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Clinical Report

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Survival over 2 years of autosomal-recessive renal tubular dysgenesis

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Abstract
Autosomal-recessive renal tubular dysgenesis (AR-RTD) is a rare disorder caused by a genetic defect in the renin–angiotensin system. Although AR-RTD has typically been known as a lethal disease due to refractory hypotension and renal failure immediately after birth, few cases have reported survival of the neonatal period. We report here an additional case of AR-RTD, who had novel *ACE* mutations and survived over 2 years and provide a review of the five previously reported surviving cases. In conclusion, AR-RTD is not a uniformly fatal disease, although factors affecting the survival remain unknown.

Keywords: *ACE* gene; angiotensin-converting enzyme; autosomal recessive renal tubular dysgenesis; renin–angiotensin system

Background

Autosomal-recessive renal tubular dysgenesis (AR-RTD) is a rare inherited disorder caused by mutations in the genes encoding any of the components of the renin–angiotensin system (RAS) including renin, angiotensinogen, angiotensin-converting enzyme (ACE) and Type 1 Angiotensin II receptor [1]. The typical revealing symptom is oligohydramnios resulting from reduced fetal urine production. Fetuses may die *in utero*, and most neonates die soon after birth with persistent anuria, respiratory failure and refractory hypotension. The histopathological hallmark of the disease is the absence or incomplete development of cortical convoluted proximal tubules [2, 3]. Since this disease was first described by Allanson *et al.* [2] in 1983, >100 cases of RTD with or without genetic defects have been reported [4]. While most previous reports have described AR-RTD as a lethal disease, five recent cases have reportedly survived the neonatal period [5–8]. Here, we report another case of AR-RTD associated with *ACE* mutations who survived for over 2 years. In addition, we provide a review of the previously reported surviving cases.

Case report

This male baby was the fourth child of healthy non-consanguineous parents. Severe oligohydramnios was detected at 29 weeks of gestation by fetal ultrasonography. His mother was a 32-year-old multipara female. The first and second pregnancies were uneventful but the third pregnancy was complicated by anhydramnios and was terminated at 28 weeks of gestation. The mother did not take any medication during her pregnancies. The patient was born at 32 weeks and 4 days of gestation due to pre-term labor. The weight was 1960 g (10–50th percentile) and the height was 41.5 cm (10–50th percentile). The Apgar scores were 1 at 1 min and 3 at 5 min. The initial blood pressure was 51/26 mmHg. The anterior fontanelle was wide and the sagittal sutures revealed wide gaps. The baby required assisted ventilation immediately after birth due to respiratory distress, and inotropes were started at 1 h after birth due to hypotension. The first urination was observed at 6 h after birth. Kidney ultrasonography revealed both normal-sized kidneys with increased parenchymal echogenicity. The patient developed a pneumoperitoneum due to ileal perforation at 7 h after birth and he underwent emergency ileostomy. Hypotension was aggravated after surgery and the patient responded poorly to plasma expanders and inotropes. The baby became anuric with gradual worsening of renal function. While urination began to increase since Day 4, hypotension persisted and was even aggravated by diuresis. Since Day 25, his blood pressure became relatively stable, and inotropes were tapered off for 2 weeks. The peak serum creatinine level was 2.2 mg/dL (194 μmol/L) on Day 6. Laboratory tests at the age of 14 days showed that the plasma renin activity was 22.3 ng/mL/h [6 ng/L/s, normal, <15 ng/mL/h (<4 ng/L/s)], serum ACE <5 U/L (normal, 8.3–21.4 U/L), plasma Angiotensin I 2114 pg/mL [2114 ng/L, normal, <180 pg/mL (<180 ng/L)], plasma Angiotensin II 61 pg/mL [61 ng/L, normal, <50 pg/mL (<50 ng/L)] and serum aldosterone 371 pg/mL [371 ng/L, normal, 5–194 pg/mL (5–194 ng/L)]. Mutational analysis of the *ACE* gene revealed novel compound heterozygous mutations, c.G776A [p.Arg(CGC)259His(GAG)] inherited from the mother and c.1454delC [p.Pro(CCT)485Leu(CTT)fs] inherited from the mother. At the age of 1 month, oral fludrocortisone treatment (0.1 mg/day) was started to correct intermittent hyponatremia and hypokalemia. The baby was discharged at the age of 4 months with a serum creatinine level of 0.6 mg/dL (53 umol/L).

Table 1. Case reports of AR-RTD patients surviving the neonatal period[a]

Patients	1	2	3	4	5	6
Reference	[5]	[6]	[6]	[7]	[8]	Present case
Gender	Female	Female	Female	Female	Male	Male
Family history	(+)	(+)	(−)	(+?)[c]	(+)	(+)
Oligohydramnios[b] (weeks)	24	32	35 (?)	26	22	29
Gestational period (weeks)	35	38	35	33	33	32
Parental consanguinity	(−)	(+)	(+)	(−)	(−)	(−)
Duration of anuria	29 days	3 days	2 months	16 days	15 days	4 days
Hypocalvaria	(+)	(+)	(+)	(+)	(+)	(+)
Lung hypoplasia	(+)	(+)	(−)	(+)	(−)	(−)
Mineralocorticoid Tx	(−)	(−)	(−)	(−)	(+)	(+)
Mutating gene	AGT	AGT	REN	ACE	ACE	ACE
Mutation 1	p.Q202X	p.R375Q	p.S135Y	p.S5GfsX136	p.13_16del4	p.R259H
Mutation 2	p.F397LfsX25	p.R375Q	p.S135Y	p.1172_1183del12	p.13_16del4	p.P485Lfs
Age at the last follow-up	18 months	15 years	10 years	3 years	3 years	2 years
Renal outcome	CKD	CKD III	Tpl at Age 4	CKD V on PD	CKD IV	CKD II

[a]CKD, chronic kidney disease; Tpl, kidney transplantation; PD, peritoneal dialysis; Tx, treatment.
[b]Gestational period when oligohydramnios was detected.
[c]The patient's elder sibling had been born at 33 weeks gestation and died of respiratory impairment just 15 h after birth. However, no autopsy was performed.

The patient is currently 2 years old with normal blood pressure and serum electrolyte levels and mild impairment of renal function [serum creatinine 0.5 mg/dL (44 μmol/L) and estimated glomerular filtration rate 69 mL/min/1.73m^2 (1.15 mL/s/1.73m^2)]. Hypocalvaria (skull ossification defect) improved spontaneously. His weight and height are below the third percentile for his age, but his motor and cognitive functions are normal.

Discussion

To date, five cases surviving the neonatal period of AR-RTD have been reported [5–8]. (Table 1) The genotypes and phenotypes were variable among the cases. All of the patients except Patient 3 had one or more affected siblings, all of which died during the perinatal period. Although all of the patients subsequently developed chronic kidney disease, their psychomotor and cognitive development was normal.

Spontaneous ileal perforation could have resulted from low perfusion pressure, and another case of RTD with multiple ileal perforation has previously been described [9]. Hypocalvaria is also the consequence of low blood pressure because skull membranous bones require high oxygen tension for normal growth [4, 10].

Renal hypoperfusion is probably the cardinal lesion leading to AR-RTD because the same tubular lesions can be produced secondarily by various fetal conditions associated with insufficient renal blood supply and consequent marked stimulation of the RAS, including renal artery stenosis and fetal exposure to RAS blockers [4]. Therefore, the presumed consequence of all mutations observed in AR-RTD is the absence of Angiotensin II production or function [4]. However, the profiles of RAS components vary according to the underlying genetic defect of individual patient [7]. A patient with *ACE* mutations revealed a high plasma renin activity, high active renin concentration and low ACE concentration [7], as shown in the present case. In addition, the present case revealed markedly increased Angiotensin I level with mildly increased Angiotensin II and aldosterone levels. The interpretation of the hormonal changes in the present case may be as follows: (i) production of Angiotensin I, the substrate of ACE, is markedly increased to overcome the defective ACE activity, (ii) the missense (p.R259H) mutant ACE has minimal residual function or other proteolytic enzyme systems are activated due to defective ACE function and (iii) a small portion of markedly increased Angiotensin I is converted to Angiotensin II by minimally functioning mutant ACE or via other proteolytic enzyme systems (Figure 1). The compensatory increase of Angiotensin II may be the cause of survival and milder course of the patient. Schreiber *et al.* [8] recommended an early trial of mineralocorticoids to overcome extreme hypotension and hyperkalemia in patients with RTD.

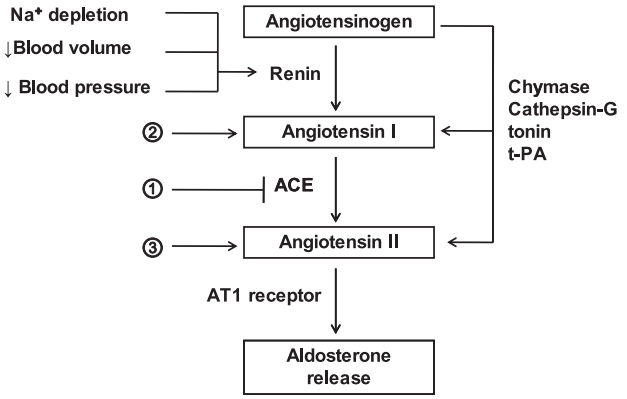

Fig. 1. Possible sequential changes in the renin–angiotensin–aldosterone system in the present case. ① decreased or absent ACE activity due to genetic mutations, ② compensatory overproduction of Angiotensin I, the substrate of ACE and ③ conversion of a small portion of Angiotensin I to Angiotensin II by minimally functioning mutant (p.R259H) ACE or via other proteolytic enzyme systems such as chymases and tissue plasminogen activators (t-PA).

In conclusion, AR-RTD is not a uniformly fatal disease, although all of the surviving cases subsequently developed chronic kidney disease. Collection of more surviving cases is required to find out possible prognostic factors and to develop effective treatment.

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Conflict of interest statement. None declared.

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