Incomplete distal renal tubular acidosis affects growth in children

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Abstract

Background. Incomplete distal renal tubular acidosis (idRTA) is recognized as an underlying aetiology in recurrent nephrolithiasis. Until the recently reported high prevalence of idRTA in adults with osteoporosis, the effect of idRTA on skeletal parameters was not known. We hypothesize that idRTA has a potential to affect height in the paediatric population.

Methods. In a cross-sectional study, the children with posterior urethral valves (PUV), with normal estimated glomerular filtration rates, were evaluated for idRTA and complete dRTA. The idRTA evaluation was done by short ammonium chloride acidification test. The height standard deviation scores (SDS) in the idRTA group were compared with PUV children without dRTA, with complete dRTA, and to age and gender matched controls with no renal issue (n = 50).

Results. The idRTA group (n = 17) manifested a significantly lower mean height SDS (−1.94 ± 0.41 vs −0.46 ± 0.28; P < 0.001) and a higher short stature prevalence (height SDS below 2) (18% vs 0; P = 0.06) as compared with those without dRTA (n = 23). The matched controls showed a significantly higher height SDS as compared with the idRTA group (−0.39 ± 0.25 vs −1.94 ± 0.41; P < 0.001). As compared with the complete dRTA group (n = 9), the children with idRTA did have significantly higher height SDS (−1.94 ± 0.41 vs −5.31 ± 1.95; P = 0.002), and a lower short stature prevalence (18% vs 78%; P = 0.001). On multivariate analysis, dRTA was significantly associated with the height SDS (β = −0.88; P < 0.001).

Conclusions. Incomplete dRTA affects height in children. This observation needs validation in longitudinal studies.

Keywords: children; clinical manifestations; distal renal tubular acidosis; height scores; posterior urethral valves

Introduction

Renal tubular acidosis (RTA) syndromes result in a systemic metabolic acidosis disproportionate to a decrease in glomerular filtration rate. The renal tubular defects could be in the excretion of hydrogen ion (H⁺), as in distal RTA (dRTA), or in the reabsorption of bicarbonate (HCO₃⁻), as in proximal (type 2) RTA. Distal RTA is further sub-classified into type 1 or type 4 RTA based on the mechanism responsible for H⁺ excretion defect [1,2].

A complete dRTA is characterized by an inability to increase urinary H⁺ excretion despite a systemic hyperchloraeic metabolic acidosis [1]. In contrast, incomplete dRTA (idRTA) does not manifest a metabolic acidosis under basal conditions; however, there remains an inability to acidify urine, which can be demonstrated in context of an induced systemic metabolic acidosis under controlled conditions [1].

Complete dRTA is known to induce systemic manifestations including short stature, rickets, hypercalciuria and nephrolithiasis due to chronic systemic metabolic acidosis [3–6]. Growth retardation is a major clinical issue in the children with complete primary dRTA [5,6]. The clinical effects of idRTA have been limited to its recognized association with recurrent nephrolithiasis and nephrocalcinosis [7,8]. Unlike complete dRTA, idRTA was not suspected to induce skeletal effects until the recently reported prevalence of idRTA in 30% of adults with osteopenia [9] and in 19% with osteoporosis [10]. Due to major skeletal growth in the paediatric age group, the clinical manifestations due to idRTA can be more severe in the childhood period; however, an association between idRTA and somatic growth has not been systematically investigated.

To test our hypothesis, we retrospectively looked at our prospectively collected data to evaluate a possible association between idRTA and the height scores in boys with posterior urethral valves (PUV).
The study group was selected due to previously reported high idRTA prevalence in this population [11,12].

Subjects and methods

Patients

The newly diagnosed children with PUV, who manifested a preserved estimated glomerular filtration rate (eGFR) after the surgical intervention, were included in the study [13]. The reasons for the referral included persistent voiding symptoms, repeated urinary tract infections (UTI), antenatal or incidental hydronephrosis, renal failure or already diagnosed PUV. The patients were on no treatment except antibiotic prophylaxis (cotrimoxazole) in five children due to recurrent UTI. Age- and gender-matched controls, with no renal issue, were selected from pre-surgery clinics.

Study period and venue. Patients were referred from January 1996 to July 2003 to Sanjay Gandhi Post-Graduate Institute (SGPGI), which is a tertiary care university hospital in India.

Exclusion criteria. A persistent renal insufficiency after surgery, or short stature diagnosed due to an alternative aetiology were reasons for exclusion from the study.

Study design. The diagnosis of PUV was confirmed on voiding cystourethrography. The data of duration of voiding symptoms prior to the surgery, age at surgery, presence and grade of VUR was collected. VUR was graded from I to V according to the criteria established by the International Reflux Study in Children [14]. The study group underwent an evaluation for complete and incomplete dRTA following the surgical intervention, after resolution of post-obstructive diuresis. The dRTA associated clinical manifestations (rickets, short stature and nephrocalcinosis), serum electrolytes, calcium, urate and phosphate, and urinary calcium, creatinine and electrolytes were recorded.

Definitions

Age at surgery. Age at the time of first surgical intervention (vesicostomy or fulguration) for PUV.

Duration of voiding symptoms. The duration since the voiding symptoms were first noticed prior to the surgery.

Renal insufficiency. eGFR was estimated by Schwartz method based on serum creatinine measured by Jaffe first-order kinetic reaction on RA 1000 auto analyser [13]. An eGFR ≥90 ml/min/1.73 m² was considered normal.

dRTA evaluation. Evaluation for dRTA was done shortly after resolution of post-obstructive diuresis following the surgical intervention, in the absence of a UTI, ketoacidosis, or urinary sodium <25 mmol/l. None of the patients were treated with a potassium-sparing diuretic, trimethoprim–sulphamethoxazole, pentamidine, angiotensin-converting enzyme (ACE) inhibitor, steroid, thyroid hormone or sodium bicarbonate at the time of the evaluation. A complete dRTA was diagnosed by a basal systemic normal anion gap metabolic acidosis and positive urinary anion gap (Na + K – Cl) [1,15]. A blood pH <7.30 and serum bicarbonate <18 mmol/l, on two separate occasions, qualified for a basal metabolic acidosis. Complete dRTA was further sub-classified based on urine pH and serum potassium levels [2]. Urine pH was measured by a pH meter on a urine sample collected under oil. In children with serum potassium ≥5.5, a urinary transtubular potassium gradient $T_{TTKG} = \text{urine potassium}/(\text{urine osmolality}/\text{serum osmolality})/\text{serum potassium}$ was calculated.

In the absence of a basal metabolic acidosis, an evaluation for idRTA was conducted by ammonium chloride acidification test. Ammonium chloride was administered orally in a dose of 100 mg/kg [16], in a gelatin capsule or a powder form depending on patient’s age or preference. A satisfactory response was a blood pH <7.30 and serum bicarbonate <18 mmol/l on a venous blood gas (VBG). The test was repeated with the same dose in children, who did not tolerate the first dose. In the absence of a satisfactory response to the first dose, the test was repeated with double the dose. Urine pH was assessed at baseline, 2, 4 and 6h after ammonium chloride administration. An incomplete dRTA was diagnosed in the presence of urine pH persistently higher than 5.5, despite an induced systemic acidosis [9,10,16,23].

In 10 randomly selected samples, the correlation ($R^2$) between VBG and arterial blood gases was 0.95 to 0.98, except for a significant difference in $pO_2$.

Growth assessment. Height or length was measured using a stadiometer or an infantometer. Height and weight were expressed as standard deviations scores (SDS). SDS was calculated (subject height–mean height/SD of mean) from the growth chart references, developed from a population with socio-economic status and ethnic characteristics similar to the study group [17,18]. Short stature was diagnosed in the presence of a height SDS score below 2. All the children with short stature underwent a complete evaluation for alternative aetiologies by subspecialists including an endocrinologist and a gastroenterologist.

Rickets. Rickets was diagnosed in the presence of widened and irregular epiphyseal–metaphyseal junctions on X-rays of wrists and long bones by a radiologist blinded to the study [5,6].

Nephrocalcinosis and hypercalciuria. Nephrocalcinosis was diagnosed in the presence of the ultrasound evidence, reported by a radiologist blinded to the study. Urinary calcium, creatinine and other electrolytes were assessed on a regular diet, with no calcium or vitamin D supplementation, on a second morning urine sample. Hypercalciuria was defined by spot urine calcium to creatinine ratio greater than the upper level for the age [19,20].

Statistical analysis. Normality of the data was assessed by Kolmogorov–Smirnov test. Chi-square analysis was used for comparison of nominal data. Continuous variables between two groups were compared by unpaired t-test, if normally distributed, and by Mann–Whitney U-test otherwise. Multiple group comparison was done by Kruskal–Wallis test. Univariate and stepwise multivariate regression analysis was used to calculate regression coefficients. Correlation was done using Spearman’s correlation analysis. Statistical differences were considered significant at $P < 0.05$. SPSS version 11.0 (SPSS, Inc., Chicago, IL, USA) software package was used for the statistical calculations. The study protocol was approved by the local research committee.
A verbal informed consent was obtained in the presence of overt metabolic acidosis; the study participants with no overt metabolic acidosis provided written informed consent prior to the study enrolment.

**Results**

Fifty-five children with PUV were reviewed during the study period. Six children were excluded; five due to persistent eGFR <60 ml/min/1.73 m² after surgical intervention and one due to a short stature secondary to hypothyroidism. Finally, 49 children constituted the study group.

**Patient characteristics.** The dRTA evaluation was done after a mean period of 8.36 ± 0.99 weeks following the surgical intervention, and this period was not significantly different among the three groups.

Incomplete and complete dRTA were diagnosed in 17 (35%) and 9 (18%) children, respectively.

The characteristics of children with idRTA, complete dRTA and without dRTA are shown in Table 1. The study group included children at different ages due to varied referral indications. As compared with the children without dRTA, the idRTA group had an older age at surgery (P = 0.01), a longer duration of prior voiding symptoms (P = 0.003) and a higher prevalence of bilateral VUR (P = 0.02).

The study patients had normal (≥90 ml/min/1.73 m²) eGFRs in three patients; while two patients had rate-limiting dRTA based on normal serum potassium levels and urine pH < 5.5 [2]. None of these children manifested glucosuria, hypouricaemia or hypophosphataemia.

In the absence of a basal metabolic acidosis, idRTA evaluation was conducted in 40 children by ammonium chloride acidification test. Eight patients required repeat ammonium chloride administration; five due to an inability to tolerate the first dose and three due to an inadequate acidification with the first dose. Incomplete dRTA was diagnosed in 17 (42%) of the investigated children, based on their inability to lower urine pH < 5.5 despite induced systemic metabolic acidosis. Children with idRTA and those without dRTA revealed normal serum electrolytes including potassium and chloride levels.

**Characteristics of dRTA.** Nine patients with complete dRTA manifested basal hyperchloremic metabolic acidosis, normal plasma anion gap and positive urine anion gap. Three of them (33%) had hypokalaemia, two (22%) had normokalaemia and four (45%) were hyperkalaemic. A TTKG below five in four hyperkalaemic patients suggested an inappropriately low potassium excretion. Complete dRTA was further sub-categorized. Hyperkalaemia and urine pH > 5.5 suggested voltage-dependent dRTA in three patients, and urine pH < 5.5 in one hyperkalaemic patient suggested reduced aldosterone bioactivity [2,21,22]. Hypokalaemia and urine pH > 5.5 suggested secretory dRTA in three patients; while two patients had rate-limiting dRTA based on normal serum potassium levels and urine pH < 5.5 [2]. None of these children manifested glucosuria, hypouricaemia or hypophosphataemia.
Clinical manifestations. As shown in Table 1, the idRTA group had a lower mean height SDS as compared with those without dRTA (−1.94 ± 0.41 vs −0.46 ± 0.28; P < 0.001); however, the difference did not reach a statistically significant level for short stature (height SDS below 2) (18% vs 0%; P = 0.06). When compared with the complete dRTA group, the idRTA group did manifest significantly higher mean height SDS (−1.94 ± 0.41 vs −5.31 ± 1.95; P = 0.002), and significantly lower prevalence of short stature (18% vs 78%; P = 0.001). Height SDS distribution among the three groups is shown in Figure 1. The mean weight SDS was significantly lower in the idRTA group as compared with those without dRTA (−0.73 ± 0.26 vs −0.08 ± 0.53; P < 0.001).

The age- and gender-matched controls, with no renal issue, showed a significantly higher corresponding height SDS (−0.39 ± 0.25 vs −1.94 ± 0.41; P < 0.001), and weight SDS (−0.03 ± 0.39 vs −0.73 ± 0.26; P < 0.001) as compared with the idRTA group. Similarly, the complete dRTA group manifested significantly lower height SDS (−5.31 ± 1.95 vs −0.35 ± 0.24; P < 0.001), and weight SDS (−3.9 ± 1.5 vs −0.04 ± 0.43; P < 0.001) as compared with the controls. However, the difference in height SDS (−0.46 ± 0.28 vs −0.50 ± 0.23; P = 0.30) and weight SDS (−0.08 ± 0.53 vs −0.06 ± 0.35; P = 0.83) was not significant between children without dRTA and the controls.

Nephrocalcinosis and rickets were not diagnosed in any patient with idRTA or no dRTA; however, the complete dRTA group manifested these clinical stigmata in 22% and 33% children, respectively.

Biochemical parameters. Despite an apparently normal acid–base profile (Table 1), the idRTA group had lower blood pH (P = 0.001) and serum bicarbonate levels (P = 0.04) as compared with no dRTA group; however, the difference was not significant for PCO2 (P = 0.12), serum calcium (P = 0.21) and serum phosphate (P = 0.39) levels.

Hypercalciuria was diagnosed in 78% of the children with complete dRTA compared with none with idRTA or without dRTA. Interestingly, despite urinary calcium to creatinine ratios being below the cut-offs for diagnosis of hypercalciuria [19,20], the idRTA group manifested higher ratios than the no dRTA group (P = 0.001). Fractional excretion of urinary sodium was high in all the three groups (Table 1); however, the difference among the groups was not significant (P = 0.41).

Factors associated with lower height SDS. On univariate analysis, height SDS was significantly associated with age at surgery (β = −0.32; P = 0.02), duration of voiding symptoms (β = −0.40; P = 0.004), bilateral reflux (β = −0.43; P = 0.002) and presence of dRTA (β = −0.88; P < 0.001). However, on multivariate analysis, the association was significant only between dRTA and the height SDS (Table 2).

On correlation analysis, height SDS was associated with weight SDS (r = 0.93; P < 0.001), blood pH (r = 0.83; P < 0.001) and serum bicarbonate levels (r = 0.85; P < 0.001). The associations of height SDS with serum bicarbonate levels and with blood pH are shown in Figures 2 and 3, respectively.

Discussion

Based on recently reported high prevalence of idRTA in adults with osteoporosis [9,10], our goal was to assess the effect of idRTA on height SDS in children. The study group was selected due to previously reported high prevalence of idRTA in children with obstructive uropathy [14,15]. The children with idRTA manifested significantly lower mean height SDS as compared with the PUV children without dRTA. The prevalence of short stature (height SDS below 2) was higher too in the idRTA group; but the difference did not turn
out statistically significant. Age-matched controls showed higher height SDS as compared with the idRTA group. We did not come across a similar study involving children with idRTA; however, idRTA prevalence of 30% in adult patients with osteopenia [9] and 19% with osteoporosis [10] has been reported. Interestingly, Pongchaiyakul C et al., in their population-based study in Thailand, did not find higher osteoporosis prevalence in adults evaluated due to diagnosed primary idRTA [23]. Their results were similar to statistically non-significant short stature prevalence (height SDS below 2) in our idRTA group.

Despite a similar methodology for idRTA evaluation (short ammonium chloride acidification) in other studies [9,10,23] and ours, the difference in the observations could be due to different study designs. Weger et al. evaluated idRTA in the presence of already diagnosed osteoporosis [9,10]; while Pongchaiyakul C et al., similar to our study, assessed skeletal manifestation in adults with already diagnosed idRTA [23]. Unlike the Thai study, we picked a trend towards lower height SDS in our idRTA patients [23]. This difference in the observation can be attributed to a more substantial effect of idRTA in children, different skeletal parameters studied or to different aetiologies of idRTA in the two studies. Similar to the results from Weger et al., lower height SDS in our idRTA group supports the hypothesis that idRTA can affect skeletal parameters; however, other concomitant factors may affect severity of the observed clinical effect.

Despite absence of a basal metabolic acidosis, the clinical impact of idRTA can be explained by the renal acid–base handling. In response to a positive acid balance, normal renal acidification mechanisms can increase compensatory renal ammonium ion excretion to more than double [24]; however, a partial renal acidification defect, due to an idRTA, can induce recurrent positive acid loads at the times of increased protein load or intermittent catabolic stress [24,25].

Despite blood pH and serum HCO₃ values being within the normal range in our patients with idRTA and without dRTA, a statistically significant difference in their absolute values signifies a tendency to develop metabolic acidosis in the presence of idRTA. Wager et al. observed a similar trend in bone mineral density scores in the presence of idRTA [10]. A strong correlation of height SDS with mean blood pH, and serum bicarbonate levels, suggests the mechanistic explanation for the lower height SDS in our patients. Furthermore, increased osteoblast and osteoclast activation is reported in the presence of idRTA [26]. In a nutshell, idRTA is a state of increased NH₃, and thus NH₄⁺ excretion, which leads to an alkaline urine and hypocitraturia in association with concomitant increased bone turnover [7].

In our study group, the patients from the idRTA and complete dRTA groups were significantly older as compared with those without dRTA. We examined the possible mechanisms that could affect height in our patients due to long-standing obstruction, independent dRTA. A confounding effect of long-standing renal insufficiency appears less likely in view of normal GFR values in the idRTA group prior to and following the surgery. Polyuria after the surgery can potentially affect growth due to recurrent dehydration episodes; however, dRTA evaluation shortly after the surgical intervention suggests a minimal effect due to excessive diuresis [27,28]. All the three groups had natriuresis at the time of evaluation; however, the difference was not statistically different enough to explain the difference in height SDS. Of note, use of height SDS, rather than absolute height, corrects for the variability in age as SDS scores are considered independent of age. A significant difference in height SDS between idRTA and the age-matched controls further supports the observation. Use of growth charts developed from a population similar to the study group for height SDS evaluation excludes confounding effect due to race or general nutritional status of the local population. A delay in PUV intervention has been previously associated with
a higher prevalence of idRTA and complete dRTA [12]. Apparently, older age in our idRTA group contributed to lower height SDS through an increased prevalence of idRTA.

Systemic alkalization does improve growth parameters in children with complete dRTA [5,6]. Alkali therapy in idRTA can prevent recurrent nephrolithiasis [7,8]; its effect on height SDS in idRTA is not defined. Sebastian et al. demonstrated an improvement in calcium and phosphorus balance, decrease in bone resorption, and increase in the rate of bone formation with oral administration of potassium bicarbonate in post-menopausal women despite no apparent acidification defect [29]. Based on these observations, diets rich in fruit or vegetables, or supplementation with potassium bicarbonate can reduce acid load and so improve bone status at the stage of idRTA. This issue needs evaluation in longitudinal studies.

The relevance of our findings in obstructive uropathy-associated idRTA to patients with primary idRTA can be debated. Obstructive uropathy induces renal injury through multiple mechanisms including increased tubular hydrostatic pressure, activated rennin–angiotensin axis, and through transforming growth factor β-mediated interstitial injury [30]; idRTA, in turn, can be a result of direct tubulointerstitial injury with or without associated aldosterone resistance. In contrast, primary dRTA is usually a result of a specific renal tubular acidification defect [2–6]. As a result of a more generalized renal injury, obstructive uropathy can potentially induce more severe growth retardation through renal insufficiency, natriuresis and polyuria as compared with primary dRTA [31].

Despite a statistically compelling trend in the clinical manifestations, cross-sectional design is a limitation of the study. However, a detailed evaluation to exclude an alternative aetiology for short stature, a single aetiology for dRTA, and a reasonably sized study cohort adds strength to the observations. Although, we did not determine vitamin D status, a significant vitamin D deficiency appears less likely due to a practice of regular vitamin supplementation in younger children and, in general, a good exposure to sunshine in our study group. Serum parathyroid hormone (PTH) levels were not available in our patients; however, both Weger M. (despite osteoporosis) and Pongchaiyakul et al. found normal PTH levels in their study cohorts [9,23].

A statistically significant association between height SDS and idRTA in children is a novel observation. Further studies are needed to confirm a place for idRTA evaluation in children at a higher risk to develop idRTA and in the presence of an unexplained slow growth velocity.

Acknowledgements. The authors are grateful to Dr. Brian Steele and Dr. Narayan Prasad for the inputs on the manuscript.

Conflict of interest statement. None declared.

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Received for publication: 22.1.07
Accepted in revised form: 24.4.07