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Chapter

Hearing Loss in Chronic Kidney Disease

Sampson Antwi and Mohammed Duah Issahalq

Abstract

Chronic kidney disease (CKD) is assuming public health significance worldwide largely driven by the surge in diabetes mellitus, hypertension and obesity. CKD patients, particularly those from resource restraint regions of the world, face huge challenge in terms of accessibility and affordability to care. Besides these challenges in care, several other co-morbidities often exist among these patients in addition to the primary disease like diabetes and hypertension. Yet, these "subtle" co-morbidities are often overlooked by Caregivers. Hearing loss is one of such co-morbidities CKD patients face but it is often overlooked. The situation is worse among children who often cannot express themselves. The etiology of hearing loss among CKD patients are multifactorial. It is hoped that this neglected aspect of care for patients with chronic kidney disease will receive the needed attention for holistic care of the CKD patient.

Keywords: chronic kidney disease, co-morbidity, hearing loss, aetiopathogenesis, Oto-renal syndrome

1. Introduction

1.1 Structure and function of the ear

The ear is the organ for hearing. The human ear consists of three parts: 1. the external ear 2. the middle ear 3. the inner ear. The inner ear, also called the labyrinth, consists of the vestibular apparatus for balance; and the cochlear for hearing.

The external and middle ear portions of this hearing apparatus are responsible for conducting sound energy from the exterior and transforming it into mechanical energy towards the inner ear. The inner ear then converts the received mechanical energy into electrical energy. The cochlear component of the inner ear is the end-organ for hearing. The organ of Corti within the cochlear is the functional processing unit for hearing aspect of the inner ear. This organ is very sensitive to the chemical environment. Changes in the physiological environment of the organ of Corti cause toxic damage to it (ototoxicity).

Variety of factors contribute to functional deterioration of the inner ear. These include aging, chemicals, medications and certain diseases both congenital and acquired [1].

1.2 The kidney and the inner ear (labyrinth)

The kidney is the organ primarily responsible for the elimination of toxic metabolites from the body and thereby creating the required milieu for the internal organs, including the inner ear, to function optimally.

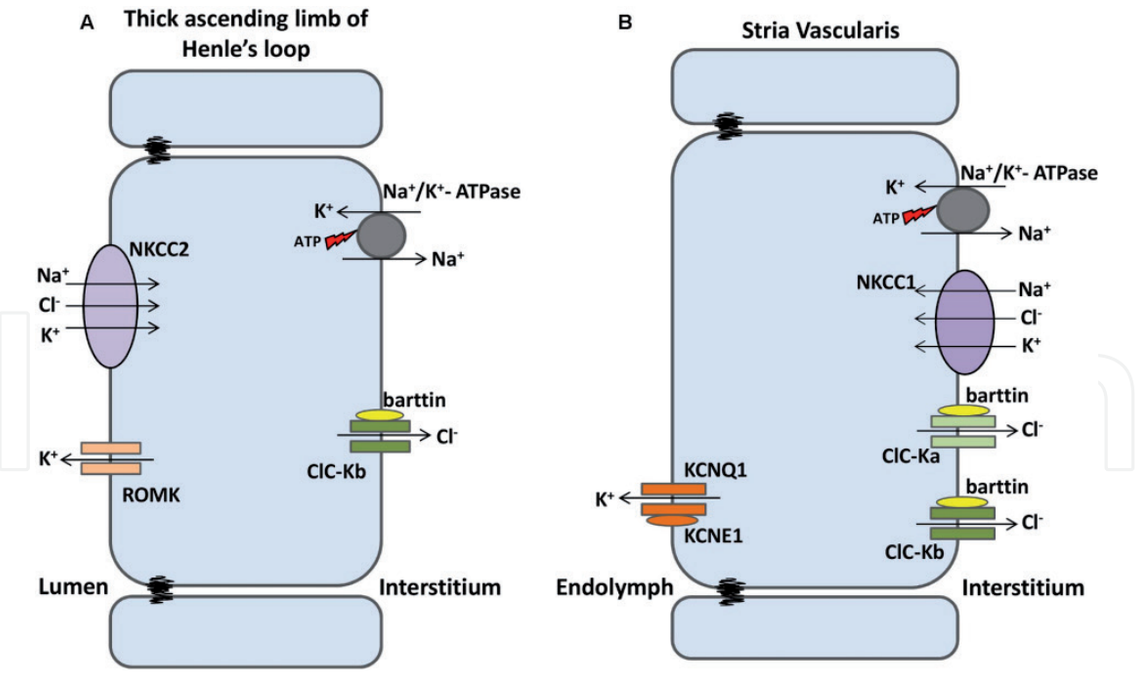

Figure 1.
ClC-K channels are expressed in kidney and inner ear. (A) At the nephrons, luminal NKCC2 transporters build up Na^+, K^+ and Cl^- into the cells. K^+ flows back to the lumen through ROMK1 channels; Na^+ and Cl^- are reabsorbed to the bloodstream separately through Na+/K+ ATPase and ClC-kb channels, respectively. (B) In the Stria Vascularis, Na^+, K^+ and Cl^- are transported into the cells by basolateral NKCC1 transporters. Na^+ and Cl^- are recycled back to the interstitium by Na+/K+ ATPase and both ClC-Ks isomers, respectively. K^+ flows through KCNQ1/KCNE1 channels and accumulates into the endolymph, a condition required for sensory transduction in inner hair cells. Figure courtesy Poroca DR et al. [4].

Diseases of the kidney have detrimental effect on the inner ear, not only because of buildup of metabolic toxins in the blood to affect the functions of the labyrinth, but also the fact that the functional unit of the kidney, the nephron, has structural and functional similarities with the stria vascularis in the labyrinth [2, 3]. These similarities make both organs vulnerable to similar agents and genetic disruptions in utero [2, 3].

1.2.1 Ion channels and transporters expressed in both the inner ear and kidney

ClC proteins are a large family of proteins that mediate voltage-dependent transport of Cl − ions across cell membranes [**4**]. They are controlled by the CLC gene family. They comprise the CLC-K channels, Cl − channels and Cl−/H+ antiporters. A critical subunit of the CLC-K channels is the protein barttin. These channels and transporters are expressed in both the inner ear and the kidney. [4–6] (**Figure 1**).

The CLC-K channels form homodimers which additionally co-assemble with the small protein barttin. ClC-K/barttin localizes at the basolateral membranes of both the thin and thick ascending limbs of Henle's loop, and in marginal cells of the stria vascularis of the inner ear [5]. In the kidney, they are involved in NaCl reabsorption; in the inner ear they are important for endolymph production (see 2.1.1.3 below).

2. Hearing loss in chronic kidney diseases

The kidney and the inner ear both suffer from the adverse effects of diseases like diabetes mellitus, hypertension and aging.

Several reports have indicated that hearing loss is more prevalent among CKD patients than the general population in different parts of the world. [7–11] In a Korean study by Seo1 JY et al. involving 5,226 participants ≥19 years of age whose estimated glomerular filtration rate (eGFR) and hearing threshold were measured, the authors found the odds of hearing impairment to be 1.25 times higher (95% confidence interval: 1.12–1.64, p-value <0.001) in participants with an eGFR <60 mL/min/1.73 m^2 (chronic renal failure group) than in those with an eGFR ≥60 mL/min/1.73 m^2 (normal or mildly impaired renal function group) after adjustments for age, sex, smoking, alcohol, body mass index, diabetes mellitus, hypertension, dyslipidemia, and microalbuminuria [7]. Among the risk parameters of CKD associated with hearing impairment, linear regression analysis adjusted for age and sex determined that each increase of serum creatinine or blood pressure was positively associated with an increase in hearing threshold (p-value <0.01) [7].

2.1 Etiology of hearing loss among patients with chronic kidney disease

The causes of hearing loss among patients with chronic kidney disease are multifactorial, ranging from genetics through uraemic complications to medication side effects [9, 12–14].

2.1.1 Genetic causes

2.1.1.1 Hereditary nephritis

Hereditary nephritis (Alport's syndrome) is a recognized cause of CKD among adolescents and young adults. Alport's syndrome is characterized by progressive kidney failure (mainly from second decade), sensorineural hearing loss and characteristic ocular findings. Cecil Alport first described the disease as hereditary haematuric nephritis with hearing loss in a family whose affected males died in adolescence [15]. The disease is caused by a defect in the gene that codes for basement membrane type IV collagen [15]. The consequence of this genetic defect is a thickened and often split basement membrane giving a characteristic "basket weave" pattern. The disease has variable pattern of inheritance but 85% of cases are X-linked and most or all of those results from mutation of COL4A5, the gene located on chromosome Xq22 that codes for the α5-chainof type IV collagen. Autosomal-recessive inheritance occurs in perhaps 15% of cases, and autosomal-dominant inheritance has been shown in a few cases with associated thrombocytopathy and in rare cases without platelet defects [15]. The disease initially manifests as asymptomatic microscopic haematuria, sometimes with superimposed episodes of gross haematuria. Progressively worsening proteinuria and end stage renal disease (ESRD) may eventually develop, although the rate of progression is quite variable [15].

Affected individuals have bilateral high-frequency sensorineural hearing loss [15]. Nonetheless, some affected individuals with the X-linked nephritis progressing to ESRD may be without hearing loss, an occurrence which might lead to missed diagnosis.

In Alport's syndrome, the similarities in connective tissue structure (collagen type IV) between basement membranes of glomeruli and the stria vascularis of the inner ear account for the affectation of both organs in most cases [15, 16].

2.1.1.2 Branchio-Oto-renal (BOR) syndrome

In Branchio-Oto-Renal (BOR) syndrome, there is concurrent occurrence of ear and renal abnormalities. Renal abnormalities include bilateral renal agenesis,

bilateral hypoplasia or dysplasia, unilateral renal agenesis with contralateral hypoplasia or dysplasia, ureteropelvic obstruction, and vesicoureteric reflux. Renal function ranges from normal to severe reduction in glomerular filtration rate [17]. The ear abnormalities range from preauricular pits, malformations in the external, middle, and inner ear; and hearing loss [7, 17].

2.1.1.3 ClC-K in renal salt loss and deafness (Bartter syndrome type IV)

ClC-Kb/barttin (see **Figure 1**) is mainly expressed in basolateral membranes of the thick ascending limb of Henle's loop, where it is involved in the reabsorption of salt and, consequently, water [18]. In this part of the nephron, the Na + electrochemical gradient (created by basolateral Na+/K+ pump) drives the secondary active transport of NKCC2 (present in the apical membrane), accumulating Na+, Cl−, and K+ into the cell. K+ is extruded back to the lumen through ROMK K+ channels (also present in the apical membrane), whereas Na + and Cl − are reabsorbed by the interstitial fluid through the Na+/K+ pump and ClC-Kb channels, respectively. Thus, the end product of this system is the reabsorption of NaCl into the blood stream (**Figure 1A**). In the inner ear, both ClC-K isomers are expressed in the basolateral membrane of marginal cells of the stria vascularis. This multilayered epithelium is responsible for both the high concentration of K+ and the positive potential (about 100 mV higher than normal extracellular fluids) of the endolymph of the scala media, both of which are important properties for hearing. In marginal cells—the more apical layer in the stria vascularis—Na+/K+ pumps and NKCC1 transporters build up K+ and Cl − inside the cells. ClC-K/barttin channels recycle Cl − back to the interstitial fluid, while apical KCNQ1/KCNE1 K+ channels secrete the excess of potassium ions into the endolymph (**Figure 1B**) [19]. In agreement with the transport models involving ClCK/barttin channels, mutations in the gene encoding ClC-Kb cause salt-losing Bartter syndrome type III [20], characterized by hypokalemia, metabolic alkalosis and secondary hyperaldosteronism with normal or low blood pressure [21]. Mutations in the gene encoding barttin cause Bartter syndrome type IV that combines the salt wasting with congenital deafness, since both ClC-K proteins are non-functional in the absence of barttin [22]. When disruption occurs in only one of the ClC-K channels, as it does in ClCKb mutations in Bartter type III, hearing is preserved; the other isomer channel still provides the necessary Cl − recycling. Deafness occurs only on disruption of both ClC-K channels or upon disruption of barttin [22, 23].

2.2 Medication toxic effect

Over 450 medicines are reported to be ototoxic [24]. These include both prescription medicines such as antibiotics, cancer medications, anti-malarias, and diuretics; and over-the counter medicines such as Non-Steroidal Anti-Inflammatory drugs (Pain killers). In most cases, this type of ototoxicity is an acute, short-lived side effect; if the patient stops taking the medication, the symptoms typically recede [24]. This is not the case, however, for aminoglycoside antibiotics and platinum derivatives used as cancer drugs which may be associated with permanent hearing loss [25]. The mechanism of drug-induced ototoxicity is varied.

2.2.1 Aminoglycoside antibiotics and high-ceiling diuretics

For the patient with CKD, the medications of importance in causing ototoxicity are the aminoglycoside antibiotics, used commonly in treating urinary tract infections and septicaemia which are quite frequent in such patients and also

furosemide; a high-ceiling diuretic commonly used in treating fluid overload and pulmonary oedema in CKD patients. Though the ototoxic effect of aminoglycoside is known among many medical practitioners, the lack of diagnostic facilities in many centers across the world lead to the neglect of full assessment for this potential side effect. Lack of treatment interventions for hearing loss in many regions take away the interest in evaluation for this side effect.

The ototoxicity of furosemide is often overlooked by physicians and nurses. Furosemide toxicity commonly occurs when the medicine is administered as intravenous push medication and in a faster fashion.

2.3 Hearing loss among hemodialysis patients

Chronic kidney disease patients in End stage who are on hemodialysis are another cohort of CKD patient who suffer from hearing loss.

Several reports indicate that sensorineural hearing loss (SNHL) is considerably more prevalent in patients with chronic renal failure (CRF) than in the general population. It ranges from 28% to 77% [26, 27].

Although all frequencies can be affected by CRF, hearing impairment at high frequencies is most common [28]. In addition to antigenic similarity [29], the cochlea and kidney have similar physiological mechanisms, namely, the active transport of fluid and electrolytes achieved by the stria vascularis in the cochlea and the glomeruli in the kidney [3].

It was previously confirmed that the cochlea is affected by the systemic metabolic, hydroelectrolytic, and hormonal alterations that are associated with CRF [30].

Several variables may contribute to the etiopathogenetic mechanisms of hearing loss in CRF including factors related to the severity and duration of the disease, electrolyte disturbances, ototoxic drugs, age, comorbid conditions such as diabetes mellitus and hypertension, and hemodialysis [31–33].

In an Iraqi study by Haider K et al. to determine the effect of hemodialysis on the hearing threshold in patients with chronic renal failure (CRF), 59 patients were followed up for 1 year with a pure-tone audiometric examination every 6 months [34]. At the beginning of the study, 39 patients (66.1%) had sensorineural hearing loss (SNHL). During the 12-month follow-up, 6 more patients developed SNHL giving a point prevalence rate of 76.3% at the end of the study. The hearing loss was more evident in the higher frequencies. Of the studied patients, 64.4% showed deterioration of the hearing threshold. The mean hearing threshold at the beginning of the study was 29.2 ± 21.1 dB versus 36.9 ± 17.3 dB at the end of the study ($P < 0.001$). No significant relation was found between age, sex, serum electrolytes, blood urea, and duration of CRF and hearing loss. Multivariate analysis showed that the duration of hemodialysis was the only significant independent predictor of SNHL [34].

3. Preventive healthcare strategies of sensorineural hearing loss

Because of the global burden of patients receiving chronic hemodialysis therapy, coupled with the high prevalence of hearing loss among this cohort which are often overlooked [26, 27], it is proper to highlight on the need to create awareness on preventive measures of hearing loss. Also, worldwide, 120 million people are estimated to be suffering from disabling hearing loss (>40 dB, average 0.5–4 KHz) [35]. Primary preventive measures should include genetic counseling targeted at families known to carry diseased genes. In the prenatal period, efforts should be made to address maternal problems like premature deliveries, and low birth weight through

improved antenatal care services. Perinatal/neonatal asphyxias, neonatal jaundices which requires exchange transfusions, neonatal meningitis etc. should be keenly addressed. There should be intensification of immunization programmes particularly those against meningitis, measles, mumps and rubella in selected populations.

There should be careful and judicious use of ototoxic drugs such as furosemide and aminoglycoside antibiotics in the clinical settings, avoiding combination of the two groups where possible. There should be education on the risk of self-medications, use of herbal products that may be both ototoxic and nephrotoxic.

Education on overcrowding in the daycare centers, poor housing systems, bottle feeding, malnutrition etc.

There should be better management of acute respiratory infections, noise control and the appropriate use of hearing protection. Education of individuals, communities and governments is an essential prerequisite to implementation [35].

Neonatal/early childhood hearing screening should be instituted for early identification, diagnosis, treatment and rehabilitation of high-risk patients.

There should be early identification and management of comorbidities like hypertension and diabetes in the adult population.

Among the dialysis population, awareness must be created and screening programmes instituted where possible.

Above all, rehabilitation programmes for affected individuals should be implemented to improve the quality of life of such individuals through the use of hearing aid and implants.

4. Conclusions

Hearing loss is not uncommonly associated with chronic kidney disease yet this co-morbidity is often overlooked by Health Care givers. The aetiopathogenesis of hearing loss in CKD patients are multifactorial; from genetic mutations that affect both the kidney and the inner ear due to similarities in structural proteins, through ototoxic medications commonly used in CKD patients, to the toxic effect of uraemia. It is hoped that this neglected aspect of care for patients with chronic kidney disease will receive the needed attention for holistic care of the CKD patient.

Conflict of interest

The authors declare no conflict of interest.

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