Survival over 2 years of autosomal-recessive renal tubular dysgenesis

Su Yeong Kim¹, Hee Gyung Kang¹,², Ee Kyung Kim¹, Jung Hwan Choi¹, Yong Choi³ and Hae Il Cheong¹,²,⁴

¹Department of Pediatrics, Seoul National University Children’s Hospital, Seoul, Korea, ²Research Center for Rare Diseases, Seoul National University Hospital, Seoul, Korea, ³Department of Pediatrics, Inje University Haeundae Paik Hospital, Busan, Korea and ⁴Kidney Research Institute, Medical Research Center, Seoul National University College of Medicine, Seoul, Korea

Correspondence and offprint requests to: Hae Il Cheong; E-mail cheonghi@snu.ac.kr

Abstract

Autosomal-recessive renal tubular dysgenesis (AR-RTD) is a rare disorder caused by mutations in the genes encoding any of the components of the renin–angiotensin system (RAS). 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, normal, <15 ng/mL/h (<4 ng/L)]. 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).
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/1.73m²). 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. 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 such as chymases and tissue plasminogen activators (t-PA), and (iii) a small portion of markedly decreased or absent ACE activity due to genetic mutations, compensatory overproduction of Angiotensin I, the substrate of ACE and 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).

![Fig. 1. Possible sequential changes in the renin-angiotensin-aldosterone system in the present case.](image)

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

| Patients | Reference | Gender | Family history | Oligohydramniosa (weeks) | Gestational period (weeks) | Parental consanguinity | Duration of anuria | Hypocalvaria | Lung hypoplasia | Mineralocorticoid Tx | Renal outcome | Present case |
|----------|-----------|--------|----------------|--------------------------|---------------------------|------------------------|-------------------|--------------|---------------|-------------------|-------------|--------------|
| 1        | [5]       | Female | (-)            | 24                       | 35                        | (-)                    | 29 days           | (+)          | (+)           | (+)               | CKD         | Male         |
| 2        | [6]       | Female | (+)            | 32                       | 38                        | (+)                    | 3 days            | (+)          | (-)           | (-)               | CKD         | Male         |
| 3        | [6]       | Female | (-)            | 35 (?                     | 35                        | (-)                    | 2 months          | (+)          | (-)           | (-)               | CKD         | Male         |
| 4        | [7]       | Female | (+)            | 26                       | 33                        | (-)                    | 16 days           | (+)          | (+)           | (+)               | CKD         | Male         |
| 5        | [8]       | Male   | (+)            | 22                       | 33                        | (+)                    | 15 days           | (+)          | (-)           | (-)               | CKD         | Male         |
| 6        |           | Male   | (+)            | 29                       | 33                        | (+)                    | 4 days            | (+)          | (+)           | (+)               | CKD         | Male         |

aCKD, chronic kidney disease; Tpl, kidney transplantation; PD, peritoneal dialysis; Tx, treatment.
bGestational period when oligohydramnios was detected.
cThe 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.

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Conflict of interest statement. None declared.

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