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Risk factors contributing to outer hair cell damage in children with chronic kidney disease

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Abstract: The study is aimed to assess the risk factors leading to outer hair cell damage in pediatric CKD patients. There are many similarities between the renal nephron and ear structures, making them vulnerable to same risk factors. Outer hair cell damage is frequent in pediatric patients with chronic kidney disease (CKD). A cross-sectional observational study including pediatric CKD patients. These patients underwent a hearing examination. Hearing examination using distortion product otoacoustic emissions (DPOAE) and tympanometry were performed. Other data were collected from medical records. Total of 58 children with CKD were included in this study. The incidence of hearing loss was 17,2%, with the most of hearing loss being in children underwent hemodialysis. The results showed factor associated for hearing loss in children with CKD were stage of CKD (OR: 3,178, p=0,000), the use of loop diuretic (OR:1,596, p=0,001), level of blood urea (OR:1,85, p=0,000), and duration of hemodialysis (OR 2,2, p<0,000). There is a significant increased risk to the development of outer hair cell damage in higher stage of CKD, longer use of loop diuretic, higher level of blood urea, and the longer hemodialysis duration. It is necessary to understand hearing loss is notable complication in pediatric CKD hence it is important to monitor comorbidities in pediatric patients with CKD and further research to identify risk factors for cochlear outer hair cell damage.

Keywords: *Chronic kidney disease, hearing loss, otoacoustic emission, outer hair cell.*

1. Introduction

Hearing loss is the fourth most common disability globally. One of the risk factors of hearing loss is chronic kidney disease (CKD) complications, either due to the disease itself or part of its therapy. Hearing loss might occur due to the damage of cochlear outer hair cells, resulting in sensorineural hearing loss. Several factors are known to play some roles in cochlear outer hair cells damage; however, previous studies show limited results.[1-4)]

Cochlear outer hair cell damage incidence in patients with CKD is an arising issue across the globe. This is because reporting of CKD in children over the past two decades has increased and monitoring of CKD complications has improved. Complications of CKD in children include hypertension, cardiovascular disease, anemia, bone and mineral disease, and proteinuria. Cochlear outer hair cell damage are complications that could be found in CKD patients, although the pathophysiology is not fully elucidated. Cochlear outer hair cell damage in CKD patients is higher than in the normal population. A study reported that 7% of patients with CKD experienced hearing loss. Another study reported that 46% CKD patients had moderate and severe hearing loss.[5-8)]

Study regarding cochlear outer hair cell damage is still scarce especially in pediatric patients, although there is evidence that hearing loss is more common in CKD patients with childhood onset.

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Based on previous studies, a study is needed to assess the risk factors for cochlear outer hair cell damage and hearing loss. This study aimed to assess the risk factors for hearing loss, especially cochlear outer hair cell damage, in children with CKD.

2. Materials and Methods

This was a quantitative study with a cross-sectional design at the Pediatric Nephrology outpatient clinic, pediatric inpatient ward, and audiology clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Data collection was conducted between October 2021 - June 2022.

Before the study began, the authors submitted ethical eligibility of the study to the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya. The confidentiality of the study subjects was well maintained by not mentioning their names, but written based on their initials. The data from this study are only used for study purposes.

The study population was pediatric patients with CKD who underwent treatment and were registered at the Pediatric Nephrology outpatient clinic of Dr. Soetomo General Academic Hospital. The population study sample met the inclusion criteria and did not fall into the exclusion criteria. The inclusion criteria in this study were pediatric patients aged 5-18 years and the patient's guardian agreed to participate as study sample and had signed an informed consent. The exclusion criteria in this study were patients suffering from ear infections that affected hearing, experiencing anatomical disorders of the hearing organ, diagnosed with hearing loss before the onset of CKD was established, and the patient's clinical condition was unstable for audiological examination. The drop out criteria in this study were results of the audiological examination could not be interpreted and the patient's guardian withdrew from the study.

Pediatric patients with CKD who have met the inclusion and exclusion criteria underwent baseline data collection. The data collected include gender, age, initial diagnosis of CKD, laboratory test results, treatment received (conservative and hemodialysis), use of ototoxic drugs, and degree or classification of CKD. In this study subject, the stages of CKD category were determined by calculating the glomerular filtration rate (GFR) with the revised Schwartz formula. The variables were based on the results of serum creatinine laboratory and the patient's height.

Further data collection in the form of hearing impairment assessment using pure tone audiometry and distortion product otoacoustic emission (DPOAE) with GSI Corti® was conducted on both ears through direct examination at the audiology clinic. The results of the examination were grouped into dichotomous categorical data types: refer if the examination results obtained a refer assessment on one or both of the subject's ears, and pass if the examination results obtained a pass assessment on both of the subject's ears. The data were analyzed statistically and presented in the form of data tabulations, graphs, and tables at the end of the study.

The data that has been collected in the data collection sheet and the results of the cochlear outer hair cell damage assessment were analyzed using descriptive and analytical statistical tests. Data processing and analysis used SPSS software program version 25. Descriptive data was displayed in a frequency table. For inferential needs, the data from this study were analyzed using statistical tests.

The bivariate analysis to determine the correlation between two variables was conducted. The bivariate analysis used chi square test to analyze whether there was a correlation between the two variables from categorical data. Analysis of variables that produced one of the columns with a value of <5 was analyzed using Fisher's exact test. Analysis of variables with categories of more than 3 (3x2 table) and variables with one of the columns with a value of 0 was conducted using simple logistic regression. A p value <0.05 indicates significant result.

3. Results

A total of 58 children with CKD consisting of several stages and underwent DPOAE examination were included in this study (Table 1). Most subjects were boys, with mean age of 13 years. The most common etiology was lupus nephritis (37.9%). Most of the subjects were patients with mild CKD

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(77.6%). Most patients had a mean blood urea nitrogen (BUN) level of <21 mg/dL (67.2%). As many as 39.7% of patients used loop diuretic drugs, mostly furosemide. Subjects undergoing hemodialysis were mostly patients with severe CKD and most (77.6%) were CKD patients with conservative therapy. Hemodialysis patients underwent hemodialysis for a mean duration of 27.8 months.

Cochlear outer hair cell damage was found in 17.2% of subjects. This study showed significant correlations between CKD stage, use of loop diuretic consumption, high blood urea level, and hemodialysis treatment, as well as hemodialysis duration of >12 months with the incidence of cochlear outer hair cell damage in children with CKD (p = 0.000). The three risk factors with the greatest influence on cochlear outer hair cell damage incidence in children with CKD were hemodialysis duration of >12 months (OR 5.5; 95% CI 1.098 – 15.933), severe CKD degree (OR 3.178; 95% CI 1.404 – 7.191), and hemodialysis treatment (OR 3.178; 95% CI 1.404 – 7.191) (Table 2).

4. Discussion

This study had 58 participants with CKD. A total of 45 patients (77.6%) did not undergo hemodialysis, indicating that patients underwent conservative therapy, with 13 patients (22.4%) having undergone hemodialysis for six months or more, indicating further impaired kidney function requiring renal replacement therapy. The mean duration of hemodialysis was 6.24 months and ranged from 0 to 53 months. Another study also reported that 43 patients had undergone hemodialysis for more than 6 months on average.[9)]

Table 1.
Characteristics of subject.

Characteristics	**N (58)**	**%**
Sex		
Boys	32	55.2
Girls	26	44.8
Etiology		
Nephritic lupus	22	37.9
Nephrotic syndrome	19	32.7
APSGN	6	10.3
IgA nephropathy	3	5.2
RPGN	3	5.2
Polycystic kidney disease	2	3.4
Renal hypoplasia	1	1.7
CAKUT	1	1.7
C3 Glomerulopathy	1	1.7
CKD stage		
Mild	45	77.6
Severe	13	22.4
BUN level		
≤ 21	39	67.2
>21	19	32.8
Loop diuretic consumption		
No	35	60.3
Yes	23	39.7
Aminoglycoside consumption		
No	57	98.3
Yes	1	1.7
Treatment type		

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Conservative	45	77.6
Hemodialysis	13	22.4
Outer hair cell damage		
No	48	82.8
Yes	10	17.2
Hemodialysis duration		
Non-hemodialysis	45	77.6
≤ 6 months	1	1.7
7 – 12 months	3	5.2
> 12 months	9	15.5

Note: APSGN: Acute post-streptococcal glomerulonephritis, CAKUT: Congenital anomalies of the kidneys and urinary tracts, RPGN: rapidly progressive glomerulonephritis.

Table 2.
Analysis of risk factors associated with cochlear outer hair cell damage in children with CKD.

Variable	Cochlear outer hair cell function, n (%)		p-value	OR (95% CI)
	Normal	Damaged		
CKD stage Mild Severe	 44 (75.9) 4 (6.9)	 1 (1.7) 9 (15.5)	0.000*	3.178 (1.404 – 7.191)
Loop diuretic consumption No Yes	 34 (58.6) 14 (24.1)	 1 (1.7) 9 (15.5)	0.001*	1.596 (1.144 – 2.226)
Aminoglycoside consumption No Yes	 48 (82.8) 0 (0.0)	 9 (15.5) 1 (1.7)	1.000	0.000
Urea level ≤ 21 > 21	 38 (65,5) 10 (17,2)	 1 (1,7) 9 (15,5)	0.000*	1.770 (1,187 – 2,641)
Treatment type Conservative Hemodialysis	 44 (75,9) 4 (6,9)	 1 (1,7) 9 (15,5)	0,000*	3,178 (1,404 – 7,191)
Hemodialysis duration				
Non-hemodialysis	44 (75,9)	1 (1,7)	Comparison	
≤ 6 months	0 (0,0)	1 (1,7)	1,000	7,108
7 – 12 months	0 (0,0)	3 (5,2)	0,999	7,008
> 12 months	4 (6,9)	5 (8,6)	0,000*	5,500 (1,098 – 15,933)

Note: *Significant result

This study reported a significant correlation between loop diuretic use and cochlear outer hair cell damage occurrence in children with CKD. Loop diuretics are commonly prescribed drugs for patients with CKD and are used to treat edema or volume overload. As many as 39.7 percent of pediatric patients in this study used the loop diuretic furosemide. Similar findings were found in other studies, reporting that 49% of patients with CKD received loop diuretic therapy, and most were used to treat complications such as edema, volume overload, or congestive heart failure.[10] Studies investigating the association between loop diuretics and cochlear outer hair cell damage in CKD patients have yielded

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mixed results. Some studies have shown a dose-dependent association, with higher cumulative doses of loop diuretics associated with an increased risk of cochlear outer hair cell damage. Other studies have suggested that individual susceptibility factors such as genetic predisposition or concomitant medications might affect this association.[11,12]

In this study, 34.5% of subjects had urea concentrations of >21 mg/dL (normal level 7-21 mg/dL). Urea level showed a significant correlation to cochlear outer hair cell damage occurrence in pediatric patients with CKD. Other studies have confirmed similar findings, where hearing loss is found alongside increasing blood urea level. One study stated that there is hearing loss in the form of increased latency with Brain Evoked Response Auditory (BERA) examination in patients with blood urea level >200 mg/dL compared to patients who have blood urea levels of <200 mg/dL.[13].

Cochlear outer hair cell damage might be due to uremic neuropathy, which could develop in CKD patients due to accumulation of urea in the blood and electrolyte imbalance. Uremic neuropathy could affect various parts of the nervous system, including the auditory nerve. Damage to the auditory nerve axons due to uremic neuropathy could cause hearing loss. Uremic neuropathy affects peripheral nerves and might occur in 60–100% of patients with CKD. Patients with uremic neuropathy have a 50–60% decrease in nerve conduction from normal. In an animal study, prolonged first wave latency and prolonged peak waves 1–5 was observed in rats with uremic condition, indicating problems with nerve conduction along the acoustic nerve. Another study comparing Auditory Brainstem Response (ABR) between CKD patients and control also showed prolonged ABR latencies in CKD patients, indicating impaired nerve signal conduction along the auditory nerve pathway.[11,12].

In this study, hemodialysis therapy was a risk factor associated with the occurrence of cochlear outer hair cell damage in pediatric patients with CKD. Other study in adult populations reported similar results. Previous study reported that patients undergoing hemodialysis experienced cochlear outer hair cell damage and osmotic imbalance.[14] Another study found cochlear outer hair cell damage occurred in 72.7% of CKD patients receiving hemodialysis therapy, accompanied by tinnitus in 68.2% of patients, vertigo in 27.3% of patients, and fullness in the ear in 45.4% of patients. Differences in CKD therapy have an effect on several aspects that cause cochlear outer hair cell disorders. Differences in drug administration, hemodialysis itself, and immunological factors have been associated with hearing loss in CKD patients. Electrolyte imbalance, creatinine level, sodium-potassium ATPase level and their inhibition during hemodialysis are thought to play a role in inner ear organ dysfunction.[15].

There was a significant correlation between hemodialysis duration and cochlear outer hair cell damage incidence in this study. The pathogenesis mechanism of inner ear organ damage resulting in cochlear outer hair cell damage in patients undergoing hemodialysis is not fully understood. One theory explains that hemodialysis is associated with vascular damage and complications, especially peripheral blood vessel and capillary disorders. Continuous contact with the dialysate membrane causes accumulation of amyloid substances and degraded membrane molecules causing inflammation which ultimately increases levels of intercellular (ICAM1) and vascular adhesion molecules (VCAM1). This increase causes endothelial dysfunction and vascular damage, especially in the cochlea. Increased level of ICAM1 and VCAM1 are found in patients with cochlear outer hair cell damage. Asymmetrical dimethylarginine (ADMA) level, which is an eNOS inhibitor, interferes with the endothelial vasodilation process in capillary blood vessels, leading to decreased oxygenation and is associated with cochlear outer hair cell damage.[15,16].

This study has several limitations. First, the limitation of the age group studied is related to hearing impairment examination because children under 5 years are difficult to cooperate. Second, hearing impairment examination is limited to the use of OAE and tympanometry.

5. Conclusion

Severe CKD, loop diuretic drug use, blood urea level >21, and hemodialysis duration >12 months are risk factors associated with cochlear outer hair cell damage occurrence in children with CKD. The results of this study could be used as considerations for early detection, prevention, mitigation, and

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comprehensive management plan of cochlear outer hair cell damage to reduce declining in quality of life in children with CKD. It is important to monitor comorbidities in pediatric patients with CKD, hence further research is needed to identify risk factors for cochlear outer hair cell disorders.

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Abbreviations:

ABR	: Auditory Brainstem Response
ADMA	: Asymmetrical dimethylarginine
ASPGN	: Acute Post-Streptococcal Glomerulonephritis
BERA	: Brain Evoked Response Auditory
CAKUT	: Congenital Anomalies of Kidneys and Urinary Tracts
CKD	: Chronic Kidney Disease
DPOAE	: Distortion Product Otoacoustic Emissions
GFR	: Glomerular Filtration Rate
OR	: Odd Ratio
RPGN	: Rapidly Progressive Glomerulonephritis

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