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Research article

Distal renal tubular acidosis in a pediatric patient with ATP6V1B1 mutation

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Abstract: Distal renal tubular acidosis (dRTA) is a very rare disease characterized by metabolic acidosis, hypokale-mia and nephrocalcinosis caused by the impaired H+ secretion in the distal convoluted tubules of the kidney.We report the case of a one-year-old girl who firstly presented to another facility at the age of two months with insidious lack of appetite, weight loss, diarrhea, vomiting and fever, interpreted as acute gastroenteri-tis. Three weeks later she presented to our institution. Physical examination indicated altered general condition, severe dehydration, skin pallor, generalized hypotonia and weight for length ratio beneath the 1st percentile. Laboratory investigations showed normochromic, microcytic anemia, mild inflammatory syn-drome, decompensated metabolic acidosis, hypokalemia and hypercalcemia. Rehydration therapy was ini-tiated. Renal ultrasonography showed bilateral nephrocalcinosis, while cerebral ultrasonography revealed subarachnoid space enlargement. Although her general condition improved under treatment and the vom-iting remitted while she gained weight, the metabolic acidosis and electrolyte imbalance persisted and as-sociated alkaline polyuria. A hearing test was performed and mild sensorineural hearing loss was discov-ered. Moreover, the genetic investigation (Next Generation Sequencing) revealed that the patient is homo-zygous for ATP6V1B1 c.242T>C, p.(Leu81Pro), a pathogenic variant suggestive for dRTA. Primary dRTA, while rare, can have great impact on the patient's quality of life. Therefore, it must be rec-ognized as quickly as possible in order to avoid complications that can ultimately lead to irreversible kidney damage.

Keywords: renal tubular acidosis, ATP6V1B1, nephrocalcinosis, metabolic acidosis

1. Introduction

Distal renal tubular acidosis (dRTA) is a very rare disease characterized by metabolic acidosis, hypokalemia and nephrocalcinosis caused by the impaired H^+ secretion in the distal convoluted tubules of the kidney. There are two types of dRTA: primary and secondary. While the secondary form, more common in adults, is caused by autoimmune disorders and certain medications, the primary type is linked with mutations in the SLC4A1, ATP6V0A4 and ATP6V1B1 genes. Both autosomal dominant and autosomal recessive forms have been described and are usually diagnosed in pediatric patients [1,2]. Frequently, dRTA manifestations are unspecific and include: muscle weakness, weight loss, nausea, vomiting and dehydration. We describe a case of a child with growth faltering, diarrhea, vomiting and lack of appetite as principal reasons for admission.

Case presentation

A one-year-old girl firstly presented to our institution at the age of 3 months with lack of appetite, weight loss, diarrhea, vomiting, and fever that started insidiously. She is the first child from a properly monitored unremarkable pregnancy, delivered at term (40 weeks). Her birth weight was 3530 grams with a length of 54 centimeters

and an APGAR score of 8, with fetal distress and meconium aspiration. She was administered vitamins and was vaccinated in accord with the international recommendations for her age.

Three weeks before the first admission in our institution, she was hospitalized at another facility, where her manifestations were interpreted as acute gastroenteritis and she was treated accordingly. However, the symptoms reappeared. Upon presentation to our institution, the initial physical examination showed altered general condition, severe dehydration weight for length ratio beneath the 1st percentile (Z score= -1.6). Laboratory investigations revealed normochromic microcytic anemia, mild inflammatory syndrome, hypokalemia, hypercalcemia, decompensated metabolic acidosis, with liver and kidney function within normal limits. Initial treatment consisted of intravenous rehydration therapy, Cefuroxime, and hydrocortisone hemi-succinate for the management of the hypercalcemia. During the hospitalization, a renal ultrasound was performed and it revealed bilateral nephrocalcinosis. Under treatment, her appetite and weight improved and the vomiting remitted. She gained 600 grams in 10 days. Further bloodwork showed persistent decompensated metabolic acidosis, hypokalemia and hypercalcemia despite the treatment with intravenous fluids. On top of that, she associated polyuria (6ml/kg/h). As a result, distal renal tubular acidosis was considered a probable diagnosis.

Figure 1. Renal ultrasound performed at the age of 7 months. Nephrocalcinosis.

Diagnostic methods

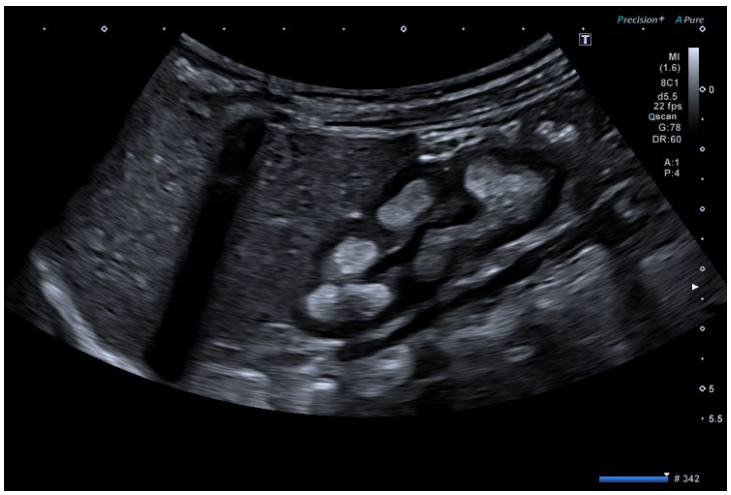
Over several assessments, her paraclinical parameters seemed to follow the same path. On the last admission, at the age of 9 months, her bloodwork indicated persistence of normochromic microcytic anemia and decompensated metabolic acidosis (pH, 7.34; pCO_2 ,36 mmHg; HCO_3^-, 19 mEq/L; base excess, -6mmol/L) with normal calcium and potassium levels. Liver and kidney function were within normal limits. Her urine biochemistry showed persistent alkaline polyuria (pH, 8) associated with leukocyturia and hypercalciuria. Urine culture was negative. Urinary amino-acids were tested to exclude metabolic conditions and the results were in the normal range.

Date	pH	pCO2 (mmHg)	HCO3 (mEq/L)	Total calcium (mg/dl)	Ionized calcium (mg/dl)	Potassium (mmol/L)	Creatinine (mg/dl)	Hemoglobin (mg/dl)
04.2024	7,25	35	15	14,8	6,6	3,5	0,32	9,3
05.2024	7,43	36	24	11,4	5	3,7	0,26	11,3
07.2024	7,37	34	20	10,7	5,1	4,07	0,24	10,9
08.2024	7,37	27	15	10,6	4,7	4,26	0,24	10,8
10.2024	7,34	36	19	10,9	4,8	4,3	0,24	11,8

Table 1. Evolution of laboratory parameters.

The evolution of the laboratory parameters is shown in **Table 1**.

Imagistic methods included renal and transfontanellar ultrasonography. Renal ultrasound revealed bilateral nephrocalcinosis with a decrease in volume of both kidneys, from 6 cm at the age of 3 months to 5.2 cm at the age of 7 months (**Figure 1**).



On the other hand, a transfontanellar ultrasound was performed at the age of 7 months because the patient's cephalic extremity increased abnormally in size (**Figure 2**). It unveiled subarachnoid space enlargement without any signs of increased intracranial pressure or other abnormalities (**Figure 3**). She was neurologically assessed at the age of 3 months and was diagnosed with generalized hypotonia.

Figure 2. Increase in size of the patient's cephalic extremity from 2 months of age (to the left) to 7 months of age (to the right).

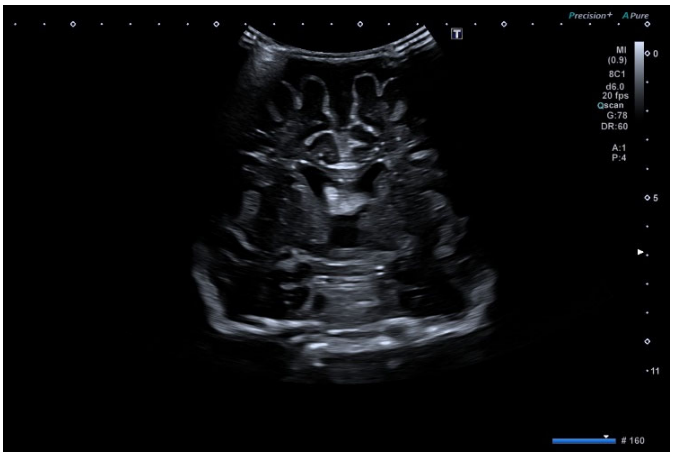


Figure 3. Transfontanellar ultrasonography at the age of 7 months. Subarachnoid space enlargement.

GENE	TRANSCRIPT	NOMENCLATURE	GENOTYPE	CONSEQUENCE	INHERITANCE	CLASSIFICATION
ATP6V1B1	NM_001692.4	c.242T>C, p.(Leu81Pro)	HOM	missense_variant	AR	Pathogenic
	ID	ASSEMBLY	POS	REF/ALT		
	rs121964880	GRCh37/hg19	2:71185243	T/C		
	gnomAD AC/AN	POLYPHEN	SIFT	MUTTASTER	PHENOTYPE	
	1/250636	probably damaging	deleterious	disease causing	Renal tubular acidosis with deafness	

SEQUENCING PERFORMANCE METRICS - NUCLEAR GENOME

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Renal Tubular Acidosis Panel	5	87	14569	14569	169	100

Figure 4. Results of Next Generation Sequencing for ATP6V1B1 gene.

Moreover, at the age of 7 months, a hearing test was performed and it presented mild bilateral neurosensorial hearing loss. The failure to thrive linked with the persistence of metabolic acidosis, hypokalemia, hypercalcemia, alkaline polyuria and the presence of bilateral nephrocalcinosis support the diagnosis of dRTA. Taking in consideration the discovery of mild hearing loss linked with generalized hypotonia and the increase in the size of the cephalic extremity, we believed that the patient is suffering from a genetic form of dRTA. Therefore, a genetic testing was performed.

The test was carried out by Blueprint Genetics, using their Renal Tubular Acidosis Panel Plus Analysis. This included sequence analysis and copy number variation analysis of the following genes: ATP6V0A4, ATP6V1B1, CA2, SLC4A1 and SLC4A4. The test is used to detect single nucleotide variants and small insertions deletions and copy number variations defined as single exon or larger deletions and duplications. The platform used to perform the test was Illumina NovaSeq and the sequencing run included in-process reference samples for quality control. The confirmation of sequence alterations was accomplished using Sanger sequencing when the results did not meet the quality metrics for a true positive call. Copy number variants were confirmed using a digital PCR assay if they covered less than 10 exons (heterozygous), less than 3 exons (homo/hemizygous) or were not confirmed at least three times previously in the laboratory.

Ultimately, the test indicated that the patient was homozygous for ATP6V1B1 c.242T>C, p.(Leu81Pro), a pathogenic variant, suggestive for dRTA (**Figure 4**).

Treatment and outcome

The patient is currently on long-term oral therapy with sodium bicarbonate 8.4% (3x5 ml/day) and potassium chloride 7.45% (3x1.5 ml/day). She was prescribed iron drops (50 mg/ml, 2x4 drops/day), and paraffin oil (2x5 ml/day) or macrogol 4000 (10 mg/day). Also, she was started on amino-acid and B12 supplementation (Tonotil) according to the neurologist's recommendations. Furthermore, she is receiving magnesium supplementation. Although pediatrics guidelines generally recommend vitamin D supplementation, in her case, this measure is contraindicated.

Discussion

This case describes a pediatric patient with persistent decompensated metabolic acidosis associated with hypokalemia and hypercalcemia. Her symptoms included failure to thrive, diarrhea, vomiting and muscle weakness. Urine biochemistry showed persistent alkaline polyuria linked with high urinary calcium levels. Further investigations revealed bilateral nephrocalcinosis associated with hearing loss. These clinical manifestations linked with the characteristic bloodwork and urinalysis as well as the discovery of hearing loss were evocative for primary dRTA. Genetic testing confirmed that the patient is homozygous for a pathogenic variant of ATP6V1B1 gene, suggestive for dRTA.

Possily the most impressive aspect of this case is that the manifestations installed at such a young age and with such quickness. Although recessive forms af dRTA are known to make their debut early, the association of neurological symptoms and kidney shrinkage in a patient just a few months-old remains remarkable.

Primary dRTA is a very rare condition. It is usually caused by mutations of ATP6V1B1, ATP6V0A4, and SLC4A1 genes. These mutations can be transmitted as an autosomal dominant (AD) or autosomal recessive (AR) trait. AD dRTA is usually caused by SLC4A1 mutations while AR dRTA is linked with ATP6V1B1, ATP6V0A4 genes.

SLC4A1 encodes the basolateral Cl^-/HCO_3^- exchanger (AE1), required for HCO_3^- reabsorption. [3,4]. There are two types of AE1 protein. The shorter isoform is expressed in the basolateral membrane of type A intercalated cells of the kidney, where it represents the principal exit route for HCO_3^- . The longer isoform is expressed by red blood cells as a part of the erythrocyte cytoskeleton. This is why SLC4A1 mutations can cause either dRTA and/or hemolytic anemia with red cell morphology anomalies [3]. The clinical signs of the AD form generally appear in adolescence or adulthood [5,6]. There are reported cases of recessive inheritance that associated dRTA and spherocytosis or, more frequently, spherocytosis without renal involvement, depending on the mutated domain of the protein. These forms were primarily described in Southeast Asia [7].

On the other hand, ATP6V1B1 and ATP6V0A4 normally encode specific subunits of vacuolar H^+ ATP-ase pump, required for urine acidification. H^+ ATP-ase is formed by two domains, V1 and V0. The various structures of these domains determine the isoform of the proton pump. For example, ATP6V0A4 encodes the A4 subunit of the V0 transmembrane domain involved in proton translocation across the membrane. ATP6V1B1 determines the structure of the B1 subunit of the V1 domain, responsible for capturing the protons from the cytoplasm. This isoform is expressed by the intercalated cells of the distal tubule of the kidney and by the endolymphatic sac cells of the inner ear. This explains why mutations in this gene are linked with early-onset sensorineural hearing loss forms of dRTA [3]. It is important to mention that the progression of sensorineural deafness is variable in patients and does not respond to alkali therapy [6].

As a result of metabolic acidosis, skeletal buffers, such as carbonate and phosphate combine with calcium are removed from the bones, causing bone demineralization and hypercalciuria. Bone demineralization can cause rickets in children and osteomalacia in adults. These conditions increase the risk of fractures and may cause bone pain. Rickets can cause bone deformities and walking impairment due to leg deformities. However, the frequency and severity of bone findings reported in the literature vary significantly [8]. Moreover, metabolic acidosis decreases the expression of calcium transport proteins, further promoting calcium excretion and thus, development of nephrocalcinosis [6,9]. Adequate alkaline therapy usually prevents its progression but does not reverse it [10]. Additionally, patients with dRTA frequently present with recurrent acute pyelonephritis, associated with the presence of potentially obstructive stones and possibly hypercalciuria.

Women with dRTA do not associate infertility. Nevertheless, during pregnancy, they may present metabolic complications associated with dRTA, mainly hypokalemia and severe metabolic acidosis. In addition, hyperemesis gravidarum may worsen the patient's condition by increasing the electrolyte loss and making oral supplementation difficult. Usually, kidney dysfunction or proteinuria are not observed in pregnant women with dRTA [10].

Ultimately, dRTA leads to irreversible kidney damage [6,10]. Lopez-Garcia *et al.*

[11] reported that a third of the children (aged 2 – 18 years old) included in their study had an impaired eGFR (<90 mL/min/1.73 m^2), mostly chronic kidney disease (CKD) stage 2 while in adults the mean eGFR at last follow-up was 75mL/min/1.73 m^2). However, no patient with end-stage renal disease was noted.

There is not much data regarding the prevalence due to the small number of reported cases. Giglio *et al.* [4] estimated that in the Italian population the prevalence for AR dRTA is approximately 1:600.000. Considering this, it is easy to understand why dRTA can easily be mistaken for more common conditions such as acute gastroenteritis.

Conclusion

Primary dRTA, while rare, it can have great impact on the patient's quality of life. This case emphasizes the importance of paying close attention to any acid-base imbalance as it can hide deeper dysfunctions. This is the reason why any electrolyte imbalances, especially in pediatric patients must be properly investigated. In order to prevent significant complications, such as chronic kidney disease or bone deformities, dRTA must be recognized as quickly as possible and patients must benefit from a thorough follow-up.

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