*Journal of Advances in Medicine and Medical Research*

***33(1): 17-28, 2021; Article no.JAMMR.64806***
***ISSN: 2456-8899***
*(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)*

# Effect of Cyclosporin A on Hearing Status in Children with Difficult to Treat Idiopathic Nephrotic Syndrome

**Mohammed Tawfik Ramadan Rageh[1*], Shimaa Basyony El-Nemr[1], Amani Mohamed El- Gharib[2] and Hend Hassan Abdelnabi[1]**

*[1]Pediatric Department, Faculty of Medicine, Tanta University, Egypt.*
*[2]Audiovestibular Department, Faculty of Medicine, Tanta University, Egypt.*

***Authors' contributions***

*This work was carried out in collaboration among all authors. Author MTRR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SBEN and AMEG managed the analyses of the study. Author HHA managed the literature searches. All authors read and approved the final manuscript.*

***Article Information***

DOI: 10.9734/JAMMR/2021/v33i130790
Editor(s):
(1) Dr. Nicolas Padilla-Raygoza, School of Medicine, University of Celaya, Mexico.
Reviewers:
(1) Panat Anuracpreeda, Mahidol University, Thailand.
(2) Nathalia Blanco Ferreiro dos Santos, Universidade Federal Fluminense, Brazil.
(3) Khemchand N. Moorani, The kidney Centre postgraduate Training Institute, Pakistan.
Complete Peer review History: http://www.sdiarticle4.com/review-history/64806

***Original Research Article***

***Received 15 November 2020***
***Accepted 19 January 2021***
***Published 20 January 2021***

## ABSTRACT

**Background**: Cyclosporin A (CsA) is an important drug regimen for difficult to treat nephrotic syndrome (NS) with few information known about its ototoxicity.
**Aims:** Assessment the hearing status in children with difficult to treat idiopathic NS on CsA treatment.
**Material and Methods:** This prospective cohort study included 2 groups: Group I: 15 children with steroid sensitive idiopathic nephrotic syndrome on steroids only as a line of treatment was used as comparing group to group II which included 15 children recently diagnosed difficult to treat NS starting CsA as steroids sparing drug, hearing functions were assessed using standard, high-frequency audiometry and transient otoacoustic emissions (TOAEs) at base line for both groups and after 6 months of CsA treatment for group II.
**Results:** There was significant elevation of hearing threshold in extended high frequency (> 8 KHz) (subclinical hearing loss) after six months of CsA. There was positive correlation between

**Corresponding author: E-mail: Rageh050@gmail.com;*

Cyclosporin A trough level and elevated hearing threshold in pure tone audiometry and extended high frequency (> 8 KHz). There was insignificant difference between groups according to TOAEs. There was statistically significant positive correlation between extended high frequency range and serum trough CsA level in group II.

**Conclusions:** CsA is a potential cause of hearing impairment in children with difficult to treat NS so all patients on CsA need routine audiological assessment especially with high serum CsA level and long duration.

*Keywords: Difficult to treat; nephrotic syndrome; children; Cyclosporine A; hearing evaluation.*

## 1. INTRODUCTION

Nephrotic syndrome (NS) is characterized by a triad of heavy proteinuria (urine protein/creatinine ratio ≥ 2 or ≥3+ proteinuria on urine dipstick), hypoalbuminemia (<2.5 g/L) and edema. It is one of the most common glomerular diseases in children, with an incidence of 1–2 /$10^5$ children, and a prevalence of 16/ $10^5$ children [1]. Although 80–90% of patients are steroid sensitive (SSNS) in the beginning, half of them will behave as frequently relapsing nephrotic syndrome (FRNS) or steroid dependent nephrotic syndrome (SDNS) which is difficult to be treated [2,3]. 10-20% will behave as SRNS. Cyclosporine A (CsA) has a main role not only in the treatment of pediatric steroid resistance nephrotic syndrome (SRNS) but it is also commonly used in SDNS and FRNS patients after trial of levamisole and cyclophosphamide when steroids side effects limit the use of steroids [4]. The kidney and cochlea have mutual physiological mechanisms, including the active transportation of fluid and electrolytes carried out by the stria vascularis and the glomerulus, respectively. In addition, they may experience a typical antigenicity. These similarities may account for analogous impacts of medications (i.e. ototoxic and nephrotoxic effects of aminoglycosides) and immunological effects on the two structures. Inner ear and kidney development are both affected by comparable genetic influences as viewed in some of the hereditary conditions such as Alport's syndrome and branchio-oto-renal syndrome [5]. Although there are extensive data on Cyclosporine A (CsA) nephrotoxicity and neurotoxicity, less is known about its ototoxicity [6]. This work is designed to evaluate effects of CsA on hearing in children with difficult to treat idiopathic nephrotic syndrome (SDNS, SRNS and FRNS).

## 2. METHODS

It was conducted on 30 children with idiopathic nephrotic syndrome (5-15y), patients were divided into 2 groups: Group I: 15 children with is steroid sensitive nephrotic syndrome (SSNS) was on steroid at least for 6 months. Group II: 15 children with difficult to treat idiopathic nephrotic syndrome (SDNS, SRNS or FRNS) who will start Cyclosporine A (5mg/kg/day) and were followed up after 6 months. We excluded children with secondary nephrotic syndrome, syndromic renal disease with extra-renal systemic affections, family history of hearing loss, audiological diseases or ear anomalies. Both patient groups subjected to the following at the beginning of the study and after 6 months of treatment with CsA for Group II only: Thorough history taking and medical records laying stress on: Disease history, duration, extra renal affection. Drug history - Steroids intake duration and dose (where low dose is less than 1 mg/kg /day and high dose is more than 1 mg/kg/day). Laboratory investigations:

**Hematological Labs**: - CBC - Serum cholesterol - Total serum protein and albumin. - Serum creatinine. - Serum trough level of CsA for group II. B. Urine: Urine protein / creatinine ratio - 24 hours urine proteins.

**Audiological Evaluation:** Otological examination, basic audiological evaluation ( Pure Tone Audiometry (PTA) Air conduction for the frequency range 0.25 KHz – 8 KHz and bone conduction for the frequency range 0.5 KHz – 4 KHz. Speech audiometry including: Speech Recognition Threshold (SRT) test and Word Discrimination score (WD) test. Immittancemetry also done including both: Tympanometry and Acoustic reflex. Extended High frequency range: at frequencies 10,12,14& 16 KHz. Transient evoked otoacoustic emissions (TOAEs): TEOAEs were elicited using non-linear click stimuli at stimulus intensity 80 dBSPL of 80µs duration, at a rate of 19/s within a time window of 20 msec. TEOAEs were analyzed by recording 260 sweeps in one session and averaged within 5 frequency bands centered at (1, 1.5, 2, 3 and 4 KHz).

**Statistics:** Analysis of data performed with SPSS statistical software version 21. Data presented as mean ± standard deviation, median, IQR and percentage. Chi-square, Mann Whitney test, Fisher Exact, Wilcoxon signed ranks test, paired-t, student-t and ANOVA tests used to compare data between studied groups. Pearson coefficient correlated the variables. P value < 0.05 is significant *. Total sample size calculated with G*Power 3.1.9 to achieve power 95% with effect size 0.8 and alpha error 0.05

## 3. RESULTS

There was no statistically significant difference between the two studied groups as regard to age and sex, but there was statistically significant difference between the two studied groups as regard duration of the disease in months Table 1. There was statistically significant difference between groups I and II before treatment and between group II before and after CsA treatment as regard to history of steroid intake (dose& duration); as most of patients were shifted from high to low doses steroid after CsA introduction. There was no statistically significant difference between groups I and II after treatment as regard to history of steroid intake (dose& duration). Regarding laboratory data, there was statistically significant difference as regard to serum albumin and 24hr urinary proteins between both groups and group II before and after CsA treatment Table 2. Basic audiological evaluation: Table 3 and Fig. 1. was done showing normal peripheral hearing in all patients. Acoustic reflex threshold was present and proportional to pure tone thresholds. Concerning speech and language evaluation, all patients had bilateral excellent and proportional word discrimination test before and after CsA treatment. Immitancemetry showed bilateral type A tympanogram reflecting normal middle ear pressure in all patients before and after CsA treatment. Pure tone audiometry threshold up to 8KHz there was no statistically significant difference between GI and GII before or after CsA treatment. However, there was statistically significant difference in higher frequencies. Comparing between group I &group II before treatment, there was statistically significant difference as regard to PTA threshold from 10 KHz and higher to be higher in group II. Comparing between groups I and II after treatment, There was statistically significant difference as regard to PTA threshold from 14 KHz to 16 KHz to be higher in group II after treatment. Comparing Between group II before &after treatment, there was statistically significant difference as regard to PTA threshold from 8 KHz to 16 KHz to be higher after treatment. TOAEs was present in all group I and group II before treatment although of 2 cases from group II after 6 months of treatment with CsA had absent TOAEs There was no statistically significant difference between the three groups of the study according to emission net results (Pass or refer) Fig. 2. There was statistically significant positive correlation between extended high frequency range and trough level of Cyclosporin A in group II after treatment at all frequencies from 8 KHz to 16 KHz Fig. 3. There was no statistically significant correlation between pure tone audiometry & extended high frequency range and (systolic & diastolic blood pressure, 24 hour urine protein, serum albumin, duration of the disease, duration of steroid intake or protein / creatinine ratio) in group II.

## 4. DISCUSSION

According to pure tone threshold and extended high frequency range threshold there was elevated threshold in only frequencies above 8 KHz after 6 months of CsA therapy. These results referred to normal peripheral hearing in conventional pure tone test and subclinical sensory neural hearing loss only in extended high frequency audiometry which is not used routinely. Also, there was non-statistically significance difference between studied groups according to transient evoked otoacoustic emissions (TEOAEs) which is coinciding with Kasap-Demir et al. [5]. This results are in accordance with other researches who detected that conventional pure tone audiometry showed that CsA treatment for at least 6 months does not cause any hearing defects in children with SDNS, FRNS or SRNS, at frequencies from 0.25 KHz to 8 KHz [5,7]. The previous two studies unfortunately did not perform Extended High frequency audiometry in which we found that there was significant difference between group II before and after CsA. In this research there is statistically significant positive correlation between pure tone audiometry and extended high frequency range (from 8 KHz to 16 KHz) and CsA trough level which agreed with Gullerglu et al. [8]. However, Gulleroglu et al. [8] found that: After dosage correction, pure-tone audiometry showed improvement of hearing loss progression. 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 hearing loss

[9]. The action of CsA on the blood/inner ear barrier has been demonstrated by Saito et al. [10] who came to the conclusion that the 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 [10]. 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 (eg, headache, tremor, peripheral neuropathy) to more severe symptoms (eg, seizures, cerebellar ataxia, motor weakness, leukoencephalopathy, blindness, psychoses, and hallucinations). 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 [11].

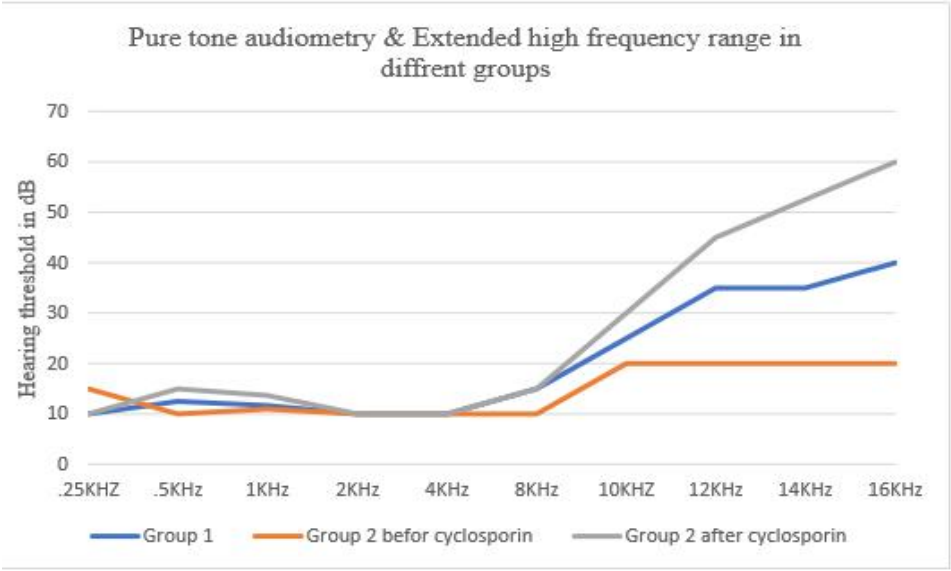



**Fig. 1. Comparison between different groups according to pure tone audiometry & extended high frequency range**

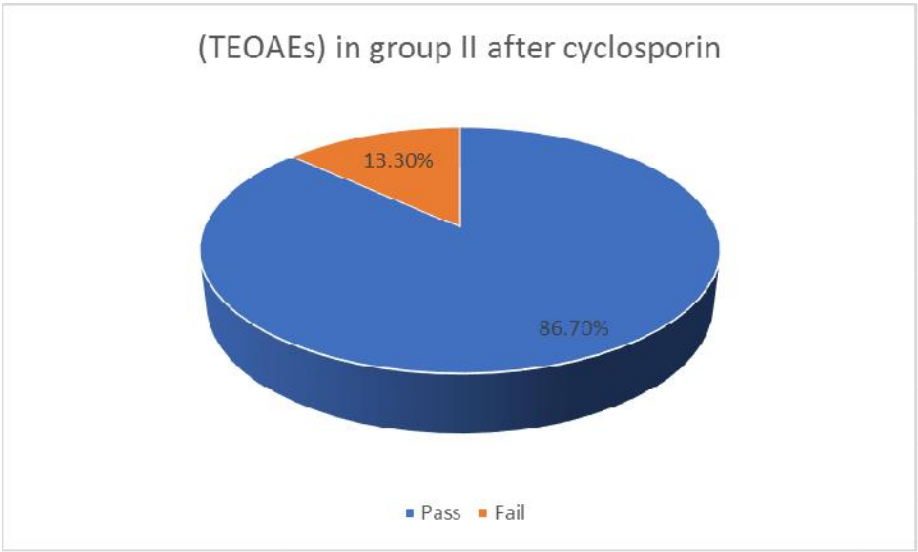
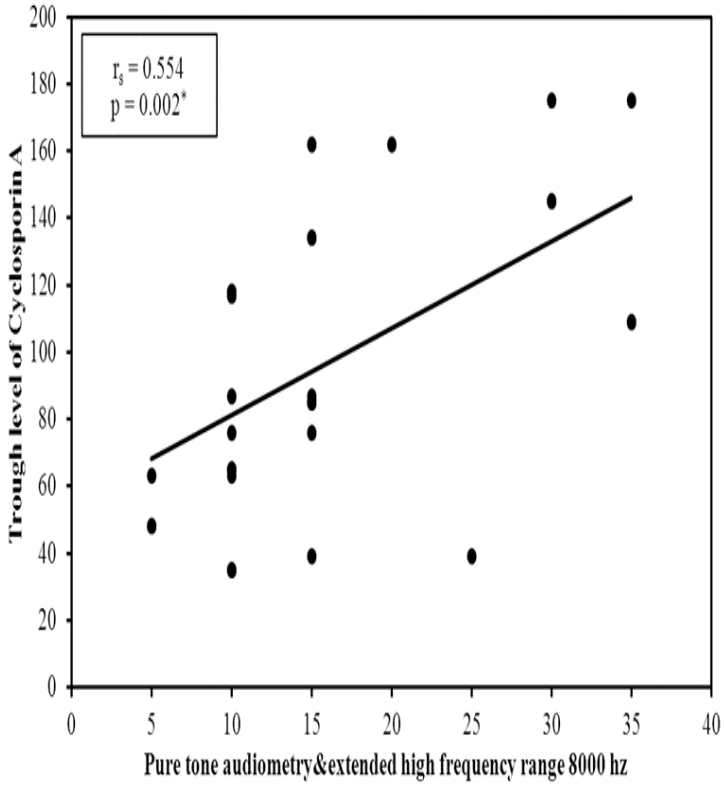
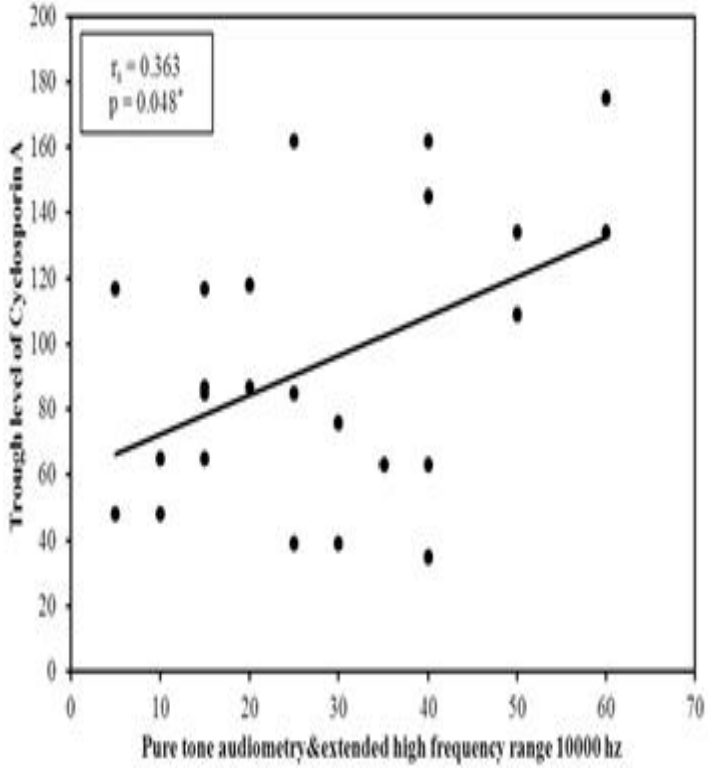



**Fig. 2. Transient evoked otoacoustic emissions (TEOAEs) in group II after cyclosporin A**


$r_s = 0.554$
$p = 0.002^*$
Trough level of Cyclosporin A
Pure tone audiometry&extended high frequency range 8000 hz

A


$r_s = 0.363$
$p = 0.048^*$
Trough level of Cyclosporin A
Pure tone audiometry&extended high frequency range 10000 hz

B

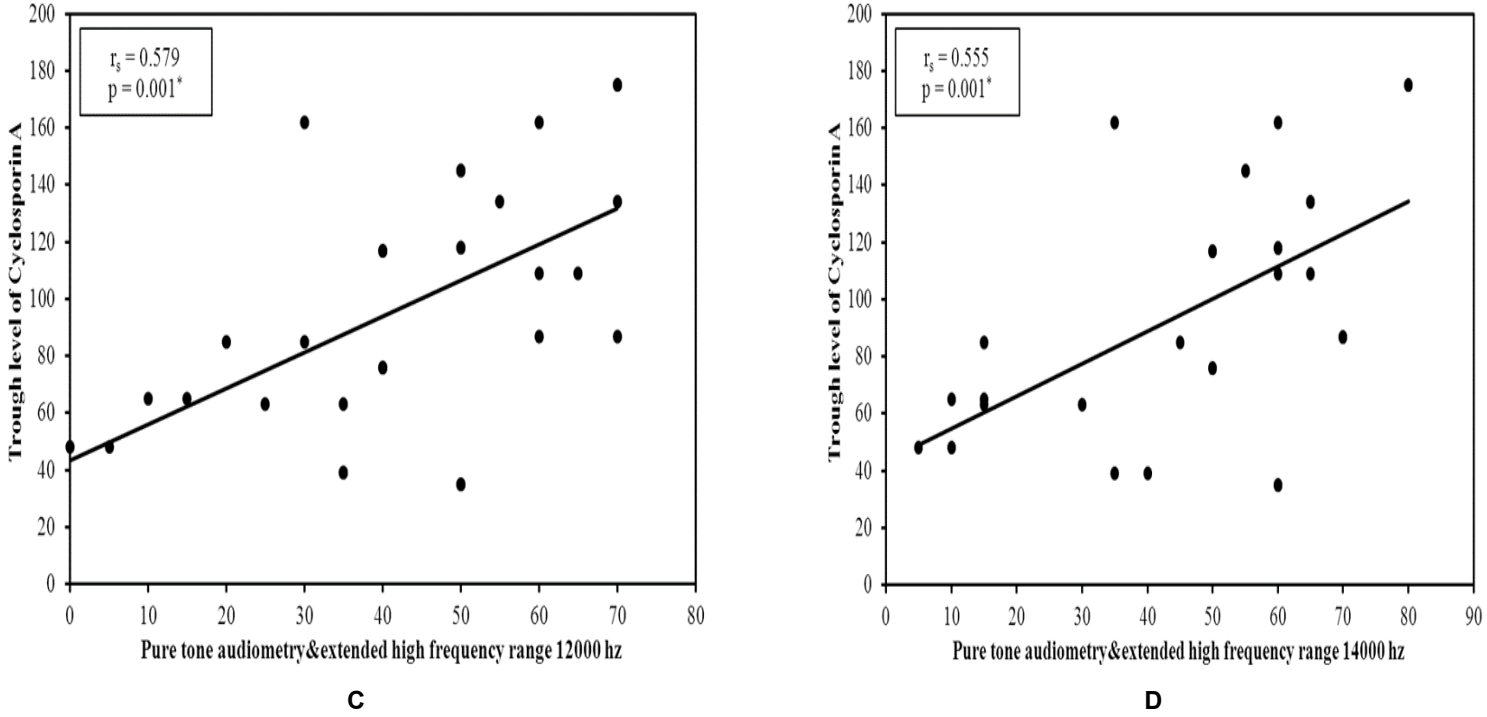



**Fig. 3. Correlation between pure tone audiometry threshold II.A; 8KHz threshold, B; 10 KHz threshold, C; 12 KHz threshold and D; 14 KHz threshold and level of Cyclosporin A in group**

**Table 1. Comparison between the two studied groups according to demographic data, examination, drugs history**

| | Group I (n = 15) | | Group II (n=15) | | | | Test of sig. |
|---|---|---|---|---|---|---|---|
| | | | Before (n=15) | | After (n=15) | | |
| | No | % | No | % | No | % | |
| **Sex** | | | | | | | $\chi$2= 0.000 |
| Male | 8 | 53.4 | 9 | 60.0 | - | - | |
| Female | 7 | 46.6 | 6 | 40.0 | - | - | |
| Male / Femele | 1.14: 1 | | 1.5: 1 | | - | - | |
| P | P1:1.000? | | - | | - | | |
| **Age (years)** | | | | | | | t=0.564 |
| Min. – Max. | 5.0 – 14.0 | | 5.0 – 13.0 | | | | |
| Mean ± SD. | 9.37 ± 2.74 | | 8.80 ± 2.76 | | | | |
| P | P1: 0.577 | | - | | | | |
| Weight (kg) | | | | | | | |
| Min. – Max. | 18.0 – 54.0 | | 18.0 – 50.0 | | | | t=0.853 |
| Mean ± SD. | 33.93 ± 10.47 | | 30.6 ± 10.92 | | | | |
| P | P1: 0.401 | | - | | | | |
| **Height (cm)** | | | | | | | t=0.853 |
| Min. – Max. | 109.0 – 162.0 | | 106.0 – 152.0 | | | | |
| Mean ± SD. | 133.53 ± 14.72 | | 128.93 ± 15.46 | | | | |
| P | P1: < 0.411 | | - | | | | |
| **Duration of the disease (m)** | | | | | | | U= 60.5* |
| in. – Max. | 6.0 – 84.0 | | 2.0 – 60.0 | | | | |
| Median (IQR) | 14.0(8.0 – 30.0) | | 36.0(24.0 – 45.0) | | | | |
| P | P1: 0.029* | | - | | | | |
| **Steroid dose** | | | | | | | x2FE McN |
| Low | 9 | 60.0 | 0 | 0.0 | 13 | 86.7 | |
| High | 6 | 40.0 | 15 | 100.0 | 2 | 13.3 | |
| P | x2FE P1: 0.001* | | x2FE P2: 0.215 | | McN P3: <0.001* | | |
| **Steroid duration (months)** | | | | | | | UZ=3.873* |
| Min. – Max. | 6.0 – 30.0 | | 1.0 – 12.0 | | 7.0 – 18.0 | | |
| Median (IQR) | 13.0(8.0 – 19.0) | | 6.0(3.50 – 8.50) | | 12.0(9.50 – 14.50) | | |
| P | U P1: <0.001* | | U P2: 0.653 | | zP3: <0.001* | | |
| **Systolic BP (mmHg)** | | | | | | | TT= 17.971* |
| Min. – Max. | 90.0 – 130.0 | | 90.0 – 130.0 | | 80.0 – 120.0 | | |
| Mean ± SD. | 107.33 ± 11.0 | | 114.0 ± 11.02 | | 102.33 ± 10.65 | | |
| P | tP1: 0.021* | | tP2: 0.076 | | TP3: <0.001* | | |

| | Group I (n = 15) | | Group II (n=15) | Test of sig. |
|---|---|---|---|---|
| **Diastolic BP (mmHg)** | | | | tT=18.582* |
| Min. – Max. | 60.0 – 90.0 | 60.0 – 90.0 | 55.0 – 80.0 | |
| Mean ± SD. | 70.0 ± 9.10 | 78.67 ± 7.30 | 68.0 ± 7.38 | |
| P | P1: <0.001* | P2: 0.354 | P3: <0.001* | |
| **Trough level of Cs A** | | | | |
| Min. – Max. | - | - | 35.0 – 175.0 | |
| Mean ± SD. | - | - | 97.2 ±44.27 | |

*$\chi^2$: Chi square test t: Student t-test T: Paired t-test*
*U: Mann Whitney test $\chi^2$: Chi square test FE: Fisher Exact*
*P1: p value for comparing between group I and group II before treatment*
*P2: p value for comparing between group I and group II after treatment*
*P3: p value for comparing between group II before and after treatment*
**: Statistically significant at p ≤ 0.0*

**Table 2. Comparison between different groups according to laboratory data**

| | | Group I (n = 15) | Group II (n=15) | |
|---|---|---|---|---|
| | | | Before (n=15) | After (n=15) |
| **CBC** | | | | |
| HB (g/L) | Min. – Max.<br>Mean ± SD. | 10.5 – 13.0<br>12.01 ± 0.76 | 8.9– 13.10<br>10.67 ± 1.69 | 9.0– 14.5<br>10.95 ± 1.55 |
| P | | P1: 0.011* | P2: 0.024* | P3: 0.616 |
| Test of sig. | | t. | t. | T=0.513 |
| TLC(x10-3) | Min. – Max.<br>Mean ± SD. | 7.6 – 13.5<br>11.58 ± 1.75 | 4.5 – 11.0<br>7.67 ± 1.97 | 4.8 – 13.0<br>8.48 ± 2.87 |
| P | | P1< 0.001* | P2: 0.002* | P3: 0.377 |
| Test of sig. | | t. | t. | T=0.912 |
| PLT(x10-3) | Min. – Max.<br>Mean ± SD. | 177.0 – 350.0<br>238.8 ± 62.4 | 170.0 – 465.0<br>240.87 ± 106.06 | 165.0 – 433.0<br>255.13 ± 86.20 |
| P | | P1: 0.949 | P2: 0.557 | P3: 0.699 |
| Test of sig. | | t. | t. | T=0.394 |
| **Serum** | | | | |
| Cholesterol (mg/dl) | Min. – Max.<br>Mean ± SD. | 185.0 – 412.0<br>287.93 ± 83.65 | 267.0 – 487.0<br>341.0 ± 68.08 | 200.0 – 290.0<br>231.47 ± 27.66 |
| P | | P1:0.067 | P2:0.024* | P3:< 0.001* |
| Test of sig. | | t. | t. | T=7.125* |
| Albumin (g/dl) | Min. – Max.<br>Mean ± SD. | 1.40 – 4.50<br>2.86 ± 1.08 | 1.4 – 2.2<br>1.81 ± 0.22 | 2.5 – 4.7<br>3.72 ± 0.63 |
| P | | P1:0.002* | P2:0.014* | P3:< 0.001* |
| Test of sig. | | t. | t. | T=13.765* |
| Urea (mg/dl) | Min. – Max.<br>Mean ± SD. | 15.0 – 30.0<br>22.4 ± 4.05 | 15.0 – 40.0<br>28.33 ± 7.27 | 25.0 – 40.0<br>32.87 ± 4.73 |
| P | | P1:0.011* | P2<0.001* | P3: 0.053 |
| Test of sig. | | t. | t. | T=2.114 |
| Creatinine (mg/dl) | Min. – Max.<br>Mean ± SD. | 0.45 – 1.03<br>0.75 ± 0.20 | 0.55 – 1.01<br>0.75 ± 0.15 | 0.60 – 1.00<br>0.80 ± 0.12 |
| P | | P1:0.959 | P2:0.424 | P3: 0.352 |
| Test of sig. | | t. | t. | T=0.962 |
| **Urine Protein** | | | | |
| Protein / creatinine ratio | Min. – Max.<br>Median (IQR) | 0.14 –10.0<br>0.78(0.16– 8.0) | 2.7 – 18.0<br>7.4(4.23 – 9.3) | 0.12 – 2.7<br>0.18(0.16 – 1.9) |
| P | | P1:0.013* | P2:0.205 | P3: 0.001* |

| | | Group I (n = 15) | Group II (n=15) | |
|---|---|---|---|---|
| | | | **Before (n=15)** | **After (n=15)** |
| Test of sig. | | U | U | Z=4.784* |
| 24 hours proteins (mg/24h) | Min. – Max. | 77.0 – 4266.0 | 1089.0 – 5621.0 | 59.0 – 820.0 |
| | Median (IQR) | 420.0(105.0 – 3627.0) | 2165.0(1765.0 –3420.0) | 102.0(87.0 – 240.0) |
| P | | P1:0.023* | P2:0.026* | P3: 0.001* |
| Test of sig. | | U | U | Z=4.784* |

*t: Student t-test* *T: Paired t-test*
*U: Mann Whitney test* *Z: Wilcoxon signed ranks test*

**Table 3. Comparison between different groups according to pure tone audiometry threshold & extended high frequency range**

| | Group I (n = 15) | Group II (n=15) | |
|---|---|---|---|
| | | Before | After |
| **0.25 KHz** | | | |
| Min. – Max. | 5.0 – 25.0 | 5.0 – 25.0 | 5.0 – 25.0 |
| Median (IQR) | 10.0(10.0 – 15.0) | 15.0(10.0 – 15.0) | 10.0(10.0 – 15.0) |
| p | P1: 0.383 | P2: 0.981 | P3: 0.537 |
| Test of sig. | U | U | Z=0.618 |
| **0.5 KHz** | | | |
| Min. – Max. | 5.0 – 20.0 | 5.0 – 25.0 | 5.0 – 20.0 |
| Median (IQR) | 12.5 (10.0 – 20.0) | 10.0(10.0 – 20.0) | 15.0(10.0 – 20.0) |
| p | P1:0.893 | P2:0.639 | P3: 0.722 |
| Test of sig. | U | U | Z=0.356 |
| **1 KHz** | | | |
| Min. – Max. | 5.0 – 20.0 | 5.0 – 25.0 | 5.0 – 25.0 |
| Mean ± SD. | 11.67 ± 3.56 | 11.0 ± 4.81 | 13.67 ± 5.07 |
| Median (IQR) | 10.0(10.0 – 15.0) | 10.0(10.0 – 15.0) | 15.0(10.0 – 15.0) |
| p | P1: 0.858 | P2: 0.932 | P3: 0.946 |
| Test of sig. | U | U | Z=0.068 |
| **2 KHz** | | | |
| Min. – Max. | 0.00 – 20.0 | 5.0 – 20.0 | 5.0 – 25.0 |
| Median (IQR) | 10.0(5.0 – 15.0) | 10.0(5.0 – 15.0) | 10.0(5.0 – 15.0) |
| p | P1:0.613 | P2:0.442 | P3:0.253 |
| Test of sig. | U | U | Z=1.144 |
| **4 KHz** | | | |
| Min. – Max. | 0.00 – 25.0 | 0.00 – 25.0 | 5.0 – 25.0 |
| Median (IQR) | 10.0(5.0 – 10.0) | 10.0(5.0 – 10.0) | 10.0(10.0 – 15.0) |
| p | P1:0.306 | P2:0.067 | P3: 0.106 |
| Test of sig. | U | U | Z=0.779 |
| **8 KHz** | | | |
| Min. – Max. | 10.0 – 35.0 | 0.00 – 20.0 | 5.0 – 40.0 |
| Median (IQR) | 15.0(15.0 – 20.0) | 10.0(5.0 – 10.0) | 15.0(10.0 – 25.0) |
| p | P1:0.236 | P2:0.078 | P3: 0.004* |
| Test of sig. | U | U | Z=2.802* |
| **10 KHz** | | | |
| Min. – Max. | 5.0 – 65.0 | 5.0 – 40.0 | 5.0 – 60.0 |
| Median (IQR) | 25.0(20.0 – 40.0) | 20.0(20.0 – 40.0) | 30.0(15.0 – 40.0) |
| P | P1:0.008* | P2:0.464 | P3: 0.005* |
| Test of sig. | U | U | Z=2.838* |
| **12 KHz** | | | |
| Min. – Max. | 5.0 – 70.0 | 5.0 – 50.0 | 0.0 – 70.0 |
| Median (IQR) | 35.0(20.0 – 45.0) | 20.0(20.0 – 45.0) | 45.0(30.0 – 60.0) |
| P | P1:0.015* | P2:0.084 | P3: <0.001* |
| Test of sig. | U | U | Z=3.667 |
| **14 KHz** | | | |
| Min. – Max. | 5.0 – 70.0 | 5.0 – 60.0 | 5.0 – 80.0 |
| Median (IQR) | 35.0(15.0 – 50.0) | 20.0(15.0 – 50.0) | 52.5(35.0 – 60.0) |
| p | P1:0.022* | P2:0.022* | P3: <0.001* |
| Test of sig. | U | U | Z=3.741* |
| **16 KHz** | | | |
| Min. – Max. | 5.0 – 75.0 | 5.0 – 70.0 | 5.0 – 90.0 |
| Median (IQR) | 40.0(20.0 – 55.0) | 20.0(20.0 – 55.0) | 60.0(40.0 – 70.0) |
| p | P1:0.005* | P2:0.016* | P3: <0.001* |
| Test of sig. | U | U | Z=3.974* |

*U: Mann Whitney test Z: Wilcoxon signed ranks test*
*P1: p value for comparing between group I and group II before treatment*
*P2: p value for comparing between group I and group II after treatment*
*P3: p value for comparing between group II before and after treatment*
**: Statistically significant at p ≤ 0.05*

## 5. CONCLUSIONS

CsA can be a potential cause of hearing impairment (high frequency hearing loss) in patients with difficult to ephrotic syndrome which is dose dependent. So routine audiological examination and extended high frequency audiometry are recommended to detect any early or sub clinical hearing affection.

## CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

This prospective cohort study was conducted at Pediatric Nephrology Unit, Pediatric Department and Audiology Unit, ENT Department of Tanta University after acceptance from ethics committee of Faculty of Medicine, Tanta University with acceptance No. 32750/12/18.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES


1. Larkins N, Kim S, Craig J, et al. Steroid-sensitive nephrotic syndrome: An evi dence-based update of immune suppressive treatment in children. Archives of disease in childhood. 2016;101:404-408.
2. Suresh kumar P, Hodson EM, Willis NS, et al. Predictors of remission and relapse in idiopathic nephrotic syndrome: A prospective cohort study. Pediatric Nephro logy. 2014;29:1039-1046.
3. Kemper M, Valentin L, van Husen M. Difficult-to-treat idiopathic nephrotic syndro me: established drugs, open questions and future options. Pediatric Nephrology. 2018; 33:1641-1649.
4. Oray M, Abu Samra K, Ebrahimiadib N, et al. Long-term side effects of gluco corticoids. Expert Opinion on Drug Safety. 2016;15:457-465.
5. Kasap-Demir B, Özmen D, Kırkım G et al. Cyclosporine causes no hearing defect in pediatric patients with nephrotic syndrome. International Journal of Audiology. 2017;56 (9):701-705.
6. Mashad ElG, Fotoh ElW, El Abedein A. 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 otorhinolaryngology. 2017;97: 206-210.
7. Ibrahim M, El-Farsy M, Fatouh F, et al. Effect of cyclosporine a on hearing in children with steroid resistant nephrotic syndrome. GEGET. 2019;14:39-47.
8. Gulleroglu K, Baskin E, Aydin E, et al. Hearing status in pediatric renal transplant recipients. Exp Clin Transplant. 2015;13: 324-328.
9. Zhang Z-J, Saito T, Kimura Y, et al. Disruption of mdr1a p-glycoprotein gene results in dysfunction of blood–inner ear barrier in mice. Brain research. 2000;852: 116-126.
10. Saito T, Zhang Z-J, Tokuriki M, et al. Cyclosporin A inhibits the extrusion pump function of p-glycoprotein in the inner ear of mice treated with vinblastine and doxorubicin. Brain research. 2001;901: 265-270.
11. Tan TC, Robinson PJ. Mechanisms of calcineurin inhibitor-induced neurotoxicity. Transplantation Reviews. 2006;20:49-60.




*Peer-review history:*
*The peer review history for this paper can be accessed here:*
*http://www.sdiarticle4.com/review-history/64806*