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ORIGINAL ARTICLE

Inner ear abnormalities in four patients with dRTA and SNHL: clinical and genetic heterogeneity

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Abstract A significant number of patients affected by autosomal recessive primary distal renal tubular acidosis (dRTA) manifest sensorineural hearing loss (SNHL). Mutations in *ATP6V1B1* are associated with early onset SNHL, whereas *ATP6V0A4* mutations have been described in dRTA and late-onset SNHL. Enlarged vestibular aqueduct (EVA) was described in patients with recessive dRTA and SNHL, and recently, this abnormality has been associated with mutations in the *ATP6V1B1* gene. In our study, we evaluated the presence of inner-ear abnormalities in four patients affected by dRTA and SNHL, characterized by molecular analysis. Two patients affected by severe dRTA with early onset SNHL showed the same mutation in the *ATP6V1B1* gene and bilateral EVA with a different degree of severity. The other two presented similar clinical manifestations of dRTA and different mutations in the *ATP6V0A4* gene: one patient, showing EVA, developed an early SNHL, whereas in the other one, the SNHL appeared in the second decade of life and the vestibular aqueduct was normal. Our study confirms the association of EVA and mutations in the *ATP6V1B1* gene and demonstrates that mutations in the *ATP6V0A4* gene can also be associated with EVA probably only when the SNHL has an early onset. The pathophysiology of SNHL and EVA are still to be defined.

Keywords *ATP6V1B1* gene · *ATP6V0A4* gene · Distal renal tubular acidosis · Enlarged vestibular aqueduct · Sensorineural hearing loss

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Introduction

Primary distal renal tubular acidosis (dRTA) is a rare genetic disease caused by impaired distal excretion of hydrogen ions (H^+). Biochemical diagnostic features of dRTA include hyperchloremic metabolic acidosis, hypokalemia, and hypercalciuria. In infants, prominent clinical features include failure to thrive, polyuria, dehydration, vomiting, and hypotonia, with psychomotor development retardation. Nephrocalcinosis and/or urolithiasis are common complications of hypercalciuria and, when untreated, may lead to chronic renal failure [1]. Both autosomal dominant and autosomal recessive forms of dRTA have been recognized; however, sporadic cases also occur [2]. Autosomal dominant dRTA has been associated with

mutations in the gene encoding the basolateral chloride/bicarbonate ion (Cl^-/HCO_3^-) exchanger (*SLC4A*) [3]. Patients display a milder phenotype compared with those with the autosomal recessive forms and, in still undiagnosed children, rickets is frequently observed [2]. The autosomal recessive dRTA, caused by mutations of H^+-adenosine triphosphatase (ATPase) pump subunits, is characterized by a wide genetic and clinical heterogeneity [4, 5]. A significant number of patients manifest sensorineural hearing loss (SNHL), which may develop from birth to late childhood [1, 2].

The association between the renal defect, with consequent trouble with urinary acidification and blood pH homeostasis, and the hearing loss, reflects the expression of the mutate H^+-ATPase proton pump in the luminal membrane of α-intercalated cells of collecting ducts and in the interdental cells of the cochlea. The normal H^+-ATPase activity seems then to be essential to normal hearing [6]. Most families with recessive dRTA and SNHL show mutations in the *ATP6V1B1* gene encoding the B1-subunit of H^+-ATPase pump [4]. Some families with recessive dRTA and a H^+-ATPase defect do not link to the *ATP6V1B1* gene and may exhibit no sensorineural deafness. These families present mutations in a different gene, the *ATP6V0A4*, which encodes for the a4 subunit of the multimeric H^+-ATPase pump [5]. Although the first descriptions of dRTA due to mutations in the *ATP6V0A4* gene concerned patients without SNHL, further studies demonstrated that mutations in the *ATP6V0A4* gene are associated with both late-onset and early onset SNHL [1, 2, 7, 8].

In different patients suffering from dRTA, the severity and the age of onset of hearing loss is then variable; however, it is progressive and irreversible, even when systemic alkali replacement therapy corrects the biochemical abnormalities [4, 7]. Recently, some authors reported radiological abnormalities in the inner ear of patients affected by dRTA and deafness [9, 10]. However, only in the study of Joshua et al. were several types of mutations in the *ATP6V1B1* gene found to be associated with inner-ear morphological alterations and a typical progressive hearing loss. Patients had EVA, with no other abnormalities being observed on imaging [11].

The aim of our study was to examine the clinical variability in four other patients showing the association of dRTA and SNHL in who we verified the presence of inner-ear abnormalities and mutations in both *ATP6V1B1* and *ATP6V0A4* genes.

Patients, materials, and methods

Four patients affected by clinically recognized dRTA were included in the study. Age at diagnosis and clinical and biochemical parameters are indicated in Table 1. Audiological data and cerebral magnetic resonance imaging (MRI) of all patients were collected (Table 2).

For molecular analysis, peripheral blood samples were obtained and genomic DNA was extracted by standard methods. Individual *ATP6V1B1* and *ATP6V0A4* coding regions, intron−exon boundaries, and flanking intronic sequences were analyzed by direct sequencing using the BigDye® Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) in association with an ABI Prism 3130xl Genetic Analyzer (Applied Biosystems). Primer sequences used for the *ATP6V1B1* gene were as described by Karet et al. [4]; *ATP6V0A4* primers were designed on the basis of the published gene sequence and are available upon request. The reference sequences used for mutation reporting are the following: NM_001692.3 for *ATP6V1B1* gene and NM_020632.2 for *ATP6V0A4* gene.

Informed consent for genetic investigations was obtained from all families who participated to the study.

Table 1 Clinical and biochemical features at diagnosis of the four patients with distal renal tubular acidosis (RTA) and sensorineural hearing loss (SNHL)

Patients, gender	Age at diagnosis	Weight (g)	Clinical manifestations	U pH	UCa/Cr	NC or UL	Blood venous pH	S HCO_3 mmol/L	S K mmol/L	S Cl mmol/L	S Na mmol/L
Case 1 M	3 months	3,350	Failure to thrive, vomiting	7	1.2	Yes	7.15	10	3.2	115	137
Case 2 F	22 months	8,400	Progressive impairment of growth, hypotonia, vomiting	6.8	0.8	Yes	7.20	13	3.3	112	134
Case 3 M	1 month	3,280	Failure to thrive and respiratory distress	7.2	1	Yes (mild)	6.99	1.5	3.5	130	141
Case 4 M	1 month	3,560	Severe failure to thrive, vomiting, hypotonia	6.8	1.1	Yes	7.10	7	3.8	113	135

NC nephrocalcinosis, *UL* urolithiasis, *S* serum, *UpH* urinary pH, *UCa/Cr* urinary calcium/creatinine ratio mg/mg, HCO_3, bicarbonate, *K* potassium, *Cl* chloride, *Na* sodium

Table 2 Sensorineural hearing loss (SNHL), enlarged vestibular aqueduct (EVA) and mutations in the *ATP6V1B1*and *ATP6V0A4* genes

Patients, gender	SNHL	EVA	*ATP6V1B1* gene mutation	*ATP6V0A4* gene mutation
Case 1 M	Early	Mild (MRI at 2 years)	c.[242T>C]+[242T>C] (p.Leu81Pro)	
Case 2 F	Early	Evident (MRI at 22 months)	c.[242T>C]+[242T>C] (p.Leu81Pro)	
Case 3 M	Late (at 17 years)	Absent (MRI at 24 months)		c.[1185delC]+[2420G>A] (deletion c.1185del C and missense mutation p.Arg807Gln)
Case 4 M	Early	Evident (MRI at 3 years)		c.[2420G>A]+[2420G>A] (p.Arg807Gln)

MRI magnetic resonance imaging

Case reports

Case 1: This boy was the first child of Albanian non-consanguineous, healthy parents and was born by normal delivery at the 38th week of an uneventful pregnancy. His birth weight was 3,350 g (>50° centile), length 50 cm (50° centile), head circumference 35 cm (>50° centile), Apgar index 9 at 1 min and 10 at 5 min. At the age of 3 months, he was referred to a pediatric unit because of failure to thrive. Laboratory data showed severe hyperchloremic metabolic acidosis with normal renal function (Table 1). Renal ultrasound (US) examination showed

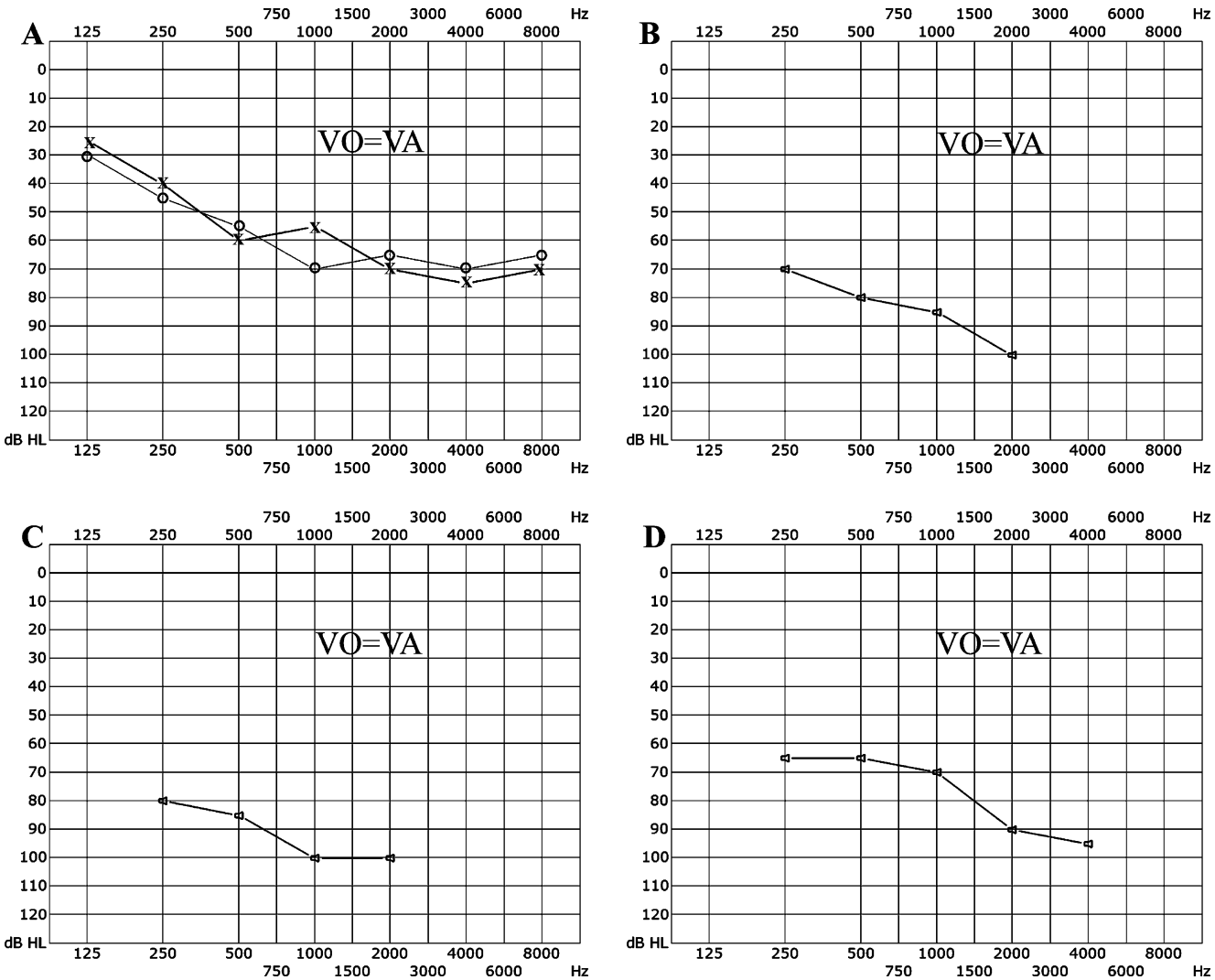

Fig. 1 Audiograms of the four patients: **a** case 1; **b** case 2; **c** case 3; **d** case 4

medullary nephrocalcinosis. The clinical diagnosis of dRTA was performed and the infant was treated with alkali. Molecular analysis of the *ATP6V1B1* gene revealed the presence of a homozygous mutation c.[242T>C]+[242T>C] (p.Leu81Pro) (Table 2). Both variants were inherited, one from each parent. At the age of 8 months, audiometric evaluation showed bilateral profound deafness (Fig. 1a) confirmed by auditory brainstem response (ABR) test, and a hearing aid was prescribed. The cerebral magnetic resonance imaging (MRI) scan performed at the age of 2 years showed mild enlargement of the vestibular duct and the endolymphatic sac (Fig. 2a).

Case 2: This patient was the sole child of Albanian nonconsanguineous healthy parents and was born by normal delivery at the 38th week of an uneventful pregnancy. From the age of 6 months, she showed a progressive impairment of growth, and at the age of 22 months, her body weight was 8.4 kg (< 3°centile) and length was 75 cm (< 3° centile). Laboratory investigations showed severe hyperchloremic metabolic acidosis (Table 1) and the diagnosis of dRTA was given. Molecular investigation showed the same homozygous mutation c.[242T>C]+[242T>C] of the *ATP6V1B1* gene described in case 1 (Table 2). Audiological and ABR tests demonstrated bilateral profound hearing loss, and a hearing aid was applied (Fig. 1b). The cerebral MRI scan showed enlargement of the vestibular duct and the endolymphatic sac (Fig. 2b). Alkali treatment normalized blood pH and ameliorated growth, and at the age of 5 years, she weighed 18.2 kg (50° centile) and was 106.3 cm tall (50° centile).

Case 3: This boy, the first child of Italian nonconsanguineous healthy parents, was referred at the age of 1 month to a pediatric unit because of failure to thrive and respiratory distress. Blood tests showed severe metabolic acidosis and hyperchloremia (Table 1), so the diagnosis of dRTA was confirmed and alkali treatment begun with normalization of parameters and improvement of growth. Audiometry performed at the age of 4 years showed bilateral normal hearing. During follow-up, a further audiological evaluation at the age of 17 years demonstrated moderate bilateral deafness requiring a hearing aid (Fig. 1c). His final height was 176.5 cm and his weight 73 kg. Despite mild nephrocalcinosis, he manifests secondary nephrogenic insipidus diabetes with polyuria (7.5 l/day); however, renal function was normal [creatinine 1.1 mg/dl; blood urea nitrogen (BUN) 15 mg/dl]. Molecular investigation of the *ATP6V0A4* gene coding region revealed the presence of two distinct mutations, the missense substitution c.2420G>A (p.Arg807Gln) and the deletion c.1185delC (Table 2). These are located in two different *ATP6V0A4* alleles, as the parents are heterozygous for a single DNA change. The cerebral MRI scan, performed at the age of 24 years, showed regular size of the vestibular duct and the endolymphatic sac (Fig. 2c).

Case 4: This patient was the second child of Italian nonconsanguineous healthy parents and was born by normal delivery at the 41st week of an uneventful pregnancy. His birth weight was 3,560 g (>50° centile), length 50 cm (50° centile), head circumference 35 cm (50° centile), Apgar index 9 at 1 min and 10 at 5 min. At the age of 30 days, he was referred to the neotatal intensive care unit (NICU) because of severe failure to thrive and vomiting. On admission, the baby weighed 2,850 g, arterial pressure was

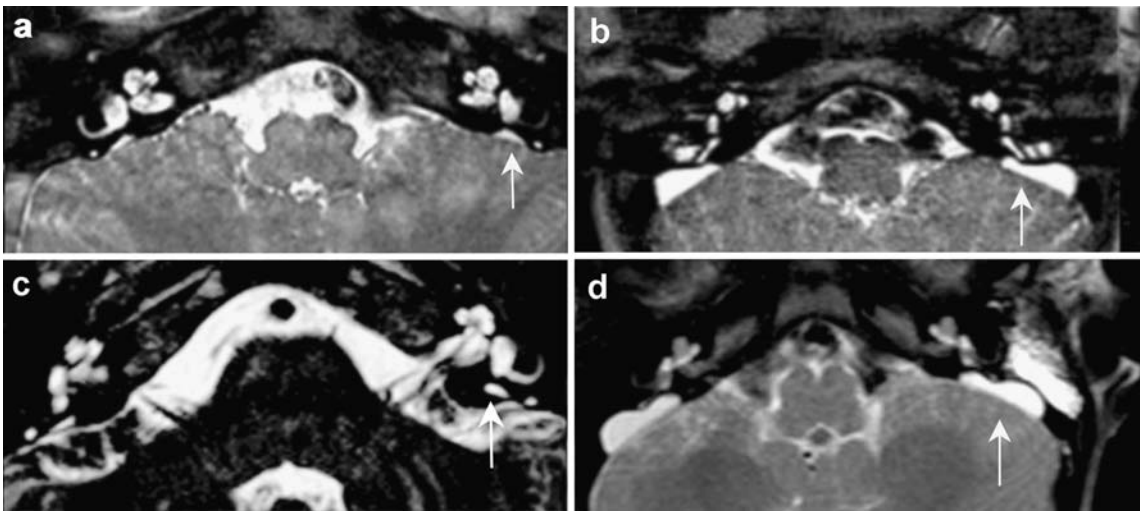

Fig. 2 Transverse T2 VISTA magnetic resonance imaging (MRI) (3D, TR 2,000 ms, TE 253 ms, voxel size 0.6 mm, matrix 512, overcontinous slice) of the inner ear of the four cases described. **a** Case 1: cerebral MRI performed at the age of 2 years showing mild enlargement (5.2×1.2 mm) of the vestibular aqueduct (*white arrow*). **b** Case 2: cerebral MRI performed at the age of 22 months showing evident enlargement (14×6 mm) of the vestibular aqueduct (*white arrow*) **c**. Case 3: cerebral MRI performed at the age of 24 years showing regular size (4.6×1 mm) of the vestibular duct (*white arrow*) **d**. Case 4: cerebral MRI performed at the age of 3 years showing evident enlargement (17.6×6.3 mm) of the vestibular aqueduct (*white arrow*)

76/51, and generalized hypotonia and clinical signs of volume depletion were detected. Laboratory data showed severe hyperchloremic metabolic acidosis (Table 1). Renal ultrasound examination showed marked echogenicity of the medullary pyramids with nephrocalcinosis. The clinical diagnosis of dRTA was confirmed, and molecular analysis of the *ATP6V0A4* gene showed the homozygous mutation c.[2420G>A]+[2420G>A] (p.Arg807Gln), inherited from each heterozygous parent (Table 2). The infant was treated with 5 mmol/kg per day of alkali in five divided doses. At the age of 8 months, audiometric and ABR evaluation showed profound bilateral deafness (Fig. 1d), and a hearing aid was prescribed. The cerebral MRI scan performed at the age of 3 years showed enlargement of the vestibular duct and the endolymphatic sac (Fig. 2d). Growth was normal, and when the boy was 3 years old, his body weight was 13 kg (25° centile) and height was 94 cm (50° centile).

Discussion

The association of dRTA and SNHL has been well known since 1967 [12]. Karet et al. demonstrated for the first time, after genome-wide linkage screening, the relationship between mutations of the *ATP6V1B1* gene, dRTA, and SNHL [4]. This gene is expressed in the renal collecting duct α-intercalated cells and endolymphatic sac epithelial cells. Furthermore, Stover et al. provided evidence that mutations of the *ATP6V0A4* gene were associated with hearing loss, demonstrating its expression not only in the kidney but also inside the cochlea [7]. *ATP6V1B1* and *ATP6V0A4* genes encode, respectively, the B1 and a4 subunits of vacuolar H^+-ATPases pump, which, through a large multisubunit complex, hydrolyses ATP to pump protons across biological membranes [13]. The function of H^+-ATPase in the kidney is to acidify the urine and to stabilize blood pH. In the inner ear, this pump helps regulate ion composition and pH of the endolymph [6]. The endolymph has a high concentration of K^+ and a high positive potential, termed endocochlear potential, which are both critical during activation of hair cells in order to transform the mechanical stimuli produced by sounds into electrical signals transmitted to the brain [14, 15]. Regulation of the composition and homeostasis of the endolymph requires normal function of transporters/channels of the epithelial cells lining the various compartments of the inner ear. Because the inner ear and renal tubules share several common transporters/channels, in case of abnormalities of one of them, hearing disturbances may be associated with renal tubular disorders, and, beside dRTA, SNHL is also observed in patients affected by Bartter syndrome due to barttin or Ka and Kb subunits defects, and by Pendred syndrome [6].

The various fluid compartments of the normal inner ear are characterized by different pH values: in the cochlear endolymph, pH is maintained at 7.4, whereas in the endolymphatic sac, it is between 6.7 and 7.1 [6, 16]. This variability is apparently a prerequisite for adequate hearing, and the pH of the cochlear fluids is in turn fundamental to regulate the activity of ion channels, transporters, and metabolic enzymes. The effects of pH might therefore be indirect, because acidification of the endolymph inhibits Ca^{++} reabsorption via pH-sensitive calcium-selective channels TRPV5 and TRPV6 and elevates the endolymphatic Ca^{++} concentration, with impairment of cochlear function [16, 17]. On the other hand, a possible explication for the development of deafness in dRTA is that the H^+-ATPase pump functional defect might cause alteration of both extracellular and intracellular pH. This could influence the mechanisms that regulate the endolymphatic potential and the K^+ concentration, which involve several K^+ transporters such as K^+ channels Kcnq1/Kcne1, Na^+-$2Cl^-$ -K^+ cotransporter, and Na^+ - K^+ - ATPase subunits ATP1A1 and ATP1B1 [14, 16, 18, 19]. A unifying hypothesis to understand the pathophysiological mechanisms causing hearing loss in different metabolic diseases is prompted by recent studies showing that, with the cochlear cells having a high metabolism, the reduction or breakdown in the function of antioxidant enzymatic systems increase reactive oxygen species (ROS) production, which are negative regulators of gap-junction channels (GJCh) [15, 20, 21].

Whereas acidification of pH and its metabolic negative effects appears to be the main mechanism for hearing loss in patients with Pendred syndrome, no scientific information is available on the composition and pH of endolymph in patients with dRTA and SNHL. Gil et al. reported two siblings who have the same *ATP6V1B1* gene homozygous splicing mutation (IVS6+1G>A), but whereas the older sister was severely deaf, her brother, diagnosed and treated early with bicarbonate supplementation, has normal hearing. The authors hypothesize that prompt alkali therapy might avoid the development of deafness [22]. As a matter of fact, whereas the perilymph of the scala vestibuli originates from the capillary network in the inner ear, the perilymph of the scala timpani, precursor of the endolymph, originates primarily from the cerebrospinal fluid [6]. Therefore, the composition and pH of the endolymphatic fluids are maintained by specialized epithelial cells of compartments separate from systemic circulation. So, it is presumably impossible that alkali treatment, which ameliorates systemic pH, could influence the pH of the cochlear endolymph and/or impede other negative metabolic consequences. Besides ion composition and pH homeostasis, some ion channels of the inner ear appear useful for maintaining fluid volume stability also, and other authors

have described some conditions characterized by a variation of fluid content with repercussions on hearing [6, 14, 23, 24].

The enlarged vestibular aqueduct (EVA) syndrome indicates an anomaly of the structures of the inner ear, which might manifest with normal hearing, congenital total deafness, progressive SNHL, fluctuating SNHL, or sudden SNHL. The definition of EVA varies among the authors, but it encompasses an anteroposterior diameter from 1.5 mm to 2 mm [25]. The origin of EVA in humans is commonly believed to be the result of an overaccumulation of endolymph produced in the labyrinth or in a failure of the endolymphatic sac to absorb the excess volume [26]. The mechanisms involved in detection and correction of volume status in the inner ear remain to be demonstrated, although regulation of secretory and reabsorptive activity across the epithelial cells enclosing the scala media of the inner ear appears to be essential to maintain a constant endocochlear fluid volume [23]. Failure to maintain fluid balance will result in an enlargement of the endolymphatic compartment, as seen in some genetic syndromes: Pendred, Brachio-Oto-Renal, Waarednburg's syndromes, and X-linked congenital mixed deafness or in the collapse of the scala media observed in Jervell and Lange-Nielsen syndrome [6, 14, 24].

In 2002, Berrettini et al. described the association of dRTA, SNHL, and EVA in two patients [9]. Another dRTA patient suffering from progressive SNHL and vertigo and showing the same aspect of EVA has been reported by Shinjo et al. [10]. In both studies, no molecular analysis were performed. Recently, Joshua et al. described five patients affected by dRTA and SNHL, four of whom showed mutations of the *ATP6V1B1* gene. Imaging studies of temporal bones showed bilateral EVA [11]. According to the theory of Pyle, Berrettini et al. suggested that also in EVA associated with dRTA, a hydroelectrolytic imbalance provokes aberrant growth of the vestibular aqueduct during fetal life and in the first 3 or 4 years of postnatal life [9, 27].

We looked for EVA in our patients affected by dRTA and SNHL and documented a large vestibular aqueduct in three of four patients, although of different entity. Both the Albanian patients had the same mutation on the B1 subunit of the H^+-ATPase pump and, in accordance with literature data, these children manifested early and profound SNHL. However, whereas case 2 manifested an evident EVA, case 1, at the same age, showed only a mild EVA, demonstrating that SNHL and EVA are not always strictly related, in contradiction with the hypothesis of Berrettini et al. [9].

Both the Italian patients showed different mutations on a4 subunit of the H^+-ATPase pump, with phenotypic differences. In case 4, profound SNHL developed unusually early with EVA. In case 3, moderate but progressive SNHL developed during the second decade of life, as usually reported, although the clinical symptoms of dRTA were severe and manifested during the first weeks of life; furthermore, no EVA has been demonstrated.

Stover et al. supposed that the lack of a severe auditory phenotype in patients with *ATP6V0A4* mutations could be explained by the fact that the ubiquitous a1 isoform encoded by *ATP6V0A1* could compensate for a4 function in the inner ear [7]. This mechanism should probably be excluded, as the c.[2420G>A]+[2420G>A] homozygous mutation observed in our patient and in another one described by Stover et al. is related with severe early onset SNHL [7].

The phenotypical variability of dRTA could be caused by mutations or polymorphic variations in genes functionally involved in the H^+-ATPase pump activity. For example, Blomqvist et al. and Kurth et al. have shown that the *Foxi1* gene activates transcription of two other ion transporter genes, *Slc4a9* encoding AE4 (an HCO_3^-/Cl^- exchanger in the type B intercalated cells of the renal collecting-duct epithelium) and *Atp6v1b1* [28, 29]. Further studies will be needed to clarify the question of why mutations in the same subunits of the proton pump apparently have different effects on the severity of hearing loss and how these variations can contribute to causing EVA.

In conclusion, in our study, we confirmed that EVA may be associated with dRTA due to *ATP6V1B1* gene mutations, although the severity could be of variable degree, and we demonstrated for the first time that EVA can be observed also in patients with *ATP6V0A4* gene mutations, perhaps with a relationship between type of mutation, precocity, and severity of the SNHL and morphological abnormalities of the inner ear. Furthermore it is evident that in the absence of a large vestibular aqueduct, there is no relationship between the severity of dRTA and precocity of SNHL.

More studies are necessary to clarify the facets of physiological mechanisms regulating the inner ear functions and the relationship between dRTA, SNHL, EVA, and gene mutations.

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