Oto-renal syndromes: disorders of shared developmental gene polymorphisms and overlapping physiology

MO Hassan[1], AO Ogundapo[2] and AO Lasisi[3]
Departments of Medicine[1], Family Medicine[2] and OtoRhinoLaryngology[3], Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Osun State, Nigeria

Abstract

Background: – Although, it has been documented that infants with ear malformations are among the highest-risk cohorts for renal malformations of any studied population with congenital birth defects, however report from meta-analyses have showed an insignificant relationship between minor ear malformations and kidney anomalies. In order to explain the intractable link between kidney and ear syndromes, we discussed the molecular regulation of development of both organs. In addition, the role of shared developmental control gene polymorphisms and dysfunction of shared transport or structural proteins in the ear-kidney syndrome were reviewed.

Methodology and review criteria: – A narrative review of ear and kidney syndrome. Pubmed Medline and Online Library search was conducted for literature/studies in English from their conception until September 2016 (without any date restrictions) using the relevant search words.

Results: – An overview on the development of ear and kidney and their molecular regulation, indicated that ear and kidney develop from primordial cells that arise at different time and grow at dissimilar rate, and the development of both organs is synergistically regulated by PAX-SIX-EYA regulatory cascade.

*Conclusion:*The molecular regulation of development of the ear and the kidney and the presence of some shared developmental control gene polymorphisms and structural/transport proteins are documented in this review. A careful clinical analysis of these pathologies will facilitate better understanding and diagnosis of ear-kidney syndromes in affected patients. Furthermore, there is need for continued research especially among the Nigerian population as part of the global data.

Keywords: *Ear-kidney syndromes, Hearing impairment, Renal dysplasia, Genetic disorders, Nephrotoxicity and Ototoxicity*

Correspondence: Dr. Muzamil O. Hassan, Department of Medicine, Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Osun State. Nigeria. Email muzlamide@yahoo.com

Résumé

Contexte: - Bien qu'il ait été documenté que les nourrissons présentant des malformations auriculaires sont parmi les cohortes les plus à risque pour les malformations rénales de toute population étudiée présentant des anomalies congénitales, cependant les méta-analyses ont montré une relation insignifiante entre les malformations mineures de l'oreille et les anomalies durein. Afin d'expliquer le lien insoluble entre les syndromes du rein et de l'oreille, nous avons discuté de la régulation moléculaire du développement des deux organes. En outre, on a passé en revue un certain nombre de polymorphismes du gène de contrôle du développement et du dysfonctionnement du transport partagé ou des protéines structurales dans le syndrome de l'oreille et du rein.

Méthodologie et critères d'examen: - Examen narratif du syndrome de l'oreille et du rein. PubMed, Medline et la recherche en ligne de bibliothèque a été menée pour la littérature / les études en anglais de leur conception jusqu'à septembre 2016 (sans aucune restriction de date) en utilisant les mots recherchés pertinents.

Résultats: - Fournir une vue d'ensemble sur le développement des oreilles et des reins et leur régulation moléculaire, indiquant que l'oreille et le rein se développent à partir de cellules primordiales qui apparaissent à différents moments et croissent à des taux différents, et le développement des deux organes est de manière synergique régulé par PAX-SIX-EYA cascade réglementaire.

Conclusion: - La régulation moléculaire du développement de l'oreille et du rein et la présence de certains polymorphismes du gène du développement partagés et des protéines structurelles / de transport sont documentées dans cette revue. Une analyse clinique minutieuse de ces pathologies facilitera une meilleure compréhension et un meilleur diagnostic des syndromes auriculo-rénal chez les patients atteints. En outre, il est nécessaire de poursuivre les recherches, en particulier auprès de la population nigériane, dans le cadre des données mondiales.

Mots-clés: *Syndromes auriculo-rénal, Troubles auditifs, Dysplasie rénale, Troubles génétiques, Néphrotoxicité et Ototoxicité.*

Introduction

Edith Louise Potter first described an association between kidney and ear abnormalities in 1946 when she reported occurrence of wrinkled and flattened ears in 20 infants dying in perinatal period with bilateral renal agenesis [1]. Isolated minor ear malformations, with intact inner ear structure and function, occur with a frequency of 5-10/1000 live births [2,4] while the incidence of structural renal anomalies among paediatric population is reported to be 1-3/100 live births [5]. Reports from various studies have documented evidence of significant association between renal and ear abnormalities [6,8]. In studies of children with isolated pre-auricular tags who had renal ultrasonography done, 3-8% of the cohorts were documented to have various urinary tract abnormalities, including renal agenesis, hypoplasia, horse-shoe kidney and hydronephrosis [6,7]. Data from a previous study which analysed 32,589 consecutive fetuses over 10 years reported renal anomalies in 1.2% of the fetuses [8]. The study further suggested a strong association between external ear deformities and renal malformations, even after excluding patients with syndromic diagnoses.

Of greater interest is the value of chronic kidney disease (CKD) staging in predicting cochlear dysfunction among patients with progressive chronic renal failure. Govender *et al.* [9] investigated cochlear function in a spectrum of CKD patients using pure tone audiometric testing and Distortion Product Oto-acoustic Emissions (DPOAEs). Patients in CKD stages 1 and 2 presented with normal cochlear functioning defined by normal pure-tone thresholds and DPOAEs, while early cochlear dysfunction was identified by DPOAE testing in patients with advanced CKD, particularly patient with CKD stage 5.This was also shown in an earlier study in Nigeria by Lasisi *et al.* [10] who investigated pre- and post-haemodialysis hearing function in patients initiating maintenance haemodialysis. They found that hearing threshold was significantly reduced in patients with end stage renal disease (ESRD) following three sessions of haemodialysis. In combination with the profound fluid and electrolytes derangements seen in CKD patients, comorbidities such as high blood pressure [11] and ototoxic drugs including frusemide [9,12] play a role in the development of auditory dysfunction, which is very common in advanced CKD [13,14] .

Even though previous studies have postulated that infants with auricular pits or cup ears are among the highest-risk cohorts for renal malformations of any studied population with congenital birth defects, report from meta-analyses however showed a weak correlation between minor ear malformations and kidney anomalies [15].This is not surprising because kidneys and ears are formed from separate primordial cell lineages at different times, and grow at different rates. Metanephric mesenchyme and ureteric bud are derived from intermediate mesenchyme while external ear structures are derived from first branchial pouch, a derivative of surface ectoderm. Therefore, the intractable link between ear and kidney abnormalities could not be explained just by an isolated embryonic insult that may simultaneously affect both developing organs during morphogenesis. However, it is increasingly being recognized that various syndromes evidently link structural renal abnormalities to hearing impairment [16,17]. Moreover, molecular as well as the genetic basis for many of these syndromes have so far been elucidated, thus, providing an insight into the overlap between the renal and inner ear physiology. The objective of this review is to further explore the link between kidney and ear by systematically grouping human ear-kidney syndromes into two distinct pathologic mechanisms including; disorders of shared developmental control gene polymorphisms, and disorders involving dysfunction of shared transport or structural proteins. This review will also provide an overview of ear and kidney syndromes, while highlighting their molecular mechanisms and gene expression.

Materials and methods

This is a narrative review of ear and kidney syndrome. Pubmed Medline and Online Library search was conducted for literature/studies in English from their conception until September 2016 (without any date restrictions) using the following search words: ear-kidney syndromes, Oto-renal syndromes, hearing impairment, renal dysplasia, inheritable hearing disorders, nephrotoxicity, ototoxicity, Branchio-Oto-Renal syndrome, Townes-Brocks syndrome, Kallmann syndrome, Hypoparathyroidism, Deafness and Renal Dysplasia, HDR syndrome, Bartter syndrome, Distal Renal Tubular Acidosis with Deafness, dRTA, Alport syndrome.

Ear and kidney development: focus on molecular regulation

Embryology of ear

During human development, ear develops into three different structural parts; the inner ear, the middle

ear and the outer ear. The inner ear is formed by the third week of embryonic life.Otic placode develops on each side of the posterior aspect of the brain and subsequently grows to form otic vesicles. The saccule, cochlear duct and ductus reuniens are derived from the ventral part of each vesicle while the utricle, endolymphatic duct and semicircular canals are derivatives of the dorsal component. Approximately during the 6th week of embryonic life, saccule, a group of sensory cells that form epithelium of the inner ear, give rise to a tubular outgrowth representing primitive cochlear duct at its lower border and subsequently connect to cochlear duct through the ductus reuniens. The cochlear duct penetrate the surrounding mesenchyme up till the 8th week of embryonic life, following which, the cochlear duct's mesenchyme differentiate into a cartilage within which vacuolization later occur, leading to the formation of three cavities namely; the scala vestibule, the scala tympani and the scala media. Perilymphatic spaces (comprising both the scala vestibule and scala tympani) contain perilymph while the scala media contains endolymph. The cochlear duct, separated from scala vestibule by vestibular membrane (Reissners membrane) and from scala tympani by basilar membrane, is attached to the cartilage laterally by the spiral ligament. During the 6th week,statoacoustic ganglion is formed from otic vesicle, and then divides into cochlear and vestibular branch of cranial nerve VII to supply sensory cells in organ of Corti, saccule, utricle and semicircular canals [18].Following the development of otic vesicle, the transcriptional regulator EYA1, expressed in the otic ectoderm triggers a molecular signaling pathway involving SIX1, a transcription factor that regulates the growth and functions of all sensory cells in the inner ear [19]. Moreover, PAX2 is expressed by the cells of otic vesicle, endolymphatic duct and cochlear hair cells while GATA3 is expressed mainly in the otic vesicle [20]. Available evidence showed that EYA1-deficient or SIX1-deficient mice undergo apoptosis of otic epithelium with the growth of the inner ear arrested at the stage of otic vesicle [21,22]. Furthermore, mice with homozygous PAX1 mutation lack endolymphatic duct and cochlear outgrowth [23] while heterozygous GATA3-deficient mice showed progressive loss of cochlear hair cells [20].

The middle ear is derived from the endoderm of first pharyngeal pouch, which gives rise to primitive tympanic cavity [18]. The distal portion of this primitive cavity form tubotympanic recess while the auditory tube develops from the proximal portion of the cavity [18]. The malleus and incus are derived from the first pharyngeal arch while the stapes is derived from the second arch. Even though, auditory ossicles are formed during the first half of the fetal life, they remain embedded in the surrounding ectoderm-derived mesenchymal tissue until 8th month when the tissues surrounding the ossicles undergo apoptosis, leading to the formation of tympanic cavity wall and eventual appearance of mastoid process [24,25].

External auditory meatus is formed from pharyngeal cleft during the 5th week of embryonic life and grows to its full length by the 18thweek [18,24,26]. Under no circumstances, did the pharyngeal cleft extend to its corresponding pouch, and as a result of this, the eardrum is a tridermal structure, originating from three different layers comprising; ectoderm, endoderm and connective tissue. The auricles are formed between 6th and 8th months, originating from the auricular hillocks, the 6 mesenchymal condensations of the first and second pharyngeal arches [18,24,26].

Embryology of the kidney

The permanent kidney originates from the metanephros, one of the three main structures initially derived from intermediate mesoderm [27]. The other two temporary kidney-like structures, the pronephros and the mesonephros, atrophy and disappear except in males where the mesonephric portion gives rise to male reproductive organs [27]. The cells of the intermediate mesoderm produce ODD1, a factor that functions to facilitate the formation of progenitor cells of metanephric blastema which expresses EYA1 and PAX2 in the developing kidney[28]. These regulating factors activate a cascade of transcription factors involving SIX1 and SALL1, leading to expression of Glial cell line-derived neutrophic factor (GDNF) gene, which induces budding of RET-containing nephric duct. The appearance of ureteric duct, an epithelial outgrowth of nephric duct, is positively regulated by PAX2/8, which regulates expression of GATA3(another transcriptional factor) and activation of RET gene which encode for a tyrosine kinase receptor that is localize to the cell surface[29,30]. Accordingly, homozygous mutations involving PAX2, GATA3 or RET gene have been shown to be associated with kidney defects in mice lacking tyrosine kinase receptor [31-33]. Similarly, humans with inactivating PAX2 mutation exhibit signs of renal-coloboma syndrome and renal hypoplasia [34]. The process of nephrogenesis is initiated when the ureteric bud penetrates the metanephric tissue thereby leading to induction of metanephric

mesenchyme and subsequent aggregation of mesenchymal cells around the tip of the ureteric bud, thus, triggering mesenchyme-epithelial transformation and formation of renal vesicles. As a result of the invasion of metanephric mesenchyme by the ureteric bud, there is repetitive branching of the bud leading to the formation of about 15 branch generations, with induction of new nephron by the interactions between corresponding newly formed ureteric branch tip and the adjacent metanephric tissue cap. Hence, the final nephron mass is a function of total number of resultant ureteric bud branches that arise during branching morphogenesis. Successive appearance of two clefts in the renal vesicles leads to the formation of S-shaped tubule, with the proximal cleft invaded by angioblasts and ultimately giving rise to glomeruli. The mature nephron is united to the collecting duct which in turn converges with other ducts in the medulla to form renal papilla. Approximately, by the 22nd and 34th week of gestation, the definitive cortex and medulla of the embryonic kidney are fully formed. In summary, ear and kidney develop from primordial cells that arise at different time and grow at dissimilar rate, and the development of both organs is synergistically regulated by PAX-SIX-EYA regulatory cascade.

Disorders of shared developmental control gene polymorphisms

Branchio-Oto-Renal Syndrome

Branchio-oto-renal Syndrome (BOR) syndrome, first described in 1975, is characterized by mixed conductive or sensorineural deafness, ear malformations, branchial cleft and renal abnormalities including renal hypoplasia, pelvic-ureteric junction obstruction and vesico-ureteral reflux [35].The prevalence was estimated at 1:40,000, with 2% of children with severe deafness affected [36,37].It is a heterogeneous genetic disorder caused by a variety of mutations affecting genes in the EYA/SIX pathway, with clinical expression extremely variable from one family to another, as minor anomalies have been documented in about 20% of BOR families [38]. Ear abnormalities include pre-auricular pits and appendages, atresia or stenosis of the external auditory meatus and auricular deformities, cervical fistulas and cysts as well as ossicular malformation relating to the developmental abnormalities arising from the first and the second brachial arches. Furthermore, the cochlea is underdeveloped; exhibiting fewer turns than normal, and occasionally there may be dilatation of the vestibular duct [17]. Renal hypoplasia is not pathognomonic, and when present only 5-10% of patients with BOR syndrome develop advanced chronic renal failure [16].The renal anomalies are characterized by decreased kidney size and volume with associated increased echogenicity and poor corticomedullary differentiation, and histological evidence of glomerular hyalinization, mesangial proliferation and splitting of glomerular basement membrane. Moreover, available evidence suggests that there are three differentiated phenotypes of BOR syndromes. In the first phenotype, the syndrome is associated with renal anomalies; while the second phenotype lacks renal abnormalities; the third phenotype however present with brachial and renal anomalies with no associated deafness.

In 1992, mutation involving EYA1 gene, the first BOR syndrome gene was identified and localized to the long arm of chromosome 8 [39,40] and subsequently several other mutations had since been reported in humans[41,42]. More than 80 different mutations involving EYA1 gene have been documented, with heterozygous mutation of EYA1 demonstrated in 30% of BOR syndrome patients. EYA1 gene, a homologous Drosophila developmental gene is expressed very early in human embryo around 4-6 weeks. More specifically, it is expressed in mesenchymal cells of the 1st branchial arch, from which the outer and inner ear structures are derived, thus explaining the outer ear deformities and conductive deafness that is observed in BOR syndrome patients. Similarly, EYA1 is also expressed in the otic placode and hair cells of the cochlea, thus implicating EYA1 in the differentiation and/or survival of the inner ear cell populations, thereby elucidating the sensorineural deafness in BOR syndromes [43]. Expression of EYA1 in the condensing mesenchyme of the kidney induces GDNF which is required for ureteric budding and branching, thus consistent with ureteric anomalies and renal hypoplasia in BOR syndrome. Furthermore, co-expression of EYA1 and PAX2 during ear and kidney development highlights the synergistic regulatory role of these two genes in controlling the pathway leading to mesenchymal-induced renal tubule formation. Also, EYA1 triggers a signaling cascade activating the member of SIX transcription family during ear and kidney development. This is in consistent with reports that demonstrated association between BOR syndrome and heterozygous mutations involving both SIX1 and SIX5 transcription factors [44,45].

Townes-Brocks Syndrome

Townes-Brocks syndrome (TBS) also known as renal ear anal radial syndromeis a rare autosomal dominant syndrome was first described in 1972 by Townes and Brocks [46,47]. It is a multisystem disorder with variable clinical manifestation, characterized by renal hypoplasia or dysplasia, sensorineural or conductive deafness associated with dysplastic ossicles and oval windows, external ear malformations (pre-auricular tags or pits, superior helix deformity), anorectal malformations including stenosis, anteriorly placed anus and imperforate anus, and hand deformities such as bifid thumb, preaxial polydactyly or triphalangeal thumb [17]. Diagnosis of TBS is suggested when two or more of these malformations are present in an individual [48].Townes-Brocks syndrome is caused by a mutation of the SALL1 gene, encoding a developmental regulatory factor that seems to play a crucial role in the embryonic development of the ear, limb, liver, brain, kidney as well as excretory system [17,49]. Townes-Brocks syndrome from dominant negative missense mutations of SALL1 has a more severe phenotype than that cause by SALL1 haploinsufficiency [50]. Renal dysplasia is thought to occur in TBS because of inactivating mutation involving the SALL1 gene which is expressed by metanephric mesenchymal tissues capping outgrowths of ureteric bud, thereby resulting in inadequate branching of the ureteric bud that ultimately induce formation of renal tubules [51]. Accordingly, study of murine model of SALL1 deficiency showed that mice lacking SALL1 failed to develop ureteric bud outgrowths and die of renal agenesis in perinatal period. Patients with heterozygous SALL1 gene mutations have been reported to develop renal agenesis that resulted in end stage renal disease, and ultimately requiring renal replacement therapy later in life [52]. Although, the role of SALL1 in developing ear is yet to be fully elucidated, report from available study suggested that patients with TBS exhibit mixed sensorineural and conductive deafness [17], thus suggesting that SALL1 may play a role in determining the fate of the first and second branchial arches as well as the differentiation of the otic vesicle.

Kallmann Syndrome

Kallmann syndrome is a congenital disorder characterized by hypogonadism secondary to deficiency of gonadotrophin-releasing hormone and anosmia caused by underdevelopment of olfactory bulb and/or tract. Three forms of Kallmann syndrome have been recognized based on mode of inheritance: an X-linked form resulting from mutation of Kal1 gene, encoding anosmin-1[53]; an autosomal dominant form arising from mutation of Kal2 gene, encoding FGFR1 protein [54]; and autosomal recessive forms, which is associated with mutations of the genes encoding prokineticin2 and its receptor [54]. Anosmin-1, the protein encoded by Kal1 gene, is produced in the developing ear and kidney by the basal lamina cells of the outer hair cells of the cochlear and ureteric bud. Approximately a third of patients with X-linked Kallmann syndrome present with unilateral renal aplasia with associated bilateral sensorineural hearing loss but occasionally, they may also present with conductive deafness [55]. In addition, the absence of vas deferens (a derivative of mesonephric duct, which give rise to ureteric bud and expresses anosmin-1) on the same side to the missing kidney in a minority of patients, further suggests a role for anosmin-1 in the induction of mesenchymal blastemal by the ureteric branches. However, the variable penetrance of renal agenesis together with a functioning kidney in individuals with Kallmann syndrome [56,57] therefore raised a question regarding direct stimulating role of anosmin-1during branching morphogenesis and induction of nephrogenesis, while suggesting a possible compensating role for other proteins in individual with anosmin-1 deficiency. Available evidence suggest that anosmin-1 and FGFR1 (Kal2 gene product) co-localize and interact in the olfactory bulb during embryonic life, with anosmin-1 positively regulating FGFR1 signaling pathway. Taken together these findings, it was hypothesized that the higher prevalence of Kallmann syndrome in males may be explained by the gender difference in the expression of anosmin-1 [58].

Hypoparathyroidism, Deafness and Renal Dysplasia

Hypoparathyroidism, deafness and renal dysplasia (HDR) syndrome is transmitted as an autosomal dominant disorder involving mutation of GATA3 gene localized to the short arm of chromosome 10 [59]. It is characterized by undetectable parathyroid hormones levels associated with hypocalcemia, variable kidney malformations ranging from isolated vesicoureteral reflux with normal-sized kidney to renal agenesis, and moderate to severe sensorineural deafness [59]. GATA3, a developmental transcription factor is produced early in the parathyroid glands, cochlear hair cells and nephritic duct of the developing embryo. GATA3 seems to be essential for proper migration of nephric duct, with evidence from study of murine model showing failure of

induction of metanephric blastema as a result of abnormal migration of nephric duct [60]. Similarly, mice with heterozygote GATA3 mutation showed evidence of progressive perceptive hearing loss with associated outer hair cells apoptosis compared to mice with normal GATA3 gene, thus suggesting that GATA3 influence cochlear hair cell survival in the developing middle ear [60].

Disorders of shared transport and structural proteins

Bartter syndrome

Bartter syndrome is an inherited disorder of impaired salt transportation in thick ascending limb of Henle (TALH) characterized by hypokalemia, salt wasting, normal blood pressure and failure to thrive [61]. It is inherited as autosomal recessive and two types have been recognized namely; classic type and antenatal type otherwise known as Bartter syndrome with deafness (BSND) [62,63]. The classic type results from loss of function mutations affecting one of the three genes encoding sodium chloride transport proteins in the TALH. The commonest disorder is cause by mutation of the gene NKCC2, encoding sodium-potassium-chloride cotransporter on the apical membrane [64]. The second mutation affects KCNJI, encoding apical outwardly rectifying medullary potassium channel (ROMK) which recycle K^+ back to the tubular lumen in parallel to the function of sodium-potassium-chloride cotransporter [65]. A third mutation has been described in the CLCNKb gene, which encodes ClC-Kb, a voltage-gated chloride channel localized to basolateral membrane of TALH [66]. These three mutations are mild, associated only with classic Bartter syndrome, and are rarely associated with deafness [16]. Bartter syndrome with deafness has been reported in consanguineous families and is cause by mutation in BSND gene. This gene is localized to 1p31 and encodes Barttin which co-localizes with ClC-Kb channels and potassium secreting cells in the inner ear. Moreover, Barttin is co-expressed with both ClC-Ka and ClC-Kb throughout the renal tubules and the inner ear cells including; stria vascularis cells and vestibular apparatus [67-69]. Barttin seems to play a crucial role for the expression and regulation of function of the voltage-gated chloride channels because ClC-Kb is deficient when it is co-expressed with altered Barttin proteins [67]. Therefore, homozygous mutations of the BSND or heterozygous mutations in two chloride channels typically result in salt wasting and congenital sensorineural deafness [70,71].

Distal renal tubular acidosis with deafness

Classic distal renal tubular acidosis (dRTA), also known as type 1 RTA, is a disorder of distal renal tubular dysfunction characterized by the inability of α-intercalated cells to secrete hydrogen ion into the urine, thereby leading to defective urine acidification. Infants with dRTA typically present with inappropriately high urine pH, metabolic acidosis, osteomalacia, nephrocalcinosis and failure to thrive. Distal RTA is a genetically heterogeneous disorder with two patterns of inheritance identified; autosomal dominant form, which is caused by heterozygous mutation for the anion exchanger gene SLC4A1 [72] and autosomal recessive form caused by homozygous mutations of the ATP6N1B, which encodes the B1 subunit of hydrogen ion pump exclusively localized to the apical surface of α-intercalated cells of medullary collecting duct [73]. Moreover, two other autosomal recessive forms of distal renal tubular acidosis have been described in the setting of sensorineural deafness. The two responsible mutant genes encode the B1 (ATP6V1B1) and A4 (ATP6V0A4)subunits of the apical proton pump, which are co-expressed in the endolymphatic sac, cochlea as well as the kidney [74,75]. Therefore, mutations in the genes encoding these subunits of proton pump define two other categories of patients with distal renal tubular acidosis with deafness. These patients typically have inappropriately high urine pH as well as abnormal endolymph pH homeostasis, resulting in impaired auditory function. Individuals with homozygous mutations of B1 subunit gene develop dRTA and deafness at birth, with variable renal penetrance, as majority of these patients do not develop progressive renal failure in adulthood [76,77]. Compared to patients with ATP6V1B1 gene mutations, patients with ATP6V0A4 mutations are more common, have milder disease and become symptomatic later in life and is associated with variable hearing impairment [78].

Alport syndrome

Alport syndrome, a disorder of defective cross-linking of type IV collagen characterized by high frequency sensorineural deafness, ocular defects including anterior lenticonus, retinal flecks and corneal dystrophy, and progressive nephropathy. The incidence of Alport syndrome is 1:5000 and has been reported to cause end stage renal disease in 2% adults [79], usually in the 6th decade of life, although ESRD may occur earlier in young girls [80]. In approximately 85% of families, Alport syndrome is inherited as X-linked disease, which is due to

inactivation mutation of COL4A5 gene located at Xq22 and encoding α5 chain of type IV collagen. Autosomal recessive Alport syndrome involving homozygous or mixed heterozygous mutation of COL4A3 or COL4A4 genes located to chromosome 2 are responsible for the syndrome in about 15% of cases, while autosomal dominant missense mutations may be the cause in a few of kindreds [81]. Type IV collagen, comprising α3, α4, α5 chains is major constituents of basement membranes found in the kidney, ear and the eyes. The main defect in Alport syndrome usually affects the α5 chain of type IV collagen, invariably leading to faulty assembly of α3, α4, α5 collagen network of aural, ocular as well as glomerular basement membranes, thus leading to a collagen disease that usually affect the kidneys and the ears simultaneously. Affected individuals, usually males presented with persistent microscopic haematuria, which start at birth. Proteinuria is uncommon early in life, but progressively worsens with age and may occasionally result in nephrotic syndrome, indicating severe glomerulopathy as a result of damage to the podocytes. The risk of progression to ESRD is higher in affected males with X-linked Alport syndrome compared to females; greater than 90% of males progressed to ESRD by age 40, compared to 12% in females with X-linked Alport syndrome [80]. On light microscopy, histologic changes shows interstitial and tubular foam cells in young children, and as the disease progresses, there is patchy thickening of the glomerular basement membrane. In severe cases, the glomerular basement membrane may split into several layers interspersed by small clear areas, resembling a basket weave arrangement on electron microscopy. The degree of hearing loss varies, but majority may have developed hearing loss requiring hearing aids by 40 years of age.

Kidney and ear disorders caused by therapeutic agents: Gentamycin and Cisplatin

Gentamicin and Cisplatin are frequently associated with nephrotoxicity and ototoxicity in hospitalized patients. Even though the mechanism through which these agents cause injury in the kidney and ear is yet to be fully elucidated, co-localization of specialized transport proteins in the proximal tubular cells of the kidneys and cells of the stria vascularis in the middle ear, which takes up and concentrate drugs in this organs, seems to increase the vulnerability of these organs to drug toxicity [16]. The reported incidence of gentamicin induced kidney dysfunction ranges between 10-20%, characterized by a rise in serum creatinine and proximal tubular dysfunction. The degree of tubular dysfunction varies, as proximal tubulopathy, Fanconi syndrome or Bartter-like syndrome have previously been described in patients with gentamicin-induced nephrotoxicity [82]. As a result of their physicochemical properties, gentamicin binds to apical membrane via transient receptor potential cation channel (TRPV1) and subsequently concentrated by proximal renal tubular cells, cells of medullary striavascularis and cochlear hair cells [83,84]. Once gentamicin undergo endocytosis and build up inside lysosomes, ototoxicity and nephrotoxicity occurs following process involving stimulation of oxidative stress, mitochondrial dysfunction, eventually leading to interruption of functions of subcellular organelles [82]. Risk factors for nephrotoxicity includes, prolonged period of treatment usually greater 10 days, volume contraction, underlying chronic kidney disease, advanced age of patients, severe hypokalemia and co-administration with other nephrotoxins such as radiocontrast agent, cisplatin and amphotericin B. Host factor such as genetic defect may potentiate ototoxicity. The presence of a single nucleotide polymorphism in the mitochondrial DNA (A1555G) has been documented in patients who developed irreversible deafness after a single dose of gentamicin [85,86].

Cisplatin is associated with high incidence of nephrotoxicity and ototoxicity, even following prevention strategies involving volume repletion and maintenance of drugs within therapeutic range [87,88]. Although the mechanism of injury in both the kidney and ear is not very clear, nevertheless, oxidative stress, vascular injury and induction of intracellular injury pathway have been documented to play a role in the patho-mechanisms of the injury that eventually lead to apoptotic cell death [89]. Recently, OCT-2, a transport protein have been shown to contribute to the process of kidney injury [82], it remains to be seen whether OCT-2 is involved in the uptake of cisplatin in the ear.Renal manifestations of cisplatin-induced nephrotoxicity includenonoliguric AKI, Fanconi syndrome resulting from proximal tubulopathy and magnesium wasting caused by injury in the loop of Henle. Cisplatin caused hearing loss probably through induction of apoptotic process in cells of stria vascularis as well as cochlear hair cells [90].

Conclusion

The molecular regulation of development of the ear and the kidney and the presence of some shared developmental control gene polymorphisms and structural proteins are documented. The syndromes

discussed above are aimed to exemplify the overlapping physiology between ear and kidney. In addition, potential pathologies underlying human ear-kidney syndromes were grouped into two distinct groups; [1] disorders of shared developmental control gene polymorphisms; and [2] disorders of shared transport and structural proteins, including kidney and ear disorders that are caused by therapeutic agents. A careful clinical assessment of these mechanisms will facilitate better understanding and diagnosis of ear-kidney syndromes in affected patients. Furthermore, there is need for continued research especially among the Nigerian population as part of the global data.

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