Kidney function in patients with primary distal renal tubular acidosis

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Abstract

Background:

Recent reports indicate that chronic reduction of glomerular filtration rate (GFR) is common in patients with distal renal tubular acidosis (DRTA). Factors responsible for decreased GFR need clarification.

Methods:

We reviewed records of 25 patients with genetically confirmed DRTA included in the RenalTube database. Patients < 18 years at diagnosis and having at least one annual follow-up were selected and classified in two groups according to GFR ≥ 90 (normal GFR) or < 90 ml/min/1.73 m^2 (low GFR) after median follow-up of 8.8 years.

Results:

Eighteen and seven patients had normal and low GFR, (X ± SEM, 121.16 ± 28.87 and 71.80 ± 10.60 ml/min/1.73 m^2, respectively, p < 0.01). At diagnosis, these 2 subgroups did not differ in sex, age, underlying mutated gene, GFR, height SDS, or percentage of ultrasound nephrocalcinosis. Serum creatinine (SCr) was different but likely due to median ages of presentation being 0.6 and 4.0 in normal and low GFR patients, respectively. On the last recorded visit, no differences between both groups were found in serum bicarbonate, serum potassium, or alkali dosage. Height SDS of patients with normal GFR was − 0.15 ± 0.47 whereas it was − 1.06 ± 0.60 in the low GFR group (p = 0.27). Interestingly, 23% of the whole group had low birth weight (LBW; < 2,500 g), equating to 20% and 29% in the normal and low GFR patients, respectively (p = 0.65).

Conclusions:

Our findings confirm the risk of kidney function reduction in patients with DRTA of pediatric age onset, suggesting that low GFR is related with less favorable growth outcome and discloses the high frequency of LBW in primary DRTA, a hitherto unrecognized feature.

Keywords:

Distal renal tubular acidosis
Metabolic acidosis
Kidney function
Reduced glomerular filtrate rate
Low birth weight
Nephrocalcinosis

1.

2.1. Introduction

Distal renal tubular acidosis (DRTA) is characterized by normal anion gap metabolic acidosis resulting from the inability to acidify the urine due to a defect in the excretion of hydrogen (H^+) by the intercalated alpha cells of the collecting tubule [1]. The primary forms of DRTA are caused by mutations in the genes *ATP6V1B1*, *ATP6V0A4*, encoding H^+ATPase subunits and following autosomal recessive inheritance [2], or in the *SLC4A1* gene, encoding the bicarbonate/chloride exchanger or AE1 co-transporter and following autosomal recessive or dominant transmission [2]. Recessive mutations in *FOXI1* and *WDR72* genes have recently been described as causative of DRTA in a few families. *FOXI1* encodes a transcription factor important for acid secreting epithelia [3, 4] and *WDR72* is likely involved in intracellular trafficking, potentially affecting targeting of acid–base regulatory proteins [3, 4]. Laboratory findings in patients with DRTA are hyperchloremic metabolic acidosis, hypokalemia, hypercalciuria, and hypocitraturia. Major clinical manifestations are polyuria, polydipsia, vomiting and loss of appetite, failure to thrive, nephrolithiasis, and nephrocalcinosis [1, 5]. Early nerve deafness occurs in the vast majority of patients harboring *ATP6V1B1* mutations whereas in individuals with *ATP6V0A4* mutations, it is less prevalent and often debuts later [6, 7].

Although the long-term outcome of primary DRTA patients who receive adequate alkaline treatment since infancy or childhood is generally considered to be good, in 2019, Lopez-

Garcia et al. [7] reported a multicenter retrospective analysis of long-term follow-up of patients with DRTA, mostly of pediatric age onset. They found that 82% of adult patients had chronic kidney disease (CKD) stages 2–4 (estimated glomerular filtration rate (GFR) < 90 mL/min/1.73 m^2). Even more recently, Atmis et al. reported that 28% of 31 patients with primary DRTA had CKD stage 2 or 3 after a median follow-up period of 77 months (range, 2–283 months) [8]. The reasons for this mild–moderate decrease of kidney function are not clear, although it might be related to poor metabolic control, nephrocalcinosis [2, 5], and/or development of kidney cysts [2, 5].

We reviewed the RenalTube database (www.renaltube.com), a collaborative online effort aimed at the clinical and molecular diagnosis of primary tubular disorders, to find out what percentage of patients with primary DRTA had low GFR at the last follow-up and to analyze factors potentially responsible for the reduced GFR.

~~3.~~

~~4.~~2. Methods

~~4.1.~~2.1. Patients and kidney function

From a total of 50 patients with a confirmed genetic diagnosis of DRTA included in the RenalTube database, those who were < 18 years of age at diagnosis and had at least one annual follow-up were selected and classified in two groups according to whether the estimated GFR at the last follow-up was ≥ 90 mL~~ml~~/min/1.73 m^2 (normal GFR) or < 90 mL~~ml~~/min/1.73 m^2 (low GFR). GFR was calculated using the Schwartz formula with *K* of 0.413 [9] or using the CKD-EPI (Collaboration on Epidemiology of Chronic Kidney Disease) formula for those aged > 20 years. Birth weight, weight, height, body mass index (BMI), presence of ultrasound nephrocalcinosis and serum levels of creatinine (SCr), bicarbonate, and potassium were retrospectively collected from the database. Height and weight data were normalized according to national or World Health Organization reference values and expressed as standard deviation score (SDS). Low birth weight (LBW) was considered less than 2~~,~~500 g [10].

~~4.2.~~

~~4.3.~~2.2. Statistical analysis

The SPSS 26 program was used to analyze the results. Data with a normal distribution are expressed as mean ± standard error of mean (X ± SEM). For variables not following a normal distribution, median and range are given. As sample size was $n < 30$, the Shapiro–Wilk test was used to evaluate normality of the variables. For comparing categorical variables with eGFR defined as low/normal, a chi-square was performed. Data with normal distribution were compared by Student's *t*- test for two independent samples. The Mann–Whitney *U* test was used for comparison of variables not following a normal distribution. Fisher's exact test was used for comparing the presence of nephrocalcinosis. A P value ≤ 0.05 was considered indicative of statistically significant difference between groups.

~~5.~~

~~6.~~3. Results

A total of 25 cases were selected. Table 1 shows demographic, genetic, clinical, and biochemical data at diagnosis for the whole cohort of patients and for the two groups of normal (18 patients) or low GFR (7 patients). Significant differences between the two groups were only found for SCr. The low GFR group tended to be older and had lower GFR at diagnosis and tended to have higher frequency of LBW and lower height at diagnosis and at the last follow-up.

~~7.~~

~~8.~~4. Discussion

This study confirms that patients with primary DRTA diagnosed at pediatric age have a risk of developing a mild–moderate degree of CKD with low GFR, which was found in the present cohort in 7 of 25 patients (27%) after a median follow-up period of 8.8 years. This percentage is similar to that reported by Palazzo et al. [5] and Atmis et al. [8] and lower than that found by Lopez-Garcia et al. [7]. In this series, DRTA patients were followed for a longer period, some of them up to 70 years of age, and not all of them had genetic mutations identified.

The retrospective and multicentric nature of our study is a limitation that makes it difficult to know potential factors related to the clinical and metabolic control of these patients which may have influenced the evolution of kidney function. Patients with normal and low GFR were not different in gender, underlying causal gene, age, height, or percentage of LBW. Likewise, duration of follow-up, serum potassium, serum bicarbonate, and dose of alkali at the last visit were not significantly different between both groups of patients. Mean height SDS of patients

with low GFR was −1.06 vs. -0.15 in the normal GFR group, a finding that might indicate worse control of acidosis as responsible for CKD, as suggested by former studies [5, 7, 8]. It could be argued that patients with low GFR had poorer compliance with treatment. This assumption is not supported by the lack of difference in serum bicarbonate at the last visit, although this is one-time data that may not reflect the adherence during the entire follow-up period.

It is of note that patients with reduced GFR at the last follow-up visit had higher initial SCr and tended to have lower eGFR at diagnosis, in spite of being older, which suggests impairment of kidney function since diagnosis in some of these children who developed CKD with low GFR. However, it should also be considered that diagnosis of DRTA is often performed in a state of clinical and metabolic disbalance able to acutely interfere with GFR estimation, and the GFR measured at diagnosis might not reliably reflect the GFR after steady correction of acidosis and electrolyte alterations. In addition, SCr values are influenced by age and the low GFR group had a median age at diagnosis of 4.0 years vs. 0.6 years in the normal GFR group. The older age of the low GFR patients is consistent with the high percentage of patients with mutations in the *SLC4A1* gene, a form of DRTA known to debut later than those caused by *ATP6V1B1* or *ATP6V0A4* mutations. It is also of note that although there were no significant differences in the GFR, expressed as mL/min/1.73 m^2, at diagnosis between the two subgroups of patients, the median age of the subgroup with subsequent low GFR tended to be higher. Thus, GFR could have been expected to be physiologically greater in these patients. The percentages of infants younger than 1 year of age were quite similar in both subgroups: 55% and 43% in normal and low GFR, respectively, avoiding the potential bias that could result from including in a subgroup a greater percentage of individuals with physiologically lower GFR. As for the group with low GFR, 6 patients had CKD stage 2 and 1 patient had CKD stage 3. Four of these individuals already had reduced GFR when they were 18 years old (three from CKD stage 2 and one from CKD stage 3), indicating impairment of glomerular function before adulthood. The reasons for the decreased GFR in patients with ATRD are not clear. Factors such as the degree of nephrocalcinosis or the effect of sustained metabolic acidosis may play a role. In our study, all patients who developed low GFR had initial nephrocalcinosis whereas nephrocalcinosis was found at diagnosis in 61% of normal GFR patients. However, this difference was not statistically significant and could be influenced by the age of the patients.

It is interesting to emphasize that 23% of our patients with primary DRTA had LBW. This finding, to our knowledge not previously reported in the literature, cannot result from acidosis,

which is not present at birth in DRTA, and may be linked to comorbidities, like those found in patients with acquired CKD [11], and might represent a risk factor for the long-term reduction of kidney function found in primary DRTA patients and adversely influence achievement of normal adult height. Thus, the percentage of LBW in the group with low GFR at the last follow-up was 29%, much higher than that expected in terms of pregnancies. In Spain, the most recent data indicate that 8% of newborns weigh less than 2,500 g at the moment of birth, precisely 33,194 babies out of 420,290 in 2015 [12]. In addition, metabolic acidosis might interfere with the marked growth of body and kidneys normally found during the first years of life. Therefore, it could be speculated that a small adult kidney size could play a role in the development of kidney failure in DRTA. Unfortunately, no data on kidney volume at the last follow-up or at the end of childhood were available in our patients.

In summary, the study presented here confirms the high frequency of long-term CKD with reduced GFR in patients with primary DRTA, indicates that low GFR may be related to less favorable growth outcome and with reduction of kidney function since diagnosis, and points to LBW as a feature, hitherto unrecognized to be more frequent in DRTA, that which might be an additional risk factor for the development of decreased GFR in these patients.

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Availability of data and material

Data were collected from the RenalTube database and were recorded after previous informed consent.

Author contribution

JMFD and HGP contributed equally to data collection and analysis. JMFD, MAV, and HGP prepared the first draft of the report. FS came up with the original idea, wrote the final version of the article, and supervised all the work.

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Declarations

Conflicts of interest

The authors declare no competing interests.~~The authors declare no conflict of interest.~~

~~Availability of data and material: data were collected from the RenalTube database and were recorded after previous informed consent.~~

~~Authors' contributions: JMFD and HGP contributed equally to data collection and analysis. JMFD, MAV and HGP prepared the first draft of the report. FS came up with the original idea, wrote the final version of the article, and supervised all the work.~~

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able 1. Data of all patients and of the two groups, normal (GFR ≥ 90 mL/min/1.73 m^2) and reduced kidney function (GFR < 90 mL/min/1.73 m^2) at the last-follow-up. SCr: serum creatinine. eGFR: timated glomerular filtrate rate. F: females. M: males. N: number of patients. X: mean. SEM: standard error of mean.

	Whole group	GFR ≥ 90 mL/min/1.73 m^2	GFR < 90 mL/min/1.73 m^2	*P* value
At diagnosis				
– Number of patients (%)	25 (100)	18 (72)	7 (28)	
– Sex (%)	F: 10 (40) M: 15 (60)	F: 8 (44) M: 10 (56)	F: 2 (29) M: 5 (71)	*0.47*
– Gene mutated Number of cases (%)	*ATP6V1B1*: 11 (44) *ATP6V0A4:* 8 (32) *SLC4A1*:6 (24)	*ATP6V1B1*: 9 (50) *ATP6V0A4:* 6 (33) *SLC4A1:* 3 (17)	*ATP6V1B1*: 2 (29) *ATP6V0A4:* 2 (29) *SLC4A1:* 3 (42)	*0.37*
– Age (years) Median (range)	0.8 (0.1–13.0)	0.6 (0.1–8.0)	4.0 (0.1–13.0)	*0.42*
– Low birth weight Number/reported cases (%)	5/22 (23)	3/15 (20)	2/7 (29)	*0.65*
– Nephrocalcinosis Number/reported cases (%)	18/25 (72)	11/18 (61)	7/7 (100)	*0.13*
– Urolithiasis Number/reported cases (%)	10/24 (42)	7/17 (41)	3/7 (43)	*0.94*
– SCr (mg/dldL) (*X* ± SEM)	*N* = 22 0.56 ± 0.25	*N* = 15 0.47 ± 0.22	*N* = 7 0.74 ± 0.21	*0.01*
– eGFR (mL/min/1.73m^2) (*X* ± SEM)	*N* = 22 70.44 ± 33.06	*N* = 15 74.14 ± 36.00	*N* = 7 62.53 ± 26.37	*0.46*
– Height SDS	*N* = 16	*N* = 11	*N* = 5	*0.36*

(*X* ± SEM)	1.0 ± 0.4	−0.7 ± 0.6	−1.5 ± 0.4	
–HCO_3^- (mEq/L) (*X* ± SEM)	*N* = 22 14.80 ± 0.82	*N* = 16 14.61 ± 0.81	*N* = 6 15.32 ± 2.22	*0.71*
At last ~~follow~~ follow-up visit				
–Follow-up duration (years) Median (range)	*N* = 25 8.8 (1.8–39.8)	*N* = 18 8.3 (1.8–39.8)	*N* = 7 12.0 (4.0–29.9)	*0.74*
–Age (years) Median (range)	*N* = 25 15.0 (2.0–40.0)	*N* = 18 10.50 (2.0–40.0)	*N* = 7 17.0 (15.0–30.0)	*0.10*
–BMI- SDS (*X* ± SEM)	*N* = 20 0.06 ± 0.23	*N* = 14 0.26 ± 0.24	*N* = 6 −0.40 ± 0.50	*0.20*
–Height- SDS (X ± SEM)	*N* = 21 −0.45 ± 0.38	*N* = 14 −0.15 ± 0.47	*N* = 7 −1.06 ± 0.60	*0.27*
–Nephrocalcinosis Number/reported cases (%)	20/21 (95)	13/14 (93)	7/7 (100)	*1.00*
–SCr (mg/~~dl~~dL) (*X* ± SEM)	*N* = 25 0.87 ± 0.25	*N* = 18 0.65 ± 0.31	*N* = 7 0.96 ± 0.17	*0.03*
–eGFR (mL~~ml~~/min/1.73 m^2) (*X* ± SEM)	*N* = 25 105.46 ± 33.78	*N* = 18 121.16 ± 28.87	*N* = 7 71.80 ± 10.60	*< 0.01*
–Serum potassium (mEq/l) (X ± SEM)	*N* = 25 3.95 ± 0.08	*N* = 18 3.98 ± 0.10	*N* = 7 3.87 ± 0.15	*0.56*
–Serum bicarbonate (mEq/l) (*X* ± SEM)	*N* = 23 22.82 ± 0.56	*N* = 16 23.07 ± 0.62	*N* = 7 22.29 ± 1.23	*0.53*
–Dosage of alkali (mEq/kg/day) (*X* ± SEM)	*N* = 21 1.7 ± 0.2	*N* = 14 1.8 ± 0.2	*N* = 7 1.6 ± 0.2	*0.41*

Cr serum creatinine, *eGFR* estimated glomerular filtrate rate, *F* females, *M* males, *N* number of patients, *X* mean, *SEM* standard error of mean