Clinical and Biochemical Characteristics of Patients with Renal Tubular Acidosis in Southern Part of West Bengal, India: A Retrospective Study

Partha Pratim Chakraborty*, Rana Bhattacharjee[1], Shinjan Patra**, Ajitesh Roy[1]***, Kripasindhu Gantait, Subhankar Chowdhury[1]

Department of Medicine, Midnapore Medical College and Hospital, Midnapore, [1]Department of Endocrinology and Metabolism, IPGME and R/SSKM Hospital, Kolkata, West Bengal, India
*Present affiliation: Clinical Tutor, Department of Endocrinology and Metabolism, Medical College, Kolkata, West Bengal, India
**Present affiliation: Senior Resident, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, Jodhpur, Jodhpur, Rajasthan, India
***Present affiliation: Assistant Professor, Department of Endocrinology, Vivekananda Institute of Medical Sciences, Kolkata, Kolkata, West Bengal, India

Abstract

Purpose of the Study: Reversible proximal tubular dysfunction associated with distal renal tubular acidosis (dRTA) mimics type 3 RTA, a condition classically associated with features of both proximal RTA (pRTA) and dRTA. Proximal tubulopathy has been reported in children with primary dRTA, but the data in adults are lacking. **Study Design:** In this hospital record-based retrospective study, data from 66 consecutive cases of RTA, between January 2016 to December 2018, were retrieved and analyzed. **Results:** Mean age of the study population was 25.3 years (range: 3 months to 73 years). Six (9.1%) of them had pRTA, 58 (87.9%) had dRTA, 1 (1.5%) had type 3 RTA, and the remaining 1 (1.5%) had type 4 RTA. Ten patients (17.2%) with dRTA and 3 patients of pRTA (50%) had underlying secondary etiologies. Data on proximal tubular dysfunction were available for 30 patients with dRTA, of whom 1 had isolated dRTA, and the rest 29 patients had accompanying completely reversible proximal tubular dysfunction. Among the 10 cases of secondary dRTA, 6 were not evaluated for proximal tubular dysfunction. Of the remaining 4, 3 had reversible form of proximal tubular abnormality. Fifty-two patients with dRTA came from a population, indigenous to the "Rarh" region of India. **Conclusions:** Proximal tubular dysfunction often accompanies dRTA; 75% of the children with primary dRTA, at least 29% of adults with primary dRTA, and at least 30% of adults with secondary dRTA manifest such completely reversible form of proximal tubulopathy. "Rarh' region of India probably is a hotspot for endemic dRTA.

Keywords: Endemic renal tubular acidosis, low molecular weight proteinuria, proximal tubular dysfunction, Rarh region, renal tubular acidosis, type 3 RTA

INTRODUCTION

Renal tubular acidosis (RTA) is a group of transport defects, associated either with reduced proximal tubular reabsorption of bicarbonate (HCO_3^-) [proximal RTA (pRTA) or type 2 RTA], or decreased capacity of the α-intercalated cells in the collecting duct (CD) to excrete hydrogen ion (H^+) [distal RTA (dRTA) type 1 RTA], or both. Combined features of pRTA and dRTA is termed as type 3 RTA, a condition typically seen in inherited or acquired defect of the carbonic anhydrase type II (CAII) enzyme. Type 4 RTA is secondary to impaired secretion of H^+ and potassium (K^+) by CD, due to reduced aldosterone secretion or action. Biochemically RTA as a group is characterized by hyperchloremic normal anion gap (AG) metabolic acidosis with relatively preserved glomerular filtration rate (GFR). All types of RTA may be primary, or secondary to a variety of systemic causes. Patients with RTA have heterogeneous clinical presentations depending on age,

Access this article online

Quick Response Code:

Website:
www.ijem.in

DOI:
10.4103/ijem.IJEM_785_20

Address for correspondence: Dr. Partha Pratim Chakraborty, Department of Endocrinology and Metabolism, MCH 4th Floor, Medical College, 88 College Street, Kolkata - 700073, West Bengal, India.
E-mail: docparthapc@yahoo.co.in

type of RTA, etiology, degree of acidification defect, duration of disease and underlying comorbidities.

Primary isolated pRTA is rare, and pRTA is often associated with generalized proximal tubular dysfunction (PTD), termed Fanconi syndrome (FS), having varying combinations of aminoaciduria, low molecular weight (LMW) proteinuria (β_2-microglobulin, retinol binding protein), glucosuria, phosphaturia, bicarbonaturia, natriuresis, kaliuresis, uricosuria and polyuria. Hypokalaemia, hypophosphatemia and urine pH <5.5 in patients with normal AG metabolic acidosis suggests pRTA. Though hypokalaemia is common to both pRTA and dRTA, urinary pH of >5.5 during systemic acidosis, hypocitraturia and nephrocalcinosis/nephrolithiasis separate classic dRTA from pRTA. Interestingly, some patients of dRTA may develop a completely reversible form of secondary PTD, simulating type 3 RTA. This has been reported particularly in children with primary dRTA due to abnormal ATPV0A4 gene, encoding A4 subunit of H^+-ATPase.[1]

dRTA is endemic in certain parts of the world, as reported in the resident population (Lao-Thai) of the north-east region of Thailand.[2] "Rarh" region is a toponym for an area in India, lying between the Chota Nagpur plateau on the west, and the Ganges delta on the east, and includes certain parts of the states of West Bengal, and Jharkhand. A large number of cases with dRTA have been reported from this region, suggesting a probable hotspot of endemic dRTA.[3] We studied the clinical presentations and biochemical characteristics of different forms of RTA admitted to a center catering to a part of this "Rarh" region. We also looked into the prevalence of accompanying PTD in patients with different forms of dRTA in this region.

PATIENTS, MATERIALS, AND METHODS

Data of all patients discharged or referred from the Department of Medicine, Midnapore Medical College and Hospital with a diagnosis of RTA between January 2016 to December 2018 were retrospectively analyzed, irrespective of etiology. Referral center was the Department of Endocrinology and Metabolism, IPGME and R, Kolkata. The study was approved by the institutional ethical committee (Ref No. IEC/2020/A-2 dated 02/11/2020); informed consent was waived due to the retrospective nature of analysis. Relevant history (including drug intake), demographic characteristics, clinical presentations, auxological parameters and biochemical details at diagnosis and follow-up (FU) were retrieved. Values of arterial pH, serum sodium, potassium, chloride, bicarbonate, albumin corrected AG, albumin corrected calcium, phosphorus, creatinine, alkaline phosphatase (ALP), 25-hydroxyvitamin D (25OHD), intact parathormone (iPTH) were evaluated along with a number of urinary parameters like daily urinary output, pH, the concentration of sodium, potassium, chloride, creatinine, calcium, and phosphorus. 24-h urinary collections were performed in adults and toilet-trained children, and measurements were performed on spot samples in non-toilet trained children. Data on

urinary excretion of glucose and albumin of all patients were available, while urinary concentrations of β_2-microglobulin and citrate were present for a small subset. All patients underwent ultrasonography (USG) of the kidneys for evidences of nephrocalcinosis/nephrolithiasis, while children older than 6 years and all adults were evaluated with pure tone audiometry (PTA) for sensori-neural deafness (SND). Radiological evidences of rickets were sought for in children and adolescents before the age of epiphyseal fusion. All adults with dRTA and all children with pRTA were thoroughly evaluated for known secondary causes, and the final diagnoses were noted. GFR was estimated by "Bedside Schwartz" formula in children (aged 1 to 18 years) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation in adults. 24-h urinary volume of >50 ml/kg body weight in adults and >2 L/M² in children was taken as polyuria, while urinary creatinine of at least 10 mg/kg in females and 15 mg/kg in males suggested adequate collection. Calcium: creatinine ratio of more than 0.2 mg/mg on second voided morning sample or 24-h urinary calcium more than 4 mg/kg was considered as hypercalciuria. 24-h urinary K^+ excretion >15 mmol/day, or K^+: creatinine ratio >2.5 mmol: mmol or >13 mmol/gram in spot sample during hypokalemia suggested inappropriate renal K^+ excretion.[4,5] Tubular reabsorption of phosphate (TRP) was calculated in all patients with hypophosphatemia, and tubular maximum reabsorption of phosphate corrected for GFR (TmP/GFR) was obtained from the valid nomogram.[6]

All values were compared to age-appropriate cut-offs.

Patients with suspected RTA but with arterial pH of >7.3 or bicarbonate >18 mmol/L and urine pH >5.5 underwent ammonium chloride (NH4Cl) challenge test. 0.2 gm/kg body weight of NH4Cl was mixed with fruit juice and was consumed over a period of 2 h. ABG analysis was performed at baseline and at 4 h after starting NH4Cl consumption. Urine pH was measured at baseline and then hourly for 6 h.[7] Arterial pH of less than 7.3 or fall of pH by at least 0.05 or bicarbonate <15 mmol/L or fall of bicarbonate by at least 3 mmol/L at 4 h of the test was considered as adequate induction of acidosis.

Standard deviation (SD) scores (SDS) for weight and height were calculated using the combined World Health Organization (WHO) standard chart and revised Indian Academy of Paediatrics (IAP) reference chart. We considered a relatively advanced degree of malnutrition to define "failure to thrive". Children having weight less than -2SDS for age and sex with failure to gain weight were considered to have failure to thrive.

Statistical analysis

Descriptive data were expressed as mean and SD for the normally distributed continuous variables, and median and interquartile range (IQR) for the non-normally distributed continuous variables. Proportions were expressed as percentages. Continuous variables were tested for normality using the Shapiro-Wilk test. Continuous variables among two groups were compared using the unpaired *t*-test. The

Chi-square test (X^2) was used to test the relationship between the two proportions. As one or more cells of the contingency tables contain values <10, all X^2 values were calculated using Yates continuity correction to avoid overestimation. Correlations between the continuous variables were assessed by Pearson's or Spearman's correlations (for normal and non-normally distributed data, respectively). Participants with one or more missing data were excluded from the analysis. The statistical analyses were performed using JASP version 0.14 (the University of Amsterdam, The Netherlands).

RESULTS

Data from 66 consecutive patients (36 males and 30 females) of RTA were retrospectively analyzed. Mean age of the study population was 25.3 (±16.8) years, ranging from 3 months to 73 years. Twenty-eight (42.4%) of them were less than 18 years of age. Hypokalemic paralysis (HP) was the dominant presenting manifestation (56%) overall, followed by short stature (42%), failure to thrive (39%), rickets (39%), skeletal fractures (7%) and nephrolithiasis (3%) in descending order of frequency. Clinical presentations of the cohort have been summarized in Table 1. The median height SDS in children was (-) 4.3 [IQR 2.6], and median weight SDS was (-) 2.9 [IQR 1.0]. Body mass index (BMI) values were available for a very few of the adults, and the mean BMI was 17.4 (±1.4) kg/M². Only one child had normal stature (11-year-old girl with quadriparesis and nephrocalcinosis without rickets), while one adult with athyreosis had severe short stature (height SDS: -6.3).

Six (9.1%) of these patients had pRTA, 58 (87.9%) had dRTA, 1 (1.5%) had type 3 RTA, and the remaining one (1.5%) patient with type 4 RTA had Gordon's syndrome (pseudohypoaldosteronism type II). Ten patients (17.2%) with dRTA had underlying secondary etiologies [Sjogren's syndrome (SS) in 9, and Wilson's disease (WD) in 1], while 3 patients of pRTA (50%) had secondary form of the disease due to cystinosis, tyrosinemia type 1 and vitamin D dependent rickets (VDDR) type 1A. One patient with WD had type 3 RTA.

Among patients aged less than 18 years (n = 28), 6 had pRTA, 1 had type 3 RTA, 1 had type 4 RTA, and remaining 20 had dRTA. Among 58 patients of dRTA, 38 patients were aged 18 years or more. All patients with secondary dRTA were adults, while those with pRTA, type 3 RTA and type 4 RTA were

children. Short stature and rickets were universal in children with pRTA, while all but one child with pRTA had failure to thrive. Vast majority of our patients had dRTA and we divided those patients into two groups (age less than 18 years and age 18 years or more) and compared the clinical presentations and biochemical parameters [Table 2]. Rickets/limb deformity, hypophosphatemia and hyponatremia were significantly higher in those aged less than 18 years, while HP was higher in adults. History of fracture was present in 2 (10%) children and 3 (7.9%) adults with dRTA. Data on urinary calcium excretion was available for 23 patients (pRTA: 4, dRTA: 18; type 3RTA: 1). All of them except one with pRTA had hypercalciuria. 32 (pRTA: 2, dRTA: 30) of 66 patients had nephrocalcinosis/nephrolithiasis on USG. Two of the adults with dRTA sought medical advice primarily for renal stones.

30 patients had arterial pH of more than 7.3 of whom 18 patients (dRTA: 17, type 3 RTA: 1) had arterial pH of 7.35 or more at baseline, suggesting incomplete dRTA. Twelve patients had arterial pH between 7.31 and 7.34 of whom 3 had urine pH less than 5.5, confirming pRTA. Seven patients had intermittent acidosis. NH4Cl challenge test was performed in 27 patients (dRTA: 26; type 3 RTA: 1) with arterial pH of more than 7.3 and simultaneous urine pH of more than 5.5. We used a relatively higher dose of NH4Cl (0.2 gm/Kg) as we had experienced earlier that some of the patients do not develop systemic acidosis with the standard dose (0.1 gm/Kg). We also compared the presenting manifestations, biochemical parameters and radiological abnormalities in patients with dRTA, who underwent NH4Cl challenge (arterial pH >7.3) with those with a baseline arterial pH of ≤7.3 [Table 3]. We could not find any meaningful difference between these two groups except lower corrected calcium in patients with pH ≤7.3. Majority of children with dRTA had arterial pH of ≤7.3 at baseline. NH4Cl challenge was performed in 6 patients aged less than 18 years and 20 patients aged ≥18 years. Rickets/limb deformity appeared significantly higher and HP seemed significantly lower in those who did not undergo challenge test, i.e, those who had relatively severe acidosis.

Serum phosphate and/or urinary β_2-microglobulin values were not available for 28 patients with dRTA. Of the remaining 30, 1 had isolated dRTA, while the other 29 patients had some form of PTD, either phosphaturia or β_2-microglobulinuria. Among the 10 cases of secondary dRTA, 6 were not evaluated for PTD.

Table 1: Clinical presentations of patients, analyzed in the study (*n*=66)					
Presenting manifestation	Overall (*n*=66)	pRTA (*n*=6)	dRTA (*n*=58)	Type 3 RTA (*n*=1)	Type 4 RTA (*n*=1)
Flaccid quadriparesis	37 (56%)	0	37 (64%)	0	0
Short stature	28 (42%)	6 (100%)	20 (34%)	1 (100%)	1 (100%)
Failure to thrive	26 (39%)	5 (83%)	19 (33%)	1 (100%)	1 (100%)
Rickets/limb deformity	26 (39%)	6 (100%)	19 (33%)	1 (100%)	0
Fracture	5 (7%)	0	5 (9%)	0	0
Renal stones	2 (3%)	0	2 (3%)	0	0

Table 2: Comparative analysis of clinical, biochemical and radiological parameters between two groups (age <18 years and ≥18 years) in all patients with dRTA (*n*=58)

Presenting manifestation and parameters (biochemical & radiological)	Total number of patients (*n*=58)		*P*
	Age <18 years (*n*=20)	Age 18 years or more (*n*=38)	
Flaccid quadriparesis	4/20 (20%)	33/38 (87%)	<0.001*
Rickets/limb deformity	19/20 (95%)	0/38	<0.001*
Polyuria	8/9 (89%)	29/31 (93%)	1.000
Acidosis	17/20 (85%)	24/38 (63%)	0.152
Hypokalemia	18/20 (90%)	37/38 (97%)	0.561
Hypophosphatemia	14/20 (70%)	13/38 (34%)	0.009*
Hypercalciuria	9/9 (100%)	9/9 (100%)	1.000
Nephrocalcinosis/Nephrolithiasis	12/20 (60%)	18/38 (47%)	0.360
Arterial pH	7.28±0.07	7.31±0.07	0.115
Urine pH	6.62±0.43	6.46±0.39	0.146
Serum bicarbonate (mmol/L)	15.34±4.09	17.05±4.35	0.154
Serum sodium (mmol/L)	137.98±5.43	141.69±4.14	0.006*
Serum potassium (mmol/L)	2.57±0.78	2.157±0.74	0.053
Serum albumin corrected calcium (mg/dl)	8.96±0.73	9.11±0.60	0.458
Serum phosphate (mg/dl)	2.98±1.06	2.87±0.81	0.749
Serum alkaline phosphatase (IU/L)	848.83±544.60	226.60±183.00	0.027*

*denotes significant difference between groups. Denominator in the categorical variables (first 8 parameters) denotes number of patients, tested for that parameter, and numerator denotes number of patients with positive finding. Data are expressed in mean±SD for the continuous variables (next 8 parameters)

Table 3: Comparative analyses between patients with dRTA (*n*=58), with or without NH4Cl challenge test

Presenting manifestation and parameters (biochemical & radiological)	Patients with dRTA (*n*=58)	Patients without NH4Cl challenge (*n*=32)	Patients, who underwent NH4Cl challenge (*n*=26)	*P*
Flaccid quadriparesis	37 (64%)	16 (50%)	21 (81%)	0.015*
Failure to thrive	19 (33%)	13 (41%)	6 (23%)	0.157
Short stature	20 (34%)	14 (44%)	6 (23%)	0.099
Rickets/limb deformity	19 (33%)	14 (44%)	5 (19%)	0.048*
Nephrocalcinosis/nephrolithiasis	30 (52%)	16 (50%)	14 (54%)	0.771
Age (years)	27.9 (± 16.3)	27.1 (± 18.3)	28.9 (± 13.6)	0.078
Arterial pH	7.29 (± 0.07)	7.24 (± 0.04)	7.36 (± 0.03)	<0.001*
Urine pH	6.52 (± 0.41)	6.49 (± 0.41)	6.56 (± 0.41)	0.527
Serum bicarbonate (mmol/L)	16.5 (± 4.3)	14.7 (± 3.9)	18.4 (± 3.8)	<0.001*
Serum sodium (mmol/L)	140.4 (± 4.9)	140.5 (± 5.2)	140.4 (± 4.6)	0.77
Serum potassium (mmol/L)	2.3 (± 0.8)	2.4 (± 0.8)	2.2 (± 0.9)	0.332
Serum albumin corrected calcium (mg/dl)	9.0 (± 0.7)	8.8 (± 0.7)	9.3 (± 0.5)	0.026*
Serum phosphate (mg/dl)	2.9 (± 0.9)	2.7 (± 1.0)	3.1 (± 0.8)	0.089
Serum Alkaline phosphatase (IU/L)	666 (± 546)	778 (± 576)	395 (± 385)	0.197

*denotes significant difference between groups. Data are expressed in mean±SD for the continuous variables (last nine parameters)

Of the remaining 4, 1 had isolated dRTA, and 3 had PTD. The relevant findings have been summarized in Tables 4 and 5.

DISCUSSION

The common presentations of RTA in children are failure to thrive, growth retardation and refractory rickets, which were also evident in our study; in fact, we noticed severe growth retardation (Height SDS < -3) in 50% of children. Secondary causes need to be sought for routinely in pRTA and one-half of our pRTA cases had secondary etiology. Interestingly we came across one child of pRTA secondary to VDDR type 1A. PTD in the form of aminoaciduria was reported in about 8%

of patients with VDDR from India.[8] In contrast, dRTA in children is almost always primary, and none of our children with dRTA had any secondary cause.[9]

56% (n = 37) of the study population presented with HP, and all of them had dRTA. The numbers of paralytic episodes ranged from 1 to 8. There was no correlation between arterial pH and serum K^+ [Spearman's rho (-) 0.144; P = 0.281] or between HCO_3^- and serum K^+ [Pearson's r (-) 0.04; P = 0.766]. The prevalence of RTA in different cohorts of HP varies significantly, not only between countries, but also between different regions of India [Table 6]. SS was detected in 9 patients of dRTA, constituting 15% of all dRTA, and

Table 4: Comparative analysis between pRTA and dRTA, and between primary dRTA and secondary dRTA (n=64). Patients with type 3 RTA (*n*=1) and type 4 RTA (*n*=1) were excluded

Parameters	pRTA (*n*=6)	dRTA (*n*=58)	pRTA vs. dRTA P	dRTA Primary (*n*=48)	dRTA Secondary (*n*=10)	Primary vs. Secondary P
Age (years)	6.6 (± 4.8)	27.9 (± 16.3)	0.002*	26.3 (± 17.1)	35.1 (± 8.3)	0.124
Arterial pH	7.29 (± 0.05)	7.29 (± 0.07)	0.945	7.26 (± 0.07)	7.33 (± 0.06)	0.052
Urine pH	5.55 (± 0.62)	6.52 (± 0.41)	<0.001*	6.51 (± 0.4)	6.41 (± 0.51)	0.495
Serum bicarbonate (mmol/L)	15.3 (± 3.1)	16.5 (± 4.3)	0.518	16.5 (± 4.5)	16.6 (± 3.4)	0.918
Serum sodium (mmol/L)	137 (± 5.5)	140.4 (± 4.9)	0.188	140.2 (± 5.3)	141.2 (± 1.5)	0.582
Serum potassium (mmol/L)	2.9 (± 0.7)	2.3 (± 0.8)	0.074	2.3 (± 0.7)	2.4 (± 0.6)	0.527
Serum albumin corrected calcium (mg/dl)	8.8 (± 1.2)	9.0 (± 0.7)	0.483	8.6 (± 0.7)	8.9 (± 0.8)	0.648
Serum phosphate (mg/dl)	1.9 (± 0.7)	2.9 (± 0.9)	0.011*	2.8 (± 0.7)	2.7 (± 0.9)	0.456
Serum alkaline phosphatase (IU/L)	1141 (± 218)	666 (± 546)	0.075	721 (± 556)	866 (± 573)	0.623

*denotes significant difference between groups

Table 5: Comparative analysis between pRTA and dRTA, and between primary dRTA and secondary dRTA (*n*=64). Patients with type 3 RTA (*n*=1) and type 4 RTA (*n*=1) were excluded

	pRTA (*n*=6) No.	pRTA (*n*=6) %	dRTA (*n*=58) No.	dRTA (*n*=58) %	pRTA vs. dRTA χ^2	pRTA vs. dRTA P	Primary dRTA (*n*=48) No.	Primary dRTA (*n*=48) %	Secondary dRTA (*n*=10)		Primary dRTA vs. Secondary dRTA χ^2	Primary dRTA vs. Secondary dRTA P
Paralysis	0 (6)	0	37 (58)	63.8	6.646	0.01*	29 (48)	60.4	8 (10)	80	0.657	0.418
Rickets/deformity	6 (6)	100	19 (58)	32.8	10.328	0.001*	19 (48)	39.6	0 (10)	0	5.887	0.015*
Hypokalemia	5 (6)	83.3	55 (58)	94.8	0.049	0.825	45 (48)	93.7	10 (10)	100	0.073	0.978
Kaliuria	5 (6)	83.3	56 (58)	96.5	0.197	0.657	46 (48)	95.8	10 (10)	100	0.061	1.00
Acidosis	6 (6)	100	41 (58)	70.7	1.128	0.288	37 (48)	77.1	4 (10)	40	3.849	0.05
Hypercalciuria	3 (4)	25	18 (18)	100	0.713	0.398	13 (13)	100	5 (5)	100	NA	NA
Nephrocalcinosis/Nephrolithiasis	2 (6)	33.3	30 (58)	51.7	0.184	0.668	24 (48)	50	6 (10)	60	0.052	0.82
Hypophosphatemia	6 (6)	100	27 (58)	46.5	4.264	0.039*	24 (48)	50	3 (10)	30	0.648	0.421
Phosphaturia	6 (6)	100	27 (58)	46.5	4.246	0.039*	24 (48)	50	3 (10)	30	0.648	0.421
Polyuria	2 (2)	100	37 (40)	92.5	0.028	1.0	29 (32)	90.6	8 (8)	100	0.023	0.881
Resident of 'rarh' region	1 (6)	16.7	52 (58)	89.6	15.547	<0.001*	43 (48)	89.6	9 (10)	90	0.015	1.0
Tribal	0 (6)	0	15 (58)	25.9	0.842	0.359	14 (48)	29.2	1 (10)	10	0.744	0.389

*denotes significant difference between groups

90% of secondary dRTA. Of these 9 cases, 6 presented with HP, 2 with recurrent fractures, and one with both HP and fracture. SS is a commonly encountered etiology of secondary dRTA, and the prevalence varies between 23-35%.[10-12] SS is more commonly associated with dRTA than pRTA.[13] In an earlier series of RTA, SS (n = 52; 34.9%) was the dominant secondary etiology, wherein 30 had dRTA, while 22 had pRTA; however, the diagnosis was based on fractional excretion of HCO_3^- of <5% and >15%, respectively; those dRTA cases with secondary PTD could have misdiagnosed as pRTA.[12] Interestingly, none of our patients had been diagnosed with SS, before the development of HP or fractures, and they also lacked the suggestive symptoms of "sicca syndrome". This study validates the earlier observation, that HP may precede classical symptoms of SS.[14]

Autoantibodies against CA or the transporters, responsible for urinary acidification have been proposed to be involved in the pathogenesis of dRTA in SS.[15] We also came across dRTA in 2 patients with type 1a diabetes mellitus and 2 patients with autoimmune primary hypothyroidism (euthyroid on levothyroxine), of whom one had SS. Like SS, immune-mediated damage to acid-secreting cells in the kidney might be responsible for dRTA in these patients. 2 of our patients with dRTA also had anti-thyroid peroxidase (TPO) antibody negative subclinical hypothyroidism (SCH), of which one child had rickets, incomplete dRTA with nephrocalcinosis, and an adult, who presented with HP, had classic dRTA with PTD. Another patient with untreated athyreosis (FT4: 0.4 ng/dl), who presented with bilateral nephrocalcinosis and nephrolithiasis, had mild hypokalemia (3.3 mmol/L), kaliuresis, hypocitraturia and incomplete dRTA. dRTA has been reported in congenital primary hypothyroidism and non-autoimmune primary hypothyroidism, both overt and subclinical.[16,17] Thyroid hormones play a role in renal tubular acidification; impaired proximal and distal acidification defects have been documented in the animal models of hypothyroidism. Moreover, mild hypothyroidism is likely to be associated with a minimal defect in proximal tubular renal acid handling, which is compensated by the distal nephron.[18,19] dRTA in anti-TPO negative SCH

Table 6: Prevalence of RTA in published series of hypokalemia paralysis (studies are listed according to year of publication)

First author (Journal)	Geographical region	Study duration	Year of publication	Total patients	RTA	pRTA	dRTA	Frequency of dRTA (patients/year)
Chandramohan G, *et al.* (Indian J Nephrol)	South India (Tamil Nadu)	6.5 years	2018	206	81 (39%)	6	75 (36%)	11.5
Singh AK *et al.* (Acta Neurol Taiwan)	North India (Uttar Pradesh)	5 years	2017	40	6 (15%)	4	2 (5%)	0.4
Mohapatra BN, *et al.* (J Assoc Physicians India)	Eastern India (Odisha)	2 years	2016	50	5 (10%)	0	5 (10%)	2.5
Jandhyala SN, *et al.* (J Clin Diagn Res)	South India (Karnataka)	3 years	2015	23	1 (4%)	0	1 (4%)	0.3
Sung CC, *et al.* (Am J Med.)	Taiwan	8 years	2014	208	8 (4%)	1	7 (3%)	0.9
Kumar V, *et al.* (Trop Doct.)	Eastern India (Bihar)	3 years	2014	84	58 (69%)	NA	NA	≤19
Kayal AK, *et al.* (Ann Indian Acad Neurol.)	North-East India (Assam)	2 years	2013	56	4 (7%)	0	4 (7%)	2
Garg RK, *et al.* (Ann Indian Acad Neurol.)	North India (Uttar Pradesh)	2.5 years	2013	29	3 (10%)	0	3 (10%)	1.2
Maurya PK, *et al.* (Postgrad Med J.)	North India (Uttar Pradesh)	3 years	2010	30	4 (13%)	1	3 (10%)	1
Rao N, *et al.* (Natl Med J India.)	South India (Tamil Nadu)	6 years	2006	31	13 (42%)	10	3 (10%)	0.5
Lin SH, *et al.* (Arch Intern Med.)	Taiwan	3 years	2004	43	6 (14%)	1	5 (12%)	1.7
Lin SH, *et al.* (QJM)	Taiwan	10 years	2001	97	6 (6%)	0	6 (6%)	0.6

perhaps suggest underlying anti-renal tubular cell antibodies in anti-TPO negative autoimmune thyroid disease, or the possibility of FT4 concentrations, which fell within the reference range, but might be low for that particular individual or just an unrelated coexistence of two common disorders.

We came across 3 patients (2 males and 1 female), aged between 20-40 years, with primary dRTA and SND presenting with HP. Of the seven identified genes (ATP6V1B1, ATP6V0A4, ATP6V1C2, SLC4A1, CA2, FOXI1 and WDR72) related to dRTA, ATP6V1B1 and FOXI1 mutations are associated with early-onset (within 1st decade) SND, while ATP6V0A4 defect may be associated with late onset (after 1st decade) SND.[1]

Metabolic acidosis of any etiology is associated with significant increase in urinary calcium excretion (excess release from bones and decreased expression of renal calcium transporters), without altering plasma-ionized calcium concentration. When severe, acidosis results in high serum calcitriol and suppressed iPTH.[20] Risk of nephrocalcinosis/nephrolithiasis is increased, particularly in dRTA. About 52% of our patients with dRTA had nephrocalcinosis/nephrolithiasis. Interestingly, one patient with primary pRTA had nephrocalcinosis and another one had nephrolithiasis, and none had glucosuria. Nephrocalcinosis/nephrolithiasis is uncommon in pRTA except in conditions like Dent disease, cystinosis, and Fanconi-Bickel syndrome.[21] Glucosuria is relatively rare in PTD associated with Lowe syndrome or Dent disease.[1,22] In absence of genetic confirmation, Dent disease is suggested by simultaneous presence of elevated urinary β2-microglobulin (>1500 μg/L), hypercalciuria and either hypophosphatemia or nephrolithiasis/

nephrocalcinosis or hematuria or renal insufficiency.[23] Those two patients had a phenotype of Dent disease, although genetic test was not performed.

Given the retrospective nature of the study, the details about proximal tubular function in patients of dRTA could only be retrieved in 30 patients. 29 of them had PTD in the form of phosphaturia (n = 29) and/or β2-microglobinuria (n = 4) or albuminuria (n = 4), and 1 had isolated dRTA. None of these 29 patients had glucosuria. We could document PTD in at least one-half of all patients with dRTA, and one-third of patients with secondary dRTA. PTD got completely reversed in all of them with alkali therapy alone. Earlier studies have reported PTD in two-thirds of patients with primary dRTA. Such cases may often be misdiagnosed as type 3 RTA. Glucosuria is typically absent in these cases, and is an important clue to differentiate dRTA with consequent PTD from the classical type 3 RTA.[1,8] In addition to CAII defect, WD and elevated iPTH are known be associated with type 3 RTA. We came across 2 patients of WD, of which one had type 3 RTA, and the other had incompletely evaluated dRTA, though without glucosuria.

While the precise mechanisms underlying PTD in patients with dRTA remain incompletely understood, there are two potential explanations, namely endosomal dysfunction in the proximal renal tubular cells secondary to intracellular acidosis, and hypokalemic nephropathy. This abnormality is completely reversible, once systemic acidosis is abated with alkali therapy, as seen in our patients. Induced metabolic acidosis in healthy volunteers led to renal loss of phosphate, and a strong direct correlation between plasma phosphate and plasma bicarbonate

concentrations was established.[20] In this study we documented a weak positive correlation between serum pH and serum phosphate (Spearman's rho 0.261; $P = 0.048$), and between serum bicarbonate and serum phosphate (Spearman's rho 0.34; $P = 0.009$). Moreover, chronic hypokalaemia *per se* may cause intracellular acidosis of the epithelial cells of PCT.[24-26] In addition, chronic hypokalaemia may induce a number of structural abnormalities within PCT like brush border damage, vacuolization, inflammatory mononuclear cell infiltration, atrophy, destruction, and interstitial fibrosis.[27] A significant proportion of patients with chronic hypokalaemia also manifest reversible form of PTD, particularly if hypokalaemia is corrected before interstitial fibrosis sets in.[28] However, there was no correlation between serum phosphate and K^+ (Spearman's rho 0.05; $P = 0.711$) in our patients with dRTA. On the contrary, hypophosphatemia and acidosis in pRTA may also lead to an acquired reversible form of dRTA.[29,30] Two children with pRTA had urine pH of 6 (cystinosis) and 6.6 (tyrosinemia) at presentation, and both of them had glucosuria. The former child (aged 1.5 years) had serum HCO_3^- of 20 mmol/L, and HCO_3^- in the latter (aged 9 years) was 13 mmol/L. Both of them had urine spot sodium of >25 mmol/L and severe hypophosphatemia (2.2 mg/dl in the former and 1.55 mg/dl in the latter). Alkaline urine pH in these cases could reflect secondary distal tubular dysfunction. In the first case, however, it may also be explained by high filtered load of HCO_3^-, which was above the resorptive threshold.

We came across 58 patients of dRTA in three years, of whom 52 (<18 years: 18; ≥18 years: 34) were from the "rarh" region. Of these 52 patients, 43 had sporadic primary dRTA and 9 had secondary dRTA. Such finding within a defined geographical area is unusually high compared to previous studies, including those performed in other regions of India [Table 6]. In addition, we also looked into studies dealing with dRTA only. 45 cases of primary dRTA (n = 96) was recorded from South India over 14 years.[31] In another study from North India, 21 cases were seen over an 8-year.[32] The only other study that reported such large number of dRTA, was conducted in Bihar, an area in close proximity to the "rarh" region[33] This finding probably suggests endemicity of dRTA. Endemic dRTA in Thailand was initially suspected following report of a large number of patients with HP within a short period of time (103 patients in 3 years).[34] Prevalence of dRTA, either overt or incomplete, was inversely related to the socioeconomic status of the indigenous population, suggesting a role of environmental factor(s) in the pathogenesis. Chronic hypokalemia due to low dietary intake of potassium and excessive sweating might be one of them.[35] All of our patients (15 of them were tribal) also belonged to poor socio-economic stratum and resided in an area with hot and humid tropical climate. We could not identify with certainty any culpable environmental factor; however, certain toxins to which these group of people are often exposed to, might have played a contributory role. Heavy metals are known to be associated with a variety of renal tubular dysfunctions, and possible chronic exposure to these environmental toxins, either environmental or occupational, needs to be investigated. However, heavy metals such as lead, cadmium and mercury have been reported to be associated with pRTA.[36] On the contrary, fluorosis may cause dRTA, and water sources of certain areas situated within the "rarh" region of West Bengal have fluoride content above the permissible limit.[31,37] Interestingly, exposure to high vanadium in soil has been implicated in endemic dRTA in north-eastern Thailand.[38] Certain ingredient(s) within the indigenous or folk medicines, this group of people is exposed to might also play a role. However, these aforementioned agents alone are unlikely to be responsible for dRTA in our cohort, and we postulate that both environmental and genetic factors might have contributed to the pathogenesis of the disease, wherein the environmental factor(s) acted as a trigger in genetically susceptible individuals. Studies focusing on possible environmental factors precipitating dRTA in the "rarh" region are warranted.

To summarize, rickets and hypokalemic weakness are dominant presenting manifestations of dRTA in children and adults, respectively. Adults with dRTA have significantly higher prevalence of HP than children, despite no difference in serum K^+. Sudden decline in serum K^+ is known to precipitate acute flaccid paralysis than in chronic hypokalemia, and adults with dRTA, particularly those with incomplete dRTA perhaps are more vulnerable to acute decline in serum K^+. No clinically significant difference was observed between patients with dRTA having baseline pH ≤7.3 and those with higher pH requiring NH4Cl challenge. Combined features of pRTA and dRTA is termed as classical type 3 RTA, a condition typically seen in inherited or acquired defect of the carbonic anhydrase type II (CAII) enzyme, WD and elevated PTH. Some patients of dRTA, however, may develop a completely reversible form of PTD, simulating type 3 RTA. This has been reported in two-third of children with primary dRTA, particularly in those with ATP6V0A4 mutation. We documented some form of PTD in 15 children (75%) and 14 adults (37%) with dRTA. Of these 14 adults, 3 had secondary dRTA. PTD, thus, as a consequence of dRTA was seen in at least 75% of children and 29% of adults with primary dRTA, and in at least 30% of adults with secondary dRTA in our cohort. In addition, dRTA is endemic in the north-east region of Thailand, where renal stones, hypokalaemia, low urine citrate concentration, and urinary acidification defect are prevalent in the resident population (Lao-Thai). We came across 58 cases of dRTA in 3 years, of which 52 individuals were indigenous residents of a defined geographical area of India, known as "rarh" region. This region probably is a hotspot for endemic dRTA.

Ethics approval
The study was approved by the Intuitional Ethical Committee of Midnapore Medical College and Hospital. This has been mentioned in the "MATERIALS AND METHODS" section.

Consent for publication
All the authors provided consent for publication of the study findings and agreed to the authors' list mentioned above. The

manuscript has been read and approved by all the authors, and the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Besouw MTP, Bienias M, Walsh P, Kleta R, Van't Hoff WG, Ashton E, *et al*. Clinical and molecular aspects of distal renal tubular acidosis in children. Pediatr Nephrol 2017;32:987-96.
2. Nimmannit S, Malasit P, Susaengrat W, Ong-Aj-Yooth S, Vasuvattakul S, Pidetcha P, *et al*. Prevalence of endemic distal renal tubular acidosis and renal stone in the northeast of Thailand. Nephron 1996;72:604-10.
3. Patra S, Chakraborty PP, Biswas SN, Barman H. Etiological search and epidemiological profile in patients presenting with hypokalemic paresis: An observational study. Indian J Endocrinol Metab 2018;22:397-404.
4. Mount DB. Fluid and electrolyte disturbances. In: Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 19th ed. New York: McGraw-Hill Education; 2015. p. 295-312.
5. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis: Core Curriculum 2019. Am J Kidney Dis 2019;74:682-95.
6. Walton RJ, Bijvoet OL. Nomogram for derivation of renal threshold phosphate concentration. Lancet 1975;2:309-10.
7. Available from: http://www.baspath.co.uk/clinical_chemistry/handbook/SOP_AmmoniumCl_Loading_Test.pdf. [Last accessed on 2021 Feb 01].
8. Bajpai A, Bardia A, Mantan M, Hari P, Bagga A. Non-azotemic refractory rickets in Indian children. Indian Pediatr 2005;42:23-30.
9. Bagga A, Sinha A. Renal tubular acidosis. Indian J Pediatr 2020;87:733-44.
10. Rao N, John M, Thomas N, Rajaratnam S, Seshadri MS. Aetiological, clinical and metabolic profile of hypokalaemic periodic paralysis in adults: A single-centre experience. Natl Med J India 2006;19:246-9.
11. Kayal AK, Goswami M, Das M, Jain R. Clinical and biochemical spectrum of hypokalemic paralysis in North: East India. Ann Indian Acad Neurol 2013;16:211-7.
12. Ram R, Swarnalatha G, Dakshinamurty KV. Renal tubular acidosis in Sjögren's syndrome: A case series. Am J Nephrol 2014;40:123-30.
13. Sandhya P, Danda D, Rajaratnam S, Thomas N. Sjögren's, renal tubular acidosis and osteomalacia - An Asian Indian Series. Open Rheumatol J 2018;12:114.
14. Kulkarni N, Chopra A. Clinical profile of primary Sjogren's syndrome with hypokalemic periodic paralysis. J Assoc Physicians India 2018;66:69-70.
15. Vallés PG, Batlle D. Hypokalemic distal renal tubular acidosis. Adv Chronic Kidney Dis 2018;25:303-20.
16. Laway BA, Ali I, Bashir MI, Mir SA, Ganie MA, Wani IA. Distal renal tubular acidosis associated with non-autoimmune hypothyroidism. Saudi J Kidney Dis Transpl 2012;23:846-9.
17. Misgar RA, Mubarik I, Choh NA, Wani AI. Congenital hypothyroidism due to thyroid dysgenesis associated with distal renal tubular acidosis and hypoplastic kidney, an unknown association. Thyroid Res Pract 2016;13:40-2.
18. Morales MM, Purchio Brucoli HC, Malnic G, Gil Lopes A. Role of thyroid hormones in renal tubule acidification. Mol Cell Biochem 1996;154:17-21.
19. Mohebbi N, Kovacikova J, Nowik M, Wagner CA. Thyroid hormone deficiency alters expression of acid-base transporters in rat kidney. Am J Physiol Renal Physiol 2007;293:F416-27.
20. Krapf R, Vetsch R, Vetsch W, Hulter HN. Chronic metabolic acidosis increases the serum concentration of 1,25-dihydroxyvitamin D in humans by stimulating its production rate. Critical role of acidosis-induced renal hypophosphatemia. J Clin Invest 1992;90:2456-63.
21. Joshi RR, Patil S, Rao S. Clinical and etiological profile of refractory rickets from western India. Indian J Pediatr 2013;80:565-9.
22. Bockenhauer D, Bokenkamp A, van't Hoff W, Levtchenko E, Kist-van Holthe JE, Tasic V, *et al*. Renal phenotype in Lowe syndrome: A selective proximal tubular dysfunction. Clin J Am Soc Nephrol 2008;3:1430-6.
23. Bhardwaj S, Thergaonkar R, Sinha A, Hari P, Hi C, Bagga A. Phenotype of dent disease in a cohort of Indian children. Indian Pediatr 2016;53:977-82.
24. Tannen R. Effect of potassium on renal acidification and acid-base homeostasis. Semin Nephrol 1987;7:263-73.
25. Schoolworth A, Culpepper R. Measurement of intracellular pH in suspensions of renal tubular cells from potassium-depleted rats. Miner Electrolyte Metab 1990:16:191-6.
26. Adam W, Koretsky A, Weiner M. 31 P-NMR *in vivo* measurement of intracellular pH: Effect of acidosis and K^+ depiction in rats. Am J Physiol 1986:251:F904-10.
27. Alpern RJ, Toto RD. Hypokalemic nephropathy—A clue to cystogenesis? N Engl J Med 1990;322:398-9.
28. Emery C, Young RM, Morgan DB, Hay AW, Tele-Donker D, Rubython J. Tubular damage in patients with hypokalemia. Clin Chim Acta 1984;140:231–8.
29. Arruda JA, Julka NK, Rubinstein H, Sabatini S, Kurtzman NA. Distal acidification defect induced by phosphate deprivation. Metabolism 1980;29:826-36.
30. Donnelly S, Kamel KS, Vasuvattakul S, Narins RG, Halperin ML. Might distal renal tubular acidosis be a proximal tubular cell disorder? Am J Kidney Dis 1992;19:272-81.
31. Jha R, Muthukrishnan J, Shiradhonkar S, Patro K, Harikumar K, Modi KD. Clinical profile of distal renal tubular acidosis. Saudi J Kidney Dis Transpl 2011;22:261-7.
32. Koul PA, Saleem SM, Bhat D. Sporadic distal renal tubular acidosis and periodic hypokalaemic paralysis in Kashmir. J Intern Med 1993;233:463-6.
33. Kumar V, Armstrong L, Seshadri MS, Finny P. Hypokalaemic periodic paralysis in rural northern India--most have secondary causes. Trop Doct 2014;44:33-5.
34. Nilwarangkur S, Nimmannit S, Chaovakul V, Susaengrat W, Ong-aj-Yooth S, Vasuvattakul S, *et al*. Endemic primary distal renal tubular acidosis in Thailand. Q J Med 1990;74:289-301
35. Vasuvattakul S, Nimmannit S, Chaovakul V, Susaengrat W, Shayakul C, Malasit P, *et al*. The spectrum of endemic renal tubular acidosis in the northeast of Thailand. Nephron 1996;74:541-7.
36. Haque SK, Ariceta G, Batlle D. Proximal renal tubular acidosis: A not so rare disorder of multiple etiologies. Nephrol Dial Transplant 2012;27:4273-87.
37. Available from: https://maps.wbphed.gov.in/fluoride/index.html. [Last accessed on 2021 Feb 01].
38. Tosukhowong P, Tungsanga K, Eiam-Ong S, Sitprija V. Environmental distal renal tubular acidosis in Thailand: An enigma. Am J Kidney Dis 1999;33:1180-6.