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Clinical and biochemical findings in Mexican patients with distal renal tubular acidosis

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ABSTRACT

Introduction. Renal tubular acidosis (RTA) is a rare disease characterized by a normal serum anion gap, sustained metabolic acidosis, low concentration of plasma bicarbonate, variable hyperchloremia and hypokalemia and conserved glomerular filtration rate. RTA is developed during the first year of life and produces failure to thrive and anorexia. Primary distal RTA (type 1) is a renal syndrome with a reduced ability to excrete the acid load through the collecting ducts and impairment to concentrate the urine causing polyuria and dehydration. **Objective.** Evaluate the current health status and describe the clinical findings and progress of Mexican patients with distal RTA. Demonstrate the distal urinary acidification defect by measuring the urinary pCO_2 tension in alkaline urines. **Material and methods.** We looked for infants in tertiary care hospitals with a clinical history of normal serum anion gap, metabolic acidosis, hypokalemia, hyperchloremia, nephrocalcinosis, sensorineural hearing loss and inability for urine acidification under systemic metabolic acidosis. Biochemical analysis were performed periodically. Alkali medication was not suspended in one patient to assess urinary acidification with oral administration of sodium bicarbonate (2 mEq/Kg) and acetazolamide (500 mg/1.73 m^2 body surface). Urinary pCO_2 levels were determined at 60 and 90 min. **Results.** Three children, one adolescent and one adult with distal RTA were found. They had an infant history of dehydration, failure to thrive, anorexia, vomiting, muscle paralysis, hypercalciuria, urinary infections, polyuria, polydipsia and polyhidramnios during pregnancy. Severe nephrocalcinosis was detected in all patients whereas sensorineural hearing loss was developed in four cases. Under the alkali medication all cases but one were normocalciuric. A patient developed kidney failure. The urinary acidification test confirmed the innability to eliminate the acid load. **Conclusion.** Early diagnosis in infancy and continuos alkali medication were of great benefit for most of the patients. Urinary pCO_2

Hallazgos clínicos y bioquímicos en pacientes mexicanos con acidosis tubular distal

RESUMEN

Introducción. *La acidosis tubular renal (ATR) es una enfermedad rara que se caracteriza por una brecha aniónica sérica normal, acidosis metabólica persistente, concentración disminuída de bicarbonato sérico, hipercloremia e hipocaliemia variable y función glomerular normal. La ATR se presenta durante el primer año de vida y produce fallo de medro y anorexia. La ATR distal primaria (tipo 1) es un síndrome renal caracterizado por una excreción reducida de la carga ácida a través de los conductos colectores e incapacidad para concentrar la orina, lo que produce poliuria y deshidratación.* ***Objetivo.*** *Evaluar el estado actual de salud y describir los hallazgos clínicos, así como la evolución de pacientes mexicanos con ATR distal. Demonstrar la incapacidad de la acidificación urinaria en la nefrona distal con la determinación de la pCO_2 urinaria en orinas alcalinas.* ***Material y métodos.*** *Se buscaron pacientes en hospitales de tercer nivel con historia clínica de acidosis metabólica y brecha aniónica sérica normal, hipocaliemia, hipercloremia, nefrocalcinosis, hipoacusia e incapacidad para acidificar la orina en condiciones de acidosis metabólica sistémica. Se realizaron análisis bioquímicos periódicos. La prueba de acidificación se realizó con un paciente sin retirar el tratamiento alcalino y administración oral de bicarbonato de sodio (2 mEq/Kg) y acetazolamida (500 mg/1.73 m^2 de superficie corporal). Se determinaron los niveles de la pCO_2 urinaria a los 60 y 90 min.* ***Resultados.*** *Se encontraron tres niños, un adolescente y un adulto con ATR distal. Presentaron una historia clínica de cuadros de deshidratación, fallo de medro, anorexia, vómitos, parálisis muscular, hipercalciuria, infecciones urinarias, poliuria, polidipsia y polihidramnios en el embarazo. En todos los pacientes se detectó nefrocalcinosis severa mientras que cuatro casos desarrollaron hipoacusia*

levels in alkaline urine provided an index for collecting duct hydrogen-ion secretion. To our knowledge this is the first report of mexican patients with distal RTA.

Key words. Renal tubular acidosis. Hypokalemia. Nephrocalcinosis. Hyperchloremia. Hypercalciuria. Hypocitraturia. Sensorineural hearing loss.

neurosensorial. Con la terapia alcalina todos, excepto un caso, fueron normocalciúricos. Un paciente desarrolló daño renal. La prueba de acidificación urinaria confirmó la incapacidad de un ATR distal para eliminar la carga ácida. ***Conclusión.*** *El diagnóstico temprano en la infancia y el tratamiento alcalino continuo fueron de gran beneficio para la mayoría de los pacientes. Estos casos representan el primer reporte de pacientes mexicanos con ATR distal.*

Palabras clave. *Acidosis tubular renal. Hipocaliemia. Nefrocalcinosis. Hipercloremia. Hipercalciuria. Hipocitraturia. Hipoacusia neurosensorial.*

INTRODUCTION

The kidney maintains and controls the serum acid-base balance through filtration and reabsorption of bicarbonate, acid or alkali excretion and synthesis of ammonium and bicarbonate. Urinary acidification together with citrate excretion, are essential for removing organic and inorganic salts in soluble form. The intake of an acid load such as a high protein meal, produce an acidic urine (pH 5.5), increasing the rate of phosphate and ammonium excretion, being ammonium/ammonia the main urinary buffer.[1-4]

Patients with distal renal tubular acidosis (distal RTA) have reduced urinary ammonium excretion, causing variable hyperchloremic, hypokalemic, sustained metabolic acidosis, a drastic drop in serum bicarbonate, hypercalciuria, nephrocalcinosis, hypocitraturia and early or late neurosensory hearing loss.[5-7] Distal RTA diminishes serum pH < 7.35 and the urine pH becomes > 6 due to the inability of the kidney to produce an acidic urine in the presence of metabolic acidosis.[5-7] Potassium wasting in distal RTA can result in sudden life-threatening hypokalemic muscle paralysis, periodic paralytic attacks, and chronic persistent muscle weakness.[8,9] Hypocitraturia is developed with or without hypercalciuria.[7] Distal RTA is a rare hereditary monogenic disease with an estimated prevalence of less than 1:100,000.[10-14]

The clinical picture of our patients was prototypic of the disease with vomiting, stunted growth, dehydration, polydipsia, polyuria, loss of appetite, muscle weakness and paralysis; nephrocalcinosis and early (childhood) or late sensorineural hearing loss. Alkali treatment does not avoid polydipsia, polyuria and hearing loss. Importantly, distal RTA was accompanied by hyperchloraemia as a result of lack of plasma bicarbonate. Hypokalemia was developed reaching potassium concentrations as low as 1.5 mEq/L. From five, four individuals already developed bilateral hearing impairment; all presented bilateral nephrocalcinosis and one, kidney failure.

Previously, we called the attention to distal RTA over-diagnosis in Mexico.[15]

The aim of this work is to present the first report of the clinical findings and progress of mexican patients with distal RTA.

MATERIAL AND METHODS

Pediatric patients were diagnosed in the tertiary care hospitals Centro Médico Nacional La Raza, Instituto Mexicano del Seguro Social (IMSS), in Mexico city and Unidad Médica de Alta Especialidad (UMAE), Hospital de Especialidades Núm. 25, Centro Médico Nacional del Noreste, in Monterrey city. The adult patient was contacted by the web site: www.funatim.org.mx (currently, www.acidosistubular.unam.mx).

All participants signed an informed consent. Progress of patients was followed up from one to more than ten years. For the acidification test, the bladder was emptied before oral sodium bicarbonate (2 mEq/Kg) and acetazolamide (500 mg/1.73 m^2) administration. An hour later, the bladder was emptied and the urine was discarded. Urine was collected at 60 and 90 min later.[16-18] Urine samples were aspirated with a syringe under anaerobic conditions. The urinary pH (PH-200 Meter, HM Digital Inc.), sodium, potassium and pCO_2 (gasometer GEM Premier 3000, Instrumentation Lab Werfen Group) were determined immediately.

RESULTS

Case report 1

He had failure to thrive, developmental delay and hypotonia since birth (Table 1). He achieved head control at age six months, ability to sit at age one and walked until age two, having a delayed onset of

expressive oral vocabulary. He needed frecuent hospitalizations due to episodes of hypotonia, flaccidity and general paralysis, accompanied by dehydration and prolonged sleep; initially without and later with loss of consciousness. At the emergency room, venous blood gases showed persistent metabolic acidosis: pH 7.25, pCO_2 26 mmHg, bicarbonate 13.3 mEq/L, severe hypokalemia with potassium 1.1 mEq /L and normocalciuria: urinary calcium (mg/dL)/creatinine (mg/dL) index UCa/UCr 0.04. Three days after receiving endovenous alkali treatment with potassium chloride and bicarbonate (2 mEq/Kg/day), medication with oral potassium citrate (6 mEq/Kg/day) was introduced. Normal potassium levels (3.9 mEq/L) were reached a month later. He developed bilateral sensorineural hearing loss at age three. An ultrasound was performed confirming bilateral nephrocalcinosis (Figure 1). Physical examination at age four showed weight on the 10th percentile (Z-score -1.20) and height on the 11th percentile (Z-score -1.25). At age of five the 44th percentile on weight (Z-score -0.13) and the 25th percentile on height (Z-score -0.67) was attained. Serum creatinine 0.47 mg/dL, urea 19.26 mg/dL, sodium 143 mEq/L, potassium 5 mEq/L, chloride 107 mEq/L, pH 7.39, pCO_2 43 mm Hg and bicarbonate 26 mEq/L.

Case report 2

He was hospitalized at birth due to severe hyperbilirubinemia and gastroparesis. At age two months he developed diarrhea and dehydration (Table 1)

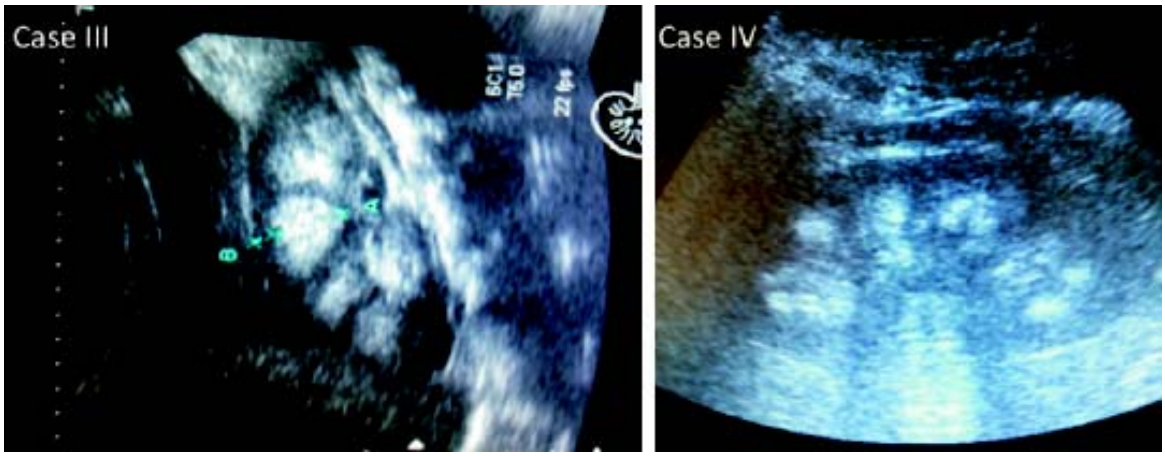

Figure 1. Medullary nephrocalcinosis at renal ultrasound.

Table 1. Clinical feature at diagnosis and current conditions.

Patient	1	2	3	4	5
Age at diagnosis (months)	41	9	12	12	4
Gender	M	M	F	M	M
Clinical features	Dehydration, failure to thrive, muscle paralysis, delayed motor skills.	Deshydration, failure to thrive, diarrhea	Vomiting, dehydration pneumonia, malnutrition	Vomiting, dehydration failure to thrive	Lack of appetite, vomiting, dehydration, urinary infections
Sensorineural hearing loss	Yes	Yes	No	Yes	Yes
Body weight kg (z score)					
At birth	2-95 (-1.67)	3.0 (-1.59)	3.1 (-1.28)	3.15 (-1.37)	3.3 (-1.14)
Present	14.4 (-0.13)	15 (-2.22)	13.9(-1.99)	80 (1.11)	95 (1.61)
Height cm (z score)					
At birth	50 (-1.06)	53 (0.12)	49 (-1.16)	52 (-0.27)	51 (-0.67)
Present	97 (-0.67)	96 (-3.19)	99 (-2.15)	167 (-1.17)	182 (0.58)

followed by metabolic acidosis with normal anion gap (Table 2), starting alkali medication with sodium bicarbonate. Nephrocalcinosis was detected at age nine months. Even with sodium bicarbonate prescription (10 mEq/Kg/day), he developed hypokalemia (potassium 2.2 mEq/L) and metabolic acidosis (plasma pH = 7.2, bicarbonate 12.4 mEq/L) at one year of age. Severe hypercalciuria was developed: UCa/UCr 2.9 at age nine months and UCa/UCr 0.8 at age one year, but it was progressively diminished at age five years UCa/UCr 0.28, following a potassium citrate therapy (20 mEq/Kg/day). Normal plasma glucosa 88 mg/dL, BUN 14 mg/dL, urea 35 mg/dL, creatinine 0.3 mg/dL, calcium 10.3 mg/dL and sodium 145 mEq/L. He followed a motor therapy due to his physical developmental delay, achieving the 8% percentile on weight (Z-score -2.36) and 0% on height (Z-score -1.40) at age four years and eight months. At five years three months his weight was 14.7 Kg (Z-score -2.22) and height 98 cm (Z-score -3.19) (Table 1).

Case report 3

A female infant was admitted to the Hospital at the age of seven months due to dehydration, vomiting, severe malnutrition, polyuria, polydipsia, failure to thrive, weight 3.4 kg (Z-score -6.35), length 53 cm (Z-score -5.06), pneumonia, polypnea, severe hyperchloremia (chloride 117 mEq/L), acidosis (serum pH 6.7, bicarbonate 7 mEq/L) and severe hypokalemia (potassium 1.7 mEq/L) (Tables 1 and 2). Antimicrobial therapy was given with vancomycin and cefotaxime. The alkali treatment for distal RTA was provided with sodium and potassium bicarbonate solutions. She had bilateral nephrocalcinosis (Figure 1). At age four she was switched from bicarbonate to potassium citrate medication. Hearing was assessed by auditory evoked response showing normal audition. She weighed 13.9 kg (percentile 0, Z-score -2.80) and her height was 100 cm (percentile 0, Z-score -2.50) at age five years seven months. Urinary citrate < 0.2 mg/24 h; urinary index: calcium, Ca/Cr 0.09, magnesium, Mg/Cr 0.21, phosphate, P/Cr 1.15, uric acid/Cr 0.38 and proteinuria 0.21 (albumin/creatinine). At six years eleven months old her weight was 17.2 kg (p2% Z-score -1.99) and height 109.5 cm (p1% Z-score -2.15). Venous blood gases: pH 7.37, pCO_2 40 mmHg, bicarbonate 23.1 mEq/L; serum sodium 137 mEq/L, potassium 3.5 mEq/L, chloride 101 mEq/L and calciuria: 3 mg/kg/day and UCa/UCr 0.18.

Case report 4

Polyhydramnios during pregnancy giving birth by cesarean section at 38 weeks. He was admitted at age four months to the hospital due to failure to thrive, vomiting, lack of appetite, moderate dehydration, diarrhea, polyuria, polydipsia, polypnea and severe hypokalemia (Tables 1 and 2). He developed bilateral sensorineural hearing loss at age eight years. Potassium citrate was given at age one, but changed to sodium and potassium bicarbonate due to gastritis. Currently, alkali treatment consists of potassium citrate (4 mEq/kg/day). Weight and height are within normal range percentiles with polyuria (10.4 L/day) and hypocitraturia (14 mg citrate/g creatinine). Kidney failure started at age fourtheen with serum creatinine 1.58 mg/dL, urea 51 mg/dL and a glomerular filtration rate of 73.54 mL/min/1.73 m^2. At this moment he is seventeen years and two months old with a creatinine clearance of 80 mL/min/1.73m^2, plasma chloride 109 mEq/L, sodium 139 mEq/L, potassium 3.2 mEq/L, bicarbonate 22 mEq/L, pH 7.38. UCa/UCr < 0.03 (mg/dL); his height is 1.67 m (Z-score -1.17) and weight 80 Kg (Z-score 1.11). He has mild neu-

Table 2. Biochemical analysis in metabolic acidosis and calcium excretion (UCa/Cr) after alkali supplementation.

Case	Blood venous pH	S HCO_3 mEq/L	BE mmol/L	S K mEq/L	S Cl mEq/L	UpH	UCa/Cr after alkali therapy
1	7.25	13.3	-12.7	1.1	120	7.6	0.04
2	7.33	13.7	-12.1	3.4	114	8	0.28
3	7.2	11.3	-14.1	1.8	120	7.1	0.15
4	7.27	6.6	-17.0	2.4	118	8	0.55
5	-	-	-	1.7	-	6.5	0.21

$SHCO_3$: serum bicarbonate. BE: base exess. SK: serum potassium. SCl: serum chloride. Cr: creatinine. UpH: urinary pH under metabolic acidosis. UCa/Cr: calcium to creatinine index. Normal values for UCa/Cr at different ages are: 0-6 months < 0.8 mg/mg; 6-12 months < 0.6 mg/mg; 1.2 years < 0.5 mg/mg, 0.3 mg/mg for children aged 5-7 years.[5,17,18]

rosensorial hearing impairment with normal cognitive development.

Case report 5

He was admitted at age four months to the Hospital due to vomiting, lack of appetite, dehydration, polyuria, polydipsia and frecuent urinary infections. We could not retrieve the gasometry performed when distal RTA was diagnosed during his infancy. Bilateral sensory hearing loss appeared during adolescence. He is twenty-seven years old. Five months ago he was at the emergency room with muscle paralysis and inability to stand up as a consequence of severe hypokalemia (serum potassium 1.7 mEq/L). Twelve days after potassium citrate and potassium bicarbonate administration, serum potassium was still low (3.2 mEq/L) with sodium 137 mEq/L. Recovering was completed after two months of alkali treatment with the following serum measurements: potassium 4.2 mEq/L, sodium 148 mEq/L, bicarbonate 23.7 mEq/L, chloride 106 mEq/L, pH 7.33, creatinine 1.3 mg/dL, urea 52.3 mg/dL, without hypercalciuria (Table 2). The glomerular filtration rate was 115.7 mL/min (Cockcroft-Gault). He is 1.82 m tall (Z-score 0.58) and weighs 95 kg (Z-score 1.61).

Clinical and biochemical data for all patients are summarized in tables 1 and 2. They had a variable growth development. Normal growth results from interactions between several mechanisms: genetic, nutritional, environmental, social and economic, that lead in concert to gain in weight and height. Many systemic diseases as RTA and environmental conditions do impair linear growth. However, RTA growth often resumes with alkali medication and may be complete or incomplete depending upon the final height with reference preferably to the genetic target height.

The acidification test was performed in case 3 and accomplished 24 h after stopping alkali therapy at the Hospital, requiring intravenous sodium bicarbonate and potassium handling. Development of hypokalemia was accompanied with electrocardiographic changes characterized by flatted T waves (not shown). Close monitoring showed hyperchloremic hypokalemic metabolic acidosis after 18 h. At the end of the acidification assessment, alkali supplementation was given immediately. Biochemical analysis under metabolic acidosis reported serum sodium 143 mEq/L, severe hypokalemia (potassium 1.7 mEq/L) and hyperchloremia (chloride 120 mEq/L), venous blood pH 7.2, pCO_2 20 mmHg and bicarbonate 11.3 mEq/L; creatinine 0.36 mg/dL and alkaline urine (pH 7.2). Urinary index (mg/dL/mg/dL): Ca/Cr 0.15, uric acid/Cr 0.38, P/Cr 1.15, Mg/Cr 0.21, proteinuria (albumin/Cr) 0.21 and hypocitraturia (6.5 mg/g Cr, < 0.2 mg/24 h).

The acetazolamide test was performed with alkali therapy. The urinary acidification results are shown in table 3. The urine pH (7.8-8.0) was greater than blood pH (7.36) and the urinary pCO_2 level (49 mmHg) was below the normal value (pCO_2 > 70 mmHg). This result together with the fact that the urine pCO_2 minus blood pCO_2 (U-B pCO_2) was 8 mmHg, confirmed the acidification defect of a distal RTA. In normal subjects the $UpCO_2$ and the U-B pCO_2 levels increase markedly in alkaline urine: pCO_2 > 70 mmHg and U-B pCO_2 > 33 mmHg.[19]

All patients showed persistent polydipsia and polyuria (urine output exceeding 3 L/day), normal serum sodium, calcium, magnesium and phosphate levels. Urinalysis showed inappropriate alkaline urine (pH > 6.0) and a positive urinary anion gap (23.1 mmol/L).

DISCUSSION

The aim of this study was to present the clinical findings and progress of five Mexican patients with distal RTA. Patients had dependence of a hearing prothesis except for case 3. However, it has been found that sensorineural hearing loss develops later during the adolescence in some distal RTA.[5-7,10-13]

Case 4 showed renal injury in spite of early alkali treatment with bicarbonate. In contrast, case 1, who was diagnosed until age three, had a normal glomerular filtration rate. These patients had also normal serum creatinine (0.3 mg/dL), calcium (9.7 mg/dL), phosphate (4.3 mg/dL) and magnesium (2.0 mg/dL). Regarding the clinical manifestations, all had dehydration episodes, 4/5 (80%) failure to thrive/malnutrition, 3/5 (60%) vomiting, and 1/5 (20%) diahrrea. It is worth to mention that patients with distal RTA are prone to constipation and inability to concentrate the urine due to renal water and potassium losses.[20-21] One patient had a history of urinary infections cases, which we consider unrelated to RTA, with no structural urinary anomalies.

The most common cause of a hyperchloremic metabolic acidosis in pediatrics is acute diarrhea disease. Potassium losses can be substantial enough in either RTA or diarrheal, disease to provoke hypokalemia, but they can be distinguished from each other in the infant. In a diarrhea or a kidney affected by proximal RTA (type II), there is an increase of am-

Table 3. Acidification test with acetazolamide (180 mg) and sodium bicarbonate (30 mEq).[16,19] The assay was performed with case 3.

	Plasma	Urine	Urine
Gasometry	-	60 min	90 min
pH	7.36	7.8	8.0
pCO_2	41	49	49
pO_2	37		
HCO_3	23.2		
BE	-2.2		
UNa		101	132
UK		49.71	53.42
$UHCO_3$		67.83	112.8

monium production and chloride excretion, and hence, a decreased value of the urinary anion gap: urinary [Na^+] + urinary [K^+]-urinary [Cl-], which should be small to negative. On the contrary, a positive and elevated urinary anion gap is determined in a distal RTA, besides all the parameters described for this syndrome in this work.

Our results illustrates the clinical heterogeneity of distal RTA and maintain open questions respect to the evolution of this renal disease.

Primary distal RTA is characterized by a renal failure to produce appropriate acidic urine in the presence of systemic metabolic acidosis or after an acidic load, owing to impairment in hydrogen ion secretion in the distal nephron.[20] The aim of the acidification test with bicarbonate and acetazolamide was to produce alkaline urines (bicarbonaturia was promoted by inhibition of the carbonic anhydrase, type IV, at the proximal tubules), to increase the urine pCO_2 tension and then, acid excretion into the luminal collecting ducts. In contrast to distal RTA patients, there is abundant data of the urine pCO_2 determination with alkaline urines from hypercalciuric children.[7] Urine pH was > 7.8, the bicarbonate excretion index ($UHCO_3$-) was > 80 and the urine pCO_2 was 49 mmHg with the acidification test. These results confirmed distal RTA impairment to acidify the urine since a value of $pCO_2 \geq 70$ mmHg is expected for a normal urine acidification.[17-19] Therefore, the urine pCO_2 test with alkaline urines is useful and affordable to determine the acid secretion function in the distal nephron.

Levels of urinary calcium excretion are normally high in infants but decline progressively with age. Urinary Ca/Cr normal ratio in infants is: 0-6 months < 0.8 mg/mg, 6-12 moths < 0.6 mg/mg, 1-2 years < 0.5 mg/mg.[5,17,18] With alkali therapy, all patients exept case 4 were normocalciuric for their age (Table 2). This result has been described as well with other distal RTA.[22-24] Urinary excretion of calcium is the result of a complex interplay between the gastrointestinal tract, bone, and kidney and is finely orchestrated by hormones. Genetic and/or metabolic disorders are the main reason for childhood nephrocalcinosis and urolithiasis. Furthermore, hypercalciuria is also influenced significantly by the diet.[24-26] In addition, development of nephrocalcinosis in the absence of hypercalciuria supports the important role of hypocitraturia in developing calcium deposits in distal RTA. Early treatment with potassium citrate reduces urinary saturation by providing crystallization inhibitors, preventing progressive nephrocalcinosis and consequently, deterioration of the renal function.

It is important to underline that distal RTA is a rare disease;[27] therefore, a low prevalence is expected in any population. For example, distal RTA in Tunisia, a country with a mean endogamy rate of 26%,[28] has found in less than 1:100,000.[13] Consequently, a professional health has a very low probability of finding a tubulopathy and, in particular, a distal RTA. Primary tubulopathies comprise a variety of entities with a genetic origin that affect the function of the proximal and distal tubules; they are considered rare diseases or orphans, chronic, life-threatening and without cure.[29]

We hope that our study helps to understand the clinical features of this rare renal syndrome. The genetic and clinical heterogeneity of hereditary tubular diseases together with their low prevalence, constitute a challenge for health professionals, basic researchers and epidemiologists.[14]

These patients represent the first distal RTA to be studied in México.

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