

Case Report
Pediatrics



A Premature Baby with Severe Oligohydramnios and Hypotension: a Case Report of Renal Tubular Dysgenesis

Jeesu Min ,¹ Myung Hyun Cho ,¹ Seong Phil Bae ,² Seung Han Shin ,^{1,3} Il-Soo Ha ,^{1,3,4} Hae Il Cheong ,^{1,3,4} and Hee Gyung Kang ,^{1,3,4,5}

¹Department of Pediatrics, Seoul National University Hospital, Seoul, Korea

²Department of Pediatrics, Soonchunhyang University Hospital, Seoul, Korea

³Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea

⁴Kidney Research Institute, Seoul National University College of Medicine, Seoul, Korea

⁵Wide River Institute of Immunology, Seoul National University, Seoul, Korea



Received: Feb 21, 2020

Accepted: Jun 14, 2020

Address for Correspondence:

Hee Gyung Kang, MD, PhD

Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
E-mail: kanghg@snu.ac.kr

© 2020 The Korean Academy of Medical Sciences.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Jeesu Min

<https://orcid.org/0000-0003-1535-7769>

Myung Hyun Cho

<https://orcid.org/0000-0002-3237-3173>

Seong Phil Bae

<https://orcid.org/0000-0002-6447-418X>

Seung Han Shin

<https://orcid.org/0000-0002-7008-4073>

Il-Soo Ha

<https://orcid.org/0000-0001-5428-6209>

Hae Il Cheong

<https://orcid.org/0000-0001-7556-1265>

Hee Gyung Kang

<https://orcid.org/0000-0001-8323-5320>

ABSTRACT

Renal tubular dysgenesis (RTD) is a rare fatal disorder in which there is poor development of proximal tubules, leading to oligohydramnios and the Potter sequences. RTD occurs secondary to renin-angiotensin system (RAS) blockade during the early stages of fetal development or due to autosomal recessive mutation of genes in the RAS pathway. A boy born at 33+1 weeks due to cord prolapse was found to be anuric and hypotensive. Pregnancy was complicated by severe oligohydramnios from gestational age 28+4 weeks. Abdominal sonography revealed diffuse globular enlargement of both kidneys with increased cortical parenchymal echogenicity. Infantogram showed a narrow thoracic cage and skull X-ray showed large fontanelles and wide sutures suggestive of ossification delay. Basal plasma renin activity was markedly elevated and angiotensin-converting enzyme was undetectable. Despite adequate use of medications, peritoneal dialysis, and respiratory support, he did not recover and expired on the 23rd day of life. At first, autosomal recessive polycystic kidney disease was suspected, but severe oligohydramnios along with refractory hypotension, anuria, skull ossification delay and high renin levels made RTD suspicious. *ACE* gene analysis revealed compound heterozygous pathogenic variations of c.1454.dupC in exon 9 and c.2141dupA in exon 14, confirming RTD. Based on our findings, we propose that, although rare, RTD should be suspected in patients with severe oligohydramnios and refractory hypotension.

Keywords: Renal Tubular Dysgenesis; Oligohydramnios; Hypotension; Premature Birth

INTRODUCTION

Fetal oligohydramnios is defined as an amniotic fluid index (AFI) below 10 percentile corresponding to the gestational age (GA). Severe fetal abnormalities, preterm pre-labor rupture of membranes, and impaired placental function are common causes.¹ Severe oligohydramnios, commonly known as AFI less than 5 cm, has a poor prognosis, leading to high mortality after birth. This is due to respiratory failure from pulmonary hypoplasia, especially in the settings of renal dysfunction.^{1,2} Renal causes of oligohydramnios include posterior urethral valve, bilateral renal dysplasia, autosomal recessive polycystic kidney disease (ARPKD), and tubular dysgenesis.²

Funding

This research was supported by a grant of the Korea Health Technology Research & Development Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant No. HI18C0013).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kang HG. Data Curation: Ha IS, Cheong HI. Resources: Bae SP, Shin SH, Cho MH. Supervision: Kang HG. Writing - original draft: Min J. Writing - review & editing: Kang HG.

Renal tubular dysgenesis (RTD), is a fatal disorder characterized by faulty developmental of proximal tubules caused by impairment of the renin-angiotensin system (RAS) as a result of mutations of relevant genes (*AGT*, *REN*, *ACE*, and *AGTRI*) or pharmacological blockade of RAS during early embryogenesis.³⁻⁷ RAS plays important roles in regulation of blood pressure and development such as ureteric bud branching.^{3,8} Therefore, RTD shows deranged renal tubular development, as well as flat-bone ossification because of hypoxemia resulting from hypotension.⁹ After birth, the patient suffers from persistent hypotension and anuria, which are unresponsive to treatments with volume expanders or high dose catecholamine.¹⁰

Here we present a case of RTD in a preterm baby from a pregnancy complicated by severe oligohydramnios from GA 28 weeks. After birth, the patient suffered from persistent anuria and hypotension, and although suspicion for ARPKD was high, identification of *ACE* gene mutation confirmed the diagnosis of RTD.

CASE DESCRIPTION

A boy, weighed 2,010 g, was born prematurely at GA 33+1 weeks by emergency cesarean delivery due to preterm labor and umbilical cord prolapse in November 2017. Pregnancy was complicated by severe oligohydramnios from GA 28+4 weeks with an AFI close to zero. Fetal kidneys were slightly enlarged (length of 4.2 cm) at GA 29+1 weeks. The mother denied taking any medication during pregnancy and she had no intervention to correct her oligohydramnios.

After birth, his heart rate was less than 60 per minutes and no cry was noted. His Apgar score was 1, 5, and 6 at 1, 5, and 10 minutes after birth, respectively. Resuscitation, including chest compression and intubation, was applied upon delivery. Oxygen saturation remained between 70% to 80%, despite surfactant administration, high-frequency oscillation ventilation or nitro oxide and treprostinil administration. Initial cord blood gas analysis showed metabolic and respiratory acidosis with a pH of 6.97, pCO₂ 104 mmHg, HCO₃⁻ 23.9 mmol/L. Initial laboratory findings from cord blood showed urea nitrogen of 5 mg/dL and creatinine 0.34 mg/dL. He was hypotensive; thus, inotropes (dopamine, dobutamine, epinephrine, and vasopressin) and stress dose hydrocortisone for adrenal insufficiency were initiated. However, twenty-four hours after birth, he was noted to have persistent hypotension and remained anuric. His initial infantogram showed a narrow thoracic cage (**Fig. 1A**). Suspicious of RTD because of anuria and persistent hypotension, skull X-ray was performed and it revealed large fontanelles and wide sutures, suggestive of ossification delay (**Fig. 1B**). Abdominal sonography on the second day after birth revealed diffuse globular enlargement of both kidneys (right kidney 4.6 cm and left kidney 4.7 cm) with increased cortical parenchymal echogenicity (**Fig. 2A**). The bladder was collapsed. Abdominal sonography on the third day after birth revealed new bilateral small perinephric fluid collections and multiple dot-like or linear echogenic spots in the right kidney (**Fig. 2B**). Also, thrombi in inferior vena cava were shown in ultrasonography (**Fig. 2C**). Heparin was initiated; however, two days later, expansion of the thrombi was noted now involving both renal veins.

Serum basal renin was 120.0 ng/mL/hr and 22.09 ng/mL/hr at 4 days and 10 days after birth, respectively. Basal aldosterone was 17.09 ng/dL and 24.5 ng/dL at 4 days and 10 days after birth, respectively. Also, on the 10th day, serum angiotensin-converting enzyme (ACE) was not detectable (below 5.0 U/mL) and angiotensin II (ANG II) was 312 pg/mL. Serum

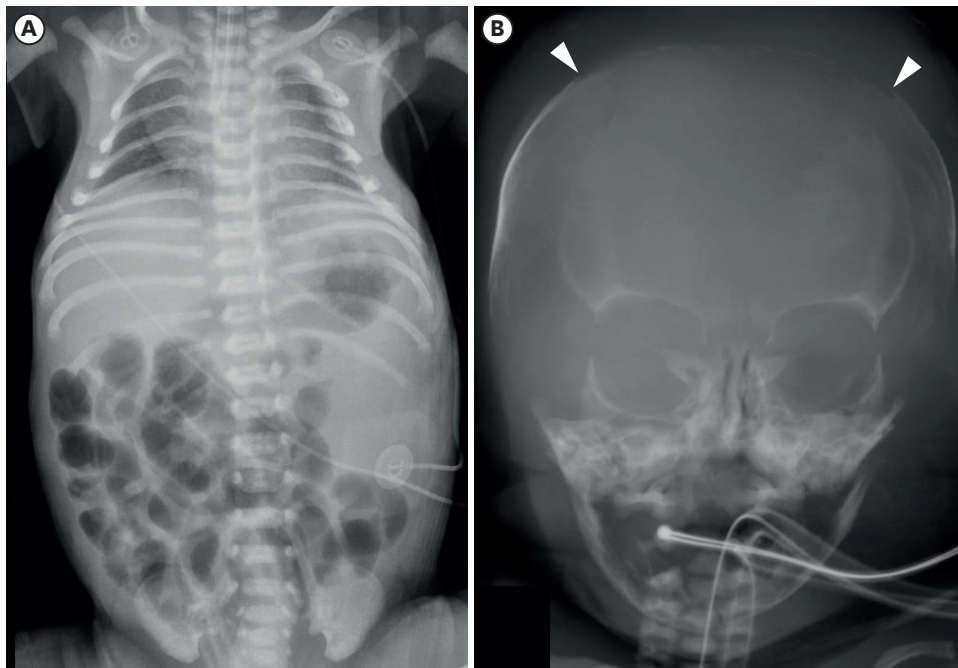


Fig. 1. The simple X-ray images of the patient showing characteristics of RTD. **(A)** Initial infantogram showing narrowing thoracic cage with the intubated state. **(B)** Large fontanelle and wide suture suggesting ossification delay.

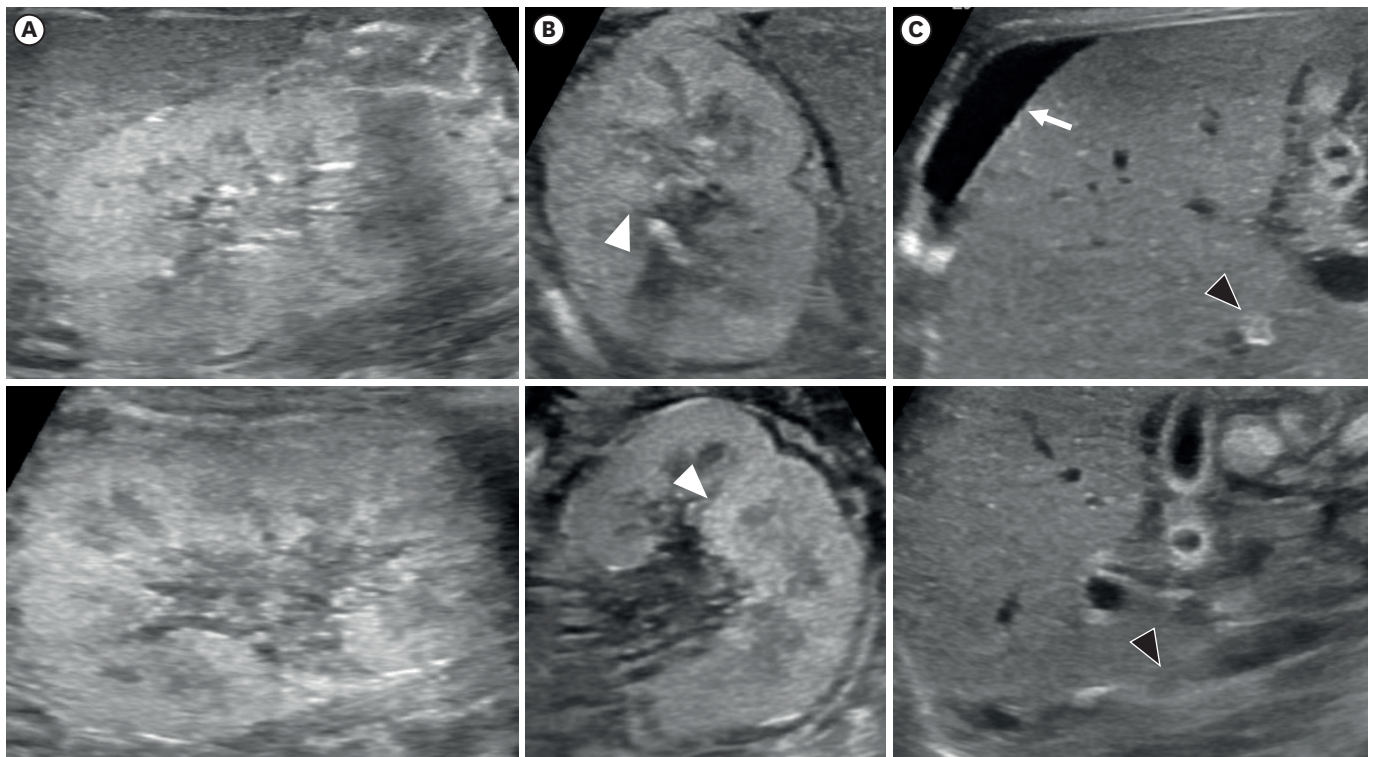


Fig. 2. Kidney sonography of the patient (the upper row: right kidney, the lower row: left kidney). **(A)** At the next day after birth, sonography showed diffuse globular enlargement of both kidneys (right kidney 4.6 cm and left kidney 4.7 cm) with increased cortical parenchymal echogenicity. **(B)** Third day of birth, newly-occurred multiple dot-like or linear echogenic spots (white arrow heads) were found in the both kidney. **(C)** Also, new bilateral small perinephric fluid collection (white arrow) and segmental obstructions of IVC in intrahepatic and suprarenal segment were detected, suggesting thrombi in the IVC (black arrow heads). IVC = inferior vena cava.

Table 1. Reference interval of serum hormone at age of 1 week to 3 months^a

Variables	Median	Range
Basal renin, ng/mL/hr ^{b,c}	12.0	7.1–23.8
Aldosterone, ng/dL ^{b,d}	62	30–201
ACE, U/mL ^e	21.6	12.1–32.9
ANG II, pg/mL ^f	58	30–117

ACE = angiotensin-converting enzyme, ANG II = angiotensin II.

^aAll blood sample was taken between 8:30 and 9:00 in the morning with supine posture and fasting since midnight (Infants fasted 3 hours before blood sample) in healthy patients and put into ice-cooled tubes. Plasma was immediately separated and frozen at -20°C until assay; ^bThe tube had 10 mg potassium EDTA; ^cMeasured by Clinical Assays, the commercial kit; ^dMeasured by direct radioimmunoassay; ^eThe tube had heparin. The sample was measured using hiuppuryl-L-histidyl-L-leucine as a substrate and spectrophotometrically at 228 nm; ^f0.125 M EDTA and 0.025 M O-phenanthroline in distilled water as inhibitors. The sample was measured by direct radioimmunoassay in unextracted plasma.

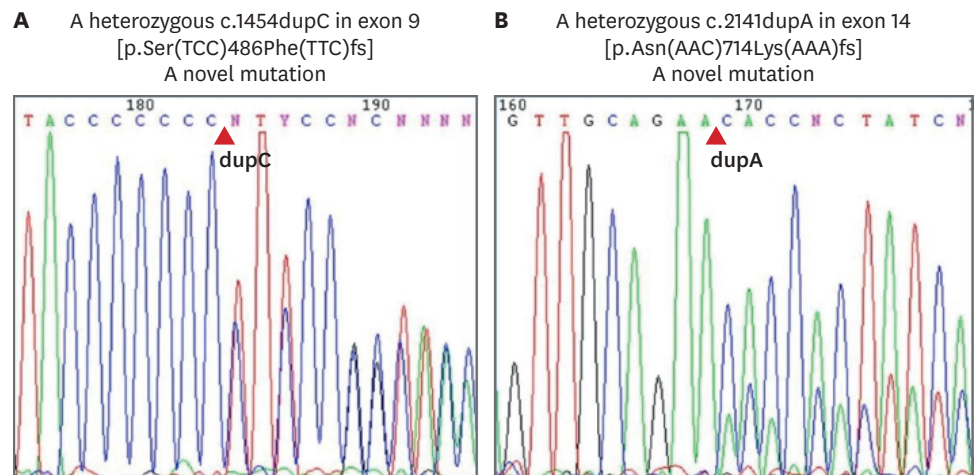


Fig. 3. The result of genetic analysis showing variations in *ACE* gene. **(A)** A heterozygous c.1454dupC in exon 9 (p.Ser486Phefs). **(B)** A heterozygous c.2141dupA in exon 14 (p.Asn714Lysfs).

creatinine increased to 3.09 mg/dL at the 10th day. Normal reference intervals of serum hormones are described in **Table 1**.¹¹ Genetic analyses revealed 2 frame-shifting duplications in the *ACE* gene (REFSEQ: NM_000789.3): c.1454dupC in exon 9 (p.Ser486Phefs) and c.2141dupA in exon 14 (p.Asn714Lysfs) (**Fig. 3**). Both variations have not been previously reported. Genetic testing of the parents was not available.

Despite the continuous infusion of inotropes and antibiotics, his hypotension persisted and he remained anuric. Peritoneal dialysis was started from the second day after birth for suspicious ARPKD but with frequent interruptions. Hyponatremia as low as 123 mmol/L on day three, improved, without reflex hyperkalemia, after 0.05 mg fludrocortisone was initiated on day six. The changes of blood pressure with interventions were shown in **Fig. 4**. On the 23rd day after birth, desaturation and bradycardia rapidly worsened, resulting in cardiac arrest. He then expired without further resuscitation following the wishes of his parents.

Ethics statement

This case was reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 0812-002-264). Requirement for informed consent was waived after review of IRB because it was practically impossible and this study was of retrospective design.

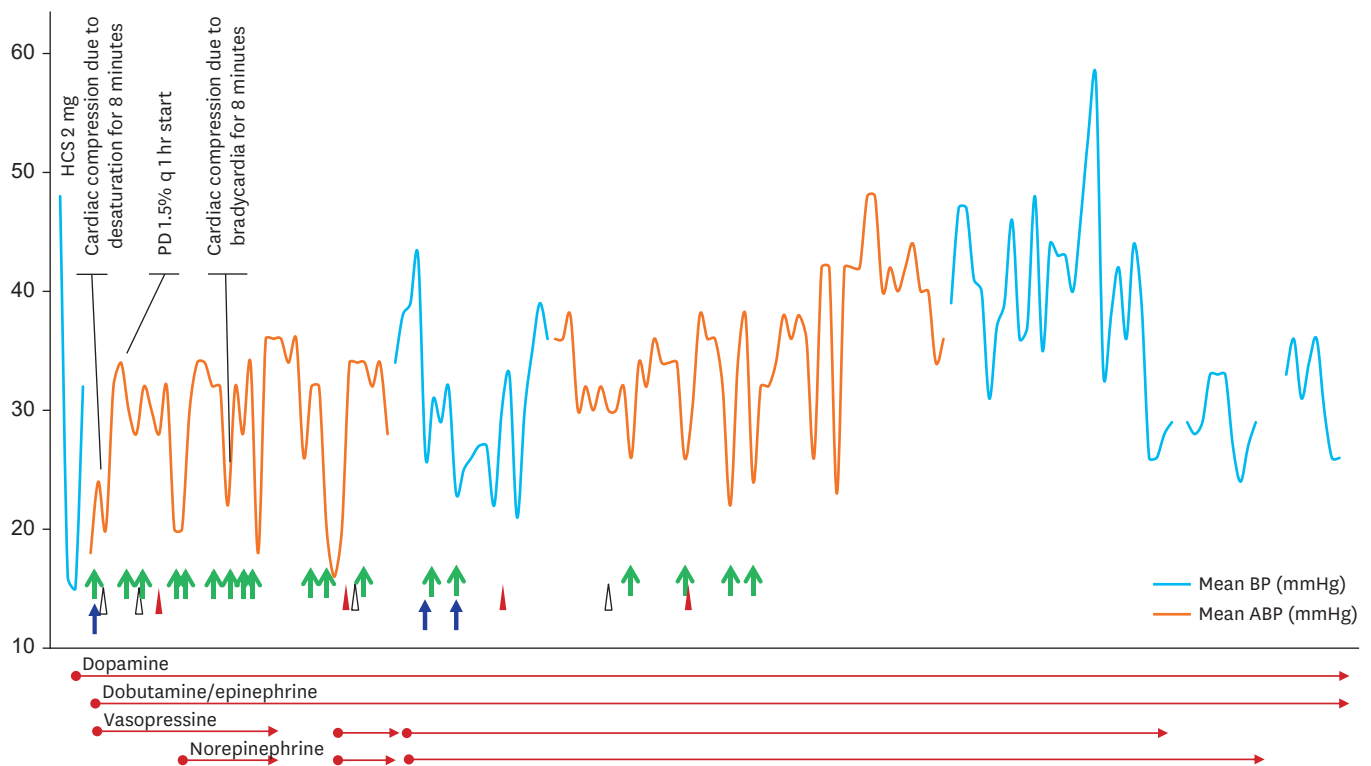


Fig. 4. The changes of patient's mean blood pressure associated with interventions such as inotropes, volume repletion or PD. 5% albumin (green arrows), normal saline (blue arrows), and blood (red arrow heads for red blood cell and white arrow heads for fresh frozen plasma) was used for volume repletion. HCS = hydrocortisone, PD = peritoneal dialysis.

DISCUSSION

RTD is a fatal and rare disease with an unknown incidence.^{4,9} RTD is caused by loss of function of the renal proximal tubule and chronic hypoperfusion of the fetal kidney, similar to what occurs in twin-twin transfusion syndrome, renal artery stenosis, or fetal exposure to RAS blockers.^{3,10} RTD is usually inherited in an autosomal recessive pattern.³ Variations result in the absence or decrease of ANG II production or function, leading to refractory hypotension.^{4,10} Thrombosis and skull ossification defect, as seen in our case, can be explained by this persistent fetal-neonatal hypotension.^{4,12}

In our patient, RTD was induced by two novel 1-base pair duplications confirmed in genetic analysis. Both variations result in frame-shifting with functional impairment (functional impact scores predicted by MutationAssessor [<http://mutationassessor.org/>] were 3.015 [c.1454dupC] and 2.375 [c.2141dupA]). Although there is a limitation interpretation because genetic testing in the parents were not performed, both variations were considered to be 'pathogenic variations' according to the guidelines¹³ developed by the American College of Medical Genetics and Genomics (1 very strong [PVS1], 1 moderate [PM2], and 1 supporting [PP4] evidence).

Laboratory findings also supported the diagnosis of genetic RTD in this case; In RTD with RAS mutations, except *REN*, the renin expression is usually increased as a result of negative feedback on the RAS pathway.^{3,4,12} Since *ACE* was mutated in our patient, serum ACE and aldosterone levels were low,¹⁴ but, serum ANG II was increased above the normal range of

age. Considering that serum ANG II increases after birth in preterm babies,¹⁵ it can explain the increase of ANG II in our patient.

Initially, we suspected ARPKD, since oligohydramnios was severe along with anuria. However, ultrasonography findings were not typical of ARPKD; kidneys in ARPKD are highly echogenic and enlarged.¹⁶ On the other hand, kidneys affected by RTD have normal or slightly enlarged sizes with or without normal echogenicity and loss of corticomedullary differentiation as seen in our case. Because these findings are not specific, it is difficult to diagnose RTD by fetal kidney sonography only, although the sensitivity of prenatal ultrasonography screening for renal malformation is now up to 80%.¹⁷ In addition to renal ultrasonography, a typical pre-natal finding of RTD is severe oligohydramnios, which manifests around GA 20 weeks.⁹ In our patient, oligohydramnios was first detected at GA 24 weeks and severe oligohydramnios at GA 28 weeks. Also, antenatal renal ultrasonographic findings were compatible with RTD.

Hypotension is the major challenge during the first days of life in patients with RTD. While vasopressin was reported as helpful to remedy hypotension in survived cases,^{14,18} it was not effective in our case. Volume repletion using volume expanders such as fresh frozen plasma, which reversed hypotension in a few cases,^{4,14} was not effective either. There are reports that fludrocortisone can be used for electrolyte stabilization and can significantly improve clinical outcomes,^{14,18} but in our patient, fludrocortisone was helpful only in electrolyte stabilization.

Despite rigorous management, our patient did not survive. To date, 14 patients with genetically confirmed RTD have survived according to the literature. Almost all the reported patients, similar to our patient, needed renal replacement therapy, and all the survived cases except one had chronic kidney disease.^{12,14,19,20} In Korea, only one case was reported until now, and that patient survived with chronic kidney disease stage 2.¹⁹

Interestingly, prognosis, severity, or the phenotype of RTD is not correlated with locus heterogeneity or differences in the mutated genes.^{4,12} Rather than the specific type of variations or causative gene, response to supportive care for respiratory difficulty and hypotension is more important for the neonatal survival;¹⁰ rapid recovery of diuresis is considered a favorable prognostic factor.^{10,14,19}

As presented in this report, despite its rarity, suspicion for RTD should be high in preterm neonates with refractory hypotension whose gestational course was complicated by severe oligohydramnios.¹² Faulty ossification of skull bones with wide sutures and high renin levels support the diagnosis of RTD. For genetic analysis, molecular identification of pathogenic variations in RAS-associated genes can confirm the disease, opening the possibility for genetic counseling.¹²

REFERENCES

1. Kozinszky Z, Sikovanyecz J, Pásztor N. Severe midtrimester oligohydramnios: treatment strategies. *Curr Opin Obstet Gynecol* 2014;26(2):67-76.
[PUBMED](#) | [CROSSREF](#)
2. Klaassen I, Neuhaus TJ, Mueller-Wiefel DE, Kemper MJ. Antenatal oligohydramnios of renal origin: long-term outcome. *Nephrol Dial Transplant* 2007;22(2):432-9.
[PUBMED](#) | [CROSSREF](#)

3. Gribouval O, Gonzales M, Neuhaus T, Aziza J, Bieth E, Laurent N, et al. Mutations in genes in the renin-angiotensin system are associated with autosomal recessive renal tubular dysgenesis. *Nat Genet* 2005;37(9):964-8.
[PUBMED](#) | [CROSSREF](#)
4. Gubler MC, Antignac C. Renin-angiotensin system in kidney development: renal tubular dysgenesis. *Kidney Int* 2010;77(5):400-6.
[PUBMED](#) | [CROSSREF](#)
5. Plazanet C, Arrondel C, Chavant F, Gubler MC. Fetal renin-angiotensin-system blockade syndrome: renal lesions. *Pediatr Nephrol* 2014;29(7):1221-30.
[PUBMED](#) | [CROSSREF](#)
6. Vivante A, Kohl S, Hwang DY, Dworschak GC, Hildebrandt F. Single-gene causes of congenital anomalies of the kidney and urinary tract (CAKUT) in humans. *Pediatr Nephrol* 2014;29(4):695-704.
[PUBMED](#) | [CROSSREF](#)
7. Lee KH, Gee HY, Shin JI. Genetics of vesicoureteral reflux and congenital anomalies of the kidney and urinary tract. *Investig Clin Urol* 2017;58 Suppl 1:S4-13.
[PUBMED](#) | [CROSSREF](#)
8. Yosypiv IV. Renin-angiotensin system in ureteric bud branching morphogenesis: implications for kidney disease. *Pediatr Nephrol* 2014;29(4):609-20.
[PUBMED](#) | [CROSSREF](#)
9. Lacoste M, Cai Y, Guicharnaud L, Mounier F, Dumez Y, Bouvier R, et al. Renal tubular dysgenesis, a not uncommon autosomal recessive disorder leading to oligohydramnios: role of the Renin-Angiotensin system. *J Am Soc Nephrol* 2006;17(8):2253-63.
[PUBMED](#) | [CROSSREF](#)
10. Gubler MC. Renal tubular dysgenesis. *Pediatr Nephrol* 2014;29(1):51-9.
[PUBMED](#) | [CROSSREF](#)
11. Fiselier TJ, Lijnen P, Monnens L, van Munster P, Jansen M, Peer P. Levels of renin, angiotensin I and II, angiotensin-converting enzyme and aldosterone in infancy and childhood. *Eur J Pediatr* 1983;141(1):3-7.
[PUBMED](#) | [CROSSREF](#)
12. Gribouval O, Morinière V, Pawtowski A, Arrondel C, Sallinen SL, Saloranta C, et al. Spectrum of mutations in the renin-angiotensin system genes in autosomal recessive renal tubular dysgenesis. *Hum Mutat* 2012;33(2):316-26.
[PUBMED](#) | [CROSSREF](#)
13. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17(5):405-24.
[PUBMED](#) | [CROSSREF](#)
14. Ruf K, Wirbelauer J, Beissert A, Friauff E. Successful treatment of severe arterial hypotension and anuria in a preterm infant with renal tubular dysgenesis- a case report. *Matern Health Neonatol Perinatol* 2018;4(1):27.
[PUBMED](#) | [CROSSREF](#)
15. Miyawaki M, Okutani T, Higuchi R, Yoshikawa N. Plasma angiotensin II concentrations in the early neonatal period. *Arch Dis Child Fetal Neonatal Ed* 2006;91(5):F359-62.
[PUBMED](#) | [CROSSREF](#)
16. Bergmann C. ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies. *Pediatr Nephrol* 2015;30(1):15-30.
[PUBMED](#) | [CROSSREF](#)
17. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C, Group ES, et al. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. *Eur J Med Genet* 2005;48(2):131-44.
[PUBMED](#) | [CROSSREF](#)
18. Richer J, Daoud H, Geier P, Jarinova O, Carson N, Feberova J, et al. Resolution of refractory hypotension and anuria in a premature newborn with loss-of-function of ACE. *Am J Med Genet A* 2015;167(7):1654-8.
[PUBMED](#) | [CROSSREF](#)
19. Kim SY, Kang HG, Kim EK, Choi JH, Choi Y, Cheong HI. Survival over 2 years of autosomal-recessive renal tubular dysgenesis. *Clin Kidney J* 2012;5(1):56-8.
[PUBMED](#) | [CROSSREF](#)
20. Fila M, Morinière V, Eckart P, Terzic J, Gubler MC, Antignac C, et al. Bi-allelic mutations in renin-angiotensin system genes, associated with renal tubular dysgenesis, can also present as a progressive chronic kidney disease. *Pediatr Nephrol* 2020;35(6):1125-8.
[PUBMED](#) | [CROSSREF](#)