Al-Azhar Med. J . (Medicine). *Vol. 51(2), April, 2022, 1133 – 1144*
DOI: 10.21608/amj.2022.230476
https://amj.journals.ekb.eg/article_230476.html

AUDIOMETRIC EVALUATION FOR CHILDREN WITH IDIOPATHIC NEPHROTIC SYNDROME

By

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ABSTRACT

Background: The nephrotic syndrome (NS) is a glomerular disease, in which the glomerular capillary wall becomes no longer impermeable to proteins. The organs of the inner ear bear a physiological similarity to the kidney, both being concerned with maintaining the electrolyte concentration gradient. There is an association between renal and inner ear disorders, either genetically determined as in Alport syndrome and branchio-oto-renal syndrome or acquired as in acute kidney injury and chronic kidney disease.

Objective: To evaluate hearing status in children with idiopathic nephrotic syndrome and to identify the underlying etiology.

Subjects and methods: This was a case controlled study which included 40 patients with idiopathic nephrotic syndrome. Patients were selected according to a certain inclusion and exclusion criteria from those attending the pediatric nephrology clinic, Al-Hussein University Hospital. Those patients have been classified into 2 equal groups: Group 1: Steroid sensitive nephrotic syndrome (SSNS) and Group 2: Steroid resistant nephrotic syndrome (SRNS). Twenty apparent healthy age and gender matched children were included as a control group (group3).

All patients and control subjects were subjected to detailed history, full clinical examination and laboratory assessment including CBC, renal function, serum electrolytes (Na, K, Ca), investigations specific for nephrotic syndrome and audiometric evaluation, and repeated after remission for those who were in relapse.

Results: Sensorineural hearing loss (SNHL) was detected in 8 of the 40 patients (20%). Six out of the 20 patients with SRNS (30%) had SNHL (4 mild, 2 moderate) and 2 out of 20 patients with SSNS (10%) had mild sensorineural loss.

Conclusion: Hypocalcemia, hypercholesterolemia, and hyponatremia seemed to affect hearing and should be followed up in childhood nephrotic syndrome. Disease flare and steroids using for a long period may also be risk factors for SNHL in children with NS.

Keywords: Hearing loss; nephrotic syndrome; Audiometry, Steroid.

INTRODUCTION

Nephrotic syndrome refers to the tetrad of edema, nephrotic- range proteinuria, hypoalbuminemia, and hyperlipidemia *(Uwaezuoke, 2015)*.

Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are the two major causes of nephrotic syndrome in children *(Müller-Deileet al., 2019)*.

Minimal change nephrotic syndrome (MCNS) has been considered a T-cell disorder, which causes the impairment of the glomerular filtration barrier with the release of different circulating factors *(Kim et al., 2016).*

Nephrotic syndrome can be classified into two entities. SSNS if there is response to steroids within the first 4 weeks or as SRNS if there is no response to steroids after the first 4 weeks of commencing steroids *(Wang et al., 2019).*

Children with INS 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 *(Saha et al., 2013).*

The present work aimed to evaluate hearing status in children with idiopathic nephrotic syndrome and to identify the underlying etiology.

PATIENTS AND METHODS

This was a case controlled prospective study included 40 patients with idiopathic nephrotic syndrome. Patients were selected from those attending the pediatric nephrology clinic, at Al-Hussein University Hospital; those patients have been classified into 2 equal groups:

Group 1: SSNS, two of them were in relapse.

Group 2: SRNS, six of them were in relapse.

Control group: Twenty apparent healthy age and gender matched children were included as a control group (group 3).

Inclusion criteria: Age from 4-18 years, of both genders, diagnosed as SSNS and SRNS.

Exclusion criteria: NS with renal insufficiency, children with comorbid condition that can affect hearing, children with secondary nephrotic syndrome, children with previously known hearing impairment, children having chronic suppurative otitis media, and children having middle ear effusion or positive family history of hearing affections.

All patients were subjected to the following:

I. History included: Age and sex, onset and duration of the disease, detailed history especially of renal troubles or hearing affection, family history of hearing or renal diseases and history of treatment of nephrotic syndrome as well as other medications.

II. Examination: Physical examination included: weight in kg, height in cm, vital signs especially for blood pressure and detailed examination of all body systems.

III. Investigations included the following: CBC, urine analysis, blood urea, serum creatinine and serum electrolytes (Na, K, Ca), investigations specific for nephrotic syndrome including nephrotic range proteinuria (by estimation of Albumin/ Creatinine Ratio in urine), serum albumin and cholesterol.

IV. Audiometric examination: Audiometric examination had been done to detect the level of hearing using pure tone audiometer model MAICO53 in a sound treated room, including:air conduction had been done at frequencies from 250 to 8000 Hz. boneconduction had been done at frequencies from 500 to

4000 Hz. Speech audiometry including speech reception threshold (SRT), most comfortable level (MCL)and speech discrimination (WD%).

Hearing loss was graded into mild (26–40 dB), moderate (41–55 dB), moderately severe (56–70 dB), severe (71–91 dB), and profound (>91 dB).

Ethical consideration: Informed consents have been taken from all parents of our patients before the study, and they have all rights to refuse participation in the study without giving any reason. This study had been approved by the ethical committee of pediatric department.

Statistical analysis: Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent Quantitative data were described using range (minimum and maximum), mean and standard deviation. For non-parametric data, Mann-Whitney U test was used to compare between the two groups. Chi-square (X2) test of significance was used in order to compare proportions between qualitative parameters. ANOVA test was used to compare quantitative data. Significance of the obtained results was judged at the 5% level. In all statistical tests P value < 0.05 was considered significant.

RESULTS

No statistically significant difference between the three groups as regard to gender, age, and residence and no statistically significant difference between the two patients groups as regards duration of steroid intake but showed statistically significant difference among the three groups as regard air conduction audiometry **(Table1)**.

Table (1): Comparison between the three studied groups according to different parameters

Groups / Parameters	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	p
Gender				
Male	13 (65%)	12 (60%)	9 (45%)	0.414
Female	7 (35%)	8 (40%)	11 (55%)	
Age (years)				
Min. – Max.	4 – 18	4 – 18	4 – 18	0.609
Mean ± SD.	8.3 ± 3.6	9.2 ± 3.6	8.3 ± 3.8	
Residence				
Rural	7 (35%)	9 (45%)	6 (30%)	0.605
Urban	13 (65%)	11 (55%)	14 (70%)	
Duration of steroid intake (years)				
Min. – Max.	1 – 6	1 – 6	–	0.925
Mean ± SD.	2.8 ± 1.4	3.6 ± 1.2	–	
Duration of cyclosporine intake				
Min. – Max.	–	1– 5	–	–
Mean ± SD.	–	2.4 ± 1	–	
Air conduction frequency (Hz)				
250				
Min. – Max.	20 – 30	20 – 40	20 – 25	0.058
Mean ± SD.	22.8 ± 3.4	24 ± 6	20.8 ± 1.8	
500				
Min. – Max.	20 – 35	20 – 45	15 – 25	0.040
Mean ± SD.	23.5 ± 4	25 ± 7.8	20.8 ± 2.5	
1000				
Min. – Max.	10 – 40	10 – 50	10 – 20	0.003
Mean ± SD.	16 ± 8.2	22.8 ± 13.4	12.3 ± 3.4	
2000				
Min. – Max.	10 – 35	10 – 55	10 – 20	0.013
Mean ± SD.	16 ± 7.5	22 ± 15	11.8 ± 2.9	
4000				
Min. – Max.	10 – 40	10 – 50	10 – 20	0.201
Mean ± SD.	16 ± 8.8	21.3 ± 15.4	12.3 ± 3.4	
8000				
Min. – Max.	10 – 40	10 – 55	10 – 20	0.250
Mean ± SD.	15.5 ± 9.2	21.5 ± 16.1	12 ± 3	

Group 1:Steroid sensitive nephrotic syndrome
Group 2:Steroid resistant nephrotic syndrome
Group 3:Control group

There was a statistically significant difference among the three groups as regard to cholesterol and serum albumin but there was no statistically significant difference as regard to Hb, and showed that serum Na levels were significantly lower in both SSNS and SRNS groups than the control group (p= 0.001). Serum Ca levels also were significantly lower in both SSNS and SRNS groups than control group (p=0.004), but there was no statistically significant difference as regard serum K **(Table 2)**.

Table (2): Comparison between the three studied groups according to different parameters

Groups / parameters	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	p
Hb (g/dl)				
Min. – Max.	11.2 – 12.8	10.5 – 12.8	10.2 – 13.2	0.256
Mean ± SD.	12.3 ± 0.4	12 ± 0.7	12 ± 0.8	
Serum albumin (g/dl)				
Min. – Max.	2.6 – 4.4	2.5 – 4.2	3.5 – 3.9	0.041
Mean ± SD.	3.7 ± 0.5	3.6 ± 0.6	4 ± 0.4	
p_1=0.45, p2=0.048, p3=0.034				
Cholesterol (mg/dl)				
Min. – Max.	218 – 372	314 – 458	135 – 255	<0.001
Mean ± SD.	269 ± 43.8	394 ± 40.1	183.1 ± 29.2	
p_1<0.001,p_2=0.001,p_3<0.001				
Na (mEq/l)				
Min. – Max.	130 – 139	130 – 139	135 – 142	0.001
Mean ± SD.	135.2 ± 2.7	135.1 ± 2.6	138 ± 2	
p_1=0.998,p_2=0.002,p_3=0.002				
K (mEq/l)				
Min. – Max.	3.8 – 4.7	3.7 – 4.8	3.6 – 4.8	0.559
Mean ± SD.	4.2 ± 0.3	4.2 ± 0.3	4.1 ± 0.4	
Ca (mg/dl)				
Min. – Max.	8.2 – 9.2	8.2 – 9.2	8.4 – 9.9	0.020
Mean ± SD.	8.7 ± 0.3	8.7 ± 0.3	9 ± 0.5	
p_1=0.867,p_2=0.023,p_3=0.006				

Group 1:Steroid sensitive nephrotic syndrome
Group 2:Steroid resistant nephrotic syndrome
Group 3:Control group

There was a positive correlation between the cumulative dose of steroid and hearing loss detected by audiometric examination, but there was no definite correlation between the cumulative dose of cyclosporine and hearing loss **(Table 3)**.

Table (3): Correlation between audiometric examination for patients with hearing loss (N=8) and cumulative dose of both steroid and cyclosporine

Doses / Audiometric Examination frequency (Hz)	Cumulative dose of steroid (mg/kg)		Cumulative dose of cyclosporine	
	r_s	P	r_s	P
Air conduction				
250	0.902	0.002	0.054	0.931
500	0.982	<0.001	0.054	0.931
1000	0.945	<0.001	-0.162	0.794
2000	0.805	0.016	-0.433	0.467
4000	0.932	0.001	-0.342	0.573
8000	0.784	0.021	0.135	0.828
Bone conduction				
500	0.982	<0.001	0.054	0.931
1000	0.945	<0.001	-0.162	0.794
2000	0.741	0.036	-0.342	0.573
4000	0.932	0.001	-0.342	0.573

Hyponatremia was observed in 80% Hypocalcemia in 87%, and hypercholesterolemia in 100% **(Table 4)**.

Table (4): Distribution of the cases with hearing loss according to the electrolyte disturbance (n = 8)

	No. (%)
Hyponatremia	
Negative	2 (25%)
Positive	6 (75%)
Hypocalcemia	
Negative	1 (12.5%)
Positive	7 (87.5%)
Hypercholesterolemia	
Negative	0 (0%)
Positive	8 (100%)

Audiometric evaluation for all patients with hearing loss (n=8) showed that no significant difference detected between those cases either in relapse or in remission (p value>0.05), but there was significant difference between patients with hearing loss during relapse and control group (p value <0.05).Also, there was a significant difference between patients with hearing loss during remission and control group (p value <0.05). This indicated that the hearing impairment in those children still present even after remission **(Table 5)**.

Table (5): Data of cases with hearing loss (during relapse and after remission) and control group

Groups / Air conduction Frequency(Hz)	Group 1b (n= 8)	Group 2b (n= 8)	Group 3 (n=20)
250			
Mean ± SD.	26.25 ± 7.44	26.67 ± 8.76	20.8 ± 1.8
500			
Mean ± SD.	29.38 ± 8.63	30.0 ± 10.0	20.8 ± 2.5
p_1=0.889,p_2=0.023 ,p_3=0.020			
1000			
Mean ± SD.	32.50 ± 14.64	30.83 ± 16.86	12.3 ± 3.4
p_1=0.869,p_2=0.022 ,p_3=0.021			
2000			
Mean ± SD.	31.25 ± 19.04	28.33 ± 21.37	11.8 ± 2.9
4000			
Mean ± SD.	31.25 ± 17.06	28.33 ± 19.15	12.3 ± 3.4
8000			
Mean ± SD.	31.88 ± 19.45	30.0 ± 22.58	12 ± 3

p1: p value for comparison between Group 1b and Group2b
p2: p value for comparison between Group 1band Group3
p3: p value for comparison between Group 2band Group3

Group1b: cases of hearing loss during remission
Group2b: cases of hearing loss during relapse
Group3: control group

DISCUSSION

The prognosis of NS in children correlates with the spectrum of responsiveness to steroid therapy, from SSNS to SRNS. SRNS is the most common acquired cause of end-stage renal disease (ESRD) in children *(Uwaezuoke, 2015).*

Nephrotoxic drugs and biochemical impairments which occur in Children suffering from NS are the main risk factors of hearing impairment in those children *(Saha et al., 2013).*

In the study of *Vilayur et al. (2010),* they reported several physiological, ultra structural and antigenic similarities between the kidney and the cochlea that strongly support the link between the hearing impairment and chronic kidney disease.

Children with acute kidney injury and chronic kidney disease are known to have hearing impairment. Children with INS have biochemical impairments which include hyponatremia, hypocalcemia, and hyperlipidemia *(Saha et al., 2013).*

In our study, regarding comparison between the three studied groups according to demographic data, there was no statistically significant difference between groups in gender, age, and residence. These data were consistent with *Braun et al. (2019)* and *Gooding et al. (2020). Braun et al. (2019)* concluded that

NS can affect children of any age, from infancy to adolescence.

As regard comparison between the two studied groups according to duration of steroid intake (years), there was no statistically significant difference between groups in duration of steroid intake.

In our study, only 12.5% were under hypertensive drugs with controlled blood pressure. Those were consistent with *Ghobrial et al. (2013)* who found that 15% of nephrotic patients were hypertensive.

In our results, there was statistically significant difference among groups as regard serum albumin this was consistent with the study of *El Mashadet al. (2017)* who reported that serum albumin was significant lower in cases than in controls.

Regarding audiometry measurements, there was a statistically significant difference among groups as regard air conduction audiometry. Also, comparison between the three studied groups according to bone conduction showed statistically significant differences among groups as regard bone conduction audiometry. Our results were supported by those obtained by *El Mashad et al. (2017)* who reported similar results.

In our study, there was SNHL in 20% of patients. These data matched with the results of *Mahfouz et al. (2016)* who reported that 22% of patients had SNHL. Also, *Marie et al. (2019)* showed that 23.7% of patients showed hearing impairment, while 76.3% had normal hearing. 45% had SNHL due to electrolyte disturbance; while 55% had conductive hearing loss which may be attributed to recurrent ear infections caused by immune suppression by steroids.

The eight patients who showed hearing losses were in relapse were distributed as follow two out of twenty patients in the SSNS group (10%) and six out of twenty patients in the SRNS group (30%).

Audiometric evaluation for all patients with hearing loss showed that no significant difference was detected between those cases either in relapse or in remission. This indicates that the hearing impairment in those children is still present even after remission. This can be explained by the effect of the disease itself as well as the electrolyte disturbance.

Orendorz et al. (2010) concluded that disease exacerbation is a risk factor for hearing loss in children suffering from nephrotic syndrome and be explained by the electrolyte impairment and edema of different tissue which is worse during exacerbation.

Saha et al. (2013) noticed that children with FRNS/SDNS had a statistically significant higher threshold for hearing (SNHL) 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.

Furthermore, *Orendorz et al. (2010)* realized that children with NS had worse hearing outcome than the healthy children even after remission. These are concordant with our results.

Regarding laboratory investigations, there were statistically significant differences among groups as regard serum calcium and serum sodium which were

lower in SRNS and SSNS than the control group. This can be explained by the frequent use of diuretics and steroids which cause this side effect. In agreement with our results, *Marie et al. (2019)* showed a statistically significant lower serum calcium (due to urinary loss of vitamin D), and serum sodium in cases with SNHL.

Hyponatremia was observed in 80%, hypocalcemia in 87%and hyper cholesterolemiain 100%. There was a statistically significant difference regarding Na and Ca, but no statistically significant difference regarding serum K.

We observed that there was no statistically significant difference in cumulative dose of cyclosporine in patients with hearing loss as regard audimetric examination. In agreement with our results, *Kasap-Demir et al. (2017)* concluded that cyclosporine causes no hearing defect in pediatric patients with nephrotic syndrome. They reported that cyclosporine is not responsible for permanent SNHL with NS, and there is no sufficient evidence to consider routine hearing assessment in children with NS treated with cyclosporine.

CONCLUSION

NS is a common pediatric problem with many complications. Children with different phenotypes of nephrotic syndrome were at risk of hearing impairment. Hypocalcemia, hypercholesterolemia, and hyponatremia seemed to affect hearing and should be followed up in childhood nephrotic syndrome. Also, disease flare up was well recognized association for transient hearing loss in that group of patients. Using steroids for a long period may also be a risk factor for SNHL in children with NS.

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الفحص السمعي لأطفال المتلازمة الكلوية

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خلفية البحث: المتلازمة الكلوية من الأمراض الشائعة في الأطفال ولا يؤثر على الكلى فقط وإنما يؤثر على أجهزة الجسم المختلفة ومنها السمع خصوصا في الأطفال الذين يتناولون عقار الكورتيزون لفترات طويله ويتعرضون لانتكاسات متكرره من المرض.

الهدف من البحث: معرفة تأثير المتلازمة الكلوية عند الأطفال على درجة السمع لديهم ومعرفة السبب الكامن وراء ذلك.

اجري هذا البحث على أربعين طفلا من الذين يعانون من المتلازمة الكلوية والمترددين على عياده كلى الأطفال بمستشفى الحسين الجامعي وتراوحت أعمارهم مابين (٤-١٨) سنة وقد تم تقسيمهم الى مجموعتين متساويتين:

- **المجموعة الأولى:** وشملت عشرون طفلا من المستجيبين للعلاج بالكورتيزون منهم ١٣ ذكرا و٧ إناث.
- **المجموعة الثانية:** وشملت عشرون طفلا من غير المستجيبين للعلاج بالكورتيزون منهم ١٢ ذكرا و٨ إناث.

وقد تم استبعاد الذين يعانون من فشل كلوي او ضعف بالسمع او أمراض مزمنة تؤثر على السمع او يتناولون أدوية قد تؤثر على السمع، وذلك حتى لا تتأثر نتائج البحث بعوامل خارجة عن أهداف البحث.

ملحوظة: لقد تم أخذ مجموعة عشرين طفلا من الأطفال الاصحاء المماثلين في السن والجنس للأطفال المرضى كمجموعة مقارنة وذلك لمقارنة نتائج الأطفال المرضى بنتائجهم.

المرضى وطرق البحث: لقد خضع هؤلاء الأطفال جميعا للاتي:

1. أخذ طريق مفصل للمرض.
2. فحص إكلينيكي شامل لجميع أجهزة الجسم.
3. اجراء التحاليل اللازمة خاصة اللي تتعلق بالمتلازمة الكلوية.
4. عمل مقياس سمع لهؤلاء الأطفال جميعا بما فيهم الأطفال الاصحاء.

نتائج البحث: ثبت ان تمانية طفلا من الأربعين طفلا المرضى يعانون من ضعف في السمع وهؤلاء الأطفال الثمانية كانوا في الحالة النشطة للمرض وكانوا موزعين كالآتي:

- عدد طفلين من المجموعة الأولى (المستجيبة للكورتيزون).
- عدد ستة أطفال من المجموعة الثانية (الغير مستجيبة للعلاج بالكورتيزون).

وقد أثبتنا ان السبب في ضعف السمع لديهم هو الحالة النشطة للمرض وتناول عقار الكورتيزون لفترات طويلة بالإضافة الى اختلال في عنصري الصوديوم والكالسيوم لدى الأطفال المرضى حيث توصلنا الى ان مستوى الصوديوم والكالسيوم في دم الأطفال المرضى كان اقل بكثير من الاصحاء وكان الفرق له دلالة إحصائية.

الاستنتاج:

- متابعة الأطفال اللي يعانون من المتلازمة الكلوية بصورة منتظمة وعمل التحاليل اللازمة لهم عند كل زيارة.
- عمل مقياس سمع لهؤلاء الأطفال خاصة الذين يكونون في الحالة النشطة للمرض.

الكلمات الدالة: فقدان السمع، المتلازمة الكلوية، اختبار السمع، الكورتيزون.