Clinical Outcome of Children with Primary Distal Renal Tubular Acidosis

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Objective: *To evaluate the clinical course of children with primary distal renal tubular acidosis and to determine parameters correlated with the outcomes.*
Material and Method: *A retrospective review of medical records was carried out. The parameters at initial diagnosis and the last visit were collected including height standard deviation score (SDS), weight SDS, ultrasonography of kidneys, serum electrolytes, urine electrolytes, urine calcium to urine creatinine ratio (urine Ca/Cr), serum creatinine, bicarbonate dosage and glomerular filtration rate estimated by Schwartz's formula (eGFR).*
Results: *Fifteen patients were included with median follow-up time of 12 years (range 4.5 to 19 years). Median age at diagnosis was 3 years (range 0.25 to 9 years). At the last visit, median height SDS increased significantly from -3.1 to -0.8 ($p = 0.04$). Height SDS at the last visit correlated with age at diagnosis ($r = -0.54$, $p = 0.038$) and serum bicarbonate at the last visit ($r = 0.68$, $p = 0.008$). Moreover, at the last visit, eGFR correlated with urine Ca/Cr ($r = -0.84$, $p = 0.001$).*
Conclusion: *After treatment, growth of patients improved satisfactorily. The outcomes were associated with age at diagnosis, compliance of bicarbonate therapy and urine Ca/Cr at the last visit.*

Keywords: *Renal tubular acidosis, Nephrocalcinosis, Children, Outcome*

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Distal renal tubular acidosis (distal RTA) is characterized by inadequate urinary acidification of the distal nephron[1]. Patients with distal RTA usually present with failure to thrive, rickets and intermittent weakness. Increased bone resorption due to chronic metabolic acidosis leads to hypercalciuria and development of nephrocalcinosis. The plasma anion gap remains normal while that of urine anion gap becomes positive reflecting the decrease of urinary ammonium excretion.

Distal RTA includes both primary and secondary forms. Secondary distal RTA is usually associated with diseases of distal nephron such as autoimmune diseases, calcium disorders, metabolic diseases, obstructive uropathy, drugs and toxins. Primary distal RTA is a genetic disorder that can be transmitted by autosomal dominant or autosomal recessive mode[2]. Autosomal recessive distal RTA often presents in infancy, whereas autosomal dominant distal RTA may not present until adolescence or young adulthood. Principal of treatment includes alkaline therapy and correction of hypokalemia. Compromised final height despite adequate treatment has been reported[3-7]. Primary distal RTA is uncommon in children. Adedoyin O reported that distal RTA was confirmed in only 1 out of 36 patients who had been referred to a pediatric nephrologist to exclude RTA[8]. During the past 20 years, a few studies had reported regarding long-term renal outcomes and growth outcomes of children with primary distal RTA[3-5,9]. This retrospective study, therefore, was set out to study the outcomes of treatment and to find the factors correlated with the outcomes.

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Material and Method

Patients

The present study was approved by the ethic committee on human research at the Faculty of Medicine Ramathibodi Hospital (ID 10-53-14). Medical records of children with the diagnosis of primary distal renal tubular acidosis who had been followed up for at least 2 years in Ramathibodi Hospital between the years

1995 and 2010 were reviewed. Primary distal renal tubular acidosis was diagnosed in the presence of[3-5]: A: inability to lower urinary pH below 5.5 during the spontaneous normal anion gap metabolic acidosis, B: glomerular filtration rate estimated by Schwartz's formula (eGFR)[10] is normal for age (eGFR > 70 ml/min/1.73 m^2 if age < 2 years and eGFR > 100 ml/min/1.73 m^2 if age > 2 years), C: positive urine anion gap and D: exclusion of structural kidney anomalies *e.g.*, hydronephrosis, cystic kidney diseases, etc.

Clinical features and laboratory parameters

Clinical features at diagnosis were collected including presenting symptoms, age at first onset, age at diagnosis, weight standard deviation score (SDS), actual height and height SDS. The growth data including weight and height of patients was compared with the national standard reference of weight and height in Thai citizens[11].

Height SDS = (subject height - mean height)/standard deviation of mean
Weight SDS = (subject weight - mean weight)/standard deviation of mean
Weight for height per cent = 100 x (actual weight/mean weight for height)

Laboratory parameters were collected including serum sodium (serum Na), serum potassium (serum K), serum chloride (serum Cl), serum bicarbonate (serum HCO_3), serum anion gap (serum Na-serum Cl-serum HCO_3), urine pH during period of metabolic acidosis, urine sodium (urine Na), urine potassium (urine K), urine chloride (urine Cl), urine anion gap (urine Na + urine K-urine Cl), urine calcium to urine creatinine ratio (urine Ca/Cr), serum creatinine (serum Cr), and eGFR. Serum creatinine was measured by modified Jaffe method. Estimated GFRs were calculated by Schwartz's formula (using k = 0.45 if age was under 2 years, k = 0.55 if age was over 2 years and k = 0.7 if age was over 12 years in male patients). All patients were investigated by ultrasonography of kidneys for detection of bilateral nephrocalcinosis. All parameters were displayed in metric unit. Records of initial treatment with bicarbonate or bicarbonate precursors such as potassium citrate or sodium citrate were collected and displayed in millimole per kilogram per day (mmol/Kg/day).

Data at the last visit

The parameters at the last visit were collected including weight SDS, actual height, height SDS, serum K, serum HCO_3, urine Ca/Cr, serum Cr, and eGFR. Dosages of bicarbonate or bicarbonate precursors at the last visit were also collected and displayed in millimole per kilogram per day (mmol/Kg/day).

Statistical analysis

Institutional licensed SPSS version 17.0 was used for statistical analysis in the present study. The demographic data and clinical parameters were expressed as median and range. Comparisons between parameters at initial diagnosis and the last visit were tested by Wilcoxon Signed Ranks test. Comparisons between the two groups of patients with the different outcomes were tested by Mann Whitney U test. Correlation was tested to evaluate factors associated with the outcomes at the last visit. P-value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

Fifteen patients (6 males, 9 females) were included. The median age at first onset was two years, ranging from three months to nine years. The median age at diagnosis was three years, ranging from three months to 11.5 years. The presenting symptoms were failure to thrive (8 patients), intermittent weakness (5 patients), and rickets (2 patients). Two of them also had bilateral sensorineural hearing loss while the others were normal hearing. Bilateral medullary nephrocalcinosis was detected by ultrasonography in every patient. One patient also had a 2-mm stone on the left kidney and one patient had a 1.3-cm cyst at the left kidney.

Parameters at initial diagnosis

The laboratory parameters at initial diagnosis and the last visit are shown in Table 1. At initial diagnosis, underweight (weight SDS < 2.0) was found in nine patients and short stature (height SDS < 2.0) in 11 patients. All patients had hypokalemia (K < 3.5 mmol/L) and normal eGFR.

The treatment and the parameters at the last visit

The median follow-up time was 12 years, ranging from 4.5 years to 19 years. Four patients had reached final adult height according to the national standard reference of weight and height in Thai citizens (more than 18 years of age at the last visit). All 15 patients had normal eGFR at the last visit. Bicarbonate therapy was initiated with the median dosage of 3.6 mmol/Kg/day. Comparing between parameters at

Table 1. Clinical parameters of patients at initial diagnosis and the last visit (n = 15)

Clinical parameters	Units	Initial diagnosis	Last visit	p-value
		Median (min and max)		
Serum potassium	mmol/L	2.5 (1.6-3.5)	3.5 (2.9-4.2)	0.007*
Serum bicarbonate	mmol/L	10 (6-13)	21.5 (12-28)	0.007*
Serum anion gap	mmol/L	11 (5-16)	NA	
Urine pH		7.2 (7-8.5)	NA	
Urine anion gap	mmol/L	13 (7-61)	NA	
Urine Ca/Cr	mg/mg	0.34 (0.17-0.7)	0.22 (0.01-0.78)	0.34
Weight SDS		-3 (-7.2 and 7.2)	-0.8 (-4.4 and 2.4)	0.028*
Height SDS		-3.1 (-8.2 and 1.8)	-0.8 (-6.2 and 0.8)	0.041*
Serum creatinine	mg/dL	0.4 (0.3-0.9)	0.9 (0.5-1.2)	0.02*
eGFR	ml/min/1.73 m^2	110 (72-192)	102.5 (84-162)	0.16
Bicarbonate dosage	mmol/Kg/day	3.6 (0.7-8.8)	1.4 (1.0-3.0)	0.028*

* Statistical significant
eGFR = estimated glomerular filtration rate; NA = not applicable; r = correlation coefficient

initial diagnosis and the last visit, height SDS and weight SDS improved significantly after treatment. Median height SDS increased significantly from -3.1 to -0.8 (p = 0.04) and similarly for median weight SDS from -3.0 to -0.8 (p = 0.028). Urine Ca/Cr also decreased but was not statistically significant. eGFR were still the same as initial diagnosis. Moreover, median dosage of bicarbonate was reduced from 3.6 to 1.4 mmol/Kg/day at the last visit (p = 0.028). Nutritional parameters at the last visit were favorable. Median weight SDS was -0.8 ranging from -4.4 to 2.4 and median weight for height was 107% ranging from 94% to 166%.

Factors correlated with the outcomes at the last visit

Factors that had effects on outcomes at the last visit are presented in Table 2. Height SDS at the last visit had negative correlation with age at diagnosis (r = -0.54, p = 0.038) but had positive correlation with serum HCO_3 at the last visit (r = 0.68, p = 0.008) (Fig. 1, 2). Comparing between groups of patients with height SDS were shorter than -2.0 and higher than -2.0 at the last visit, median age at diagnosis was 5 years and 2.4 years respectively. This was statistically different (p = 0.026). Moreover, eGFR at last visit had negative correlation with urine Ca/Cr at the last visit (r = -0.84, p = 0.001) (Fig. 3). At the last visit, comparing between groups of patients with eGFRs were less than 100 ml/min/1.73m^2 and more than 100 ml/min/1.73m^2, median urine Ca/Cr was 0.44 mg/mg and 0.04 mg/mg respectively. This was statistically significance different (p = 0.021).

Table 2. Univariate analysis of parameters correlated with height SDS and eGFR at the last visit (n = 15)

	Height SDS at the last visit		eGFR at the last visit	
	r	p-value	r	p-value
At diagnosis				
Age	-0.54	0.038*	-0.46	0.13
Height SDS	0.43	0.14	-0.50	0.14
Weight SDS	0.18	0.54	-0.31	0.38
Serum potassium	-0.07	0.82	0.50	0.16
Serum bicarbonate	-0.54	0.08	0.50	0.20
Urine Ca/Cr	0.5	0.39	0.40	0.60
eGFR	-0.38	0.24	0.07	0.86
Bicarbonate dosage	-0.22	0.49	0.36	0.39
At the last visit				
Height SDS	NA		-0.23	0.47
Weight SDS	0.82	0.001*	-0.37	0.23
Serum potassium	0.51	0.06	0.06	0.85
Serum bicarbonate	0.68	0.008*	0.39	0.20
Urine Ca/Cr	0.12	0.7	-0.84	0.001*
eGFR	-0.23	0.47	NA	
Bicarbonate dosage	0.42	0.11	-0.04	0.90

*Statistical significant, NA; not applicable

Discussion

The criteria for diagnosis of distal renal tubular acidosis vary by the different opinions among pediatric nephrologists. The authors use a core defect of distal renal tubular acidosis (inability to acidify urine

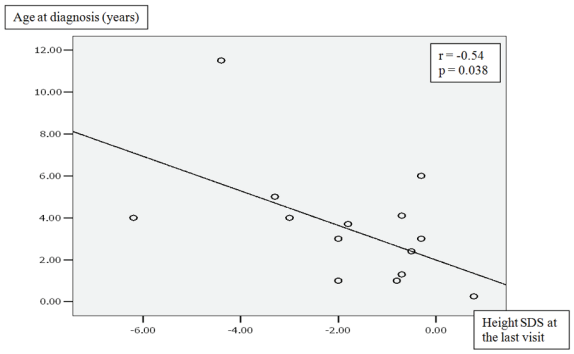

Fig. 1 Correlation between age at diagnosis and height SDS at the last visit

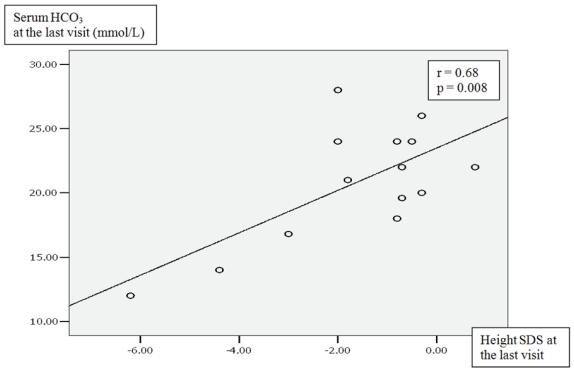

Fig. 2 Correlation between serum bicarbonate and height SDS at the last visit

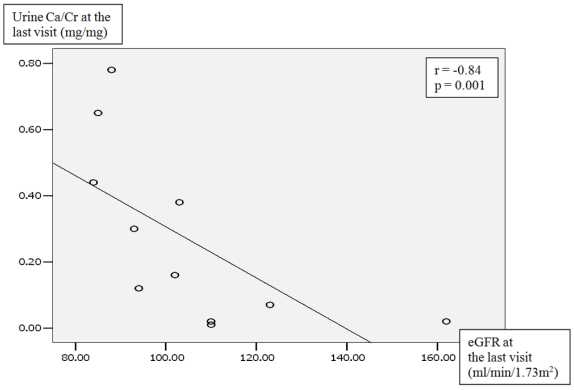

Fig. 3 Correlation between urine Ca/Cr and eGFR at the last visit

in the presence of metabolic acidosis) as the criteria and exclude patients whose eGFRs were abnormal for age and who had other kidney anomalies. The criteria the authors use are the same as that reported by Caldas A[4]. Bajpal A also added positive urine anion gap as a marker of decreased urine ammonium, which was also used by the authors[3].

The most common symptom at initial diagnosis of patients was failure to thrive. This finding was concordant with the previous studies of Caldas A and Chang CY[5]. The authors also found that 26% of patients had weakness as the first presentation, but this was the case in only 3.5% in the present study of Caldas A. There is no available data on what factors determine development of weakness in patients with hypokalemia from primary distal RTA. Regarding nephrocalcinosis, it is common to be detected in primary distal RTA. Mantan M had found that 50% of children with nephrocalcinosis resulted from primary distal RTA[12] while previous studies had reported that nephrocalcinosis were found in up to 75% of patients with primary distal RTA[3-7]. Interestingly, all patients the authors followed had bilateral medullary nephrocalcinosis. The variation of ultrasonographic equipment and criteria of diagnosis might cause difference of the detection.

Bajpai A found that the average height SDS at diagnosis was very short at -5.2 but it was only -2.8 in the study of Chang CY and -3.1 in the present study. The report with lower height SDS of Bajpai A could be due to the different of standard growth reference. They reported height SDS reference of patients in their study comparing with standard reference of children in the United States[13], while the authors reported height SDS comparing with our national standard reference in Thai citizen[11]. The other explanation of this finding was age at diagnosis that was made relatively late in the study of Bajpai A of about 6 years, but diagnosis was made only at 3 years in the present study and the study of Chang CY. This suggested the longer the patients were left untreated, the shorter the patients were.

At initial diagnosis, there was no data regarding bone status by radiological evidence but the authors found external features of rickets in two patients who presented with bowed legs. Chang CY also reported that 88% of patients had delayed bone age but their data after treatment was incomplete. In the study of Bajpai A, they showed that all patients had radiological features of rickets and 95% of them resolved after four months of treatment without vitamin D supplement. It is generally agreed that the cause of rickets and failure to thrive in primary distal RTA is chronic metabolic acidosis but the other mechanism might contribute to this finding. Caldas A reported low plasma levels of 25(OH) vitamin D in four out of

11 patients, thereby linked the finding as the cause of rickets. The data from McSherry E[14] showed that growth hormone release might be impaired during acidosis. Chan JC[15] also reported that bicarbonate should be given at the night time while the growth hormone is released and the optimal correction of metabolic acidosis during this period will have a significant beneficial effect.

At initial treatment, median dosage of bicarbonate was 3.6 mmol/Kg/day whereas the effective dosages were 7.2 mmol/Kg/day and 4-7.3 mmol/Kg/day in the study of Bajpai A and Caldas A, respectively. However, the authors reported that optimal dosage of bicarbonate for correction of children with primary distal RTA to be only 3-4 mmol/Kg/day[16]. After treatment, growth of patients improved to nearly normal level. The authors found that median height SDS and weight SDS gained from -3.1 to -0.8 and from -3.0 to -0.8, respectively after median follow-up of 12 years. The dosages of bicarbonate could be reduced to 0.8 mmol/Kg/day at the last visit. The reduction in bicarbonate used also reported in the studies of Bajpai A and Caldas A. In the present study of Bajpai A, they reduced the dosage of bicarbonate from 7.2 to 3.4 mmol/Kg/day, while Caldas A. reported the dosage decreased from 4-7.3 to 2 mmol/Kg/day.

The authors have followed all patients with median follow-up time of 12 years, which is, as the authors' best knowledge, the longest time ever been reported. Many factors that had influence on the outcomes were found including age at diagnosis, urine Ca/Cr at the last visit and serum bicarbonate at the last visit. Some reports also showed that early treatment had influence on the outcomes[4,14]. The authors found age at diagnosis was negatively correlated with height SDS at the last visit ($r = -0.54$, $p = 0.038$). This might be assumed that the earlier the diagnosis was made, the better the height outcome was achieved. The authors further grouped the patients according to their height SDS at the last visit. The group of patients with height SDS at the last visit were shorter than -2.0, they had median age at diagnosis of five years while the group of patients with height SDS at the last visit were taller than -2.0, they had median age at diagnosis of only 2.4 years that was statistically different ($p = 0.026$). This finding was also reported by Caldas A that height SDS at the last visit of patients who had been diagnosed before two years of age were -1.1 but patients who had been diagnosed after two years of age, their height SDS at the last visit was -2.0. In contrast, Bajpai A did not find this correlation. They explained that it would be caused by the delayed diagnosis of their patients. Moreover, the authors found that serum HCO_3 at the last visit had positive correlation with height SDS at the last visit ($r = 0.68$, $p = 0.008$). This correlation was also reported in patients with secondary distal RTA from posterior urethral valve[17]. The data also showed that median serum creatinine was increased after follow-up. Because the patients were taller comparing with before treatment, therefore this finding was meaningless in term of change in renal function.

However, interestingly, four patients who reached final adult height had their height SDS as follows: -0.7, -0.8, -2.4, -6.2 and they had been diagnosed with distal RTA at four, one, three, and four years respectively. Although these patients had been diagnosed before five years of age, variation in their height SDS at the last visit was obvious. This finding supports that the early diagnosis is not the only factor determining the outcomes. The authors found that patient whose height SDS was -6.2 at the last visit had serum HCO_3 at the last visit only 15 mmol/L. This shows that the compliance to treatment is also an important factor. The authors also found that eGFR at the last visit was negatively correlated with urine Ca/Cr at the last visit ($r = -0.84$, $p = 0.001$). At the last visit, patients with eGFRs were less than 100 ml/min/1.73m^2 had median urine Ca/Cr of 0.44 mg/mg while patients with eGFRs were more than 100 ml/min/1.73m^2 had median urine Ca/Cr of only 0.04 mg/mg. This data showed that urine Ca/Cr had correlation on eGFR of patient with primary distal RTA. Thus, metabolic acidosis is not only factor that should be followed but hypercalciuria is also important. On the other hand, nutritional status in the present study was favorable. Median weight SDS at the last visit was only -0.8 comparing with -2.4 in the study of Bajpai A. This might also contribute to the height outcome that it was better in the present study.

The data was somewhat incomplete as no patient had been tested for urine HCO_3 at diagnosis, therefore fractional excretion of HCO_3 cannot be reported. The other limitation was the lack of data regarding puberty achievement and parental height SDS. This might have an effect on height SDS. A larger and longer study is needed to confirm the authors' finding.

Conclusion

Primary distal RTA is not common in children. However, the authors should be aware of patients who presented with failure to thrive by checking their serum

electrolytes and venous blood gas. Age at diagnosis, compliance of treatment, monitoring of electrolytes and hypercalciuria are the main factors in determining the outcomes.

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Potential conflicts of interest

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การศึกษาผลลัพธ์ทางคลินิกของผู้ป่วยเด็กโรค distal renal tubular acidosis ชนิดปฐมภูมิ

ขวัญชัย ไพโรจน์สกุล, กาญจนา ตั้งนรารัชชกิจ, วิวัฒน์ ตปนียโอฬาร

วัตถุประสงค์: *เพื่อศึกษาผลลัพธ์ทางคลินิกของผู้ป่วยเด็กโรค distal renal tubular acidosis ชนิดปฐมภูมิ และหาปัจจัยที่มีผลต่อผลการรักษาของผู้ป่วย*

วัสดุและวิธีการ: *เก็บข้อมูลย้อนหลังผู้ป่วยโดยการทบทวนเวชระเบียน ปัจจัยที่เก็บรวบรวมเมื่อแรกเริ่มวินิจฉัยและหลังการรักษาครั้งสุดท้าย ได้แก่ คะแนนส่วนเบี่ยงเบนมาตรฐานของความสูง น้ำหนักตัว ผลตรวจไตด้วยคลื่นเสียงความถี่สูง ค่าอิเล็กโทรไลต์ในเลือดและปัสสาวะ ค่าแคลเซียมในปัสสาวะเทียบกับครีแอทินินในปัสสาวะ ค่าครีแอทินินในเลือด ปริมาณไบคาร์บอเนตที่ได้รับและอัตราการกรองของไตประเมินโดยสูตรของ Schwartz*

ผลการศึกษา: *ผู้ป่วยจำนวน 15 ราย ค่ามัธยฐานของระยะเวลาการติดตามรักษาเท่ากับ 12 ปี (4.5-19 ปี) ค่ามัธยฐานของอายุที่เริ่มวินิฉัยเท่ากับ 3 ปี (0.25-9 ปี) การติดตามรักษาครั้งสุดท้ายพบว่าคะแนนส่วนเบี่ยงเบนมาตรฐานของความสูงเพิ่มจาก -3.1 เป็น -0.8 อย่างมีนัยสำคัญทางสถิติ ($p = 0.04$) ปัจจัยที่มีผลต่อคะแนนส่วนเบี่ยงเบนมาตรฐานของความสูงที่การรักษาครั้งสุดท้าย คือ อายุที่เริ่มวินิฉัย ($r = -0.54$, $p = 0.038$) และค่าไบคาร์บอเนตในเลือดที่การรักษาครั้งสุดท้าย ($r = 0.68$, $p = 0.008$) ปัจจัยที่มีผลต่ออัตราการกรองของไตที่การติดตามรักษาครั้งสุดท้ายคือ ค่าแคลเซียมในปัสสาวะเทียบกับครีแอทินินในปัสสาวะที่การรักษาครั้งสุดท้าย ($r = -0.84$, $p = 0.001$)*

สรุป: *ความสูงของผู้ป่วยหลังการรักษาเพิ่มขึ้นอย่างน่าพอใจ ปัจจัยที่มีผลต่อผลการรักษาได้แก่ อายุที่เริ่มวินิจฉัย ค่าไบคาร์บอเนตในเลือดที่การรักษาครั้งสุดท้าย และค่าแคลเซียมในปัสสาวะเทียบกับครีแอทินินในปัสสาวะที่การรักษาครั้งสุดท้าย*