements
Authors would like to thank all patients and their family members for their valuable contributions to the study.

Submitted **16/04/2021**
Accepted **28/05//2021**
Published online **28/07/2021**