

Clinical Types and Outcome of Renal Tubular Acidosis in Children

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ABSTRACT

Background: Renal tubular acidosis (RTA) is a tubulopathy characterized by polyuria, polydipsia and failure to thrive with hyperchloremic metabolic acidosis and normal serum anion gap.

Aim: To determine the clinical types and outcome of children with RTA.

Methods: This was a retrospective observational study carried out in the Department of Nephrology at The Children's Hospital and The Institute of Child Health Lahore, Pakistan from January 2009 to December 2017.

Results: 120 subjects were selected - 70% distal, 29% proximal and only one with mixed type of RTA. There were 61% males and 39% females with parental consanguinity identified in 67% and family history positive in 36% cases. Cystinosis, Lowe's syndrome and Dent disease were found to be the underlying etiologies in 12.5%, 6% and 2% participants with proximal RTA. Failure to thrive and short stature was noted in all patients at the time of diagnosis. The mean serum creatinine on the last visit after 5 years of follow-up was 1.04 ± 0.95 mg/dl (distal), 1.01 ± 1.12 mg/dl (proximal) and 0.9 mg/dl (mixed) and 12% children were found to develop renal insufficiency.

Conclusion: The overall prognosis of RTA is generally good provided the diagnosis is made early with a good compliance to alkali treatment. The findings of our study reiterate the need for early diagnosis in order to institute appropriate treatment for improving outcome regarding growth and preserving renal function.

Keywords: Renal tubular acidosis, Types, Clinical outcome, Growth, Chronic kidney disease

INTRODUCTION

Renal tubular acidosis (RTA) is a group of disorders characterized by defective renal acid-base regulation¹. In absence of a gastrointestinal origin, the capacity for normal urinary acidification is impaired in RTA resulting in net acid retention and hyperchloremic metabolic acidosis despite normal glomerular filtration rate^{2,3}. RTA can be due to several causes ranging from primary varieties to secondary disease processes, the former being the most common and resulting from inherited genetic defects in the tubular proteins involved in the renal regulation of acid-base homeostasis⁴. RTA is classified into 4 major forms based on pathophysiology: distal, proximal, mixed and hyperkalemic types^{5,6}. Distal RTA is associated with reduced urinary acid secretion, proximal type is characterized by impaired bicarbonate reabsorption and hyperkalemic variety is an acid-base disturbance generated by aldosterone deficiency / resistance^{7,8}. In neonatal life and infancy, RTA is often detected incidentally through an abnormal blood workup while older children present with typical clinical features of poor growth, polyuria and polydipsia. A positive family history may facilitate the diagnosis because of the disease's hereditary transmission but the final diagnosis of primary RTA requires mutation analysis of involved genes studied by next-generation sequencing⁹⁻¹⁴. Treatment requires sustained alkali supplementation aiming at normalization of blood pH and bicarbonatemia¹⁵. Prognosis varies and often depends on the type of RTA and its underlying cause. Growth retardation is a recognized problem in these patients, however, good catch-up growth has been

observed with adequate treatment. Some patients lead normal lives with minimal treatment while others progress to chronic kidney disease (CKD) as a consequence of nephrocalcinosis and hypokalemic nephropathy^{16,17}.

As there is paucity of published data, we conducted this single-centre retrospective study to elucidate the clinical entities of RTA which will enable us to find out the pattern and outcome of the disease.

SUBJECTS AND METHODS

The retrospective data was obtained and reviewed from medical files of patients diagnosed as RTA presenting between January 2009 to December 2017 in the Pediatric Nephrology Department at The Children's Hospital Lahore Pakistan. Each subject was followed up for a period of 5 years with enrolment of the last child done by December 2012. The information was gathered from records regarding age of presentation, type and duration of disease, underlying etiology, anthropometric data and the investigations performed - arterial blood gases, serum electrolytes, serum and urine anion gap, renal function tests, serum calcium, phosphorus and alkaline phosphatase, urinalysis, spot urine for calcium and creatinine ratio and renal ultrasound. The diagnosis of RTA was made on the basis of hyperchloremic metabolic acidosis with normal serum anion gap. Height, weight and growth velocity were plotted on percentile charts during different periods of follow-up. Final height achieved on last follow-up visit was correlated with malnutrition and renal failure. The glomerular filtration rate (GFR) was calculated by the Schwartz formula in patients who developed renal insufficiency and CKD was defined as creatinine clearance <60 ml/min/1.73m² (KDIGO guidelines). Neonates,

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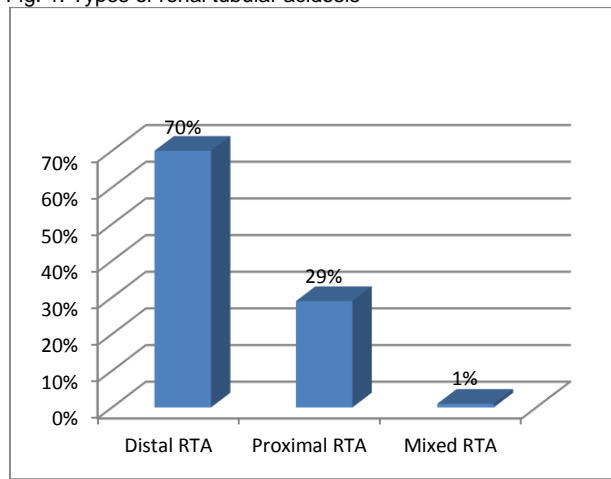
participants with renal insufficiency at the time of presentation and those who were lost to follow-up during the study period were excluded from the trial. Treatment was advised in the form of sodium / potassium citrate solution to all patients while phosphate supplementation (Joule's solution) was prescribed for children with proximal RTA. The dose of bicarbonate was adjusted in all the patients with the aim of maintaining the serum bicarbonate level $\geq 22\text{mmol/L}$ which was considered to be adequacy of treatment. The daily bicarbonate requirement decreased from the mean of 18.4mmol/kg to 4.2mmol/kg in the first 3 years of therapy with correction and normalization of bicarbonate levels except children with poor therapeutic compliance and those who progressed to renal failure.

Data was analyzed by using SPSS version 20.0 and p-value was calculated for the statistical significance of the results. The ethical approval was obtained from the Institution Review Board prior to the study and informed written consent taken from the parents.

RESULTS

Out of 158 patients diagnosed as RTA during the study period, only 120 were selected who were on regular follow-up - 85 (70%) with distal, 34 (29%) proximal and only one child (0.6%) with mixed type of RTA (Fig. 1). The mean age of onset of symptoms in distal RTA was 7.01 ± 4.77 months, 6.91 ± 3.18 months in proximal and 11.00 months in mixed type, while the mean age of diagnosis was 39.95 ± 43.27 , 37.58 ± 41.71 and 96 months respectively. There were 73 (61%) males and 47 (39%) females. Parental consanguinity was identified in 80 children (67%) while family history significant for similar illness / death in siblings was found in 43 participants (36%). Cystinosis, Lowe's syndrome and Dent disease were found to be the underlying etiologies in 6(12.5%), 3(6%) and 1(2%) subjects presenting with proximal RTA.

Fig. 1: Types of renal tubular acidosis

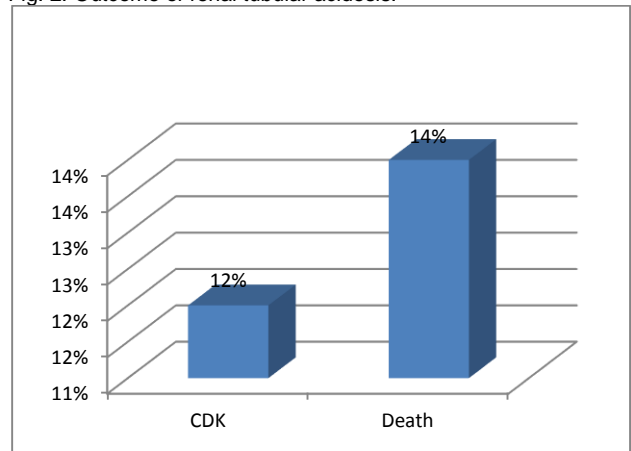


The most common presentation of polyuria, polydipsia and failure to thrive was present in all the subjects with the mean weight being 7.9 ± 4.1 kg (distal), 7.48 ± 3.42 kg (proximal) and 13.0 kg (mixed) and mean height of 83.98 ± 25.04 cm, 78.60 ± 20.82 cm and 99 cm respectively. Renal ultrasound findings of nephrocalcinosis were present in all children with distal RTA and Dent

disease while clinical as well as radiological evidence of rickets was seen in 72 (60%) subjects – 25 (73%) proximal and 40(47%) distal RTA. Pathological fractures were found to occur in 4(12%) and 7(8%) patients of proximal and distal RTA respectively.

Renal function tests were monitored on annual basis to assess for development of CKD during the course of disease. The mean serum creatinine at presentation was 0.62 ± 0.17 mg/dl (distal), 0.69 ± 0.13 mg/dl (proximal), 0.7 mg/dl (mixed) while that on the last visit after 5 years of follow-up was 1.04 ± 0.95 mg/dl, 1.01 ± 1.12 mg/dl and 0.9 mg/dl respectively. The GFR was calculated by the Schwartz formula and found to be 60–90 ml/minute/1.73m² consistent with CKD stage 2 in 14(12%) subjects–11(13%) distal and 3(9%) proximal RTA (2 out of 6 pts with cystinosis developed renal insufficiency). 17(14%) children expired during the study period 15(17%) with distal and 2 (6%) of proximal RTA (Fig 2).

Fig. 2: Outcome of renal tubular acidosis.



DISCUSSION

Renal tubular acidosis constitutes a group of disorders characterized by hyperchloremic metabolic acidosis with a normal anion gap. We presented a retrospective clinical data on the follow-up of 120 children with RTA in a single tertiary care centre with each patient followed up for 5 years. The analysis enlightens about the management and prognosis of patients with this rare disease.

In our experience, distal RTA was found to be the most common type of renal tubular acidosis comprising 70% cases followed by proximal (29%) and mixed (1%) types in contrast to a study by Kiran et al who reported 46% patients with distal RTA. In consistence with the published literature, the latter also established cystinosis to be the principal cause of Fanconi syndrome which was seen in majority of our children with primary proximal RTA and only 12.5% cases of cystinosis¹⁸. A significant gap between the onset of symptoms and diagnosis was observed in majority of our patients. This could be explained by the fact of misdiagnosis made by the physician at the first presentation or delay in seeking medical advice on the part of patients' parents which is not uncommon in developing countries. In the series of distal RTA by Bajpai et al., the onset of symptoms was at the age of 1.8 years (3 months to 7.5 years) and age at diagnosis was 6 years (1.5-13 years)¹⁹. Comparatively, the mean age

of onset of symptoms in our cases of distal RTA was 7.01 ± 4.77 months, 6.91 ± 3.18 months for proximal and 11.00 months in mixed type, while the mean age of diagnosis was 39.95 ± 43.27 , 37.58 ± 41.71 and 96 months respectively.

Our study showed that appropriate treatment in RTA with good compliance was associated with correction of acidosis and statistically significant increase in height although final height remained compromised. These findings were similar to those of Besouw, et al²⁰ who observed the same results. Another study reports that significant improvement in height was noticed in distal RTA only ($P < 0.001$) and there was no significant catch-up growth in children with Fanconi syndrome^{21,22}. As growth is also influenced by nutritional status of the child, malnutrition present in all our subjects was considered a major factor contributing to growth retardation. As growing children have a higher metabolic rate and protein intake than adults, they may need relatively higher doses of alkali treatment when corrected for body weight to maintain a normal pH and serum bicarbonate level. This requirement for increased bicarbonate dose was previously reported in a study in which five children with distal RTA were followed for a period of less than 10 years²². The fact that children in general need higher doses of alkali was confirmed in our study as well stating that the average initial daily bicarbonate requirement was 18.4mmol/kg particularly in patients with proximal RTA.

Nephrocalcinosis is an important feature as an essential outcome variable in distal RTA. It was present in all our children with distal RTA and Dent disease with no resolution observed during follow-up. The high rate of nephrocalcinosis at presentation may be due to the delay in diagnosis and institution of therapy. Deterioration of renal function was seen in patients with distal RTA, mainly in those with hypercalciuria, nephrocalcinosis / nephrolithiasis, but progression to end-stage renal disease has been related to the underlying etiology rather than the degree of calcification^{21,22}. In our series, 12% patients had progressed to renal insufficiency during a follow-up period of 5 years out of which 13% were cases of distal RTA and 9% with proximal RTA (2 out of 6 patients with cystinosis developed renal insufficiency).

CONCLUSION

The overall prognosis of RTA is generally good provided the diagnosis is made early with a good compliance to alkali treatment. The findings of our study reiterate the need for early diagnosis in order to institute appropriate treatment for improving outcome in terms of growth and preserving renal function. Increasing awareness of the pediatricians about tubular disorders may ensure early referral and diagnosis and the risk of progression to end-stage renal failure warrant prenatal diagnosis in order to establish early neonatal management.

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