Clinical case

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Distal renal tubular acidosis: case series report and literature review

Acidosis tubular renal distal. Serie de casos y revisión narrativa

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Abstract

The distal renal tubular acidosis presents due to a defect in the excretion of hydrogen ions at the distal tubular level, causing an increase in the pH of the urine and a decrease in the plasma pH, with several associated clinical manifestations. This article makes a thorough review of distal renal tubular acidosis and presents the case of three siblings with the entity, two men and one woman, this being one of the first family cases reported in Colombia. All three received the diagnosis during the lactation period, presented nephrocalcinosis and good response to the alkali therapy started early, eventually achieving their suspension. Interestingly, one of them also presented mevalonate-kinase deficiency with hiperinmunoglobulinemia D, alteration not previously described. This association and the apparent lack of need for continued management with alkali are atypical in the light of current knowledge, deserving special consideration.

Key words: Acidosis, renal tubular, nephrocalcinosis, genetics, kidney tubules, distal, rare diseases.

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Resumen

La acidosis tubular renal distal es causada por un defecto en la excreción de iones de hidrogeno a nivel tubular distal, lo que aumenta el pH de la orina y disminuye el pH plasmático; esta es una enfermedad con varias manifestaciones clínicas asociadas. En este artículo se hace una revisión profunda sobre la acidosis tubular renal distal y se presenta el caso de tres hermanos (dos hombres y una mujer) con la entidad, siendo este uno de los primeros casos familiares reportados en Colombia. Los tres pacientes recibieron el diagnóstico durante el período de lactancia, presentaron nefrocalcinosis y tuvieron buena respuesta a la terapia con álcali iniciada de forma temprana, logrando eventualmente su suspensión.

De manera curiosa, uno de los pacientes también presentó deficiencia de mevalonato quinasa con hiperinmunoglobulinemia D, una alteración no descrita con anterioridad. Esta asociación y la aparente falta de necesidad de continuar el manejo con álcali son atípicas a la luz del conocimiento actual, mereciendo especial consideración.

Palabras clave: acidosis tubular renal, nefrocalcinosis, genética, túbulos renales distales, enfermedades raras.

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Introduction

Renal tubular acidosis refers to a heterogeneous group of diseases in which, despite having a relatively normal glomerular filtration rate (GFR), metabolic acidosis occurs due to a defect in the renal tubules, which alters their regulatory capacity of the normal acid-base status.[1] In this group of diseases, metabolic acidosis with normal (hyperchloremic) anion gap (AG) occurs, which is secondary to losses of bicarbonate, mainly in the proximal tubules, or due to defects in the excretion of hydrogen chloride or of some salts that are metabolized to hydrogen chloride (such as ammonium chloride) distal to the nephron.[1,2] This disorder can be primary, secondary, acquired or hereditary, and is sometimes associated with other systemic diseases.[3-8]

Three main forms of renal tubular acidosis have been defined: distal (type 1), proximal (type 2), and hyperkalemic (type 4); type 3 corresponds to a mixed distal and proximal form.[9-11]

In type 1 renal tubular acidosis (RTA1), the excretion of acid in the distal tubule is altered[12] and in the absence of alkalizing therapy, a progressive accumulation of hydrogen in plasma is generated, that leads to a decrease in plasma pH and is accompanied by urine pH> 5.5.[5,6,12] Likewise, RTA1 can be accompanied by hypokalemia secondary to potassium loss due to the acidemia.[13] In Colombia its incidence is unknown due to the lack of records, but in Spain, with a population of about 45 million inhabitants, 50 cases of hereditary RTA1 have been registered in Renaltube; of these, only 20 are Spanish[5,6,9]; likewise, in most European countries the prevalence is low[5,6,11]; in England and France, genetic studies estimate a ratio of 1 case per million inhabitants.[1,3,8] According to several investigations, the population with RTA1 is concentrated in immigrants of Arab origin.[8,9,13]

This article presents one of the first reports of RTA1 with family commitment in Colombia; three siblings with this pathology and with a typical autosomal recessive presentation are identified here. Given the importance of the issue, a review of the literature on this disease is also made.

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Presentation of case 1

A male patient who was admitted for the first time to a hospital of third level of complexity when he was 12 years old. His mother brought an extra-institutional medical history that showed a diagnosis of RTA1 and reported that she had two other children, both minors, who had the disease.

The child had a history of pyloric hyperplasia during his first days of life, for which he required surgical management before reaching his first month of age. Later he developed gastroesophageal reflux disease (GERD), for which he received medical management during the following years. When he arrived at the institution, he was taking antiemetic and antisecretory drugs.

At 10 months of age, the gastroenterology service referred him to nephrology for suspected kidney disease due to persistent emesis and evidence of altered renal function. After some studies, nephrology diagnosed RTA1 and established a management and follow-up plan. At the age of 16 months, nephrocalcinosis was detected and by audiometries performed at 4 and 12 years of age, hearing alterations were ruled out.

Likewise, in their first extra-institutional evaluations, the child had a growth deficit that was corrected with alkalizing therapy. He arrived at the hospital of third level of complexity being managed with polyethylene glycol (PEG) 7 g/day for chronic constipation; otherwise he had adequate symptomatic control.

At the time of his first assessment at the intra-institutional pediatric nephrology service, the patient was being managed with Shohl's solution (1 liter = citric acid 140 g + sodium citrate 70 g + potassium citrate 70 g) 5 cm^3 orally every 8 hours and was asymptomatic. The physical examination showed a weight of 40 kg (41st percentile), height of 144 cm (14th percentile), and vital signs within normal limits for age. The mother delivered paraclinical tests taken 1 month before at the altitude of Bogota, Colombia, which showed venous gases (VG) with pH: 7.383; PCO_2: 38.4; HCO_3: 22.4; BE: -2.3; BUN: 8.7;

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creatinine: 0.45 (GFR: 176 mL/min/1.73 m^2), calciuria: 70.9 mg/day (1.7 mg/kg/day) and urinalysis with pH=6, with the rest of parameters normal. Likewise she brought a ultrasound scan of the same date which showed a right kidney of 100x37 mm and a left kidney of 87x46 mm (Hodson index 10.8), without other alterations.

Subsequently, the patient was evaluated by the genetics service, which requested an international consultation for genetic mapping. This study was carried out by Renaltube (Spain) and its results ruled out the presence of mutations of ATP6V0A4, the most frequently associated with RTA1, without being able to rule out other mutations that are not described in the literature.

In one of the institutional controls by pediatric nephrology, it was evidenced that the mother had suspended treatment with citrate solution one month earlier; however, the patient had totally normal blood gases at the altitude of Bogota, serum electrolytes and urinalysis. Therefore, a possible remission was considered, management was not continued and follow-up exams were requested. In the last control, 8 months later, the child was asymptomatic with normal vital signs and physical examination and the paraclinical tests requested showed VG with pH: 7.381;PCO_2: 47; HCO_3: 21: BE: 3, urianalysis with pH=6 y electrolytes within normal ranges. With this, it was corroborated that he overcame the RTA1 and it was decided to continue without alkaline therapy.

Presentation of case 2

A male patient with an extra-institutional medical history which evidenced that, in addition to ATR1, he had a diagnosis of mevalonate kinase deficiency associated with hyperimmunoglobulinemia D.

During his first two years of life, he presented recurrent bronchoobstructive symptoms for which he required intrahospital management on multiple occasions, eventually receiving a diagnosis of asthma.

In one of his bronchoobstructive episodes at 10 months of age, the patient required hospitalization and management with corticosteroids; on that occasion, through paraclinical results, a persistent hydroelectrolytic deficit was evidenced. Taking into account these electrolyte alterations and the recent diagnosis, at that time, of RTA1 in his older brother, a diagnosis of renal tubular acidosis was suspected. Therefore, at discharge the child was referred to the extrainstitutional pediatric nephrology service with a request for extension studies. At one year of age he was assessed, confirming the diagnosis of RTA1 with pertinent studies. Since then, this service established management with citrate solution and follow-up, which was progressively adjusted to achieve therapeutic goals. However, repeated emetic episodes were evident.

The child was assessed by the extra-institutional pediatric gastroenterology service where a diagnosis of GERD was established and occasional antisecretory management was given with symptomatic improvement. Likewise, at 7 years of age, nephrocalcinosis was detected and hearing alterations were ruled out by audiometry. Like his older sibling, this patient also had short stature during his first extra-institutional evaluations, which was corrected, and did not present additional repercussions during extra-institutional follow-ups for about a year and a half more.

Since the patient was 6 years old he began to have multiple episodes of fever, arthralgia, sporadic headache, appearance of aphthae and asthenia, for which he received different diagnoses and treatments for 6 months, until finally superimposed immunodeficiency was suspected, for which he was referred to extra-institutional pediatric rheumatology and infectious diseases, who carried out extension studies and corroborated the diagnosis of mevalonate kinase deficiency associated with hyperimmunoglobulinemia D when he was 8 years old. Since then, management with lovastatin and colchicine was started to modulate the inflammatory process and prevent the development of renal amyloidosis.

At 9 years of age, he was taken for the first time to the institution for multidisciplinary management, being initially assessed by pediatric nephrology. The patient was being managed with Shohl's solution 5

cm^3 orally every 12 hours, lovastatin and colchicine. The physical examination showed a weight of 28 kg (37^{th} percentile), height of 128 cm (13^{th} percentile), and vital signs within normal limits for age. The last paraclinical tests that the mother brought showed VG (at the altitude of Bogota) with pH: 7.363; PCO_2 41.9; HCO_3: 23.3; BE: -2.1, BUN: 6-7, creatinine: 0.4 (GFR: 132 mL/min/1.73 m^2), calciuria: 55.6 mg/day (1.98 mg/kg/day) and serum calcium in 9.35. She also brought an ultrasound scan performed one week before the control in which a right kidney of 98x40 mm and a left kidney of 98x45mm were evidenced (Hodson Index 9.9), without additional positive findings.

Subsequently, the child was assessed by the institutional pediatric rheumatology service, which considered that the patient could benefit from biological therapy with etanercept for mevalonate kinase deficiency associated with hyperimmunoglobulinemia D. Later, the genetics service requested sequencing of the MVK gene due to the risk of retinitis pigmentosa given the described autoinflammatory condition and sent samples for genetic mapping in search of ATP6V0A4 mutations compatible with RTA1, whose result was not known at the time of writing this article.

The mother discontinued the citrate solution one month before the control by nephrology. The control paraclinical tests reported VG (at the altitude of Bogota) with pH: 7.356; PCO_2: 44: HCO_3: 23.2; and serum electrolytes and urianalysis within normal limits. She also brought a new ultrasound and an audiometry performed three months before the control which showed no alterations. A possible remission of the disease was considered, so management was not continued and control tests were requested. In his last control, 8 months later, the paraclinical tests showed arterial blood gases (at the altitude of Bogota) with pH: 7.317; PCO_2: 50.9; HCO : 26.1; BE: -0.1; BUN: 19.2, creatinine: 0.62 (GFR: 93.3 mL/min/1.73 m^2), calciuria120 mg/day (3.2 mg/kg/day) and urinalysis with pH=6; a renal ultrasound was also performed in which no lithiasis was found and the electrolytes were normal. The service of nephrology considered stability for RTA1 based in the previous paraclinical tests, the absence of pathological symptoms and signs and the remission of the brother, so the medical management established by rheumatology continued without adding alkalinizing therapy.

Presentation of case 3

A female patient in whose extra-institutional clinical history was evident, like in qher siblings, a diagnosis of RTA1.

This patient had no immediate complications during her first days of life. However, the mother, taking into account the diagnosis of RTA1 in her first two children, decided to take her to an extra-institutional pediatric nephrology evaluation at one month of age to rule out the presence of this disease. The paraclinical tests performed revealed alterations compatible with tubulopathy similar to those of her brothers. Subsequently, the diagnosis of RTA1 was confirmed and follow-up was established without introducing alkaline supplementation therapy initially. However, during the following 6 months, she presented recurrent emetic episodes and paraclinical control tests with alterations regarding the initial ones, for which management with citrate solution was initiated.

During the follow-ups, nephrocalcinosis was detected by renal ultrasound scans performed in her nursing nperiod and at 5 and 6 years of age. Likewise, hearing alterations were ruled out with normal audiometries at 3 and 8 years of age. Due to the detection of nephrocalcinosis, her management was progressively adjusted to meet therapeutic objectives. Her height was constantly below 1 standard deviation for age, without being short stature as such.

This patient received extra-institutional assessment by the genetics service, who, taking into account the clinical context and family history, requested a specific genetic study, which, like in the older sibling, was performed in Renaltube and did not show any usual ATP6V0A4 gene mutations compatible with RTA1, again without being able to exclude other mutations. Gastrointestinal symptoms persisted and she was subsequently diagnosed with

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GERD and chronic constipation, with adequate symptomatic control for the latter.

In her first evaluation by the institutional pediatric nephrology service, the girl was being managed with Shohl's solution 13 cm^3 orally every 8 hours and presented gastrointestinal symptoms given by burning epigastric abdominal pain, heartburn, dysphagia and rumination. The physical examination showed a weight of 25 kg (49^{th} percentile), a height of 123 cm (26^{th} percentile), and vital signs within normal limits for age. The mother brought paraclinical tests that had been taken 1 week before and that showed VG (at the altitude of Bogota) with pH: 7.432; PCO_2: 31.1; HCO_3: 20.3; BE: -2.8; BUN: 6.4; creatinine: 0.37 (GFR: 137 mL/min/1.73 m^2), calciuria: 248.5 mg/day (9.7 mg/kg/day), as well as an ultrasound scan of the same date that showed a right kidney measuring 93x33 mm and a left kidney measuring 91x43 mm (Hodson index 9.6), without other alterations. Therefore, the therapy was adjusted by increasing citrate solution 15 cm^3 every 8 hours and trying management with low sodium diet and restriction of calcium intake.

Subsequently, the patient was evaluated by the pediatric gastroenterology service, who considered an exacerbation of GERD symptoms and uncontrolled constipation, for which they requested extension studies and adjusted management with PEG 15 g per day and indicated an increase in oral fluid intake.

During a year and a half of follow-up, pediatric nephrology adjusted the management with alkaline therapy and dietary measures and one month before the follow-up appointment the mother of the patient suspended the treatment. The results of the paraclinical tests without medication were VG (at the altitude of Bogota) with pH: 7.344; PCO_2 : 43; HCO_3: 23; BE: -2.5 and normal serum electrolytes and urianalysis. As with her siblings, it was considered a possible RTA1 that has been overcome, so management was not continued and control tests were requested.

Eight months later, in the last control, the girl was asymptomatic, with adequate development and with VG (at the altitude of Bogota) with pH: 7.24; PCO_2: 63; HCO_3: 27; BE: -1.6, electrolytes without alterations and urine test with pH 5. However, as in her sibling, RTA1 was considered stable, urine with adequate acidification and concentration, so it was decided to continue without management until the next control to evaluate evolution.

It is important to mention that none of the three siblings had significant additional antecedents, that neither the pregnancies nor the deliveries had complications and that all were born full-term. The family is of mixed race, natural and coming from Duitama (Boyacá) and has always lived in adequate economic conditions in a home with all the basic services. The parents, who did not undergo genetic extension studies, were apparently healthy, denied consanguinity, did not have low weight or stature in a constitutional way, did not have significant antecedents, and have not presented pathological conditions suggesting renal alterations such as those observed in their children.

Type 1 renal tubular acidosis (distal)

Pathophysiology

In the distal tubule, the excretion of hydrogen ions into the tubular lumen is carried out by intercalated cells (type A), which are present in the final section of the distal convoluted tubule and in the collecting tubule (Figure 1).[13] Intracellular H_2O dissociates into H+ and OH- ions; the former are secreted into the tubular lumen by means of the H+-ATPase and H+-K+- ATPase pumps and the latter are combined with CO_2 to form HCO_3 - in a reaction catalyzed by carbonic anhydrase II (CAII). The HCO_3 - passes to the peritubular space through the anion exchanger (AE1), which allows the entry of Cl- through a counter-transport mechanism with HCO_3-.

Thus, in the distal RTA1, the decrease in H+ secretion can be caused by a decrease in the net activity of the proton pump or by an increase in the permeability of the luminal membrane to H+.[13-16]

The decrease in the net activity of the proton pump is the main mechanism that produces RTA1 and may

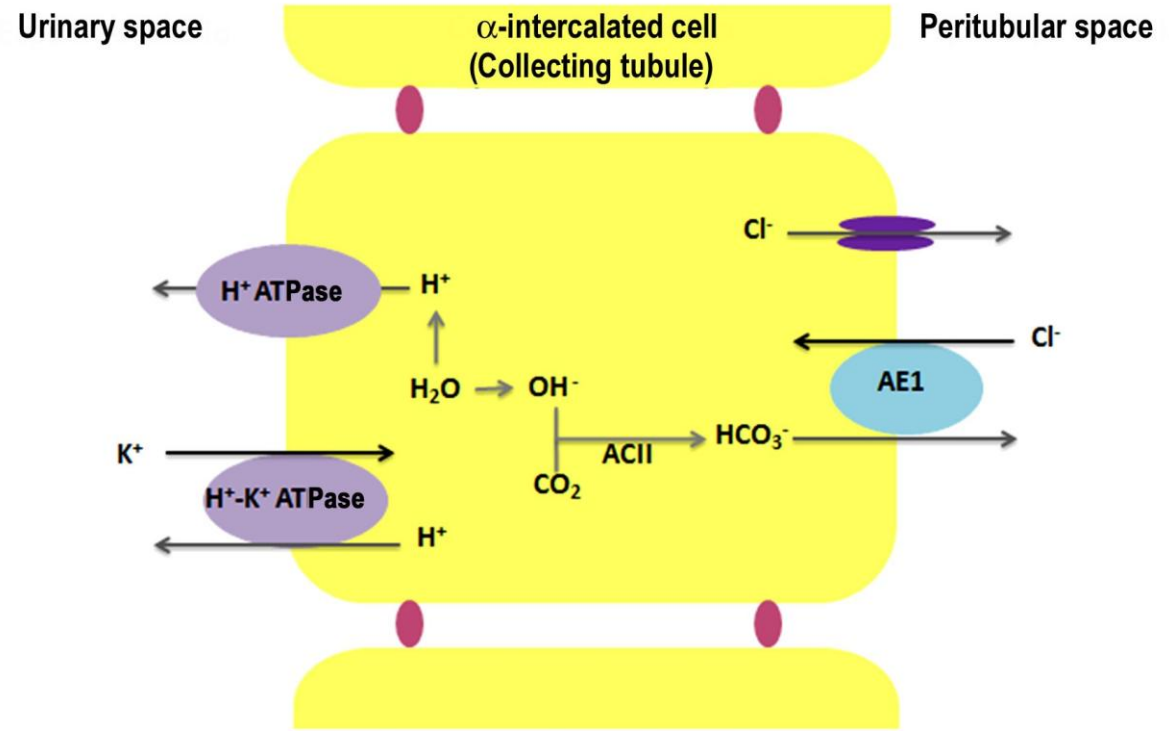

Figure 1. Role of the α-intercalated cell in the maintenance of the acid-base balance. Source: Elaboration based on Batlle & Haque.[6]

be due to several alterations that affect it directly or indirectly.[16-18] For example, several mutations have been found in genes that encode subunits of the H+-ATPase pump and that lead to a loss in their function of proton secretion.[8,19,20] On the other hand, in Sjögren's syndrome (SS) with RTA1 it has been evidenced a complete absence of the H+-ATPase pump, which occurs due to poorly understood immunological mechanisms.[21,22] Likewise, high titers of autoantibodies against CAII that decrease its activity, the generation of H+ ions in the intercalated cell, and its secretion by the proton pump have been identified in this syndrome.[23] Finally, mutations in AE1 have been identified in several families with hereditary forms of RTA1, which by decreasing the activity of this transporter would lead to the accumulation of HCO_3- in the cell A with a consequent decrease in the generation of intracellular H+.[24-28]

A less frequent mechanism of production of RTA1 is related to the permeability of the luminal membrane to H+. Since in many occasions the concentration of H+ is higher in the urine than in the extracellular space, this membrane must be relatively impermeable to prevent these ions from returning to the tubular cells and subsequently to the systemic circulation. When the permeability of this membrane decreases, as occurs in nephrotoxicity associated with the use of amphotericin B, these ions tend to return to the extracellular space, leading to hyperchloremic metabolic acidosis.[29,30]

Etiology

In children, RTA1 almost always has a primary origin, being identified several genetic mutations that are transmitted in an autosomal dominant or autosomal recessive manner. However, in about 20% of cases, no known mutation can be identified.[1,5,19,31] The three main genetic forms of primary RTA1 are distinguished in Table 1.

In addition to the genetic disorders described, Ehlers-Danlos syndrome and sickle cell anemia can

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Table 1. Classification of primary distal renal tubular acidosis

Classification	Type 1a RTA	Type 1b RTA	Type 1c RTA
Compromised gene	SLC4A1	ATP6V1B1	ATP6V0A4
Locus	17q21-22	2p13	7q33-34
Defective transporter	AE1	B1 subunit of the H+-ATPase	A4 subunit of the proton pump
Clinic	It can coexist with hereditary spherocytosis and Southeast Asian ovalocytosis	Alteration in endolymphatic homeostasis of the pH and cilia cell function with associated deafness. Acidification on semen maturation occurs.	Renal or ear involvement is generated, even leading to late deafness.

Source: Elaborated based on[31-42].

also be a genetic etiology of RTA1, although of secondary type.[43,44]

Some acquired secondary causes and less frequent in children are the consumption of some medications and autoimmune disorders. Among the former stands out amphotericin B, which can produce irreversible RTA1[29,30]; lithium, which can generate an incomplete form of RTA1 in which there is a decrease in acidification of the urine despite the plasma pH being normal,[45] and isophosphamide.[46] SS and systemic lupus erythematosus has been reported as associated autoimmune disorders, which can cause this disorder by immunological mechanisms still unknown.[21-23,47,48]

Clinical manifestations

The manifestations vary considerably depending on the etiology. In the case of the primary forms of RTA1, more stereotyped clinical pictures appear at more characteristic ages.

Recessive RTA1 is the most frequent and severe; it courses with severe hyperchloremic metabolic acidosis and moderate to severe hypokalemia.[19,49-51] Therefore, its manifestations usually appear early and the diagnosis is generally established earlier in relation to the dominant form of the disease.[19,49,50,52]

Figure 2 summarizes the clinical manifestations of RTA1 according to the involved organ systems, being present mainly in the recessive form of the disease.

Patients with the recessive form of RTA1 present with abdominal or lumbar pain secondary to nephrocalcinosis and/or renal litiasis[7,50] which are explained by the alkaline urine that favors the precipitation of calcium phosphate crystals.[54] On the other hand, there is a decrease in the concentration of urinary citrate (a powerful inhibitor of the formation of calcium stones), which favors the precipitation of this last mineral.[55,56] In addition, the acidemia promotes hypercalciuria by increasing the release of calcium phosphate from the bone by the bone buffer system and by directly decreasing the tubular reabsorption of these minerals.[57,58]

These alterations are frequent in patients with RTA1 in such a way that a late diagnosis can compromise the size of the kidneys or even lead to end-stage renal failure, for which it is recommended

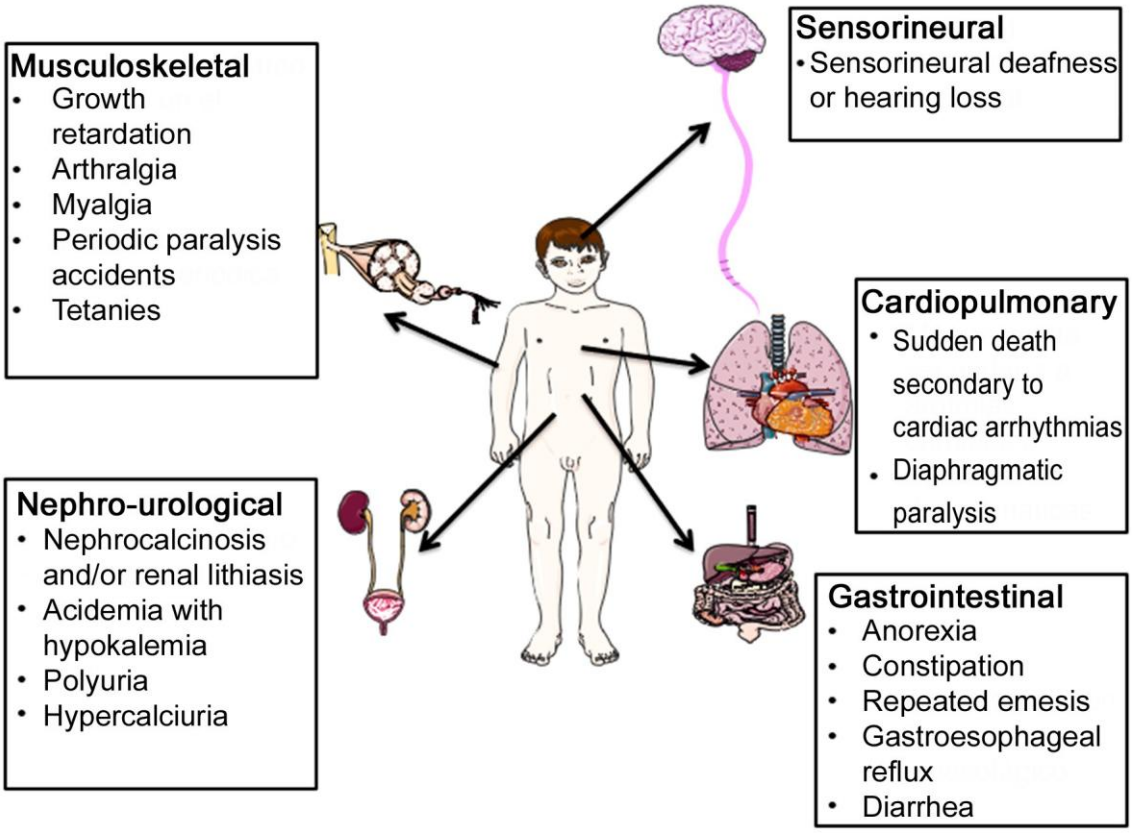

Figure 2. Clinical manifestations of distal renal tubular acidosis according to compromised organ systems. Source: Elaborated based on[53-66].

to perform renal ultrasonography annually during follow-up.[6,59]

On the other hand, sensorineural hearing alterations occur exclusively in the recessive form of RTA1.[37,42,49] However, the recessive forms of RTA1 are not necessarily accompanied by deafness, in addition, the associated hearing alterations exhibit considerable phenotypic heterogeneity.[20,41,42] In situations where genetic studies are available, the hearing status of the patient should not influence *a priori* a decision about which genes to study, and the finding of mutations associated with sensorineural hearing alterations obliges to perform periodic hearing tests.[20,37,49,60]

In the case of RTA1 of dominant inheritance, the manifestations are usually mild, being nephrocalcinosis and renal lithiasis the most frequent,[7,50] and can occur with mild or without metabolic acidosis (incomplete RTA1), as well as with normokalemia or mild to moderate hypokalemia.[25,50] Bone diseases or growth retardation occur rarely[25,50] and other alterations described for the recessive RTA1 are not common. Therefore, the dominant form of RTA1 is usually discovered late, even in adulthood.[50,67]

Diagnosis

Figure 3 illustrates the initial approach upon the clinical suspicion of renal tubular acidosis.

To diagnose a possible case of RTA1 is important to evaluate the urinary excretion of NH4+, which due to a decrease in the secretion of H+ to the tubular lumen in RTA1 is always decreased (<20-40 mEq/day).[17,69,74] This measure is of particular relevance in the differential diagnosis of metabolic acidosis secondary to inhalation of toluene, which,

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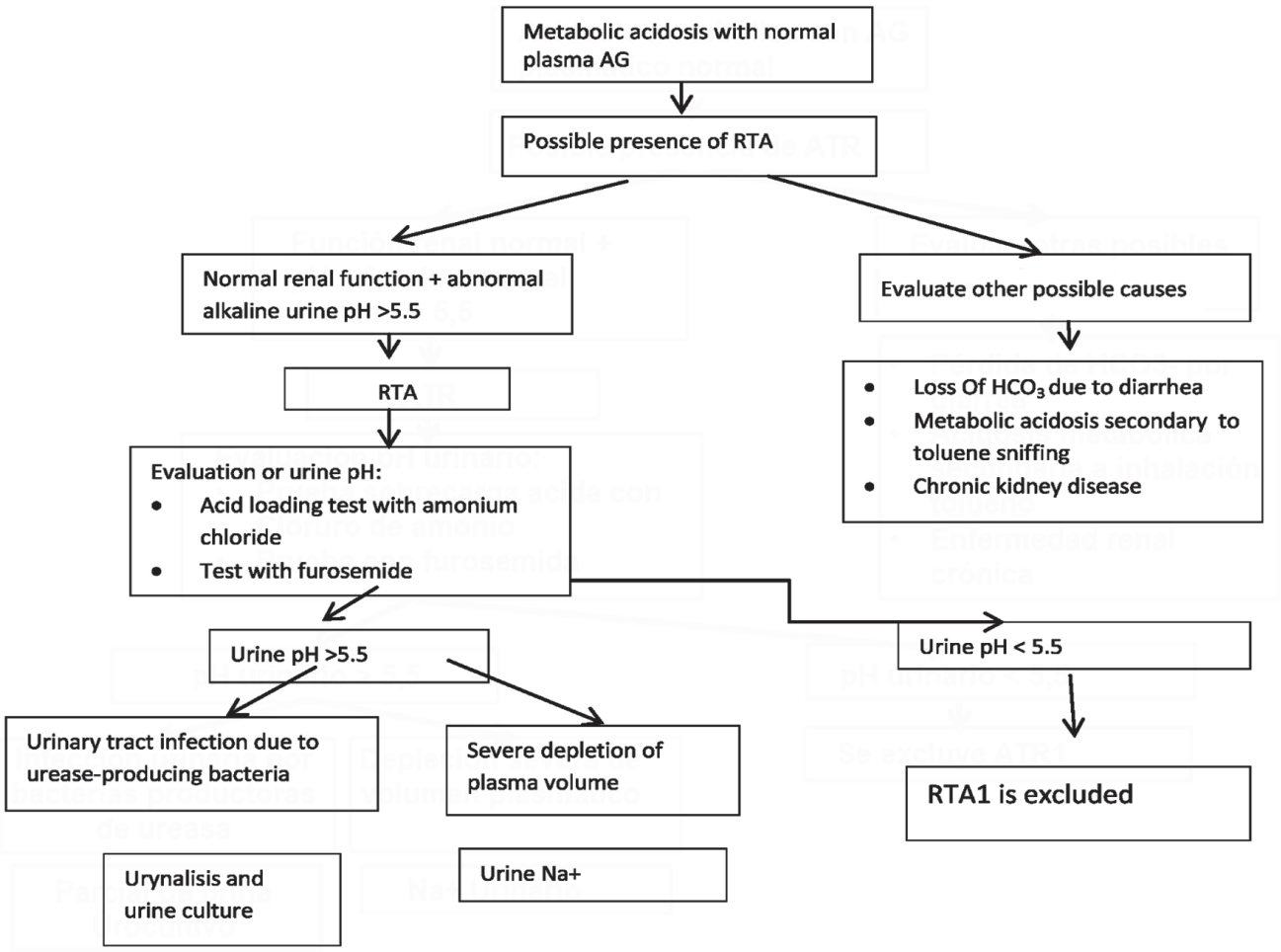

Figure 3. Diagnostic approach to renal tubular acidosis. Source: Elaborated based on[68-73]

although it presents normal AG and hypokalemia as in RTA1, it occurs with normal or elevated ammonium excretion (> 40 mEq/day).[75] Since very few laboratories can directly measure ammonium, urinary AG (uAG) has emerged as an indirect measure of NH4+ in urine.[74] Figure 4 illustrates concepts for understanding the use of uAG.

According to this, the uAG would become more negative as the concentration of NH4+ increases, which would simultaneously increase the Cl. The relationship between uAG and the urinary concentration of NH4+ was evaluated in some studies, finding an inverse linear relationship and developing the formula [NH4+ = -0.8 uAG + 82] for the estimation of NH4+.[74,76]

Likewise, in these studies the uAG of individuals with normal tubular function was averaged between -20 and -50 mEq/L and higher values (less negative) were observed in patients with low excretion of NH4+.[74,76] Therefore, in RTA1 it will be found an increased uAG, usually positive, and a decreased NH4+, either estimated or measured directly.[17,69]

Treatment

Correction of acidemia has demonstrated great efficacy in RTA1, as it reduces renal potassium loss, restores normal growth, delays nephrocalcinosis and urolithiasis, prevents progression to chronic renal failure and even reduces bone alterations associated with this

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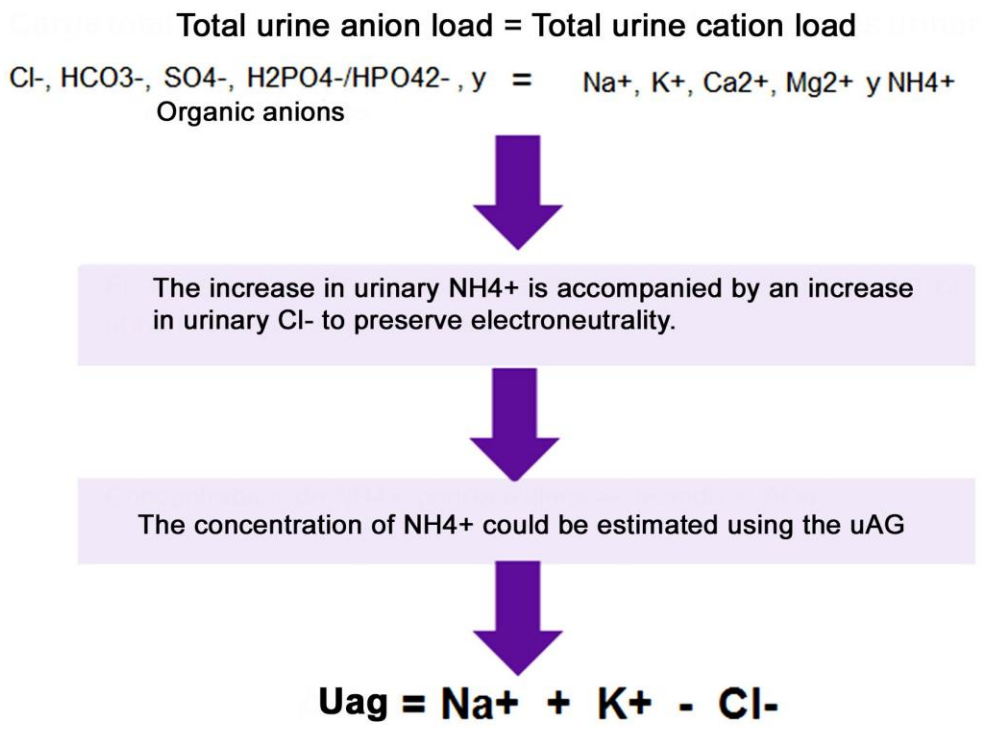

Figure 4. Basic concepts about the urine anion gap. Source: Elaborated based on[74-76]

disease.[77-80] Alkalinizing therapy is therefore the indicated management for RTA1, since it seeks to achieve relatively normal plasma levels of bicarbonate.

Sodium bicarbonate and sodium citrate are viable alternatives; however, the first occasionally generates digestive intolerance, which is one of the main obstacles.[81] The required doses in children can reach up to 4-8 mEq/kg/day, while in adults 1-2 mEq/kg/day are usually sufficient.[1,82] Potassium citrate is also an excellent alternative, mainly due to its usefulness for the replacement of K+ and its tolerability[83]; furthermore, the citrate provided when it is filtered in the kidney can directly increase the urinary excretion of citrate, although the main mechanism for this increase is the decrease in acidemia, which causes increased tubular reabsorption of citrate in RTA1.[55,56,78,79]

RTA1 is almost always a permanent disease, which is why alkali therapy must be continued lifelong.[84] When diagnosed early, the patients may have fewer complications and their prognosis will improve.[1,85] Likewise, a low sodium diet could have beneficial effects, due to mild volume depletion, increasing the reabsorption of Na+ at the proximal tubule and, secondarily, of HCO_3-.[86, 87]

Discussion

Some characteristics of the clinical picture presented in the three patients draw attention and deserve to be analyzed in the light of current knowledge about RTA1:

The three siblings presented different comorbidities since the first months of life; however, the initial manifestation of RTA1 in the three siblings consisted in refractory emetic syndrome at a young age, which is frequently reported in the literature on RTA1.[7,88,89] The patients also had early development of nephrocalcinosis and short stature, although the younger sister only had measurements within the risk range of short stature, all of which were common clinical findings.[6,7,11,50] These cases also coincided with that is reported in the literature regarding clinical

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alterations that manifest at a very young age in recessive hereditary presentations of RTA1.[19,49,50,52]

As mentioned above, early therapy usually leads to an excellent prognosis,[1] which was reflected in the adequate evolution and development of these patients. Thus, as previously reported,[77-80] both nephrocalcinosis and short stature improved with proper management.

Although a control renal ultrasound scan was not performed annually, as recommended,[6,59] at least four renal ultrasound scan were made during follow-up, which evidenced the remission of the nephrocalcinosis. On the other hand, calciuria, arterial gases and serum potassium improved during the follow-ups with alkalizing treatment, which coincides with what has been described in the literature.[77-80]

It is highlighted that none of the patients had hearing impairment, which is compatible with RTA1 type 1c.[8] Nevertheless, the studies carried out by Renaltube were not able to identify the main mutations of the ATP6V0A4 gene that are compatible with this presentation. This does not rule out the diagnosis, since it is probably a mutation not described so far in the international literature. This is not unusual taking into account that, although the main cause of RTA1 in the pediatric population is genetic, in up to 20% of primary RTA1 cases in children the underlying mutation cannot be identified.[1,5,19,31] The description of these mutations is not the main objective of this publication, however, their report can be the basis for future studies.[19,20,37,41,42]

It is curious that in one of the siblings there was a concomitant presence of mevalonate kinase deficiency associated with hyperimmunoglobulinemia D, a metabolic disease that definitely alters the prognosis and the evolution of the patient. The association between congenital RTA1 and metabolic diseases has not been clearly described in the literature, so it is worth reporting this event in order that in future studies and case reports some type of relationship will be determined.

Something that also attracted attention was the persistence of clinical improvement in the three patients after the discontinuation of alkalizing therapy and that within the biochemical alterations derived from this disease they only presented a decrease in pH to clear ranges of acidemia, but with normal urinalysis, serum electrolytes and urinary calcium. The main goal in management was achieved in the three patients: correction of symptoms associated with RTA1, remission of nephrocalcinosis, and avoiding permanent kidney damage.[1] The main goal in management was achieved in the three patients: correction of symptoms associated with RTA1, remission of nephrocalcinosis, and avoiding permanent kidney damage.[1] The caveat should be made that the follow-ups are still continuing and that future studies and evaluations will define whether the alkaline therapy requirements will indeed not be necessary again. Another possibility is that the needs for alkaline therapy have decreased without disappearing completely, as has been clearly described as patients with RTA1 grow older,[82] which will also be confirmed with the follow-up.

Conclusions

Although the clinical manifestations of the cases presented are in concordance with that is reported in the literature on RTA1, this publication highlights some uncommon facts that merit to be taken into account in future research. On the one hand, the association of one of the cases with mevalonate kinase deficiency with hyperimmunoglobulinemia D and, on the other, the disappearance of the need for alkalinizing therapy, particularly in the first case, which is not usual according to current knowledge about RTA1.

The study of relatives of patients affected by this pathology is important, since there are different genetic mutations with various forms of transmission and associated clinical manifestations. An active search should then be carried out in relatives, evaluating the risk factors previously described. Even though at this moment there are no protocols validated with an adequate scientific methodology for cost-effectiveness analysis for this type of study, its possibility is something that should be contemplated and investigated in future studies.

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It is striking that mutations previously associated with RTA1 have not been evidenced in these patients. However, there is a possibility that they have had undescribed mutations that should be studied in the future.

This type of pathology in pediatrics must be studied and managed in a multidisciplinary way by pediatric nephrology, general pediatrics, genetics, pediatric endocrinology and even nutrition, and it must be established a periodic follow-up plan that includes genetic counseling when indicated by the results of the studies.

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Conflict of interest

None declared by the authors.

Ethical responsibilities

For the preparation of this case report, informed consent was obtained from the legal guardian of the patients.

Contribution of the author

JSFO summarized the case and conducted the search of scientific literature. JAUD and JSFO reviewed the content of the articles found and created a preliminary version of this article. CJLT and GLM reviewed, completed and corrected this version.

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