

## Distal renal tubular acidosis and sensorineural deafness with mutation in the ATP6V1B1 gene

### Acidose tubular renal distal e surdez neurosensorial com mutação no gene ATP6V1B1

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#### ABSTRACT

Distal renal tubular acidosis is a rare disorder characterized by the inability in acidification of urine, conditioning hyperchloraemic acidosis, hypokalaemia, hypercalciuria and nephrocalcinosis, which can cause growth retardation, abnormal bone metabolism and, when untreated, chronic renal failure.

Distal renal tubular acidosis and sensorineural deafness is an autosomal recessive disease caused by mutations in the gene encoding B<sub>1</sub> subunit of H<sup>+</sup>-ATPase (ATP6V1B1).

The authors report the cases of two sisters who presented failure to thrive, changes in ionic and acid-base balance and sensorineural deafness. A homozygous mutation in ATP6V1B1 gene was detected in both girls.

These two cases are intended to highlight the importance of an early diagnosis in this rare disease.

**Keywords:** Distal renal tubular acidosis, sensorineural deafness

#### RESUMO

A acidose tubular renal distal é uma doença rara, caracterizada pela incapacidade na acidificação da urina, condicionando acidose metabólica hiperclorémica, hipocaliémia, hipercalciúria e nefrocalcinose, o que poderá causar atraso de crescimento, alteração do metabolismo ósseo e insuficiência renal crónica.

A acidose tubular renal distal associada a surdez neurosensorial é uma doença de herança autossómica recessiva, causada por mutações do gene que codifica a subunidade B<sub>1</sub> da H<sup>+</sup>-ATPase (ATP6V1B1).

Os autores relatam os casos de duas irmãs que apresentaram má progressão ponderal, alterações iónicas, do equilíbrio ácido base e surdez neurosensorial. Foi detectada em ambas as crianças a mutação homocigótica no gene ATP6V1B1.

Com estes dois casos pretende-se destacar a importância de um diagnóstico precoce nesta patologia rara.

**Palavras-chave:** Acidose renal tubular distal, surdez neurosensorial

## ■ INTRODUCTION

Primary distal renal tubular acidosis (dRTA) is a rare entity, caused by the inability of the  $\alpha$  intercalated cells of the cortical collecting tubules to secrete acid to the tubular lumen, resulting in severe hyperchloraemic metabolic acidosis, hypokalaemia, hypercalciuria, hypocitraturia, nephrocalcinosis and nephrolithiasis<sup>1-4</sup>.

The most frequent defects found in the paediatric population are in the  $H^+$ -ATPase, a proton pump containing several subunits encoded by different genes<sup>5</sup>. It can be sporadic or hereditary, with autosomal dominant or recessive transmission<sup>2,4,6</sup>.

The wide spectrum of clinical findings may vary from asymptomatic mild compensated acidosis to severe acidosis with growth retardation, nephrocalcinosis, urinary lithiasis, rickets and osteomalacia. If untreated the progression of nephrocalcinosis might lead to chronic renal failure<sup>1,2,3</sup>.

The authors report two cases of dRTA and sensorineural deafness in a Portuguese family, highlighting the importance of an early diagnosis and treatment of this disease.

## ■ CASE REPORTS

The cases presented are of two Caucasian siblings, of non-consanguineous parents, born and living in Portugal.

**First case:** third daughter of a family with four children, resulting from a full-term pregnancy, without any complications. The child was born by eutocic delivery, with a birth weight of 2570 g (10-25th percentile). She was apparently healthy until the third month of life, when the hospitalization occurred due to severe dehydration, metabolic acidosis and failure to thrive. Investigation showed: partially compensated metabolic acidosis (pH 7.27,  $pCO_2$  29.6 mmHg, bicarbonate 14 mmol/L), hypokalaemia ( $K^+$  2.8 mEq/L), increased plasma anion gap (21.8 mmol/L), urinary pH  $>7$  and increased urinary calcium to creatinine ratio (1.3 mg/mg). The renal ultrasound revealed alterations suggestive of nephrocalcinosis. The child began alkali supplementation with

potassium and sodium citrate and was referred to a paediatric nephrology unit for follow-up. At 32 months old, the otorhinolaryngology evaluation revealed severe sensorineural deafness, requiring auditory prosthesis. The child is now nine years old, while on oral alkali supplementation attained a well-controlled acidosis with growth improvement (weight 24Kg, 10-25th percentile; height 132 cm, 50th percentile), and normal renal function (urea 37 mg/dL, creatinine 0,37 mg/dL).

**Second case:** fourth daughter of the same family, born from a poorly monitored full-term pregnancy, by eutocic delivery, with a birth weight of 2810 g (10-25th percentile). At 14 months old, she was referred to a Paediatric appointment due to failure to thrive and chronic constipation. The laboratory results revealed a normal renal function, partially compensated metabolic acidosis (pH 7.26,  $pCO_2$  25 mmHg, bicarbonate 11.2 mmol/L, base excess of -14.2 mmol/L), hypokalaemia ( $K^+$  3.1 mEq/L), hyperchloraemia ( $Cl^-$  115 mEq/L), plasma anion gap of 11 mmol/L; increased urinary pH (pH7.2), slightly increased urinary calcium to creatinine ratio (0.64 mg/mg) and increased urinary anion gap (16 mmol/L). The renal ultrasound showed nephrocalcinosis. Taking into account the family history, she performed auditory evoked potentials test that was abnormal. The audiometry confirmed severe bilateral, permanent sensorineural deafness. She was then referred to a paediatric nephrology unit and started oral alkali supplementation treatment with potassium and sodium citrate. She is now 4 years old, has normal growth (weight 14 kg, 10-25th percentile; height 94cm, 5-10th percentile), and normal renal function (urea 33mg/dL, creatinine 0.34 mg/dL). Follow-up of both sisters is still maintained in Paediatric Nephrology and Otorhinolaryngology departments.

The ATP6V1B1 gene sequencing was performed in both children, showing a frameshift mutation on exon 12, in gene ATP6V1B17, with both siblings being homozygous.

## ■ DISCUSSION

Distal renal tubular acidosis is a rare disorder, primary or secondary, and has a wide spectrum of clinical variability<sup>4</sup>.

Primary distal renal tubular acidosis (dRTA) may be sporadic or familial. Both autosomal dominant and autosomal recessive forms of dRTA have been recognized.

There is a subgroup of patients with dRTA, with an autosomal recessive inheritance, conferring progressive and irreversible sensorineural deafness, caused by a mutation in the gene coding a B1 subunit of the H<sup>+</sup>-ATPase (ATP6V1B1)<sup>1-4,8</sup>. At least 15 mutations causing the disease in homozygous form have been described. Most of these mutations cause a disruption in the structure of the protein or diminish the production of the normal B1 subunit. There is a loss of expression of this gene in the human cochlea and endolymphatic sac epithelium<sup>1,9</sup>. This loss leads to a decrease in the function of the H<sup>+</sup>-ATPase, responsible for maintaining the endolymph pH at 7.4, causing irreversible hair cell damage, in the organ of Corti<sup>5</sup>. The clinical manifestations, aside from deafness, are similar to those of the other types of dRTA<sup>1,2</sup>. There are other mutations, namely the ATP6VoA4 encoding the  $\alpha_4$  subunit and the ATP6N1B encoding the 116-kD subunit of the H<sup>+</sup>-ATPase, also associated with deafness, particularly after the second decade of life<sup>8,10,11</sup>. The correlation between the genetic mutation and deafness is not absolutely clear, since there are some patients with the ATP6V1B1, who do not present the same typical severe early-onset sensorineural deafness<sup>5</sup>.

Failure to thrive, a relatively common occurrence in the paediatric age, was the initial symptom in both cases, as previously described in other published cases<sup>12</sup>, therefore not contributing significantly

for a swift diagnosis. In the first case, dehydration was the motive for an early evaluation in the emergency department, favouring earlier diagnosis of the disease.

Laboratory results confirmed that both children have a rare hereditary form of dRTA, of recessive autosomal inheritance. Taking into account that the parents are probably heterozygous for the same mutation, there is a 25% risk of recurrence in future gestations.

The diagnosis of this disease requires a high degree of suspicion, since the symptoms are usually non-specific and highly variable. Initially one might only find fatigue, constipation or myalgia, due to the neuromuscular effect of hypokalaemia<sup>5,12</sup> or, on the contrary, the first manifestation may be dehydration with severe metabolic acidosis.

## CONCLUSION

The authors intend with these two cases to highlight the importance of the family history and a high degree of suspicion for the diagnosis of dRTA.

Delaying the diagnosis of this pathology has important implications in the ionic balance, growth<sup>5</sup> and development of a child, as well as the progression to nephrocalcinosis and, eventually, chronic renal failure<sup>11</sup>. Most complications are reduced with adequate treatment, however, nephrocalcinosis will not regress despite the correction of acidosis and

**Table 1**

Clinical and biochemical features of the two patients with distal renal tubular acidosis and sensorineural deafness

	First sibling	Second sibling
Clinical features	Severe dehydration	Failure to thrive Chronic constipation
Otorhinolaryngology	Severe sensorineural deafness	Severe sensorineural deafness
Renal ultrasound	Nephrocalcinosis	Nephrocalcinosis
pH	7.27	7.26
pCO <sub>2</sub>	29.6 mmHg	25 mmHg
Bicarbonate	14 mmol/L	11.2 mmol/L
Potassium	2.8 mEq/L	3.1 mEq/L
Plasma anion gap	21.8 mmol/L	11 mmol/L
Urinary pH	>7	7.2
Urinary calcium/creatinine	1.3 mg/mg	0.64 mg/mg

therapy with diuretics<sup>5,12</sup>. Patients with ATP6V1B1 mutations, as in our cases, are more likely to develop progressive loss of kidney function, probably secondary to nephrocalcinosis<sup>13</sup>.

The authors would also like to stress the importance of a careful follow-up of these patients in specialized centres, with Paediatric Nephrology, for a well-controlled alkali supplementation and monitoring of glomerular-filtration rates, and otorhinolaryngology, for educational support and speech therapy to help improving deafness-related disabilities.

A genetic evaluation is also of great importance, not only to confirm the suspected diagnosis, but also for genetic counselling.

**Conflict of interest statement:** None declared.

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