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ORIGINAL ARTICLE

Treatment and long-term outcome in primary distal renal tubular acidosis

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ABSTRACT

Background. Primary distal renal tubular acidosis (dRTA) is a rare disorder, and we aimed to gather data on treatment and long-term outcome.

Methods. We contacted paediatric and adult nephrologists through European professional organizations. Responding clinicians entered demographic, biochemical, genetic and clinical data in an online form.

Results. Adequate data were collected on 340 patients (29 countries, female 52%). Mutation testing had been performed on 206 patients (61%); pathogenic mutations were identified in 170 patients (83%). The median (range) presentation age was 0.5 (0–54) years and age at last follow-up was 11.0 (0–70.0) years. Adult height was slightly below average with a mean (SD score) of −0.57 (±1.16). There was an increased prevalence of chronic kidney disease (CKD) Stage ≥2 in children (35%) and adults (82%). Nephrocalcinosis was reported in 88%. Nephrolithiasis was more common with *SLC4A1* mutations (42% versus 21%). Thirty-six percent had hearing loss, particularly in *ATP6V1B1* (88%). The median (interquartile range) prescribed dose of alkali (mEq/kg/day) was 1.9 (1.2–3.3). Adequate metabolic control (normal plasma bicarbonate and normocalciuria) was achieved in 158 patients (51%), more commonly in countries with higher gross domestic product (67% versus 23%), and was associated with higher height and estimated glomerular filtration rate.

Conclusion. Long-term follow-up from this large dRTA cohort shows an overall favourable outcome with normal adult height for most and no patient with CKD Stage 5. However, 82% of adult patients have CKD Stages 2–4. Importance of adequate metabolic control was highlighted by better growth and renal function but was achieved in only half of patients.

Keywords: chronic kidney disease, distal renal tubular acidosis, nephrocalcinosis, nephrolithiasis, sensorineural hearing loss

INTRODUCTION

Primary distal renal tubular acidosis (dRTA) is a rare disorder with an estimated incidence of <1:100 000. Often referred to as type 1 RTA, it is characterized by impaired ability of the α-intercalated cells in the collecting duct to secrete protons with consequently disturbed acid–base homoeostasis [1]. Currently, five genes are recognized, mutation in which can cause dRTA: *SLC4A1* [2], *ATP6V0A4* [3], *ATP6V1B1* [4], *FOXI1* [5] and *WDR72* [6]. *SLC4A1* encodes the anion exchanger AE1 expressed on the basolateral aspect of the intercalated cells. Mutations in this gene are not only inherited in an autosomal dominant fashion, but can also be recessive. *ATP6V0A4* and *ATP6V1B1* encode subunits of the proton pump, expressed on the apical side of the intercalated cells, as well as in the inner ear. *FOXI1* encodes a transcription factor important for acid-secreting epithelia. *WDR72* is thought to be involved in intracellular trafficking, potentially affecting targeting of acid–base regulatory proteins. So far only recessive mutations in the latter four genes have been recognized.

Clinically, dRTA is characterized by hyperchloraemic (normal anion gap) metabolic acidosis with excretion of insufficiently acidified urine. Hypokalaemia is common and has been attributed to the altered balance between potassium and proton secretion in the collecting duct in exchange for sodium reabsorption, potentially augmented by increased aldosterone levels [7, 8]. The excess acid in the blood is mainly buffered by the bone, leading to release of calcium from the skeleton, which, together with impaired tubular calcium reabsorption in acidosis, results in hypercalciuria that can be associated with nephrocalcinosis and/or nephrolithiasis [9]. Faltering growth is a common presenting symptom in children with dRTA [10].

Due to the importance of proton secretion into the endolymph for normal inner ear function, dRTA can also be associated with sensorineural deafness, most prominently with mutations in *FOXI1*, *ATP6V1B1* and, to a lesser degree, *ATP6V0A4*, because of their shared expression and functional relevance in kidney and inner ear.

Due to its rarity, few long-term outcome data exist to inform prognosis and management of patients with dRTA. Recently, a European initiative of reference networks for rare disease was launched to improved the diagnosis and management of affected patients. As part of the European Rare Kidney Disease Reference Network (ERKnet) and together with the working groups on inherited kidney diseases (ERA-EDTA) and inherited renal disorders [European Society for Paediatric Nephrology (ESPN)], we aimed to collect long-term outcome data on a large multinational cohort of primary dRTA patients.

MATERIALS AND METHODS

Clinical data

An e-mail was sent to the membership of ERA-EDTA and ESPN, inviting clinicians to provide data on patients with a clinical diagnosis of primary dRTA. The e-mail contained a link to an online data form that was open from 6 to 31 August 2017.

A total of 28 questions were asked, pertaining to demographics, treatment, as well as kidney function and complications, such as nephrocalcinosis and hearing impairment. A list of all questions is provided in Supplementary data, Table S1.

In case of missing information or if the provided data points were noted to be outliers, the corresponding clinicians were contacted via e-mail for completion and/or verification of data. Data were deemed adequate for analysis if fewer than five items were missing, and the information provided was confirmed by the responsible clinician. Details of data completion are provided in Supplementary data, Table S2.

Genotype–phenotype analysis

To facilitate the detection of potential genotype–phenotype associations, the total cohort was divided according to the genetic information supplied into the following four groups: (i) *ATP6V1B1*; (ii) *ATP6V0A4*; (iii) *SLC4A1*; and (iv) *Unknown*. For selected analyses, the genetically proven cases were subdivided into those with AE1 mutations (*SLC4A1*, mostly autosomal dominant) or proton pump subunit mutations (*ATP6V1B1* and *ATP6V0A4*, all autosomal recessive). The most recently discovered dRTA disease genes *FOXI1* and *WDR72* had not been described at the time of data collection and thus were not included. Genetic testing results were provided by the contributing clinicians according to their best knowledge, and in some patients testing may have been performed on a research basis only without confirmation in a clinical laboratory. Mutation details, as provided, were reviewed by a clinical geneticist (D.I.) to ensure that they accorded to the ACMG (American College of Medical Genetics and Genomics) standard [11].

Growth

Height data were normalized and expressed as standard deviation score (SDS) based on data from the World Health Organization for children [12, 13] or the 2000 Center for Disease Control data for adults [14]. Normal height was defined as a calculated score −2.00 or more.

Kidney function

Estimated glomerular filtration rate (eGFR) in adults (≥20 years old) was calculated using the Modification of Diet in Renal Disease (MDRD) equation; no data on ethnicity were available. Based on the population in the participating countries, only a small number of black patients were expected and therefore no correction for ethnicity was performed [15]. For children and young adults (2–20 years), we used the modified 'Schwartz' formula [16]. Prevalence of chronic kidney disease (CKD) was calculated and expressed in Groups 1–5 according to KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, based on the history of chronic tubular disorder ± abnormal imaging, no data on sediment abnormalities, proteinuria or histopathology were collected [17]. For comparison with the third National Health and Nutrition Survey (NHANES III) cohort [18], data from patients aged 20–60 years ($N = 61$) were used for subsequent analysis of CKD prevalence. As there were only two patients >60 years, meaningful comparison for that age group was not possible.

Metabolic control

Adequate metabolic control was defined as plasma or serum bicarbonate ≥22.0 mmol/L and the absence of hypercalciuria. For simplification, only the term serum bicarbonate will be used although in some patients, it may have been measured in plasma or calculated from whole blood gas analysis. Normal ranges for serum bicarbonate increase slightly during the first year of life. Yet, since treatment typically aims at a value in the middle in the normal range, we defined 22.0 mmol/L as the general lower limit for all age groups. Hypercalciuria was defined as a urinary calcium/creatinine ratio result above upper limit of normality for age range [19].

Nephrocalcinosis and nephrolithiasis

Data on nephrocalcinosis and nephrolithiasis were provided by the clinicians and thus reflect the local imaging protocols and interpretation. Age at diagnosis of nephrocalcinosis is presented in Supplementary data, Figure S3. Insufficient data were available regarding age at diagnosis of nephrolithiasis; therefore, meaningful analysis was not possible.

Classification according to gross domestic product per capita

For analyses according to country of residence of the patients, countries were classified according to gross domestic product (GDP) per capita based on the data from the World Bank [20]. Countries with GDP per capita >$35 000 were classified as 'high GDP', between $10 000 and $35 000 as 'medium GDP' and <$10 000 as 'low GDP' (see Supplementary data, Table S3).

Statistics

Analysis was done in IBM SPSS Statistics for Windows Version 24.0 (IBM Corp., Armonk, NY, USA). Kolmogorov–Smirnov test was performed to assess normality of the data. Data following a normal distribution were expressed as mean (±SD) and non-normally distributed data as median [range or interquartile range (IQR)]. Statistical significance for categorical/dichotomous variables was performed with the Pearson Chi-squared test. The Student's *t*-test was used to compare the means between two groups of parametric data and one-way analysis of variance test for three or more different groups. We used two different non-parametrics tests during the analysis for medians comparison, Mann–Whitney U-test for dichotomous and Kruskal–Wallis for polychotomous variables.

RESULTS

Responses and demographic data

A total of 340 cases (from 29 countries, Supplementary data, Table S4) were available for final analysis. An overview of the cohort is given in Figure 1.

Gender distribution was equal with 177 (52%) females and 163 (48%) males. The median age (range) was 11.0 (0–70) years at last follow-up and 83 (24%) were adults (≥18 years old) with the following age distribution 18–20 years: 20; 21–40 years: 45; 41–60 years: 16; and > 60 years: 2.

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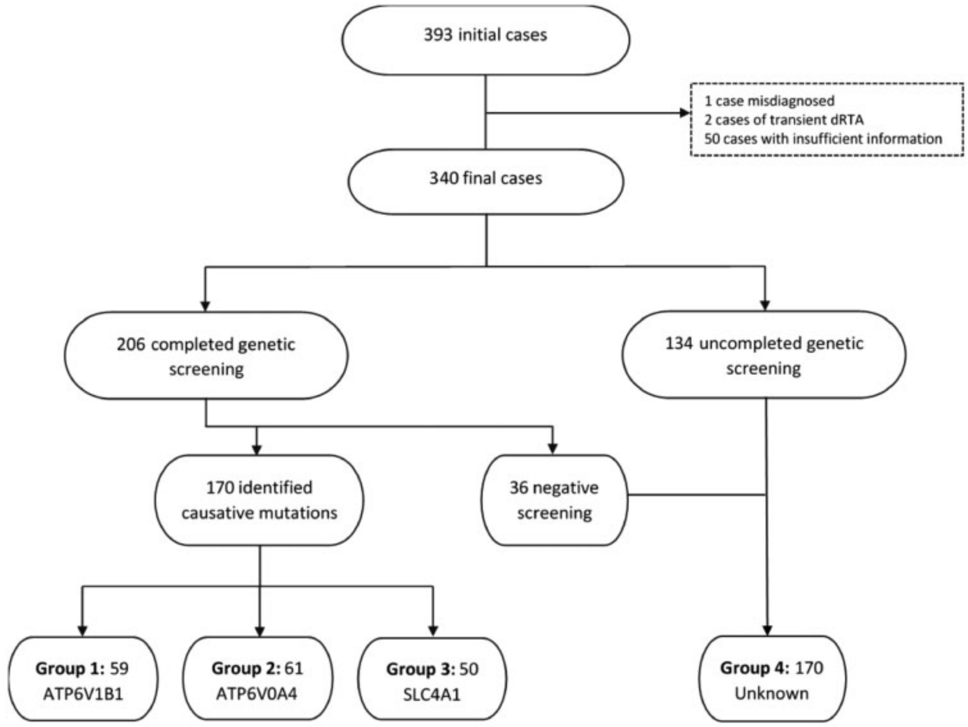

FIGURE 1: The patient cohort: patients were grouped for analysis according to the underlying gene. Patients without genetic testing or with no causative mutations in the tested three genes were classified as '*Unknown*'.

Genetic information

Genetic analysis in the three-classical known dRTA genes had been performed in 206 cases (61%) and of these 170 (83%) were found to have causative mutations. The overall distribution of the patients according to genetic cause is detailed in Figure 2A. A list of all reported mutations is provided in Supplementary data, Table S5.

Of the 36 patients who had undergone complete genetic testing yet with no clear causative mutation(s), 6 patients were heterozygous for the same variant in *ATP6V1B1*: c.1181G>T, p.(Arg394Gln) without a second mutation identified.

Age at presentation

The median age (IQR) at presentation was 0.5 (0.1–2.5) years with a significantly ($P < 0.001$) later onset in patients with *SLC4A1* mutations (Figure 2B): *ATP6V1B1* 0.5 (0.1–1.9), *ATP6V0A4* 0.2 (0.1–0.3), *SLC4A1* 4.0 (1.9–12.0) and *Unknown* 0.5 (0.2–2.8). A total of 307/336 (91%) patients presented before the age of 10 years.

Age at last clinic follow-up

Median (IQR) age at last follow-up was 11.0 (5.0–17.5) years and for the specific subgroups: *ATP6V1B1* 11.5 (6.0–18.0), *ATP6V0A4* 11.0 (3.6–17.2), *SLC4A1* 16.0 (7.9–26.3) and *Unknown* 9.0 (4.0–15.0) (Figure 2C). Consistent with the older age at presentation, patients with *SLC4A1* mutations were also significantly ($P < 0.019$) older at last clinic visit.

Long-term outcome: growth

The most recent height SDS mean (±SD) for the adult population was −0.57 (±1.16), with no significant difference ($P = 0.059$) between the genetic groups: *ATP6V1B1* −0.86 (±0.92), *ATP6V0A4* −0.54 (±1.19), *SLC4A1* −1.15 (±0.67) and *Unknown* −0.16 (±0.89) (Figure 2D).

Long-term outcome: kidney function

A third (34.7%) of the children (aged 2–18 years) had an impaired eGFR (<90 mL/min/1.73 m^2), mostly CKD Stage 2 (Figure 3A). Mean (SD) eGFR at last follow-up in adults ($N = 83$) was 75 mL/min/1.73 m^2 (±23) and was broadly similar across the genetic groups: *ATP6V1B1* 81 (±27), *ATP6V0A4* 79 (±26), *SLC4A1* 66 (±20) and *Unknown* 75 (±20) ($P = 0.2$). No patient with end-stage renal disease was noted, yet of the 83 adult patients (≥18 years), eGFR was < 90 mL/min/1.73 m^2 in 68 (82%) as shown in Figure 3B. In adults, the overall rate of eGFR decline was 0.8 mL/min/1.73 m^2/year (Figure 3C). The prevalence of CKD Stage ≥2 was significantly higher (50/61 = 82%) in dRTA patients aged 20–60 years compared with the NHANES III population (2729/10 444 = 26%) (Figure 3D).

Treatment

More than 30 different alkali formulations were used. A total of 84 patients (25%) were treated with oral bicarbonate, 141 (42%) with oral citrate and 113 (33%) with both. Two patients (both with *SLC4A1* mutations) were not treated with alkali. A sodium-containing salt was used in 21%, potassium in 29% and a combination in 50%. Sodium salts were more commonly used in countries with low per capita income (Supplementary data, Figure S1a). There was no statistically significant difference in hypercalciuria (and indirectly in metabolic control) according to the salt used (Supplementary data, Figure S1b).

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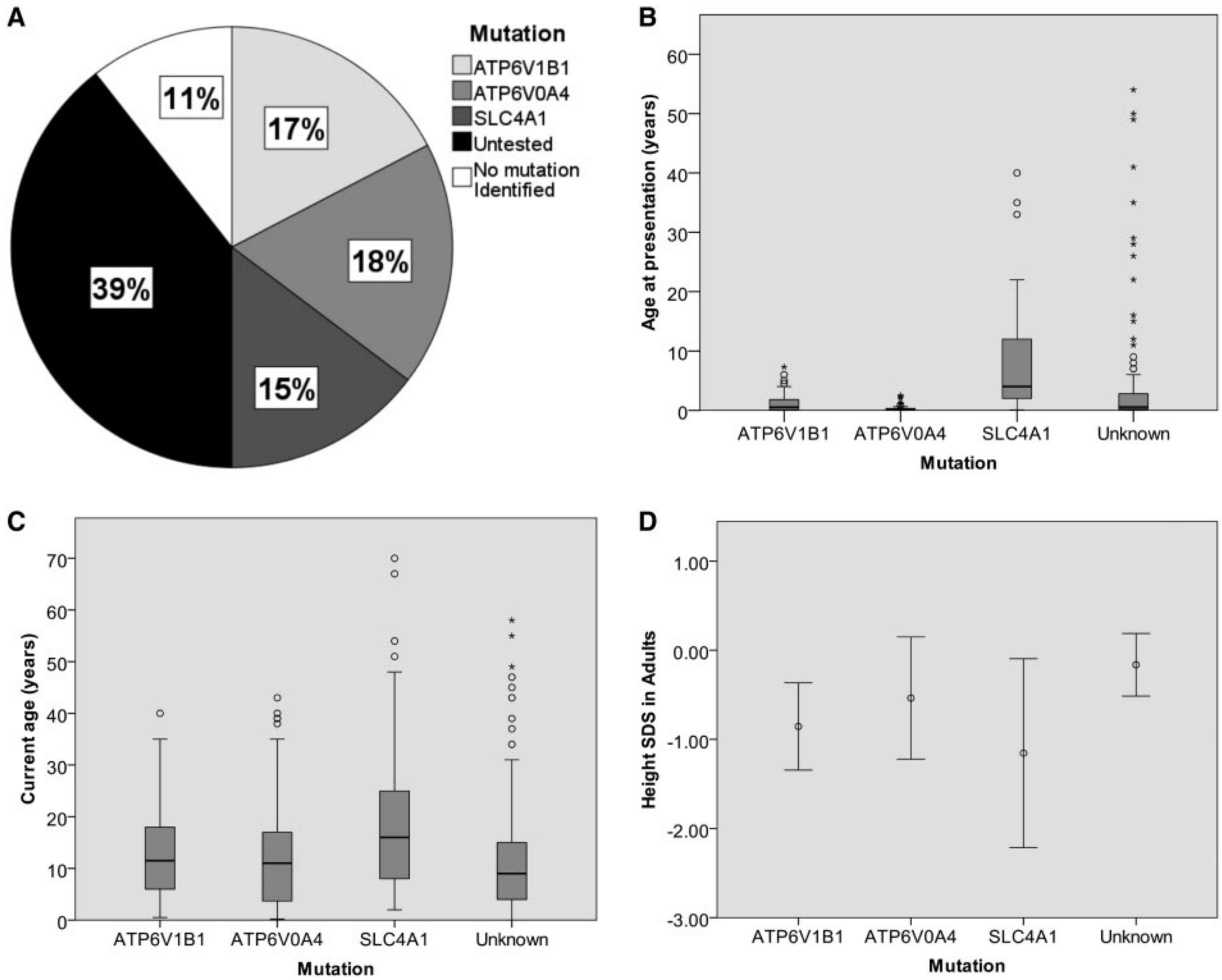

FIGURE 2: Demographics, genetics and growth. Box plot graphs represent the median and IQR; the upper and lower whiskers include data points within 1.5 × IQR. Outliers are plotted individually. (**A**) Population distribution according to genetic testing. (**B**) Age at presentation in years. Note that patients with proton pump mutations all present below the age of 10 years and the significantly ($P < 0.001$) older age at presentation in the *SLC4A1* group. (**C**) Age at last clinic visit. Note again the significantly ($P = 0.019$) older age in the *SLC4A1* group. (**D**) Adult height (mean and SDS) according to genetic group. No significant difference was seen between the genetic groups.

The median (IQR) prescribed dose of alkali treatment (mEq/kg/day) was 1.9 (1.2–3.3) and comparable across groups: *ATP6V1B1* 1.7 (1.1–2.3), *ATP6V0A4* 1.9 (1.2–3.3), *SLC4A1* 1.5 (0.9–2.7), *Unknown* 2.2 (1.4–4.1). However, median (IQR) prescribed doses of alkali equivalent were significantly higher in younger patients compared with older ones ($P < 0.001$) (Figure 4A).

Metabolic control

Serum bicarbonate (mmol/L) levels and urinary calcium/creatinine ratio (mmol/mmol) at last follow-up were used as markers for metabolic control. Data for both items were available in 312 patients. Median (IQR) serum bicarbonate level at last follow-up was just at the lower limit of the normal range at 22.0 mmol/L (20.0–24.0), with no significant difference between the genetic groups (Figure 4B). The prevalence of hypercalciuria was similar between genetically diagnosed groups, with 12% in *ATP6V1B1* (7/58), 14% in *ATP5V0A4* (8/56), 11% in *SLC4A1* (5/47) and 19% in *Unknown* (28/151).

In total, 43% of patients had a serum bicarbonate <22 mmol/L and 15% had hypercalciuria. Overall, 49% had one or both abnormalities and therefore were considered as not having adequate metabolic control at last clinic visit (Figure 4C).

To assess the importance of metabolic control, we compared growth and kidney function between those with and without adequate metabolic control. For growth, we analysed the last documented height from patients who presented and thus started treatment at an age with presumed growth potential (defined as <15 years of age). Median (IQR) height SDS significantly ($P < 0.001$) increased at −0.52 (−1.32 to +0.36) in those with adequate metabolic control compared with −1.31 (−2.50 to −0.52) in those without (Figure 4D). As a marker for the long-term effect on kidney function, we compared eGFR in adults with or without adequate metabolic control: mean (±SD) eGFR was significantly higher ($P = 0.023$) in those with adequate metabolic control at 79 (±19) compared with those without at 67 (±22) mL/min/1.73 m^2 (Figure 4E). Adequate metabolic control was achieved in a significantly ($P < 0.001$) higher proportion (67%) of patients in the countries with high GDP, compared with 50% in countries with medium and 23% in countries with low GDP (Figure 4F).

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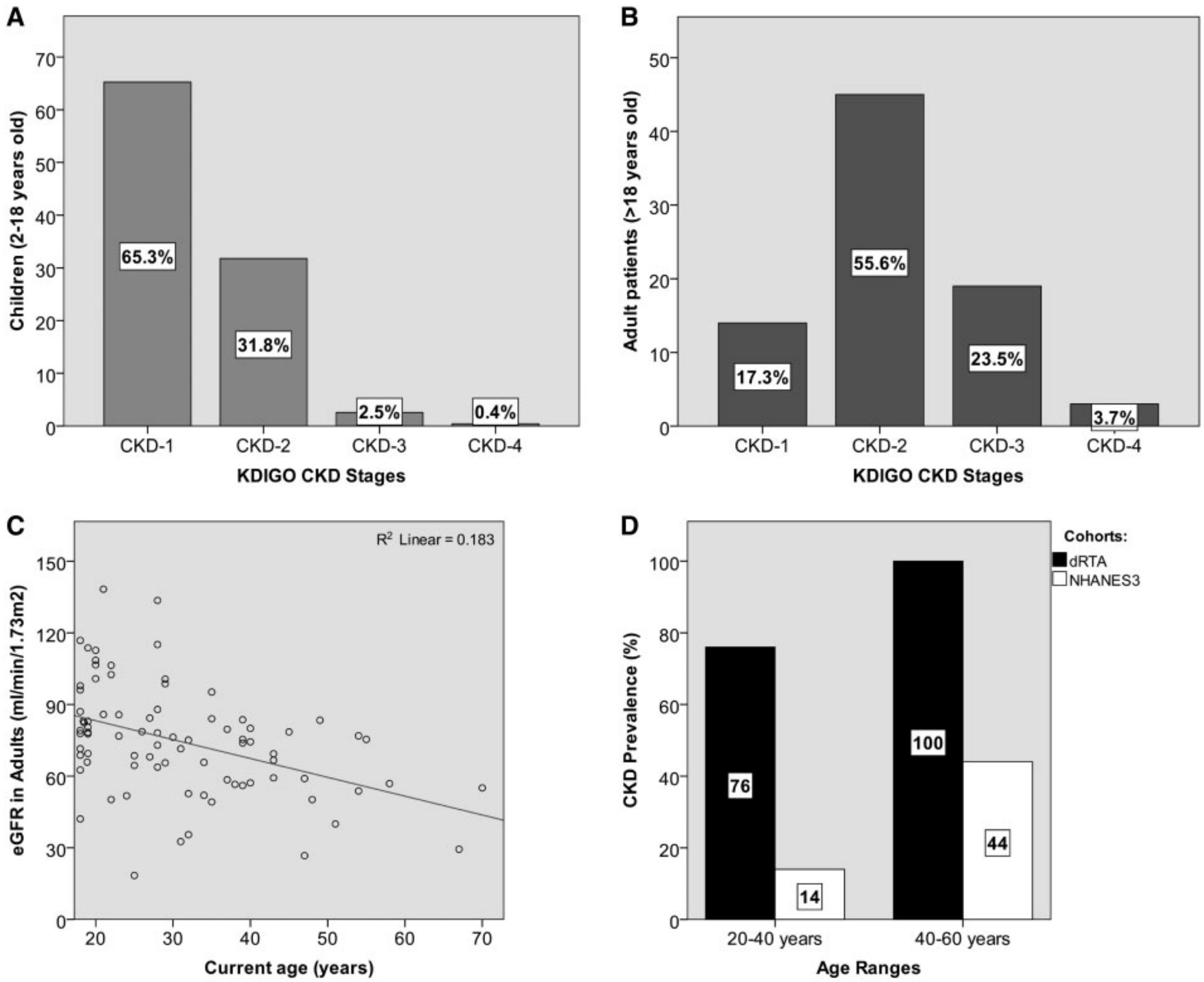

FIGURE 3: Renal function and CKD. (A) Prevalence of CKD stages in the paediatric age group. Note that 35% have CKD Stage ≥2. (B) Prevalence of CKD stages in the adult age group. Note that 82% of the adult patients analysed had CKD Stage ≥2. (C) Plot of eGFR versus age at last clinic visit. The solid line represents a regression line suggesting a linear correlation between age and loss of renal function with a calculated decline of 0.8 mL/min/1.73 m^2/year. Note that the eGFR at age 18 years is already impaired, consistent with CKD Stage 2. (D) Comparison of CKD Stage ≥2 prevalence in adults between our cohort (dRTA) and controls (NHANES III) according to two different age ranges (20–39 years and 40–59 years old). Note the significantly ($P < 0.001$) increased prevalence of CKD Stage ≥2 in the dRTA cohort.

Nephrocalcinosis and nephrolithiasis

Nephrocalcinosis was common in all groups, but had a significantly higher ($P = 0.004$) prevalence in patients with *ATP6V0A4* mutations 98% (59/60) compared with *ATP6V1B1* 90% (53/59), *SLC4A1* 94% (47/50) and *Unknown* 82% (140/170). Nephrocalcinosis was already noted at presentation in most of the patients (229/261 = 88%, see Supplementary data, Figure S3). Nephrolithiasis was significantly ($P = 0.014$) more common in patients with *SLC4A1* mutations 42% (21/50) compared with *ATP6V1B1* 21% (12/57), *ATP6V0A4* 20% (12/59) and *Unknown* 21% (34/165) (Figure 5).

Hearing loss

Hearing loss was significantly ($P < 0.001$) more prevalent in patients with *ATP6V1B1* mutation 88% (50/57) compared with *ATP6V0A4* 36% (21/59), *SLC4A1* 6% (3/49) and *Unknown* 26% (42/161) (Figure 6A). Hearing aids were prescribed in a total of 90 (27%) patients and most commonly in patients with *ATP6V1B1* mutations ($N = 40$, 69%), compared with *ATP6V0A4* ($N = 16$, 26%), *SLC4A1* ($N = 3$, 6%) and *Unknown* ($N = 31$, 18%) ($P < 0.001$) (Figure 6B). Median age (IQR) (years) of hearing aids prescription was significantly lower ($P < 0.021$) in the *ATP6V1B1* group at 2.5 (1.2–5.0) compared with 7.0 (3.1–13.3) with *ATP6V0A4*, 5.0 (4.0–5.0) with *SLC4A1* and 3.6 (1.9–5.9) with *Unknown* mutations (Figure 6C).

Similarly, cochlear implants were significantly ($P < 0.001$) more commonly performed in patients with *ATP6V1B1* mutation 24% (14/59) compared with *ATP6V0A4* 5% (3/61), *SLC4A1* 0% and *Unknown* 4% (7/170) (Figure 6D).

DISCUSSION

We report on the treatment and long-term outcome in patients with a clinical diagnosis of primary dRTA. To the best of our knowledge, our cohort is the largest reported so far for this condition. While approximately half of the cohort did not have an identified genetic diagnosis (including 39% who were not genetically screened), the large number ($N = 50$–61) in each

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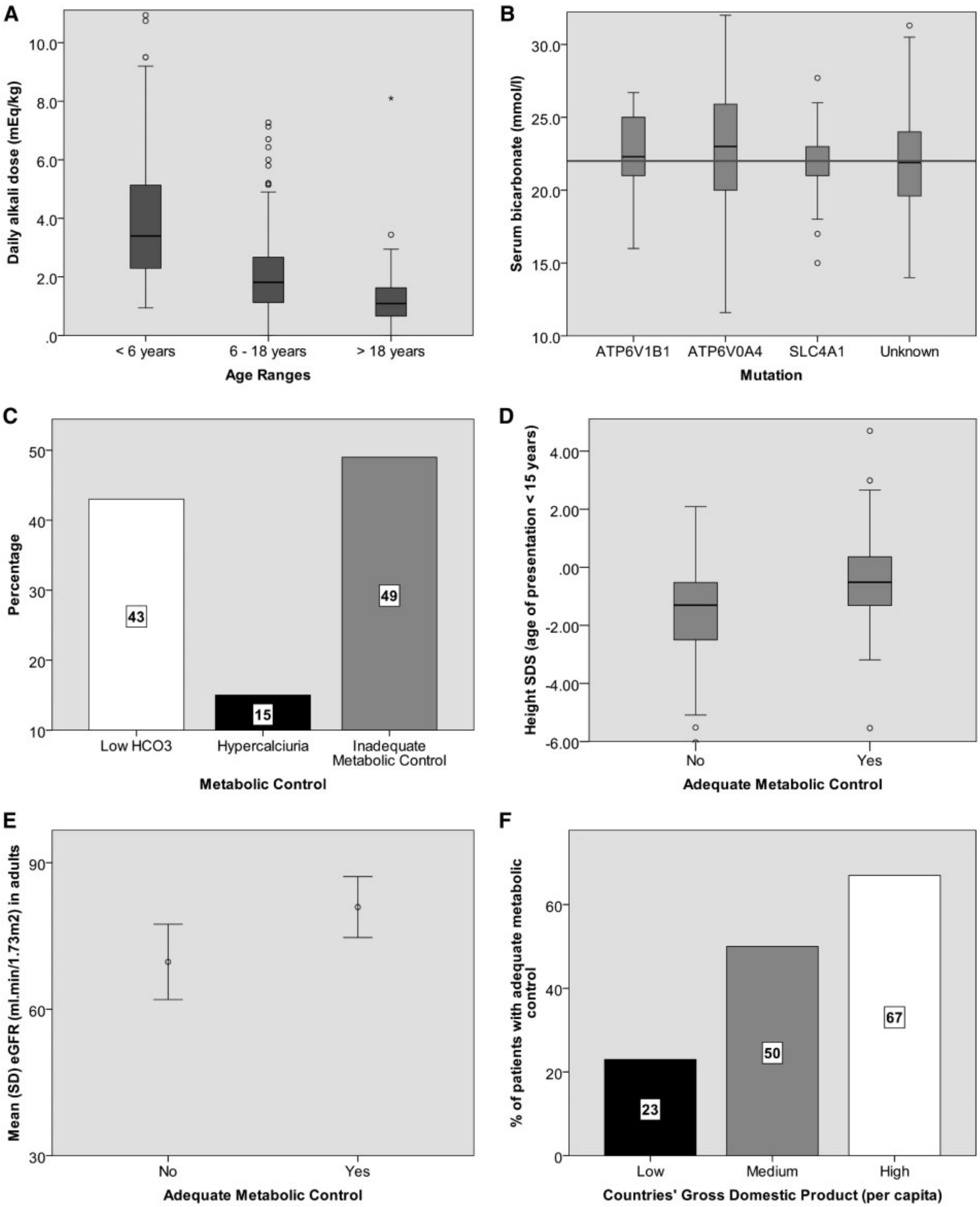

FIGURE 4: Treatment and metabolic control at last follow-up. Box plot graphs specifics are as detailed in Figure 2. (**A**) Daily weight-adjusted alkali dose according to age group (under 6 years, 6–18 years and adults). Note that the prescribed weight-adjusted dose of alkali supplement decreases with age ($P < 0.001$). (**B**) Serum bicarbonate level at last clinic visit according to the different genetic groups. The horizontal line indicates the lower limit of the normal range (defined as 22.0 mmol/L). (**C**) Prevalence of metabolic acidosis (white), hypercalciuria (black) and inadequate metabolic control (grey) within the whole cohort. Note that 49% of the whole cohort had a serum bicarbonate level below the normal range and/or hypercalciuria and were thus classified as having inadequate metabolic control. (**D**) Height SDS (in patients with presentation <15 years) and metabolic control. Note the significant ($P < 0.001$) difference in height between those with and without adequate metabolic control (for details, see text). (**E**) eGFR in adults (≥18 years) and metabolic control. Note the significant ($P < 0.023$) difference in eGFR between those with and without adequate metabolic control (for details, see text). (**F**) Prevalence of metabolic control in relation to GDP group. Note the significant ($P < 0.001$) difference in achievement of adequate metabolic control in countries with high GDP compared with those with lower GDP.

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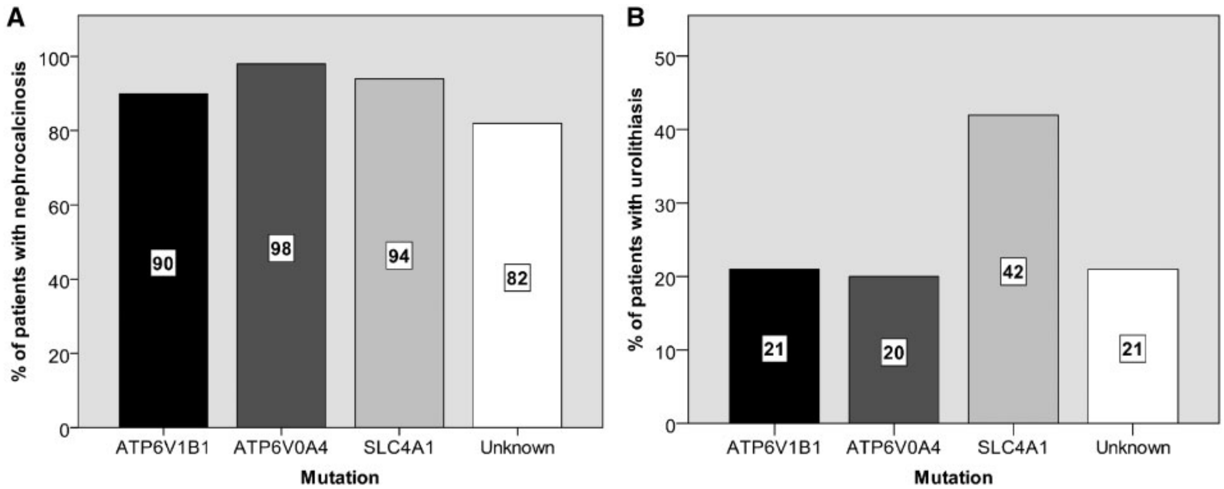

FIGURE 5: Nephrocalcinosis and urolithiasis: presence of (**A**) nephrocalcinosis and (**B**) history of urolithiasis at last clinic visit. Note that nephrocalcinosis is significantly ($P = 0.004$) more common with *ATP6V0A4* mutations, compared with the other genetic groups. Note also the significantly ($P = 0.014$) increased prevalence of urolithiasis in patients with *SLC4A1* mutations.

genetically classified group allows for meaningful interpretation of data according to genotype. Moreover, the lack of obvious differences with regards to treatment, long-term outcome and complications between the groups with unknown genetics and those with defined mutations suggests that the clinical diagnosis of primary dRTA was accurate also in most of the patients without genetic confirmation. Of those who had genetic testing performed, causative mutations were identified in about 83%, roughly comparable to other recent reports [21–23].

Of interest is the recurrent identification of the heterozygous mutation in ATP6V1B1 p.(Arg394Gln), which has been previously reported in heterozygous form in patients with clinical diagnosis of dRTA [22, 24]. It remains to be shown whether this mutation is pathogenic on its own, or whether a second mutation on the other allele has been missed by current diagnostic methods.

Genotype–phenotype analysis

Our data show some genotype-specific characteristics, comparable to previous reports [14, 15]. In general, patients with mutations in the proton pump subunits have a more severe phenotype compared with those with *SLC4A1* mutations: age of presentation is younger with the vast majority (91/118, 77%) presenting in the first year of life and all before 10 years of age, whereas 12% (6/50) of patients with *SLC4A1* mutations presented in adulthood (Figure 3B).

Treatment and metabolic control

Control of the acidosis, as assessed by plasma bicarbonate concentration and urine calcium excretion, was achieved in only about half of all patients. We recognize that there are limitations to this analysis: biochemical data were only available at the last clinic visit, which may not be representative of the entire follow-up period. Moreover, bicarbonate determinations varied, as in some instances total CO_2 was measured, whereas in others, it was calculated from a blood gas. Most importantly, bicarbonate levels in this condition depend heavily on the timing of the last alkali dose taken. Yet, these limitations reflect routine clinical practice and for these reasons, urine calcium excretion is commonly used as another indicator of metabolic control in dRTA, as urine calcium excretion increases when acidosis is present [25].

Interestingly, adequate metabolic control was significantly associated with per capita GDP (Figure 4F). Whether this reflects the affordability and/or availability of specialized medical care and medications cannot be deduced from our data. Of note, age at diagnosis was not significantly different in the three GDP groups (data not shown).

Forms of supplementation varied widely and overall, a total of 34 different alkali formulations were used (Supplementary data, Table S6). This may reflect clinician preference, as well as country-specific availability of these alkali supplements.

Interestingly, the prescribed alkali dosage is highest during the first year of life, presumably reflecting the increased metabolic rate of younger children, which necessitates a larger caloric intake relative to body size and thus an increased acid load (Figure 4A). Our results inform the initial treatment dose for newly diagnosed patients, with young children (< 6 years old) apparently needing up to 10 mEq/kg/day (median 3.3, IQR: 2.3–5.0), whereas older children and adults can achieve acid–base balance with typically 2–3 mEq/kg/day. There was no difference with regards to metabolic control between the age groups, consistent with the notion that physicians adjusted alkali supplementation accordingly.

Long-term outcome: growth

dRTA when untreated is known to have a severe impact on growth with improvement in patient's height and weight once alkaline treatment has been established [26]. Our large cohort highlights the importance of adequate treatment for optimal growth. Adult height is only mildly impaired at −0.57 SDS and, again, the majority (90%) of adult patients had achieved a final height in the normal range (SDS > −2.0). Importantly, height SDS was significantly ($P < 0.001$) better in those patients with adequate metabolic control compared with those without, suggesting that growth can be optimized with adequate treatment.

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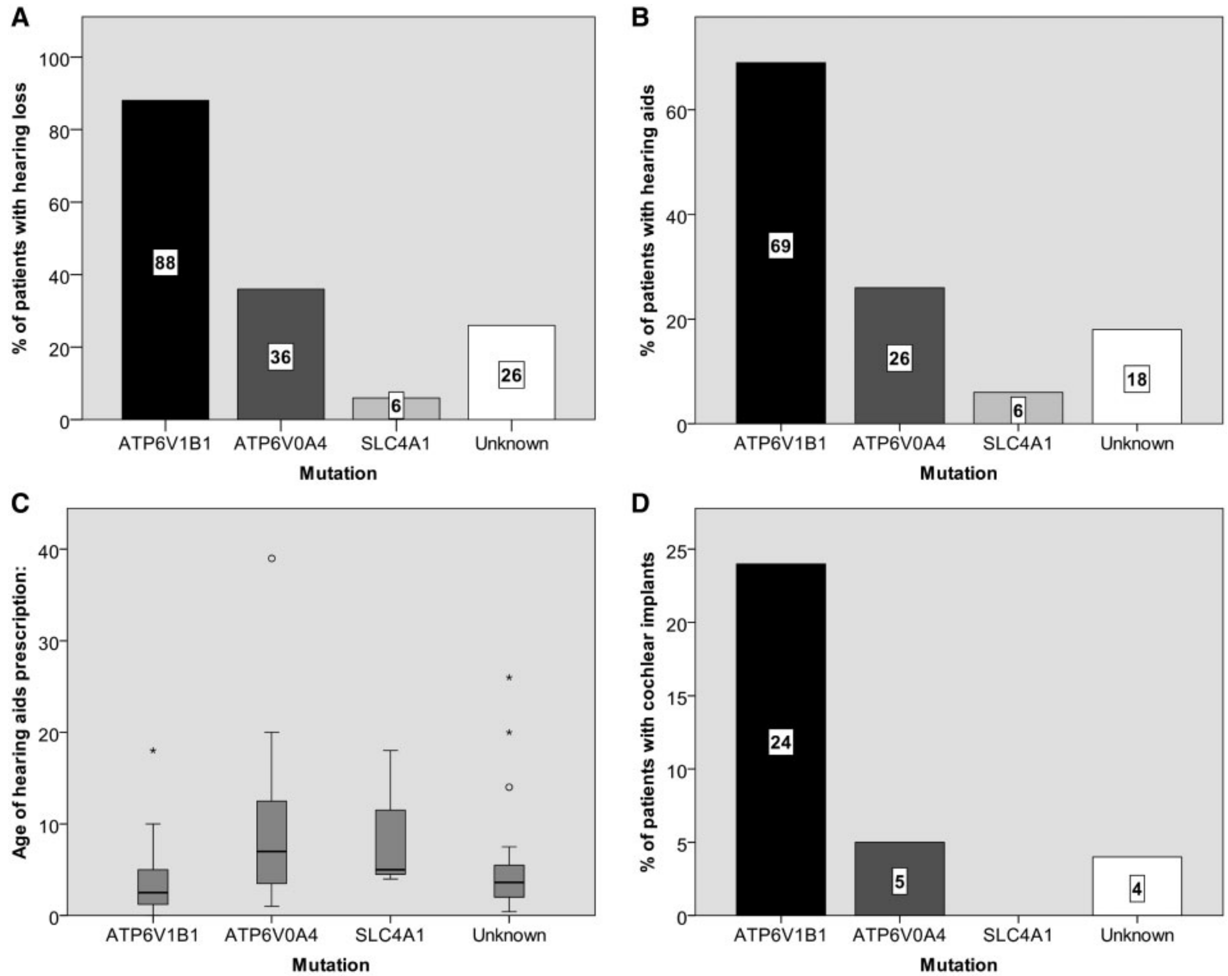

FIGURE 6: Sensorineural hearing loss. Shown is the prevalence and treatment of sensorineural hearing loss across the genetic groups. (**A**, **B** and **D**) Prevalence of hearing loss, history of hearing aids prescription and history of cochlear implantation. Note the significantly ($P < 0.001$) increased prevalence of hearing loss, prescription of hearing aids and cochlear implants in patients with *ATP6V1B1* mutations. (**C**) Patients' age at prescription of hearing aids. Note the significantly ($P < 0.021$) younger age at prescription in the *ATP6V1B1* group.

Long-term outcome: kidney function

Mean eGFR in adult patients was decreased at 75 mL/min/1.73 m^2, and the presence of CKD Stages 2–4 in >80% of adults suggests that dRTA has a long-term impact on eGFR. The high prevalence of CKD is consistent with previous studies of dRTA cohorts, which reported rates between 30% and 67%, depending on the age of the population [21, 23]. CKD may be due to nephrocalcinosis, the development of cysts, which are commonly seen, in the so-called 'hypokalaemic nephropathy' or simply because of repeated acute kidney injury due to dehydration [27].

In order to establish a meaningful comparison between the magnitude of the CKD prevalence in our cohort and in the general population, we extracted data from the NHANES III, which also estimated GFR by using the MDRD equation [28]. This comparison demonstrated a 3-fold higher prevalence of CKD in our cohort.

The observed overall decline in eGFR in adults (Figure 3C) was 0.8 mL/min/1.73 m^2/year, which is comparable to the normal population [29, 30]. However, in healthy individuals, decline starts during the fourth decade from a starting eGFR of 130–140 mL/min/1.73 m^2 [31]. In contrast, mean eGFR in the dRTA cohort at the age of 18 years was already equivalent to CKD Stage 2. This suggests that kidney damage has already occurred in childhood. Indeed, while there are no large-scale epidemiological studies in CKD in children, data from registries suggest a prevalence of CKD around 70/million of the age-related population (<0.01%) [32, 33], whereas 35% of the paediatric patients in our cohort had CKD Stage ≥2. Considering childhood as the 'vulnerable' phase for kidney injury, we assessed the impact of adequate metabolic control of eGFR in children. As with height SDS, adequate metabolic control was associated with better outcome (median 103 versus 94 mL/min/1.73 m^2, $p < 0.008$), highlighting again the importance of adequate treatment.

Nephrocalcinosis and nephrolithiasis

Nephrocalcinosis and nephrolithiasis are two classical clinical features of dRTA. Interestingly, despite a lower prevalence of hypercalciuria in the *SLC4A1* group, these patients had the highest prevalence of nephrolithiasis (11 and 42%, respectively). Yet, it is important to note that we only captured hypercalciuria at last follow-up. As patients with *SLC4A1* mutations typically present later in life, they presumably have had a longer time

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with undetected and untreated hypercalciuria, allowing stone formation.

Hearing loss

Sensorineural hearing loss is a classic-associated feature of dRTA, first described in 1971 [34]. Our data confirm the close association of deafness with mutations in *ATP6V1B1* [4]. However, we also see clinically relevant deafness in almost a third of patients with *ATP6V0A4* mutations, with hearing aids or cochlear implants present in 26 and 5%, respectively (Figure 6). We also found a 6% rate of hearing aids prescription in patients with *SLC4A1*, the youngest at 4 years of age. This reflects the prevalence of hearing loss in the general population [35, 36].

Limitations of our study

Our study is a retrospective review based on a limited number of results from the last clinical follow-up, captured via an online form. With any such study, there needs to be a balance between feasibility and the comprehensiveness of the data collected. If a large number of data are requested, then clinicians may be reluctant to participate, as data entry is time consuming. Upon conception, we therefore decided to focus only on aspects deemed most important. While hypokalaemia is a typical feature at diagnosis, it usually resolves with treatment [37] and we therefore did not consider it as a key problem. We also did not request data on haematological problems: autosomal recessive *SLC4A1* mutations may be associated with mild defects in red cell morphology, particularly if there is coincident acidosis [38]. Given the rarity of this form of dRTA in patients of European ancestry, we did not expect to be able to make meaningful statements. Indeed, only five such cases were entered in the study. Investigations into this particular problem are better performed in Asian cohorts, as has been reported before [39]. Finally, no specific data on diet were requested. As diet determines the acid load, detailed data on this may have been helpful to explain some of the variability in the treatment doses [40]. However, details of dietary habits are rarely collected by clinicians in routine practice.

The high number of patients entered validates our study design of limited data gathering even though it only allowed a focused investigation of the selected clinical aspects of dRTA.

The key limitation of our study is the assumption that data from last clinical follow-up adequately reflect treatment throughout the lifetime of the patients. This obviously is not necessarily the case, which may explain some of the variability in our results. Moreover, the 'long-term' outcome information is based on the data from adult patients, whose previous treatment may not necessarily reflect current treatment of newly diagnosed patients. These limitations clearly show the need for prospective gathering of granular data in an international registry for this rare disorder.

CONCLUSIONS

Data from this large cohort of patients with dRTA suggest an overall favourable outcome with final height in the normal range in >90%. While CKD is common, no patient with end-stage kidney disease was reported. However, almost half of all patients had inadequate metabolic control at last follow-up, suggesting difficulties with current treatment forms. The importance of adequate treatment is highlighted by its positive impact on growth and renal function. Therefore, clinicians should aim to maintain serum bicarbonate and urine calcium in the normal range.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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