Audiological findings in children with chronic renal failure on regular hemodialysis
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Introduction
The cochlea and kidney have similar physiological mechanisms, namely the active transport of fluid and electrolytes performed by the stria vascularis and the glomerulus, respectively [1]. They may also have common antigenicity [2].

Although the gross anatomy of the kidney and cochlea differs considerably, there are many similarities at the ultrastructural level. Both contain epithelial structures in close contact with their vascular supply. Basement membrane is found closely apposed to capillary endothelium in both Bowman's capsule and the proximal renal tubules of the kidney and also around the capillaries of the stria vascularis. In addition, basement membrane lined intercellular channels exist in both the glomerulus and the stria vascularis [3]. Moreover, the epithelial cells in both the cochlea and the kidney show features known to be associated with active transport of fluid and electrolytes, namely, microvilli containing numerous mitochondria.

Both organs are involved in body fluid homeostasis, and therefore have epithelium containing a sodium–potassium ion pump using ATPase. Carbonic anhydrase is also present in both the stria vascularis and the nephron [3]. They are also affected similarly by some medications (i.e. nephrotoxic and ototoxic effects of aminoglycosides) and immunological factors on the two organs. Both inner ear and kidney development are influenced by similar genetic factors in hereditary conditions such as Alport's syndrome and branchio-oto-renal syndrome [4].

Deterioration in the function of hearing organ is one of the most significant clinical problems in patients with chronic renal failure (CRF) [5]. The incidence of...
sensorineural hearing loss (SNHL) among patients with CRF is considerably higher than that in the general population [4,6]. Hearing loss (HL), mainly cochlear, is present in a high percentage of patients with CRF [7].

Otoacoustic emissions (OAEs) are low-level sounds emitted by the cochlea in the process of receiving the sound vibrations and transforming them into cellular and neural stimulation. Recording of OAEs implies a functioning cochlea and healthy middle-ear mechanism. Transient-evoked otoacoustic emissions (TEOAEs) are produced by the action of the hair cells, and they reflect special characteristics of the stimulus. Distortion production otoacoustic emissions (DPOAEs) are produced when the ear is stimulated with a combination of pure tones that are close in frequency (the primary tones). DPOAEs reflect nonlinear processes of hair cell motion. Both TEOAEs and DPOAEs are generated by the active cochlear mechanisms responsible for enhancing basilar membrane vibration; this is known as the 'cochlear amplifier' [8]. OAEs seem to be more sensitive to incipient cochlear damage than behavior thresholds in monitoring renal patients [6]. Despite a large number of studies on CRF in adult patients, there are only a few reported surveys of SNHL in children with CRF [9].

**Aim of this study**
The aim of this study was to determine the presence, type, and severity of HL, and to evaluate the relationship of reported HL with the duration of hemodialysis and hematological and biochemical data of children with CRF on regular hemodialysis.

**Patients and methods**
This study was carried out between November 2009 and March 2012 in the Otolaryngology Department, Pediatric Nephrodialysis and Audiology Units, Zagazig University Hospitals.

Thirty children with CRF on regular hemodialysis in the Nephrology Unit, Pediatric Department, Zagazig University Hospitals, were included in this study. There were 12 males (40%) and 18 females (60%), and the age of the patients ranged from 8 to 16 years. They were hemodialyzed regularly three times weekly and 2–4 h/session by a polysulfone membrane using citrate dialysate. The duration of dialysis ranged from 3 months to 8 years. All of them had arteriovenous fistula.

Children were categorized into two groups: group I, which included children on hemodialysis for 2 years or less and included 16 children (53.3%), and group II, which included children on hemodialysis for more than 2 years and included 14 children (46.7%).

All children were clinically examined (complete pediatric examination and otorhinolaryngological examination). Children who had a suggestive history of congenital HL, birth asphyxia, hyperbilirubinemia, or head trauma were excluded from the study. Any pathology of middle or external ear such as impacted cerumen or otitis media was detected and treated first to avoid fallacies in audiological tests. Children who could not cooperate during the audiomietric examination were also excluded. Audiological testing was performed 1 h after the hemodialysis session.

Tympanometry was performed in all cases using tympanometer Amplaid 724 (Amplifon, Italy); only patients with normal middle ear pressure were included in this study. Audiometric assessment by standard pure-tone audiometry (PTA) using audiometer Orber 922 (GN Otometrics, Denmark) was carried out by the audiology consultants; bone and air conduction for both ears were performed individually from 250 up to 8000 Hz. Normal hearing level was defined as hearing intensities lower than 16 dB according to Madell and Flexer [10], who suggested 15 dB as the upper limit for normal hearing in children between 2 and 18 years of age. HL was divided into five grades according to the classification documented by Madell and Flexer [10].

(1) Slight HL: hearing threshold between 16 and 25 dB.
(2) Mild HL: hearing threshold between 26 and 30 dB.
(3) Moderate HL: hearing threshold between 31 and 50 dB.
(4) Severe HL: hearing threshold between 51 and 70 dB.
(5) Profound HL: hearing threshold more than 70 dB.

HL was categorized into three types: conductive, sensorineural, or mixed. Sound frequencies between 250 and 500 Hz were considered as low frequencies, 1000–2000 Hz as middle frequencies, and 4000–8000 Hz as high frequencies [9].

Extended high-frequency audiometry was performed using an audiometer; frequencies across 10–16 kHz were examined. TEOAEs testing was carried out using IL0 version 6 (Otodynamics Ltd., UK).

Laboratory data including serum urea, creatinine, hemoglobin, platelets count, calcium, phosphorus, parathormone, iron, ferritine, albumin, electrolytes, prothrombin time, partial prothrombin time, and bicarbonate were also analyzed. Twenty normal healthy children served as controls. After normal kidney function tests were confirmed, they were subjected to clinical and otoscopic examinations, basic audiological assessment, extended high-frequency audiometry, and OAEs.

**Statistical analysis**
Data were analyzed using SPSS (Chicago, Illinois, USA). Comparison between the study and the control groups was carried out using a t-test for two independent means. Comparison of patients on hemodialysis for 2 years or less and those on hemodialysis more than 2 years was carried out using the Fisher exact test to compare two contingencies; it is a nonparametric test when the group number is small.

**Results**
Among 30 patients (60 ears), 50 ears showed SNHL (83.3%), of which 32 ears (64%) showed high-frequency
HL (Figs 1 and 2), 10 ears (20%) showed mid-frequency HL, and eight ears (16%) had low-frequency HL (Fig. 3). SNHL was found to be almost equal bilaterally in all affected patients and no unilateral affection was found (Fig. 2).

After review of the degrees of severity of SNHL, at high frequencies, SNHL was mild in 14 (43.75%) ears, moderate in 14 (43.75%), and severe in four (12.5%). At mid frequencies, the severity of SNHL was mild in eight ears (80%) and moderate in two ears (20%). Finally, at low frequencies, SNHL was mild in six ears (75%) and moderate in two ears (25%). No cases showed severe degree of HL at mid and low frequencies (Fig. 4).

PTA results showed a highly statistically significant difference between pure-tone thresholds in the patients and control groups across frequencies 500–8000 Hz (Table 1).

High-frequency audiometry with pure tones from 10 to 16 kHz was performed and it was found that the high-frequency thresholds were significantly higher for the patients with CRF (Table 2).

TEOAEs testing showed absent emission in 10 cases (cases with more than mild HL loss; 20 ears). Those with preserved TEOAEs had significantly lower amplitudes in all frequencies. No statistically significant difference was found between subgroups I and II in both PTA and TEOAEs. Also, no statistically significant differences were found between the children with SNHL and those without SNHL in terms of laboratory markers (Tables 3 and 4).

In group I, children on hemodialysis for 2 years or less, 12 of 14 patients (85.7%) had SNHL, whereas in group I, children on hemodialysis for more than 2 years, 13 of 16 patients (81.3%) had SNHL. The Fisher exact test was used to compare two contingencies (Table 5) and one-tailed $P$ value of 0.567 was found nonsignificant. There was no statistically significant relation between SNHL and duration of dialysis.

**Discussion**

Alport [11] reported a classic genetic syndrome with hearing deficit and renal failure that was named after him.
Since then, there has been a steadily growing interest in the hearing function of patients with kidney disease. The incidence of end-stage renal disease (ESRD) in children is considerably lower than that among adults. Children account for only a small fraction of the total dialysis patient population because of both the relatively low incidence of ESRD in children and the extensive use of renal transplantation among pediatric ESRD patients [12].

Table 1 Mean and SD of pure-tone thresholds in the patients and control groups across frequencies 500–8000 Hz

<table>
<thead>
<tr>
<th>Frequencies (Hz)</th>
<th>Patient group (µm)</th>
<th>Control group (µm)</th>
<th>t value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>24.5 ± 5.3</td>
<td>14.3 ± 2.1</td>
<td>9.48*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>500</td>
<td>25.33 ± 8.9</td>
<td>17.5 ± 4.69</td>
<td>4.049*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1000</td>
<td>23.67 ± 8.4</td>
<td>15.67 ± 4.69</td>
<td>4.306*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2000</td>
<td>29.17 ± 10.43</td>
<td>16.33 ± 4.34</td>
<td>6.007*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4000</td>
<td>35.67 ± 15.18</td>
<td>16.83 ± 4.45</td>
<td>6.58*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>8000</td>
<td>36 ± 19.54</td>
<td>15.83 ± 5.1</td>
<td>5.38*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Significant.

Table 2 Mean and SD of high-frequency thresholds in the patients and control groups across frequencies 10–16 kHz

<table>
<thead>
<tr>
<th>Frequencies (kHz)</th>
<th>Control group (µm)</th>
<th>Patient group (µm)</th>
<th>t value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>20.89 ± 8.21</td>
<td>35.25 ± 10.12</td>
<td>5.513*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>12</td>
<td>23.28 ± 9.88</td>
<td>46.35 ± 9.30</td>
<td>8.38*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>16</td>
<td>29.56 ± 11.88</td>
<td>50.41 ± 10.23</td>
<td>6.4207*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Significant.
Approximately one-half of pediatric ESRD patients have a congenital or a hereditary disorder and one-half have an acquired renal lesion [13], whereas more than 80% of the adult ESRD populations have an acquired renal disease [14].

Hemodialysis is a safe and effective treatment for children with acute and CRF. Although there were early problems with application of a complex extracorporeal technique in children and small infants, the availability of sophisticated equipment (particularly ultrafiltration control devices) together with skilled nursing staff make the technique applicable to even the smallest or the sickest children [15]. The two most common complications of chronic uremia are encephalopathy and peripheral neuropathy. The clinical course of encephalopathy was reversed by hemodialysis whereas peripheral neuropathy was not reversed. HL among patients with CRF has been reported as a common finding in studies investigating the effects of renal failure on auditory function [4]. However, there is a debate on the relationship between renal insufficiency and HL [16]. Hemodialysis applied in the terminal phase of CRF causes considerable metabolic and electrolyte disturbances within a few hours in humans [17]. There is also ongoing debate on the effect of regular hemodialysis on hearing acuity [18].

The results of our study indicated that 83.3% of CRF patients on regular hemodialysis had SNHL, which is almost in agreement with the results of most previous [19–21]. However, Esfahani et al. [9] reported that severe degree was the main finding in the 30% SNHL among their CRF patients and Oda et al. [22] reported that as few as 18% of CRF patients treated by regular dialysis or renal transplantation had SNHL.

In our study, SNHL was bilaterally reported in all affected cases. This result is comparable to the study by Esfahani et al. [9]; however, in the study by Nikolopoulos et al. [16], 50% of patients had unilateral HL.

In the current study, SNHL was detected mainly in the high frequencies as in previous studies [9,16], whereas low frequencies were reported to be affected in another study [23], but it was fluctuating. Fluctuation was proposed to be because of fluid imbalance because of CRF that was corrected after dialysis. This was attributed by Gatland et al. [24] to low-frequency SNHL, which is known to be a feature of endolymphatic hydrops, and the fact that hydrops is influenced by fluid balance (glycerol dehydration test). Thus, endolymphatic hydrops may be a part of the pathological process. Others have reported that of 10 temporal bone studies of patients dying from CRF, only one showed distortion of the cochlear duct to be a pathological feature of CRF [24].

Considering the severity of SNHL, it was more of mild and moderate degrees (87.5%), whereas severe SNHL was found only in 12.5% of patients and no profound SNHL was reported. This result is consistent with that of Gatland et al. [24] but not with Esfahani et al. [9], who found that severe degree was the main finding in the 30 patients studied.

We found no significant relation of SNHL with the duration of hemodialysis, which is similar to the result of Bazzi et al. [7]. This supports the hypothesis that hemodialysis does not seem to worsen hearing function for at least the first 5 years of treatment [7]; even long-term hemodialysis had no significant adverse effect on hearing [9]. It seemed that regular dialysis does not prevent the persistence of mild signs of uremic encephalopathy and peripheral neuropathy, but these

Table 3 Mean and SD of transient-evoked otoacoustic emissions in the study and control groups across different frequencies

<table>
<thead>
<tr>
<th>Frequencies (kHz)</th>
<th>Study group</th>
<th>Control group</th>
<th>t-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.78 ± 5.01</td>
<td>7.23 ± 4.35</td>
<td>-3.332*</td>
<td>0.0017</td>
</tr>
<tr>
<td>1.4</td>
<td>5.77 ± 5.24</td>
<td>9.87 ± 3.03</td>
<td>-3.497*</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>5.23 ± 4.97</td>
<td>9.3 ± 3.06</td>
<td>-3.581*</td>
<td>0.0008</td>
</tr>
<tr>
<td>2.8</td>
<td>4.79 ± 4.58</td>
<td>9 ± 4.4</td>
<td>-3.2605*</td>
<td>0.0022</td>
</tr>
<tr>
<td>4</td>
<td>6.67 ± 5.09</td>
<td>2.27 ± 4.5</td>
<td>3.2124*</td>
<td>0.0025</td>
</tr>
<tr>
<td>Overall response</td>
<td>7.16 ± 3.61</td>
<td>13.62 ± 3.03</td>
<td>-6.4535*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Significant.

Table 5 Sensorineural hearing loss in children on hemodialysis for less or more than 2 years

<table>
<thead>
<tr>
<th></th>
<th>&lt; 2 years</th>
<th>&gt; 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>With SNHL</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Without SNHL</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

SNHL, sensorineural hearing loss.

Table 4 Mean and SD of laboratory results of children with and without sensorineural hearing loss

<table>
<thead>
<tr>
<th></th>
<th>Children with SNHL</th>
<th>Children without SNHL</th>
<th>t-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>7.1 ± 1.6</td>
<td>6.9 ± 1.4</td>
<td>-0.016</td>
<td>0.9852</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>134.3 ± 39.6</td>
<td>137.3 ± 37.8</td>
<td>-0.185</td>
<td>0.8732</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.0 ± 1.2</td>
<td>9.6 ± 0.9</td>
<td>-1.28</td>
<td>0.211</td>
</tr>
<tr>
<td>Platelets count (× 10^3/cmm)</td>
<td>221.1 ± 64.7</td>
<td>212.1 ± 72.9</td>
<td>0.257</td>
<td>0.7991</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.36 ± 0.5</td>
<td>2.83 ± 0.3</td>
<td>-2.809</td>
<td>0.009</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>7.3 ± 1.1</td>
<td>7.7 ± 2.0</td>
<td>-0.872</td>
<td>0.3906</td>
</tr>
<tr>
<td>Phosphorous (mg/dl)</td>
<td>5.4 ± 1.6</td>
<td>4.8 ± 3.1</td>
<td>0.605</td>
<td>0.5501</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>138.3 ± 29.5</td>
<td>138.6 ± 33.78</td>
<td>-0.018</td>
<td>0.9585</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>5 ± 0.6</td>
<td>4.9 ± 3.0</td>
<td>0.556</td>
<td>0.5826</td>
</tr>
<tr>
<td>Iron (mg/dl)</td>
<td>98.7 ± 61.1</td>
<td>100.1 ± 45.3</td>
<td>-0.059</td>
<td>0.9534</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>988.5 ± 173.3</td>
<td>974.2 ± 180.1</td>
<td>0.163</td>
<td>0.8717</td>
</tr>
<tr>
<td>Parathormone (pg/ml)</td>
<td>452.2 ± 344.6</td>
<td>463.1 ± 332.6</td>
<td>-0.086</td>
<td>0.9478</td>
</tr>
<tr>
<td>PT (s)</td>
<td>13.5 ± 1.4</td>
<td>13.1 ± 1.1</td>
<td>0.707</td>
<td>0.4854</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>43.0 ± 10.9</td>
<td>41.0 ± 9.9</td>
<td>0.405</td>
<td>0.6886</td>
</tr>
</tbody>
</table>

PT, prothrombin time; PTT, partial prothrombin time; SNHL, sensorineural hearing loss.
signs do not appear to worsen with increasing dialytic age; this supports the result of Sobh et al. [18], who found no statistical differences between SNHL in CRF treated conservatively and those treated by dialysis.

Therefore, SNHL associated with CRF on hemodialysis mostly related to the CRF disease rather than the hemodialysis, suggesting the central component of uremic axonopathy in the pathogenesis of hearing impairment in children with CRF. This is in agreement with the Orendorz-Fraczkowska et al. [17] study. These findings are in agreement with the evidence of cochlear dysfunction reported by Samir et al. [25], corroborating the hypothesis that children with CRF (on hemodialysis) may have signs of adverse effects on cochlear function, which is predictive of upcoming HL. In addition to cochlear dysfunction, retrocochlear involvement was also reported [4,17].

Thus, SNHL rehabilitation (including SNHL precautions) and regular follow-up audiological evaluation must be considered in these children with CRF on regular hemodialysis as SNHL may affect speech, language, and social and emotional development. Behavior, attention, learning, and academic achievement may also be influenced.

High-frequency audiometry showed a statistically significant difference between the control and study groups. This is in agreement with Zeigelboim et al. [26], who concluded that high-frequency audiometry is a sensitive method for detecting hearing changes in patients with CRF and can be used to monitor these patients.

In terms of TEOAEs, almost 67% of children with CRF did not pass TEOAEs testing, even those with normal peripheral hearing; others (33%) who showed responses showed a statistically significant difference between the control and the study group in TEOAEs echo level at different frequency bands and in the overall response. This is lower than the result of Pandey et al. [27], who reported that almost all (95.65%) patients with CRF did not pass the TEOAEs.

Several factors might affect hearing in uremic patients; some of them are related to derangements dependent on CRF: uremic toxins, electrolyte and water imbalance in the inner ear fluid, destruction of the myelin sheath and axons of the medullated fibers [28], and/or involvement of the spiral organ of Corti [29]. Other factors are related to underlying disease as in Alport’s disease or drug treatment with potentially ototoxic drugs such as aminoglycoside antibiotics or diuretics such as frusemide and ethacrynic acid [30]. SNHL was greater in CRF patients treated conservatively than in those treated by dialysis (22.7 and 15.3%, respectively), but the difference was not statistically significant [18].

HL was not influenced by the various laboratory parameters (hematological and biochemical). These results are in agreement with some previous studies [3,6,18] but the results are not in agreement with the concept that electrolyte disturbances, in particular sodium, water imbalance, and elevated serum urea level, could be implicated as potential factors that could participate in deteriorating hearing acuity in CRF [19,20,28,30]. Our results may explain why even with strict control for confounding variables of hematological, biochemical, and clinical parameters, evidence of SNHL among CRF patients remains [3,6].

**Conclusion**

A high incidence of HL among children with CRF on regular hemodialysis was found in this study; thus, regular follow-up audiological evaluation must be considered in these children. Duration of hemodialysis treatment did not seem to have a significant impact on this HL.

However, the lack of a significant relationship between HL and laboratory findings precludes a detailed description of the mechanisms causing HL in CRF. The association between HL and CRF can be explained by structural and functional similarities between tissues in the inner ear and the kidney, and the fact that the kidney disease and HL share common risk factors.

**Acknowledgements**

**Conflicts of interest**

There are no conflicts of interest.

**References**