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Case report

Severe metabolic alkalosis due to diuretic treatment in a patient with distal renal tubular acidosis: a rare association

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Summary. *Introduction:* Distal renal tubular acidosis is a rare genetic disease, characterised by deficit in renal tubular transport. Clinical features are metabolic acidosis with hypercloraemia and hypokalemia, and inability in urine acidification. Hypercalciuria may also be present, often treated with the use of a diuretic therapy with thiazides. *Case Presentation:* We present a severe disease onset in a neonate with consanguineous parents, both autosomal-recessive for an ATP6VOA4 gene mutation, and a nevertheless severe episode of metabolic alkalosis, occurred in the same patient after few months, during the diuretic therapy. *Conclusion:* Biochemical results lead us to hypothesize a susceptibility to the treatment that need further investigations. (www.actabiomedica.it)

Key words: distal renal tubular acidosis, metabolic alkalosis, hydrochlorothiazide

Introduction

Distal renal tubular acidosis (dRTA), called "Classic distal" or "Type 1", is a rare genetic disease grouping in the renal tubular acidosis (RTA) syndromes. These diseases are characterized by different tubular transport defects that lead to the inability to secrete hydrogen ions (H^+) with development of metabolic acidosis (1). In children, dRTA is most of the times observed as primary entity often in families with autosomal-dominant (AD) or autosomal-recessive (AR) pattern of inheritance (2). Type 1 presents an inefficient H^+ secretion, with inadequate hydrogen ion gradient between the blood and tubule fluid (3, 4). This leads to low plasma $HCO3^-$ levels, metabolic acidosis, electrolytes alterations, as hypercloraemia and hypokalemia, and inability in urine acidification. Hypercalciuria may also be present as result of calcium phosphate mobilization from bones to compensate systemic acidosis, and hypocitraturia, as consequence of increased citrate excretion to buffer systemic acidosis. High urine pH, high calcium (Ca^{++}) and low citrate urine levels promote nephrocalcinosis, often associated with nephrolithiasis. Chronic renal failure could develop as long-term effect. Clinical manifestations may also be failure to growth, anorexia, vomiting, dehydration and hypotonia (1, 2).

RTA main treatment consists in continuous administration of the appropriate amount of alkali in the form of either bicarbonate or citrate (1, 5, 6). This leads to correct metabolic acidosis and electrolytes alterations, improves growth and prevents renal and bone diseases (2).

Thiazide diuretics (TDs) have also been used to treat renal hypercalciuria, reducing the risk of nephrolithiasis. In particular, the most used is the hydrochlorothiazide (HCT) (7, 8).

The appropriate dosage and duration of treatment is controversial (9) since literature documents several cases of pseudo-Bartter's syndrome (10-12).

We present an early diagnosis of dRTA characterized by the homozygotic mutation of the ATP6VOA4 gene, showing two severe electrolytes dysfunctional episodes: the first at the disease onset and the second during the TDs treatment, leading to speculate a possible susceptibility to the diuretic treatment.

Case presentation

XY, 29-days-old, was admitted to the Emergency Department for severe weight loss and critical dehydration (estimated loss of 520 gr in 15 days). Medical history was uneventful except for parental consanguinity (first-degree cousins).

Physical examination showed impairment of general conditions, dry skin, cold extremities, refill time of 5". Biochemical evaluation revealed critic metabolic acidosis with hypernatremia, hyperchloraemia and ipokaliemia, hyperammoniemia and acute renal insufficiency (Table 1).

Urine analysis showed an alkaline pH (6.5) with presence of leucocytes, proteins and blood. The anion gap was normal.

He was rehydrated with intravenous fluids to support the circle and electrolyte replacement (K^+ and HCO^-_3) to correct the severe electrolyte imbalance. He was rapidly transferred to Neonatal Intensive Care Unit (NICU) because of his critical conditions. Suspecting a sepsis, microbiologic samples were collected (cerebrospinal fluid, blood, urine) and empirical antibiotics therapy was started (ampicillin and gentamicin). Cultures resulted negative. Cerebral ultrasound was normal whereas the abdominal scan showed bilateral medullary nephrocalcinosis. Despite the infusive treatment with K^+ and HCO^-_3, XY continued to show a trend to maintain hypokaliemic metabolic acidosis and hypercalciuria: this led to the dTRA hypothesis.

XY was transferred to the Pediatric Unit four days later, presenting improved clinical conditions and plasma electrolyte concentrations. Continuous vital parameters monitoring, fluids balance, blood gas analysis and electrolytes status were performed. Infusive treatment was adjusted until oral administration of $NaHCO_3$ and Potassium Citrate (Kcit) was achieved.

The detection of a homozygotic mutation in ATP6VOA4 gene located on cr. 7q33-34 confirmed the suspect of dTRA. Parents and brother are heterozygotic carriers of the same mutation.

At the discharge, the oral therapy with $NaHCO_3$ and Kcit was integrated with administration of HCT (about 2 mg/kg twice a day) to reduce kidney stones formation.

One a month later, the patient was admitted again to the emergency department presenting vomiting, decreased urine output and poor appetite. He presented lost of weight and dehydrated appearance (dry skin and furred tongue).

Blood analysis revealed a severe hypocloraemic and hypokaliemic alkalosis (Table 1) and electrocardiogram showed a prolongation in QT interval (QTc >0, 50 sec). He was immediately rehydrated with intravenous fluids and electrolyte replacement, and the diuretic treatment was stopped, with good resolution. A month later the treatment with HCT was started

Table 1. Gas analysis, plasmatic electrolytes concentration and renal function at first evaluation with severe metabolic acidosis (first row) and gas analysis and plasmatic electrolytes concentration at second evaluation with severe metabolic alkalosis (during treatment with hydrochlorothiazide – second row)

	PH	pCO2 (mmHg)	pO2 (mmHg)	BE (mmol/L)	HCO3- (mmol/L)	Na++ (mEq/L)	K+ (mEq/L)	Ca++ (mEq/L)	Cl- (mEq/L)	Urea (mg/dl)	Creatinine (mg/dl)	Ammonium (mmol/l)
First episode	7,01	24,2	43,3	-23,6	6,0	157	2,44	7,40	109	231	1,54	103
Second episode	7,61	72,9	29,8	-43,3	71,9	130	1,49	--	54	--	--	--

again during a recovery at the hospital: periodic blood analysis revealed the same trend to hypocloraemic and hypokaliemic severe alkalosis, leading the doctors to stop the diuretic treatment.

No other episodes were referred and XY is still periodically evaluated by paediatric nephrologists: he now presents regular weight and height growth, no neurological deafness and no hearing loss; full blood count, renal and liver function, acid-base blood status and urines are normal; last abdominal ultrasound was unchanged. Current oral therapy of the child involves $NaHCO_3$ four times/day and Kcit.

Discussion

Clinical and biochemical features of dTRA onset can be easily confused with neonatal sepsis.

XY presented poor general conditions, with very severe hypokalemia, hypernatremia and metabolic acidosis. However, sepsis was excluded by negative microbiologic cultures, not improving with antibiotic therapy and persistent metabolic acidosis resistant to bicarbonate treatment.

The alkaline urinary pH associated to normal values of the anion gap could lead to dRTA diagnosis. In particular, in case of hyperchloraemic metabolic acidosis with normal anion gap, the presence of urine PH >5.5 and normal or low plasmatic K levels are strongly suggestive of dRTA. Moreover, the presence of nephrocalcinosis found during the first abdominal ultrasound is another sign strongly indicative of dRTA (1, 2).

Our hypothesis was confirmed by genetic investigations: in particular mutations of the ATP6V0A4 gene configuring the AR dTRA variant without sensorineural deafness (1, 4).

A family history of consanguinity (Figure 1) is the hallmark of patients with AR dTRA (2): they are more severely affected and require aggressive administration of intravenous fluids and $NaHCO_3$ and Kcit replacement.

On the second admission, XY presented a severe hypocloraemic (Cl 54 mEq/L) and hypokaliemic (K

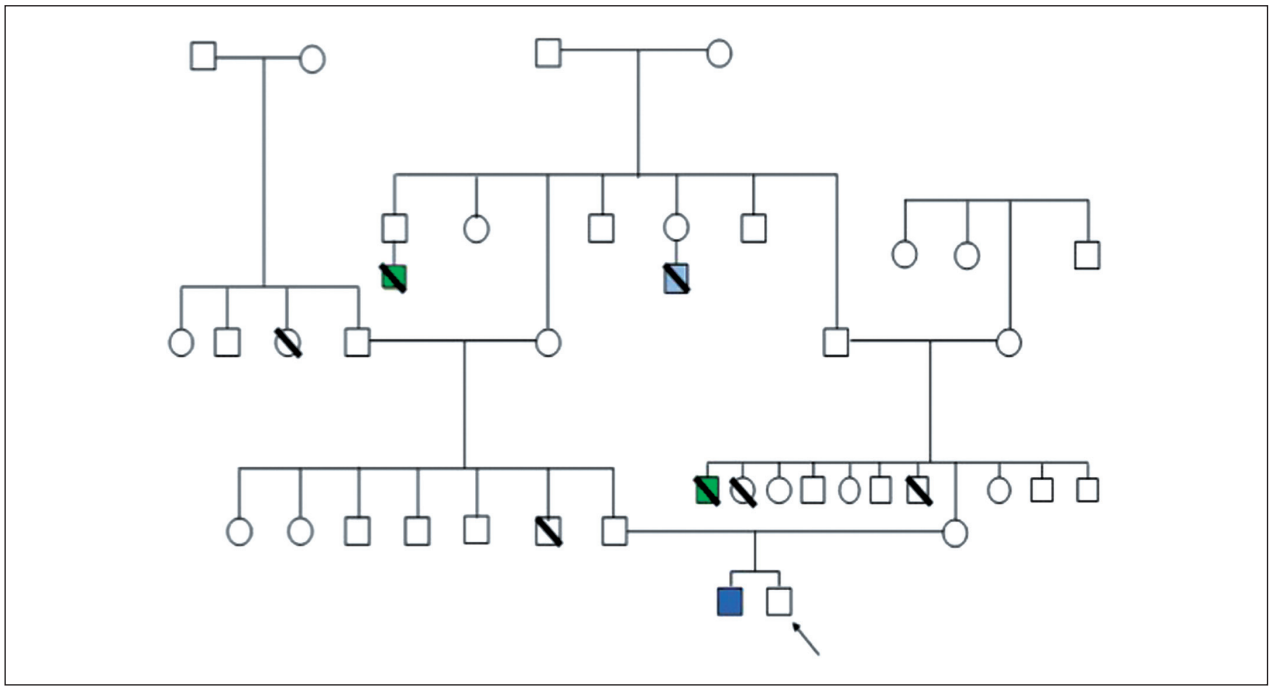

Figure 1. Family tree. In green: newborns dead after a few days of life for unknown reasons. In light blue: a 16 years old boy dead for neoplasm. In dark blue: a brother with thyroglossal duct cyst. The remnants deaths in the family were in adulthood, for unknown reasons

1,49 mEq/L) alkalosis, with life-threatening value of pH (7,61), $HCO3^-$ (71,9 mmol/L) and BE (43,3 mmol/L). The hypokaliemia caused an important prolongation in QT interval (QTc >0, 50 sec), justifying an aggressive therapeutic approach.

TDs therapy, stopped after this episode, is normally used for renal hypercalciuria treatment even in children, decreasing the risk of nephrolithiasis. In fact, TDs reduce NaCl reabsorption and renal excretion of Ca^{++}, favouring diuresis with an anti-hypertensive effect; it also increases K^+, $HCO3^-$, Mg^{++} and phosphates excretion (13).

It is controversial what dosage is appropriate and how long the treatment should be performed. It is reported that low-dose TDs (0,5-0,75 mg/kg/day) in children with idiopathic renal hypercalciuria are safe and effective in long-term control of hypercalciuria (9), however sometimes it is required to increase dosages to 1-2 mg/kg/day in children and 2-4 mg/kg/day in neonates/infants to obtain a long-lasting correction (14).

Our patient received HCT at the dosage of about 2 mg/kg twice a day, because of his age and the presence of bilateral medullary kidney stones, to prevent kidney functional impairment. In literature there are few cases of pseudo-Bartter's syndrome described from surreptitious diuretic (10-12). It is a condition characterized by hypokaliemia, hypochloremia, metabolic alkalosis and hyperreninemia with normal blood pressure and positive TDs urine excretion.

It is indeed likely that our patient developed a pseudo-Bartter episode (with severe alkalosis) although his strong predisposition to acidosis. Excluding parental difficulties on treatment administration (both HCT and bicarbonate) and errors in galenic preparation of HCT consigned to the family, and seen the biochemical trend during HCT treatment checked during a recovery, we can speculate a particular susceptibility of our dRTA patient to the thiazidic treatment that may need further investigations for understanding the pathophysiological pathway.

During the first year of life XY was evaluated every three months adjusting the treatment dosage. He did not develop hearing loss and he always maintained $HCO3^-$ level in the normality range (23-24 mmol/L). Unmodified nephrocalcinosis still persists also considering that XY may not benefit of the diuretic treatment.

Conclusion

To the best of our knowledge this is the first case of distal tubular acidosis type 1 developing a severe metabolic alkalosis due to thiazidic diuretic treatment, although appropriate regular dose administration. It is possible that our patient presents an increased susceptibility to hydrochlorothiazide that may need further investigation.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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