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ORIGINAL ARTICLE

Spectrum of clinical manifestations of renal tubular acidosis in children presenting at a Tertiary Care Hospital.

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ABSTRACT… Objective: To determine the spectrum of clinical manifestations of renal tubular acidosis (RTA) in children. **Study Design:** Cross-sectional study. **Setting:** Department of Pediatrics, National Institute of Child Health, Karachi, Pakistan. **Period:** October 2023 to September 2024. **Methods:** A total of 124 children aged 1 month to 12 years, and presenting with RTA were analyzed. Demographic, clinical, laboratory and imaging parameters were noted. Chi-square test, and independent sample t-test were applied for the comparison of data, taking $p < 0.05$ as statistically significant. **Results:** In a total of 124 children, 72 (58.1%) were male. The most frequent presenting complaints were loose stool, failure to thrive, and dehydration, noted in 71 (78.9%), 65 (72.2%), and 42 (46.7%) children, respectively. Bone deformities were observed in 50 (40.3%) children. Renal ultrasound revealed structural abnormalities, and urolithiasis in 12 (9.7%), and 40 (32.3%) children, respectively. RTA types were distal, and proximal in 90 (72.6%), and 34 (27.4%) children, respectively. Gender was found to have significant association RTA types ($p=0.032$). Comparison of laboratory parameters evaluation with respect to RTA types revealed significant patterns for chloride ($p=0.005$), and sodium ($p=0.003$). **Conclusion:** Distal RTA was the most common form of RTA. Loose stool, failure to thrive, and dehydration were the most common presenting features, while urolithiasis and structural abnormalities were identified in a significant proportion of children.

Key words: Chloride, Renal Tubular Acidosis, Sodium, Tiredness, Urolithiasis.

INTRODUCTION

Renal disease in hospitalized children can be challenging to diagnose early due to subtle symptoms, unlike in adults.[1,2] The kidneys are vital for maintaining acid–base balance through acid excretion and bicarbonate regeneration, with renal tubules playing a central role in fluid, electrolyte, and acid-base regulation. Dysfunction in these processes can lead to various renal tubular disorders.[3-5]

Renal tubular acidosis (RTA) is the most common tubular disorder, classified into proximal and distal types. Proximal RTA results from impaired bicarbonate reabsorption, often associated with Fanconi syndrome, while distal RTA stems from defective hydrogen ion secretion. Other forms include mixed RTA, combining features of both proximal and distal types, and hyperkalemic RTA, caused by inadequate urinary ammonia for bicarbonate regeneration.[6-8]

Few researchers have worked on spectrum of RTA in children and. Kiran et al analyzed clinical profile and outcome of renal tubular disorders in children and reported the distal renal tubular acidosis was the most common type, noted in 46.3% patients.[4] Al Mosawi analyzing spectrum of renal tubular disorders in Iraqi children documented distal RTA in 21.6% children.[9] A Pakistani study by Akhtar et al reported that 70.0% children had with distal RTA, 29.0% proximal RTA, and 1.0% with mixed RTA.[10] Limited research has been done analyzing RTA in children internationally, or locally. This study was planned to determine the spectrum of clinical manifestations of RTA in children.

METHODS

The cross-sectional study was conducted at the department of pediatrics, National Institute of Child

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Health, Karachi, Pakistan during October 2023 to September 2024. Using Akhtar et al prevalence of distal RTA as 29.0%[10], with 95% and margin of error 8%, the sample size was calculated to be 124. Non-probability, consecutive sampling technique was adopted. Approval was acquired from "Institutional Ethical Review Board" (IERB-15/202, dated: 25-01-2024). Written and informed consents were obtained from parents/guardians. Inclusion criteria were children of either gender, aged 1 month to 12 years, and presenting with RTA. Children with RTA secondary to drugs or transient in nature were excluded. Children with hypercalciuria, or hyperoxaluria were also not included. Parents or guardians unwilling for participation in this study were also excluded.

Demographic details of each child such as gender, and age, and height were noted. Height was measured either by using soft measuring tape or standard stadiometer. Weight of the child was measured either by using standard weighing tub or electronic weighing machine. Presenting complaints were documented. Each child was subjected to necessary laboratory and imaging evaluations. Children with urolithiasis was also investigated for 24-hour urinary examination for calcium, uric acid and oxalate. RTA was diagnosed based on presence of failure to thrive, polyuria, refectory rickets, and hypokalemia <3.5 mEq. Proximal RTA was defined as normal to mildly low serum potassium level, and hyperchloremic metabolic acidosis with spontaneous acidemia in which urine pH <5.5. Distal RTA was defined as a normal anion gap metabolic acidosis with urinary pH persistently <5.5. Data were recorded on a special proforma designed for this study.

After collection of data, the analysis was performed using "IBM-SPSS Statistics, Version 26.0". Mean and standard deviation were calculated for quantitative variable like age, height, weight, BMI, duration of symptom, potassium, chloride, sodium, calcium, phosphorus, bicarbonate, blood urea and creatinine. Frequency and percentages were calculated for qualitative variables like gender, age in group, BMI classification, duration of symptom, sign and symptoms and type of RTA. Chi-square, or independent sample t-test was applied taking $p < 0.05$ as statistically significant.

RESULTS

In a total of 124 children, 72 (58.1%) were male. The mean age, height, and weight were 5.06±3.37 years, 85.38±7.97 cm, and 10.30±1.73 kg, respectively. Th mean duration of symptoms was 7.06±2.55 months. The most frequent presenting complaints were loose stool, failure to thrive, and dehydration, noted in 71 (78.9%), 65 (72.2%), and 42 (46.7%) children, respectively. Bone deformities were observed in 50 (40.3%) children. Renal ultrasound revealed normal findings in 72 (58.1%) children, whereas structural abnormalities, and urolithiasis were identified in 12 (9.7%), and 40 (32.3%) children, respectively. RTA types were distal, and proximal in 90 (72.6%), and 34 (27.4%) children, respectively. Gender was found to have significant association RTA types (p=0.032). Th details about the comparison of RTA types with respect to various demographic and clinical characteristics of children are shown in Table-I.

Comparison of laboratory parameters evaluation with respect to RTA types revealed significant patterns for chloride (p=0.005), and sodium (p=0.003), and the details are given in Table-II.

DISCUSSION

The present study showed that distal RTA (dRTA) was the predominant form noted in 72.6% cases, while proximal RTA was identified in 27.4%. These results align closely with studies conducted by Akhtar et al.[10], and Yazici and Cakar[11], and Nassih et al.[12], who similarly reported distal RTA as the predominant type, accounting for 70-73% of RTA cases. The clinical significance of the findings of this study lies in the timely recognition and differentiation between proximal and distal RTA, as the latter is more commonly associated with complications like nephrocalcinosis, recurrent urolithiasis, and sensorineural hearing loss. Akhtar et al.[10], in their retrospective study conducted in Lahore, Pakistan, observed a male predominance (61%) in children with RTA, as was revealed in this study (58.1%). Yazici and Cakar[11], who reported familial clustering and male predominance in dRTA cases.

Characteristics		Distal RTA (n=90)	Proximal RTA (n=34)	P-value
Gender	Male	47 (52.2%)	25 (73.5%)	0.032
	Female	43 (47.8%)	9 (26.5%)	
Age (years)		5.68±3.40	3.44±2.72	0.001
Height (cm)		86.30±7.01	82.94±9.79	0.036
Weight (cm)		10.27±1.77	10.39±1.66	0.752
Duration of symptoms (months)		7.14±2.47	6.85±2.78	0.572
Presenting symptoms/features	Loose stool	71 (78.9%)	27 (79.4%)	0.949
	Failure to thrive	65 (72.2%)	26 (76.5%)	0.633
	Dehydration	42 (46.7%)	12 (35.3%)	0.255
	Bone deformity	34 (37.8%)	16 (47.1%)	0.347
Renal ultrasound	Normal	54 (60.0%)	18 (52.9%)	0.757
	Structural abnormality	8 (8.9%)	4 (11.8%)	
	Urolithiasis	28 (31.1%)	12 (35.3%)	

Table-I. Comparison of RTA types with respect to demographic and clinical characteristics of children (N=124)

Laboratory Parameters	Distal RTA (n=90)	Proximal RTA (n=34)	P-Value
Potassium (mmol/L)	3.01±0.21	2.94±0.28	0.135
Chloride (mmol/L)	106.37±4.08	109.26±6.82	0.005
Sodium (mmol/L)	135.37±4.82	131.54±8.91	0.003
Calcium (mg/dl)	9.24±0.86	9.41±0.74	0.311
Phosphorus (mg/dl)	4.61±0.35	4.46±0.49	0.060
Bicarbonate (mmol/L)	14.96±1.80	15.31±1.65	0.325
Blood Urea (mg/dl)	28.81±4.42	30.56±4.82	0.057
Serum Creatinine	0.76±0.09	0.73±0.09	0.100

Table-II. Comparison of laboratory parameters with RTA types (N=24)

Gender differences in clinical presentation may reflect underlying genetic predisposition or variations in symptom severity and disease progression.[13]

The presence of urolithiasis in 32.3% in this study is a notable finding, as it has been reported at varying rates in prior literature.[14,15] Mugdha et al.[16], found nephrocalcinosis in 62.5% of children with dRTA attributed to WDR72 gene mutations, whereas Nassih et al.[12], observed a slightly lower prevalence of nephrocalcinosis at 62.5% of dRTA cases. In contrast, Yazici and Cakar[11] reported urolithiasis and nephrocalcinosis predominantly in children with dRTA, with a significantly lower incidence in proximal RTA. This discrepancy in findings may be attributed to genetic variability across populations, environmental factors, or dietary calcium and vitamin D intake. It is noteworthy that genetic analysis was not performed in our study, limiting the ability to directly compare specific mutations implicated in RTA. Prior studies have highlighted that ATP6V1B1 and ATP6V0A4 mutations are the most common genetic defects in children with dRTA, particularly in South Asian and Middle Eastern populations, where consanguinity rates are high.[17] Laboratory parameters differences between proximal and distal RTA observed in this study, particularly serum chloride (p=0.005) and sodium (p=0.003), are consistent with the known pathophysiological differences between these two types.[18,19]

An important observation in this study was the duration of symptoms prior to diagnosis, with a mean of 7.06±2.55 months. Delayed diagnosis and subsequent initiation of alkali therapy have been shown to negatively impact growth outcomes in children with RTA.[20] Yazici and Cakar[11] reported that older age at diagnosis was associated with lower weight and height Z-scores, underscoring the importance of early diagnosis in mitigating growth failure. Besouw et al.[21], demonstrated significant improvements in height-for-age Z-scores following initiation of alkali therapy, with persistent growth retardation in only 12.5% of cases after treatment. In this

study, although detailed growth parameters (Z-scores) were not analyzed longitudinally, the high prevalence of growth failure, rickets, and bone deformities highlights the need for prompt diagnosis and treatment.

Renal ultrasound findings in this study revealed normal results in 58.1% of children, while structural abnormalities and urolithiasis were detected in 9.7% and 32.3%, respectively. This is consistent with findings from Yazici and Cakar[11], who reported nephrocalcinosis and urolithiasis predominantly in dRTA patients. Tung et al.[22], in their descriptive study of 36 children with RTA, also reported nephrocalcinosis in a majority of their cohort. The clinical implication of these findings is significant, as untreated dRTA can lead to progressive nephrocalcinosis, renal scarring, and eventual renal insufficiency. Akhtar et al.[10], reported renal insufficiency in 12% of children over a five-year follow-up period, reinforcing the need for long-term monitoring of renal function in children with RTA.

The clinical spectrum of presenting complaints in this study was broad, with tiredness (79%), muscle weakness (73.4%), and muscle cramps (43.5%) being the most frequent symptoms. These findings are comparable to those reported by Tung et al.[22], who observed slow weight gain, polyuria, and muscle weakness as the most common presenting features. Nassih et al.[12], reported polyuria-polydipsia syndrome in 90% of their patients, highlighting its role as a hallmark symptom of RTA. The presence of polyuria and polydipsia in children should raise clinical suspicion for RTA, particularly in the context of growth failure and metabolic acidosis.

A notable limitation of our study is the lack of genetic analysis, which precludes direct comparison with studies that have identified specific gene mutations associated with RTA. Mugdha et al.[16], and Besouw et al.[21], have demonstrated that ATP6V1B1 and ATP6V0A4 mutations are the most common genetic defects in dRTA, with sensorineural hearing loss being a common clinical association. While this study did not assess hearing loss, it remains an important clinical consideration in children with dRTA, particularly those with ATP6V1B1 mutations. Future studies incorporating genetic analysis and audiological evaluation are warranted to further elucidate the genetic basis and clinical spectrum of RTA in our population. Another limitation is the cross-sectional design of our study, which precludes longitudinal assessment of growth outcomes and renal function following treatment.

CONCLUSION

This study highlights the spectrum of RTA in children, with distal RTA being the predominant form. Loose stool, failure to thrive, and dehydration were the most common presenting features, while urolithiasis and structural abnormalities were identified in a significant proportion of children. Gender was found to have a significant association with RTA type, and laboratory differences between proximal and distal RTA were observed, particularly in serum chloride and sodium levels. These findings underscore the importance of early diagnosis and appropriate treatment in mitigating growth failure and renal complications associated with RTA. Future studies incorporating genetic analysis and long-term follow-up are warranted to further elucidate the clinical and molecular basis of RTA in our population. By improving awareness and diagnostic capabilities, healthcare providers can ensure timely intervention and better outcomes for children with RTA.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3	**Sadaf Asim:** Data collection, drafting, responsible for data's integrity.
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5	**Huma Mehmood:** Data analysis, proof reading, critical revisions.
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