2nd Edition of the Contest of Clinical Cases related to the non-surgical clinical management of kidney stones

Title: Prevention of nephrocalcinosis in distal renal tubular acidosis: in relation to a case

Keywords: Distal renal tubular acidosis; renal stones; urinary pH; oral chemolysis; prevention lithiasis; urinary alkalinization

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1. Summary

Distal renal tubular acidosis is due to a defect at the level of the collecting tubule avoiding proper urinary acidification, leading to metabolic acidosis with normal anion gap. It is associated with an alkaline urinary pH, hypocitraturia and hypercalciuria, thus promoting the precipitation of calcium phosphate crystals, favouring the appearance of renal stones and nephrocalcinosis.

This entity can be accompanied by multiple episodes of renal colic with the need for repeated interventions on the same renal unit, which means an increase in morbidity, worsening in the quality of life of patients, an increase in social and healthcare costs and, on occasions, ends in end-stage renal disease.

Through a clinical case we emphasise the importance of early diagnosis and non-invasive treatment with urine alkalizers, in order to prevent the appearance of these stones and avoid complications

2. Introduction

Homeostasis is an indispensable requirement for cellular life, and is carried out by multiple organs, including the kidney. Thus, the kidney plays an essential role in maintaining the acid-base balance and pH of the medium through the absorption of bicarbonate and the excretion of hydrogen ions (H+). In the distal tubules and collectors, the final regulation of this acid-base metabolism takes place (1).

Renal tubular acidosis comprises a group of congenital or acquired alterations that are characterised by an abnormal function of the kidneys making it impossible to correct urinary acidification, resulting in metabolic acidosis with normal anion gap. Specifically, distal renal tubular acidosis (dRTA) or type I, is due to a defect at the level of the collecting tubule, preventing correct excretion of H+ with the consequent renal loss of potassium (K+). The accumulation of these H+ results in the consumption and, therefore, decrease of the bicarbonate/carbon dioxide (CO_2) buffer in the blood, so that the urinary pH is raised, giving rise to a persistently alkaline urine with pH >5.6 in the presence of systemic metabolic acidosis (Image 1).

It is usually accompanied by normal or minimally impaired renal function. These alterations are associated with hypokalemia, which leads to polydipsia and polyuria due to inability to concentrate urine, and muscle weakness (3).

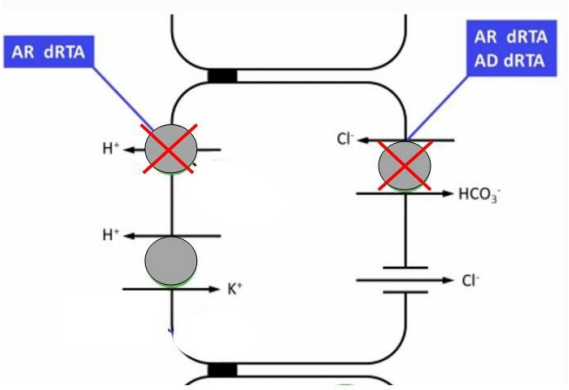

Image 1. Altered transporters in the collecting tubule in the different types of hereditary dRTA: Autosomal recessive (RA) or autosomal dominant (AD). Modified from Distal renal tubular acidosis: a systematic approach from diagnosis to treatment. Giglio S.et al. J Nephrol 2021 (2)

dRTA is also a risk factor for the development of kidney stones and nephrocalcinosis. The formation of these stones is due to 3 factors:

- The presence of an alkaline urinary pH.

- Hypocitraturia: Systemic acidemia reduces proximal water reabsorption through activation of the renin-angiotensin-aldosterone system, thus decreasing the proximal absorption of sodium (Na+). This increases CO2-dependent Na+ transporters, thereby increasing citrate reabsorption in the proximal tubule and causing hypocitraturia.

- Hypercalciuria: dRTA is also associated with an alteration of bone metabolism. The retention of H + leads to a decrease in renal absorption of calcium, thus increasing bone resorption, generating hypercalciuria.

Therefore, hypercalciuria together with hypocitraturia and alkaline urinary pH, promote the precipitation of calcium phosphate with the consequent formation of renal stones.

3. Description of the clinical case

Our case focuses on a 36-year-old male patient who has been followed up in the urology department for 7 years, referred from the nephrology service. He was diagnosed with autosomal recessive congenital distal renal tubular acidosis at the first month of life.

As a relevant urological history, the patient presents recurrent episodes of stone expulsion, often monthly, which on occasion have required extracorporeal lithotripsy for resolution.

When he came to our clinic, the patient was being treated with potassium citrate, 4 pills every 8 hours, a treatment he had been taking since the age of 18

As part of the initial study, an abdominal X-ray and ultrasound and a metabolic study were requested. The X-ray showed bilateral nephrocalcinosis, with an ultrasound scan compatible with this diagnosis (Image 2). The metabolic study showed a diuresis of 1500cc, with hypocitraturia of 130 mg/24h and mild hyperoxaliuria with normal elimination of calcium, phosphorus and uric acid, mild microalbuminuria and proteinuria, together with normal renal function.

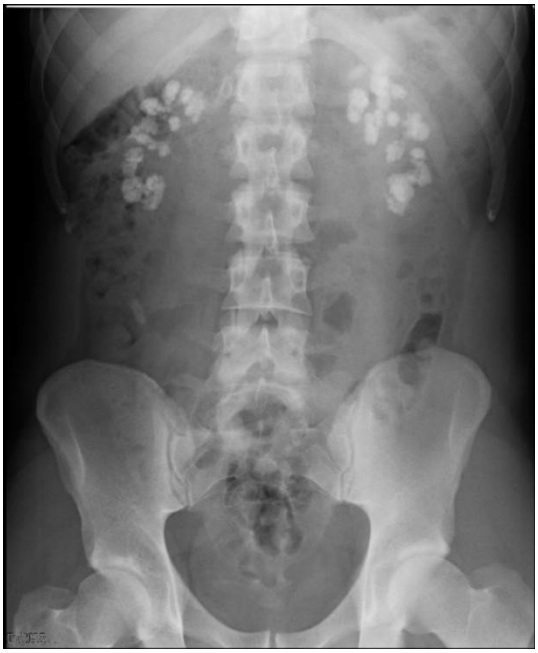

Image 2. Abdominopelvic radiography of the patient upon arrival at our service. Bilateral nephrocalcinosis is seen.

A second metabolic study 6 months after the previous one confirms hypocitraturia despite a well-conducted treatment. The rest of the parameters were within normal limits. The systematic urine test showed a pH of 7.5. Blood tests showed a parathyroid hormone level of 62pg/mL and vitamin D of 18ng/mL. It was decided to add vitamin D to the previous treatment with potassium citrate.

At this point, the patient lost follow up at our center and underwent surgery for right renal lithiasis by means of extracorporeal shock wave lithotripsy and multiple ureterorenoscopies at another centre, finally requiring distal ureterolithotomy and right ureteral reimplantation.

On resuming follow up in our consultations, a scan and a computerised axial tomography (CAT) scan were requested to assess renal function. The scan showed a right kidney with functional delay with progressive accumulation in the excretory system that was very dilated and with an obstructive curve, with a renal function of 38%.

The CT scan shows multiple calcium deposits in the pyramids of both kidneys, findings compatible with known nephrocalcinosis. On the right side there is a grade IV hydronephrosis (47 mm pelvis), with accumulation of multiple lithiasis in the proximal ureter (Image 3).

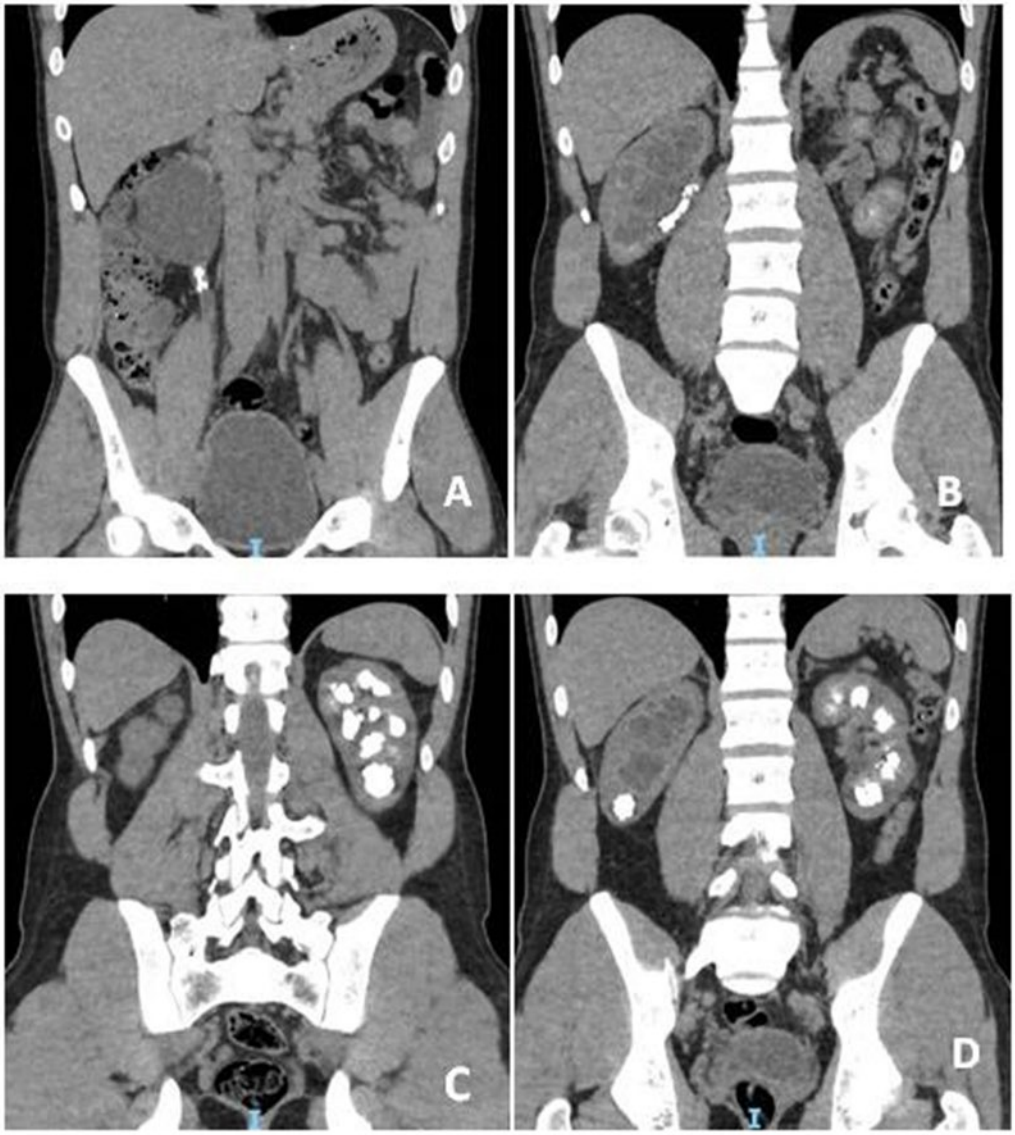

Image 3. Coronal cuts of the CT scan. Image A shows lithiasis in the right proximal ureter with grade IV hydrophenosis. In the B lithiasis accumulated in the pelvis. Images C and D show calcium deposits in the pyramids of both kidneys.

In view of these findings, it was decided to perform renal and right ureteral surgery with the intention of resolving the kidney stone, which was carried out without incident, leaving the patient stone free, with no subsequent complications. After the latter surgery, treatment was started with Lit-Control® pH Up, two pills daily. The treatment was well tolerated and the patient has since been asymptomatic, with no recurrence of calculi in the right kidney two years after surgery (Image 4).

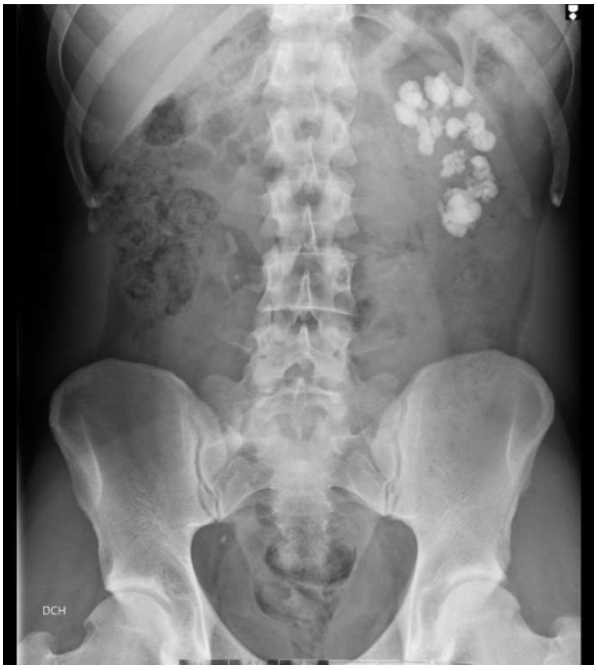

Image 4. Control abdominopelvic radiography without calculi recurrence in the right kidney.

4. Discussion

Nephrocalcinosis in patients with hereditary dRTA occurs in up to 93% of adults, leading to stage II chronic kidney disease in 82% of them. However, in patients with correct prevention of kidney stones, stage IV or V renal disease can be avoided to a considerable extent by up to 2-5% (4).

The goal of treatment of dRTA is to correct metabolic acidosis to avoid the possible consequences that it entails. These include stunted growth, rickets, osteoporosis, nephrolithiasis, and nephrocalcinosis (5). It will be of great importance to diagnose and treat this last entity, as its progression may lead to chronic renal failure and end-stage renal disease. Therefore, not only will the diagnosis and treatment of this presentation of the disease be important, but a correct prevention in the formation of calculi will be fundamental to avoid multiple interventions and symptomatic pictures, with the consequent increase in morbidity and decrease in the quality of life of patients, as well as the social and healthcare costs involved.

In this regard, the medical literature agrees on oral supplementation with salts. In the dRTA in particular, they recommend the use of alkali in the form of sodium and/or potassium bicarbonate or citrate salts to keep bicarbonate (HCO3) concentrations above 22mEq/L (5).

However, it is important to note that excess sodium bicarbonate leads to an increase in extracellular volume and thus decreases proximal HCO_3 reabsorption, which further increases the need of an alkali (6). Because of this increase in extracellular volume, special attention should be paid to patients with hypertension, a history of decompensated heart failure with decreased ventricular function, and liver cirrhosis (7).

Additionally, sodium intake in the form of sodium citrate or sodium bicarbonate salts increases urinary sodium excretion which, as previously mentioned, leads to greater secondary citrate reabsorption, and therefore favours hypocitraturia.

For this reason, potassium-based salts are more effective in this type of patients with kidney stones than those based on sodium, as they allow correction of urinary pH while helping to correct hypocitraturia. In this way they can help in the prevention of nephrolithiasis; and this means that the most widely used treatment today is potassium citrate (5).

The patient of the exposed clinical case began treatment with Lit-Control® pH Up, which is characterised by a potassium citrate base, and adds a combination of other molecules including magnesium citrate, cocoa dry extract (40% theobromine), zinc gluconate and vitamin A.

Initially, the patient started treatment with potassium citrate without a clear improvement in terms of kidney stones recurrence; however, in addition to these other molecules, he has remained asymptomatic without new stone formation in the right kidney. In support of this combination, there are studies that postulate joint treatment with magnesium, as it acts as an inhibitor of calcium oxalate crystal precipitation, since magnesium oxalate is more soluble than calcium oxalate (8).

Thus, in clinical practice, when treating each patient, we must consider the availability of the different drugs, in the same way as the possibility of acquiring them by the patient, and the organoleptic properties of the various formulas to ensure adequate adherence to treatment. In cases where we opt for a formulation based on Na+, we must bear in mind that K+ supplements may be necessary to keep the plasma levels of the same in range.

As for the follow-up of these patients in adulthood, it will depend on the clinical presentation of each individual.

In those cases in which the disease remains stable and the patient maintains adequate renal function, we may defer the revisions on an annual basis. However, if we are facing a more active disease with the formation of calculi, we should opt for a closer follow-up, as well as in those patients in whom we are initiating a new treatment.

5. Conclusions and recommendations

Although hereditary dRTA is a rare disease that affects 1 in every 100,000 people, it is not uncommon that during our professional life we are presented with a patient with this pathology associated with recurrent colic. Early diagnosis together with appropriate treatment and close follow-up is essential in those patients with the development of nephrolithiasis and nephrocalcinosis. Potassium citrate as a definitive and preventive treatment of kidney stones will be the treatment of choice in this pathology. However, future efforts should be concentrated to establish the best possible multidisciplinary management in this type of patient.

6. References

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