

## Failure to thrive in a pediatric patient

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### CASE PRESENTATION

A three-month-old boy was referred to our hospital for the study and management of metabolic acidosis and failure to thrive.

The family history was unremarkable, except for his father who had had a possible drug-induced acute kidney injury and uric acid urolithiasis.

Prenatal and perinatal periods were uneventful and he was born at term (38 weeks of gestational age). His birth weight was 3320 g (50<sup>th</sup> percentile) and his birth length was 47.4 cm (10<sup>th</sup> percentile). The neonatal screening for inherited metabolic disorders was normal. The hearing screening at birth showed no response to otoacoustic emissions on the right side. This hearing screening test was repeated one month later and the result was normal.

During the first month of life, the patient presented with constant regurgitation and constipation, associated with poor weight gain, leading to downward weight-for-age percentile crossing (from the 50<sup>th</sup> percentile to the 5<sup>th</sup> percentile). He was breast-fed for the first month of life and formula-fed thereafter. Infant formula was prepared and administered correctly. At three months of age he was admitted to his local hospital for failure to thrive.

The laboratory workup revealed hemoglobin 10.8 g/dL, leucocytes 13350/uL, sedimentation rate 26 mm/h, urea 47 mg/dL, creatinine 0.44 mg/dL, sodium 137–143 mmol/L, potassium 2.4–3.3 mmol/L, chloride 120–125 mmol/L. Venous blood gases showed pH 7.095–7.192, carbon dioxide 19.4–26.6 mmHg, bicarbonate 7–10 mmol/L, base excess -22–-18 mmol/L, anion gap 10.4–15.1 mmol/L. Urinary pH was  $\geq 6.0$ , with no glycosuria, proteinuria, or any other alterations in the urine. The sweat chloride test was normal. Transfontanelar ultrasound imaging showed no abnormalities.

At our hospital, laboratory assessment also showed non-anion gap metabolic acidosis and hypokalemia. A renal ultrasound was also performed, revealing “increased bilateral diffuse echogenicity of the medullary pyramids suggesting nephrocalcinosis”.

### IS METABOLIC ACIDOSIS ASSOCIATED WITH FAILURE TO THRIVE?

Metabolic acidosis can be caused by three mechanisms: 1) increased acid generation and bicarbonate consumption (bicarbonate acts as a buffer in the presence of increased endogenous or exogenous

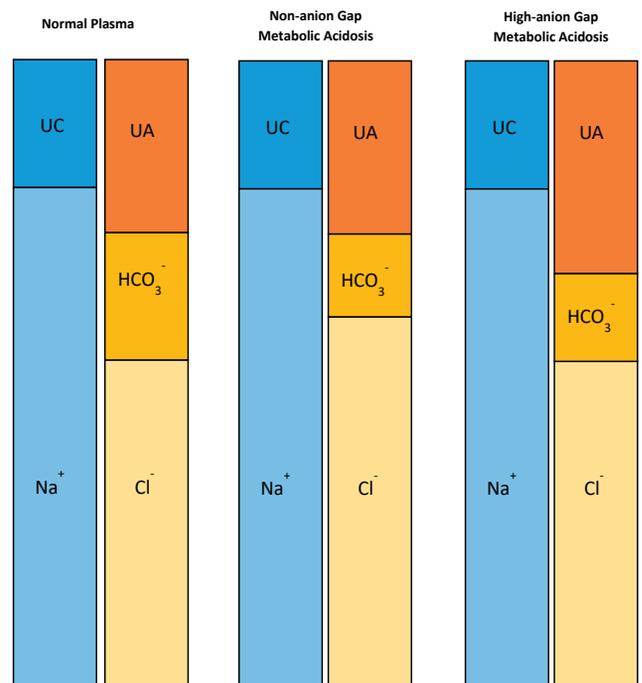
acid load); 2) loss of bicarbonate, either through the gastrointestinal tract (diarrhoea) or due to a decreased renal tubular capacity to reabsorb the filtered bicarbonate (proximal renal tubular acidosis); 3) diminished renal acid excretion, either due to a reduction in glomerular filtration rate or due to an impaired tubular capacity to acidify the urine (as in distal renal tubular acidosis).

Evaluating the anion gap ( $\text{Na}^+ - [\text{Cl}^- + \text{HCO}_3^-]$ ) is critical to understand the etiology of the metabolic acidosis (Figure 1).

Metabolic acidosis with increased anion gap is caused by acid accumulation (as occurs in metabolic diseases, intoxications, ketoacidosis, renal insufficiency, etc) with an increase in non-measurable anions concentration; bicarbonate acts as a buffer to this acid load and, therefore, there is a decrease in bicarbonate concentration and chloride concentration remains unchanged<sup>1</sup>.

**Figure 1**

High-anion gap and non-anion gap metabolic acidosis



Anion Gap =  $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$ ; UC: unmeasured cations; UA: unmeasured anions

In metabolic acidosis with normal anion gap (or non-gap metabolic acidosis), there is a decrease in serum bicarbonate concentration either due to renal causes (such as renal tubular acidosis) or due to increased intestinal bicarbonate losses (extra-renal causes). To compensate for the loss of negative charge from decreased serum bicarbonate, the serum chloride concentration increases through renal or intestinal reabsorption, in order to maintain the electroneutrality of the blood.

Measurement of the urinary anion gap ( $AGu = Na_u - Cl_u - Ku$ ) is helpful in the evaluation of patients with hyperchloremic metabolic acidosis (metabolic acidosis with normal anion gap). The normal renal response to metabolic acidosis with acedemia is to increase both the tubular secretion of protons and ammoniogenesis ( $NH_3$  synthesis). In the tubular lumen, the secreted  $NH_3$  binds to  $H^+$  generating ammonium ( $NH_4^+$ ).

The main defect in dRTA is impaired tubular hydrogen secretion<sup>2</sup>. As a result, there is a reduced ammonium formation and excretion in the urine. By contrast, ammonium urinary excretion is appropriately increased in other causes of hyperchloremic metabolic acidosis in which distal tubular capacity to acidify the urine is preserved, such as diarrhoea and proximal renal tubular acidosis. Therefore, measuring  $NH_4^+$  in the urine could help differentiate hyperchloremic metabolic acidosis due to a distal defect in urinary acidification from other causes.

Direct measurement of urine  $NH_4^+$  is not readily available in clinical practice. As ammonium is excreted with chloride, urine chloride is a “surrogate marker” for urinary  $NH_4^+$ , enabling the evaluation of ammoniogenesis in response to acedemia. A positive urinary anion gap (+20 or greater) is usually indicative of a normal or low  $NH_4^+$  urinary excretion, which in patients with non-gap metabolic acidosis suggests dRTA. A negative urinary anion gap (-20 or less) is usually indicative of an appropriately increased  $NH_4^+$  urinary excretion, as in patients with diarrhoea or proximal tubular renal acidosis. In our patient, the association of failure to thrive and hyperchloremic metabolic acidosis with normal anion gap, in the absence of intestinal losses, points to a renal cause; the presence of hypokalemia, elevated urinary pH and nephrocalcinosis prompted the diagnosis of distal renal tubular acidosis (dRTA). Unfortunately, the measurement of urinary sodium, potassium and chloride was not performed at the time our patient was admitted.

In dRTA there is wasting of sodium. This leads to polyuria and a contraction of extracellular volume, which causes secondary hyperaldosteronism and consequent potassium wasting and hypokalemia. Hypokalemia can cause constipation and may also contribute to polyuria<sup>3</sup>.

In situations of chronic metabolic acidosis, the bone will act as a plasma acid buffer, interfering with bone growth and development, thereby affecting weight progression. Furthermore, acidosis inhibits growth hormone and increases protein catabolism<sup>4</sup>. The acidosis, electrolytic disturbances and chronic dehydration observed in dRTA can therefore interfere with normal weight gain and growth.

**■ WHAT IS THE EXPLANATION FOR THE ELEVATED URINARY PH AND NEPHROCALCINOSIS?**

A urinary pH greater than 6 in the presence of systemic acidemia denotes a defect in urinary acidification. Despite metabolic acidosis, the urinary pH value does not reach values below 5.5 due to the inability to increase the secretion of hydrogen ions, impairing the elimination of the excessive acid load<sup>2,4-6</sup>. Hypercalciuria causes calcium crystal deposition, which may lead to nephrocalcinosis and nephrolithiasis<sup>7</sup>, also promoted by low urinary citrate excretion, which increases the risk of calcium crystal deposition<sup>1</sup>. Hypercalciuria can also contribute to polyuria<sup>2</sup>.

**■ CLINICAL AND LABORATORY EVOLUTION**

Due to the presumptive diagnosis of dRTA, the patient was started on oral therapy with Uralyt-U<sup>®</sup> (citric acid 145 mg/g, potassium citrate 463 mg/g, and sodium citrate 390 mg/g). Each measuring spoon (2.5 g of powder) contains 11 mEq of potassium, 11 mEq of sodium, and 27 mEq of citrate. A dose equivalent to 5.4 mEq/Kg/dia of sodium citrate (2.5 g/day of the powder) was prescribed. An improvement in weight progression, dietary tolerance, and analytical evaluation was observed (Table 1).

At 3 years-old, due to a significant language delay, an otorhinolaryngological evaluation was performed, which diagnosed bilateral sensorineural deafness. An auricular prosthesis was placed.

**Table 1**

Laboratory evolution

Age	3 m	3y 9m	4y 3m	4y 11m	6y 2m	7y 1m	8y 2m	9y 3m
Blood pH	7.21	7.46	7.42	7.38	7.46	7.40	7.41	7.36
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	9.10	24.3	22.6	19.4	25.2	22.7	24.2	21.1
Cl <sup>-</sup> (mEq/L)	124	102	103	107	105	104	106	104
K <sup>+</sup> (mEq/L)	3.9	3.9	4.8	4.6	4.2	3.5	4.6	3.9
Na <sup>+</sup> (mEq/L)	145	137	134	139	139	136	140	138
U Ca/Cr	0.53	0.17	0.22	0.10	0.30	0.48	0.32	0.29
Anion gap (mmol/L)	11.9	15.3	8.4	12.6	8.8	9.3	9.8	12.9
U pH	7	9	9	9	-	-	8	8

(y) years; (m) – months; (Cr) creatinine; (U) urinary

## ■ IS THERE A LINK BETWEEN SENSORINEURAL DEAFNESS AND THE PATIENT'S RENAL CONDITION?

There are primary and secondary causes of dRTA. The primary causes are a group of inherited genetic disorders. The most frequent mutations occur in the SLC4A1 gene, with an autosomal dominant transmission (dRTA-AD) or an autosomal recessive transmission (dRTA-AR). Mutations in the ATP6V1B1 and ATP6V0A4<sup>3,8</sup> genes are associated with autosomal recessive transmission of dRTA (dRTA-AR). In dRTA-AR the first manifestations appear earlier and are more profound: severe hyperchloremic metabolic acidosis associated with significant hypokalemia, nephrocalcinosis, vomiting, dehydration, poor weight progression, possible bone disease (rickets), and sometimes sensorineural hearing loss<sup>3,4,8</sup>

The secretion of hydrogen ions in the urine is performed by alpha intercalated cells of the collecting ducts, this process being conducted by the V-ATPase transporters (Figure 2). Carbonic anhydrase (CA2) produces hydrogen ions at the same time as bicarbonate reabsorption occurs, promoted by AE1 transmembrane glycoprotein ( $\text{Cl}^-/\text{HCO}_3^-$ ), encoded in the SLC4A1 gene. This transporter has a specific isoform in the kidney and erythrocytes. When both isoforms are mutated, it can manifest as dRTA-AD associated with hereditary spherocytic anemia.

The vacuolar hydrogen pump (V-ATPase) acts on the intercalated  $\alpha$ -cells of the collecting tubule, promoting hydrogen ion secretion. This enzyme consists of 14 subunits. Mutations in the  $\beta$ 1 (encoded by the ATP6V1B1 gene) and 4 (encoded by the ATP6V0A4 gene) subunits cause dRTA-AR. As the  $\beta$ 1 and  $\alpha$ 4 subunit are also expressed in the epithelial cells of the cochlea, mutations in this subunits may also cause sensorineural deafness.

In the occidental population, 40% of dRTA are caused by mutations in ATP6V0A4 gene, 30% in ATP6V1B1 gene, and 15% in SLC4A1 gene. Recently, mutations responsible for dRTA in FOXI1 and WRD72 genes were associated with deafness and imperfect amelogenesis, respectively. However, in 15% of patients with a clinical diagnosis of dRTA, no mutation was found, which may suggest the existence of other candidate genes<sup>9-10</sup>.

## ■ GENETIC TESTING

The patient underwent a next-generation sequencing (NGS) five-gene panel for renal tubular acidosis (ATP6V0A4, ATP6V1B1, CA2, SLC4A1, SLC4A4). The variant c.2420G>A (p.Arg807Gln) in the exon 21 of the ATP6V0A4 gene was found to be present in homozygosity. This single-nucleotide variant is known to be associated with dRTA and late-onset sensorineural hearing loss.

Genetic characterization of the father may help clarify whether the previous episode of acute kidney injury and nephrolithiasis are truly unrelated or attributable to dRTA (or at least partial dRTA).

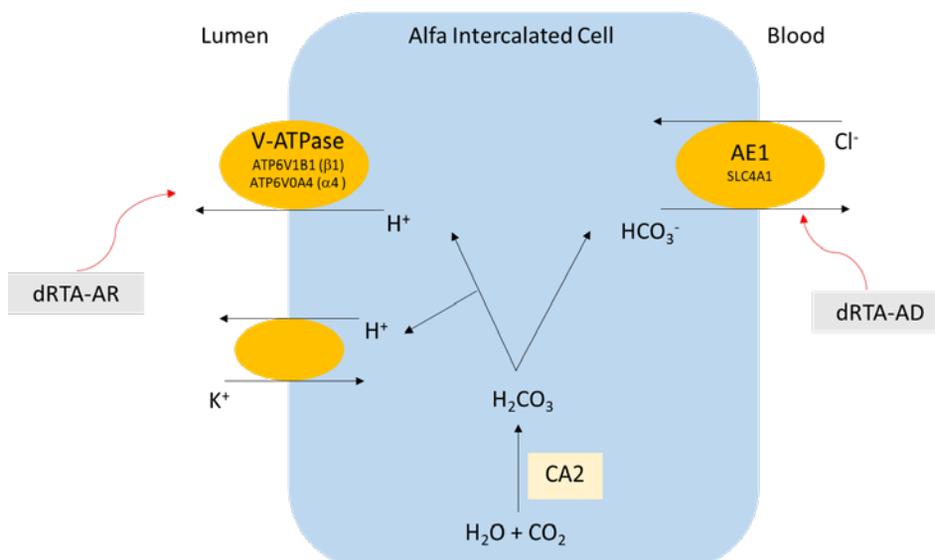
## ■ CASE FOLLOW-UP

At 5 years of age, the patient underwent a cochlear implant surgery with good adaptation and evolution.

Currently, at the age of 9, the patient remains asymptomatic and has shown a weight and height evolution between the 3<sup>rd</sup> and the 15<sup>th</sup> percentiles, under treatment with citrate. The last blood gas results showed normal pH and normal bicarbonate. The urinary

**Figure 1**

High-anion gap and non-anion gap metabolic acidosis



calcium-to-creatinine ratio was also normal. As expected, the renal ultrasound still shows nephrocalcinosis, currently grade III/IV.

The most relevant clinical outcome regarding bone health response to treatment is the improvement in linear growth. In addition, bone densitometry is not validated in this population for this purpose. The urinary calcium-to-creatinine ratio tends to normalize with citrate/bicarbonate supplementation and salt restriction. Although thiazide diuretics may be used to decrease urinary calcium excretion, this strategy is not routinely used in pediatric patients due to the risk of aggravating hypokalemia and polyuria. Thiazides are reserved for the cases in which urinary calcium excretion does not ameliorate with citrate/bicarbonate supplementation, especially if there is aggravating nephrolithiasis.

With this case, the authors intend to highlight the importance of the clinical suspicion of this pathology, given that with the correct therapy and early follow-up, it is possible to recover weight and height, and that an early diagnosis of deafness may have a profound impact on the child's development.

**Disclosure of potential conflicts of interest:** none declared

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