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Biochemical alteration in children with idiopathic nephrotic syndrome associated with an increased risk of sensorineural hearing loss; additional insights in cochlear renal relationship

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ABSTRACT

Objectives: Children with Idiopathic Nephrotic Syndrome (INS) are at risk of hearing loss due to the adverse impact of medications and related immunological and genetic factors on both cochlea and kidney. So this work was planned to evaluate hearing status in children with INS and to clarify the possible associated risk factors by interpreting the clinical and laboratory profiles of those children.
Methods: Ninety children with INS aged 5–14 years [30 patients with steroid-sensitive nephrotic syndrome (SSNS), 30 patients with steroid dependent/frequently relapsing nephrotic syndrome (SDNS/FRNS), and 30 patients with steroid-resistant nephrotic syndrome (SRNS)], and 90 age and sex matched normal controls were enrolled into this study. Laboratory measurements of serum calcium, creatinine, cholesterol, blood urea and other relevant investigations were done. Pure tone audiometry was done with the sensory-neural hearing loss (SNHL) diagnosed when the level bone conduction was >20 dB and the difference in air to the bone gap was <15 dB.
Results: 40% children with INS had SNHL, mostly of mild degree HL and primarily occurred at the lower frequencies. A highly significant statistical difference between controls and various types of nephrotic syndrome regarding pure tone audiometry measurements at frequencies 250, 500, 1000 Hz, whereas insignificant difference interpreting pure tone audiometry measurements in 2000, 4000 and 8000 Hz.
Conclusions: Children with different phenotypes of nephrotic syndrome are at risk of sensorineural hearing impairment. The hazards associated with this impairment were higher blood pressure, hypercholesterolemia, hypoalbuminemia, and hypocalcemia.

1. Introduction

Nephrotic syndrome (NS) is chiefly a pediatric disorder which is about fifteen times more common in children than adults. The majority of children have the pathological type of steroid-sensitive minimal change disease. The distinctive features of the nephrotic syndrome are hypoalbuminemia, hyperlipidemia, heavy proteinuria, and edema [1].

The kidney and cochlea have a number of shared physiological mechanisms, including the active transportation of fluid and electrolytes carried out by the stria vascularis and the glomerulus, respectively. Moreover, they may experience a common antigenicity [2]. These similarities may account for analogous impacts of medications (i.e. ototoxic and nephrotoxic effects of aminoglycosides) and immunological influences 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 [3]. Children with chronic renal disease are also recognized to have some degree of hearing impairment [4–6].

Children with INS have biochemical impairments, which include hyponatremia, hypocalcemia [7], and hyperlipidemia [8]. These biochemical abnormalities are realized to have a negative impact on hearing. Hearing organ in children with NS during chronic

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glomerulopathy is worse than in normal children. It is seemed to be linked with frequent biochemical and electrolytes changes that induce alterations in the brain stem, cochlea, and acoustic nerve. It can be also triggered by consuming ototoxic medications [9]. Few types of research studied the correlation between nephrotic syndrome and impaired cochlear function that caused hearing impairment in children. So we intended in this research paper to demonstrate this relationship among different types of idiopathic nephrotic syndrome.

2. Methods

2.1. Participants and study settings

This study was carried out in the pediatric nephrology clinic and audiology unit in Menoufia University Hospital from December 2015 to September 2016. The research was approved by the Research Ethics Committee of the Menoufia University. The study carried out on 180 children, 90 patients with INS with mean age 8.71 ± 2.7 years (42 were females and 48 males) and 90 healthy controls with mean age 8.6 ± 2.4 years (43 were females and 47 males).

The INS group consisted of 90 children (30 patients of SSNS, 30 patients with SDNS/FRNS and 30 patients with SRNS (attending the pediatric nephrology clinic and/or admitted to our hospital and were eligible for inclusion in the current research. We select an equal number of each group for concise comparison. Those with a secondary nephrotic syndrome or nephrotic syndrome with renal insufficiency (serum creatinine > 1.0 mg/dl), children with previously known hearing impairment, and those having chronic suppurative otitis media were excluded from this study.

2.1.1. The selection criteria for each group were determined

Steroid sensitive nephrotic syndrome (SSNS) described as attainment of complete remission within initial four weeks of corticosteroid therapy. *Frequent relapse (FRNS)* was described as two or more relapses within six months of the original episode or more than three relapses within any 12-month period. *Steroid dependence (SDNS)* was specified as two consecutive relapses either on every other day prednisolone or within fourteen days of stoppage of prednisolone. *Steroid resistance (SRNS)* was identified as the absence of remission even with daily prednisolone at a dose of 2 mg/kg/day for four weeks [10].

2.2. Procedures

All subjects enrolled in the current analysis underwent complete medical history; clinical assessment included a review of their medical records with respect to history, measurement of body weight, height as well as blood pressure measurements. Laboratory assessment included urine analysis, quantification of proteinuria, serum electrolytes, serum albumin, serum creatinine, blood urea, serum calcium, and cholesterol. A ultrasound-guided percutaneous renal biopsy was performed in all cases of SRNS. The audiological evaluation was performed by pure tone audiometry using a Madsen Audiometer Orbiter 922, Immitance measurements using the GSI Tempstar middle ear analyzer with the results were plotted graphically as in the pure tone audiogram and outlined both qualitatively and quantitatively [11,12].

2.3. Statistical analysis

A one-way ANOVA used to assess the equivalence of multiple means simultaneously, with Student's *t*-test applied to compare the distribution of quantitative data if parametric; and if non-parametric Mann-Whitney *U* test was used. Pearson correlation coefficient was utilized to test the correlation between two interval variables. The $\chi 2$ test and Fisher's exact test were exploited to match the distribution of qualitative data. P- value of ≤ 0.05 indicated statistical significance. The computer program used was SPSS, release 20.

3. Results

Our results demonstrated no significant statistical difference between normal children and various types of INS regarding height measurements ($P = 0.7$), but a significant statistical difference was detected between normal children and different types of nephrotic syndrome regarding weight and BP measurements ($P = 0.04$ and < 0.001) respectively.

As predictable, there were considerable alterations in serum protein-lipid parameters and 24-h proteinuria levels (lower serum albumin, serum calcium and higher urinary protein, urea protein creatinine ratio, serum creatinine and cholesterol levels in children with a nephrotic syndrome consistent with their disease as compared with healthy controls ($P < 0.001$). Additionally, children with SSNS and SDNS/FRNS and SRNS had statistically considerable higher thresholds for hearing at frequencies 250,500, 1000 Hz than the controls ($P < 0.001$) while no significant differences were detected at frequencies of 2000, 4000 and 8000 Hz (Table 1).

36 out of 90 children with INS had SNHL (40%), mostly occurred at the lower frequencies. Based on the degree of hearing loss, mild degree HL detected in 97.2% (35/36) and a moderate degree in only one patient (2.8%). The hearing loss recorded in 33.33% (12/36) of children with SSNS, 27.78% (10/36) in SDNS/FRNS and 38.89% (14/36) in SRNS.

Correlation analysis revealed a negative correlation between serum calcium, and audiometry recorded frequencies while a positive correlation between diastolic and systolic BP and audiometry recorded frequencies (Fig. 1, Table 2).

The current results also reported a highly significant difference between the patient groups with hearing loss and with a normal hearing regarding blood pressure measurements, lower serum albumin, serum calcium and higher serum cholesterol levels, but no significant difference was detected as regards to weight and height measurements (Table 3).

4. Discussion

In our study 36 out of 90 children with INS had SNHL (40%), mostly of mild degree hearing impairment that for the most part 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.

Saha et al. noticed 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 [13]. Furthermore, Orendorz et al. realized that children with nephrotic syndrome had worse hearing outcome than the healthy children even after remission had been accomplished in the former cohort [9].

In the current paper children with hearing impairment had lower serum albumin, lower serum calcium levels, and higher serum cholesterol, urea, and creatinine ratio than those with normal hearing. Some previously published papers reported that the risk parameters (urine albumin, urine creatinine, serum creatinine, BUN, SBP, and DBP) for renal dysfunction were worse in the