

Familial distal renal tubular acidosis

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Abstract

We report the case of a family in which two sisters have distal renal tubular acidosis (dRTA). Familial dRTA is a rare disorder, with both autosomal dominant and recessive transmission. This is a report of familial dRTA from China.

Keywords

Distal renal tubular acidosis, children, rare disease, autosomal dominant and recessive transmission, case report, China

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Introduction

Distal renal tubular acidosis (dRTA) is a metabolic acidosis characterized by impaired hydrogen ion (acidic) secretion in the distal renal tubules. This defect leads to an inability to excrete acid load, causing hydrogen ion retention and hyperchloremic metabolic acidosis, with inappropriately alkaline urine. The main manifestations include hyperchloremia, normal anion gap metabolic acidosis, electrolyte disturbance, bone disease, and urinary tract symptoms.^{1–8}

The inherited/primary pattern of dRTA is mostly caused by mutations in genes encoding renal acid–base transporters with autosomal dominant or recessive

transmission.^{9–12} Autosomal dominant dRTA is associated with mutations in the Cl/HCO₃[–] exchange protein (chloride/bicarbonate exchanger) gene (*AE1*) of the distal convoluted tubules in the kidney. The kidney's function is to intercalate the distal convoluted tubules and collecting ducts with type A intercalated cells during

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the acidification of urine. In red blood cells (RBCs), the function of AE1 is to maintain the integrity of red blood cells and increase the ability to carry CO₂. Autosomal recessive dRTA may be associated with sensorineural deafness and present mutations in the *ATP6V1B1* and *ATP6V0A4* gene encoding subunits of H⁺-ATPase; 7q33-34 may be a new locus of dRTA.¹³⁻¹⁷

We report the case of two patients presenting with dRTA. Both were from the same family in Baoding, Hebei Province in China. We obtained patient consent for treatment. This study complies with relevant EQUATOR Network guidelines. The study protocol was approved by the ethics committee of Baoding No. 1 Central Hospital.

Case presentation

The index case was a 20-year-old woman. She was born via full-term vaginal delivery, with birthweight 3200 g. Her parents were healthy and were not married, and she had close relatives. Her father and grandfather are about 160 cm tall. Her uncle suddenly developed kidney failure at the age of 24 years. He received a kidney transplant from a relative donor after 1 year of dialysis, and died owing to gastroenteritis after surviving 3.5 years. No patients in the family showed similar symptoms.

The patient was hospitalized at the age of 2 months because of feeding difficulties and slow weight gain. Home oral administration of active probiotics powder, such as Ofmom, was ineffective. At that time, her weight was 3.8 kg and she was alert. On examination, she was pale, her expression was indifferent, and her head and limbs were weak, but the remainder of the physical examination was normal. After admission, she had weak sucking and swallowing when feeding. Blood levels of white blood cells and platelets were normal; RBC count was $4.26 \times 10^{12}/L$ and hemoglobin (Hb)

was 84 g/L. She had 46.XX karyotype. Blood gas analysis showed urinary oxygen tension (PO₂) 92 mmHg, carbon dioxide tension gradient (PCO₂) 23 mmHg, base excess (BE) -10.6 mmol/L, potassium 2.8 mmol/L, sodium 135 mmol/L, chloride 112 mmol/L, and calcium 2.1 mmol/L. Blood pH was 7.4. Urinalysis showed a negative microscopic examination and pH 7.4. Five items of thyroid function including total thyroxine, total triiodothyronine, free thyroxine, free triiodothyronine acid, and thyroid stimulating hormone, as well as liver and kidney function, were normal. The results of an ammonium chloride loading test showed low serum pH 7.24, with BE -13 mmol/L and minimum urine pH 7.0, confirming the diagnosis of dRTA. The patient was given an oral citrate mixture (dipotassium hydrogen citrate 50 g and sodium citrate 50 g in 1000 mL of water to make a 10% solution), three times a day. Her complexion turned ruddy 3 days after initiating treatment, and she gained 0.8 kg body weight after 10 days in the hospital. Blood gas analysis and routine urine, liver, and kidney function were regularly reviewed after discharge and the dosage of citrate mixture was adjusted according to blood gas analysis. The patient's height was about -2 standard deviations behind children of the same age. Up to now, she has been followed for 19 years and has had normal puberty. She has had good academic performance and is currently a second-year university student. She underwent genetic testing at age 19 years using next generation sequencing, according to standard protocols. The genetic analysis revealed mutation in the *ATP6V0A4* gene.

Case 2 was the 11-year-old sister of the index case. She was born via full-term vaginal delivery and was breastfed after birth. She was hospitalized at the age of 6 months because of feeding difficulties and slow weight gain. She breastfed poorly, could not turn over, lift her head, sit up, and did

Table 1. Investigations in patients

Investigations	Index case		Case 2	
	Year presented		Year presented	
	2000	2016	2010	2016
Blood pH	7.40	7.47	7.28	7.45
PO ₂	92.00	107.00	87.00	105.00
PCO ₂	23.00	32.00	22.00	32.00
K ⁺	2.80	3.81	2.60	3.50
Na ⁺	135.00	134.83	128.00	136.20
Cl ⁻	112.00	102	115.00	99
Ca ⁺	2.10	2.48	2.00	—
HCO ₃ ⁻	—	23.70	—	24.00
AG	13.10	9.13	—	15.50
BE	-10.6	1.20	-17.00	-0.50
Urine pH	7.00	7.50	8.00	—
Urine protein	—	Negative	—	—

PO₂, urinary oxygen tension; PCO₂, carbon dioxide tension gradient; K, potassium; Na, sodium; Cl, chloride; Ca, calcium; HCO₃, bicarbonate; AG, anion gap; BE, base excess.

not like to cry or move. Her weight was 4.2 kg and length was 64 cm. She had a malnourished appearance, but no abnormalities of the heart, lungs, or abdomen. PO₂ was 87 mmHg, PCO₂ 22 mmHg, BE -17 mmol/L, RBCs $3.82 \times 10^{12}/L$, and Hb 79 g/L. Liver, kidney, and thyroid function were normal, and blood karyotype was 46, XX. Potassium level was 2.6 mmol/L, sodium 128 mmol/L, chloride 115 mmol/L, and calcium 2.0 mmol/L. Urinalysis showed negative microscopic examination. Blood and urine pH were 7.28 and 8.0, respectively. An ammonium chloride loading test and the medical history of her older sister confirmed the diagnosis of primary dRTA. She was also diagnosed with moderate malnutrition, moderate nutritional iron deficiency anemia, active rickets, and delayed development of major motor skills. Treatment was commenced with a citric acid mixture, and the dose was adjusted according to blood gas analysis. This was reviewed at an interval of every 3 months, which was gradually extended to every 6 to 12 months. The patient has been followed up for 9 years.

Her height is in the tenth percentile, and her mental and motor development are normal. Sanger sequencing was used to identify the mutation in the *ATP6V0A4* gene.

Ammonium chloride loading test

This was according to 0.1 g/kg/day, divided over three to four times for 3 days. Blood gas analysis and urinalysis were measured every day.

Discussion

This study reports molecular investigation of two patients with familial dRTA patients in China. The variation c.580C>T (p.Arg194*) was found in the *ATP6V0A4* gene in the homozygous state. There is evidence of a previously reported heterozygous rare variant in *ATP6V0A4* inherited from heterozygous parents, present in the two sisters.¹⁸⁻²⁰ Unfortunately, genetic screening was not performed during the second pregnancy and the parents did not receive preconception counseling. Early diagnosis

and treatment during the early stages in an infant with dRTA is of great importance for patient prognosis. The index case has been followed up for many years and no other organs are affected. She has been admitted to university, providing a useful experience of early standardized treatment. Previous knowledge of a patient's ethnic background is essential in performing molecular diagnostics, and dRTA and other Mendelian diseases must be considered.

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Author contributions

(I) Conception and design: L Zhang, B Xu; (II) Administrative support: H Tang; (III) Provision of study materials or patients: L Zhang, Y Niu; (IV) Collection and assembly of data: L Zhang, B Xu, Y Wang; (V) Data analysis and interpretation: L Zhang, H Tang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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