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ORIGINAL ARTICLE

Expanding the clinical spectrum of autosomal-recessive renal tubular dysgenesis: Two siblings with neonatal survival and review of the literature

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Abstract

Background: Autosomal-recessive renal tubular dysgenesis (AR-RTD) is a rare genetic disorder caused by defects in the renin-angiotensin system that manifests as fetal anuria leading to oligohydramnios and Potter sequence. Although the most common outcome is neonatal death from renal failure, pulmonary hypoplasia, and/or refractory arterial hypotension; several cases have been reported that describe survival past the neonatal period.

Methods: Herein, we report the first family with biallelic *ACE* variants and more than one affected child surviving past the neonatal period, as well as provide a review of the previously reported 18 cases with better outcomes.

Results: While both siblings with identical compound heterozygous *ACE* variants have received different treatments, neither required renal replacement therapy. We show that both vasopressin and fludrocortisone in the neonatal period may provide survival advantages, though outcomes may also be dependent on the type of gene variant, as well as other factors.

Conclusion: While AR-RTD is most often a lethal disease in the neonatal period, it is not universally so. A better understanding of the factors affecting survival will help to guide prognostication and medical decision-making.

KEYWORDS

fludrocortisone, renal tubular dysgenesis, survival

1 | INTRODUCTION

Autosomal-recessive renal tubular dysgenesis (AR-RTD; OMIM #267430) is a severe disorder of renal tubular development secondary to fetal renal hypoperfusion. Patients often present with oligohydramnios sequence, refractory arterial hypotension, skull ossification defects, and anuria (Allanson et al., 1983; Bacchetta et al., 2007; Gribouval et al., 2005). Most cases result in neonatal deaths due to anuric renal failure, arterial hypotension,

and/or pulmonary hypoplasia. The condition is caused by mutations in four genes that function within the renin-angiotensin system (RAS): angiotensin-converting enzyme (*ACE*), angiotensinogen (*AGT*), renin (*REN*), and angiotensin II receptor type 1 (*AGTR1*).

Since the initial characterization, over 100 sporadic or familial cases of AR-RTD have been described in the literature (Allanson et al., 1992; Gribouval et al., 2012). While the severity of AR-RTD was initially believed to invariably result in perinatal or neonatal death due to anuria and respiratory failure, in recent years, more and more patients are being described that survive past the critical neonatal period (Bacchetta et al., 2007; Danilov et al., 2010; Demirgan et al., 2021; de Oliveira et al., 2011; Gribouval et al., 2005, 2012; Hibino et al., 2015; Kim et al., 2012; Richer et al., 2015; Ruf et al., 2018; Schreiber et al., 2010; Uematsu et al., 2006, 2009; Zingg-Schenk et al., 2008). Historically, treatment has been largely supportive and includes intubation and ventilation for respiratory failure, intravenous fluid and inotrope/vasopressor support for hypotension, and dialysis for anuria. More recently, vasopressin has been used in the neonatal period to circumvent a defect component of the renin-angiotensin system in these patients (Richer et al., 2015; Ruf et al., 2018).

Herein, we present the first family with two offspring with *ACE*-related AR-RTD that survived past the neonatal period. Importantly, while they received different treatments in the neonatal period and had different clinical courses, neither sibling required renal replacement therapy (dialysis or renal transplant). We review the different treatments they received, as well as provide a review of the previous 18 reported cases with comparatively good outcomes. A more thorough analysis and understanding of the treatments for this rare genetic disorder may help to improve outcomes.

2 | RESULTS

2.1 | Clinical report: Patient 1

The proband was born to a healthy 26 year old G1. Family history was negative for consanguinity or renal disease (apart from hypertension in paternal grandfather and renal stones in maternal grandmother). The family had recently emigrated from Lebanon, with initial prenatal ultrasound in Lebanon reported as normal. Ultrasound in Canada at 31 weeks showed anhydramnios, breech presentation, and two consecutive biophysical profiles of 2/8 and 6/8. The fetal kidneys were normal-sized and isoechoic. The proband's mother was started on erythromycin for 7 days for presumed premature rupture of membranes and received two doses of betamethasone (Celestone). On examination, the proband's mother had ruptured membranes with meconium-stained fluid and the female infant was delivered thereafter by cesarean section at 33 weeks and 2 days gestational age.

At delivery, she was hypotonic with poor respiratory effort. She received initial respiratory resuscitation with positive pressure ventilation and was then stabilized on nasal continuous positive airway pressure (CPAP). APGAR scores were four, six, and nine at 1, 5, and 10 min, respectively. Birth weight was 2020 g (56th centile), length was 45.5 cm (8th centile; measured on day of life [DOL] five) and head circumference was 28 cm (6th centile; measured on DOL two). She was non-dysmorphic with a fixed right foot flexion deformity, and had no evidence of calvarial hypoplasia.

She remained on CPAP for 24 h. While initially she had intermittent low blood pressures within the first 24 h of life (as low as 38/21; normal range 56 ± 5/36 ± 4 [Pejovic et al., 2007]), she improved spontaneously and did not require any interventions for blood pressure support. She remained anuric with no response to furosemide or IV fluid. Renal ultrasound was completed, which showed normal-sized kidneys with good corticomedullary differentiation. Mercaptuacetyltriglycine (MAG-3) renal perfusion scan demonstrated good uptake of the radioactive tracer in the kidneys, but no excretion into the collecting system or bladder. During this time, laboratory markers were consistent with renal failure: her serum creatinine (sCr) steadily increased to 429 μmol/L (normal range: 27–58 μmol/L) with serum urea of 6.4 mmol/L (normal range: 2.0–5.0 mmol/L) on day of life four. At the time, her potassium level was normal.

Given her unclear prognosis, worsening anuric renal failure, and after a risks/benefit discussion of renal replacement therapy in anuric newborns with her parents, the decision was made to transition her to palliative care on the fifth day of life with breastfeeding for comfort. She unexpectedly and spontaneously started to produce small amounts of urine on DOL 10. Bloodwork at the time demonstrated a sCr of 966 μmol/L, serum urea of 10.9 mmol/L, and serum potassium of 5.7 mmol/L (normal range: 3.5–5.0 mmol/L). She was started on oral bicarbonate at this time. She continued to spontaneously produce urine at increasing quantities, and slowly became less edematous. Her sCr peaked at 1018 μmol/L (normal range: 21–46 μmol/L), serum urea at 12.5 umol/L, and serum potassium at 6.2 mmol/L on DOL 14. Kayexelate was started for hyperkalemia. Her renal function continued to improve with a sCr nadir of 52 μmol/L at 2 months of age (normal range: 15–33 μmol/L) and electrolytes within the normal range.

During follow-up assessments, the patient's renal function slowly deteriorated; she had chronic kidney disease

(CKD) stage III-IV at 8 months of age. She continued on kayexalate, vitamin D, iron, folic acid, and sodium supplementation. She was started on erythropoietin for anemia with good response. Her blood pressure remained in the low-normal range. Other ongoing medical issues included a patent ductus arteriosus, and bicuspid aortic valve. Overall, the patient was generally well throughout infancy but did have several admissions to hospital for intercurrent illnesses requiring intravenous fluid support with transient acute on chronic kidney injury.

When the patient was 20 months of age, the parents agreed to genetic testing and an autosomal-recessive renal tubular dysgenesis sequencing panel with CNV detection was conducted (PreventionGenetics, Marshfield, WI, USA). It revealed two variants in *ACE*: a paternally inherited c.38_43del (p.Leu13_Leu14del; interpreted as pathogenic) and maternally inherited c.1487G > A (p.Arg459Gln; interpreted as a variant of uncertain significance). Deletions of one or more leucine residues in exon one of the *ACE* gene, including this specific variant, have been reported to be pathogenic for AR-RTD (Fila et al., 2020; Gribouval et al., 2012; Schreiber et al., 2010). The c.1487G > A variant has been reported once in the literature and in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/variation/424035/) and is predicted to destroy the natural splice donor site in intron nine, resulting in aberrant gene splicing (Ruf et al., 2018). If it does not alter splicing, it would result in an Arg496Gln missense mutation.

At last follow-up, she was 3 years and 5 months of age with stable CKD stage III well-controlled with diet and medication. Most recent renal ultrasound at 3 years and 2 months of age demonstrated normal-sized kidneys (68 and 71 mm in length), persistent increased cortical echogenicity and slightly attenuated corticomedullary differentiation, and mild thinning of the bilateral renal parenchyma predominantly affecting the lower pole. She has not required renal replacement therapy and is otherwise developing normally.

2.2 | Clinical report: Patient 2

Patient 2 was the second pregnancy of her parents. The pregnancy was uncomplicated apart from severe oligohydramnios noted on ultrasound at 28 weeks and 4 days gestational age, which persisted on subsequent ultrasounds. The fetal kidneys were normal-sized and isoechoic on ultrasound assessment at 28 weeks and 4 days gestational age and on repeat ultrasounds thereafter. A small right pleural effusion was detected by ultrasound at 29 and 31 weeks gestational age. Her mother presented with premature rupture of membranes at 33 weeks and 3 days gestational age and underwent emergency C-section shortly thereafter. She received one dose of betamethasone (Celestone) 12 h before delivery.

At delivery, the child cried and cord clamping was delayed for 1 min. Subsequently she was noted to be cyanotic with increased work of breathing. She required CPAP initially, and then intubation and ventilation, for respiratory stabilization. APGAR scores were six, seven, and eight at 1, 5, and 10 min. Cord pH was 7.31. Birth weight was 2130 g (63th centile), length was 46 cm (68th centile; measured on DOL eight), and birth head circumference was 29.5 cm (34th centile). She was non-dysmorphic but had calvarial hypoplasia and contractures.

Neonatal course was complicated by her prematurity requiring surfactant administration, pneumothorax requiring chest tube placement, and anemia requiring red blood cell transfusion. She had hypotension (as low as 44/17; normal range 58 ± 4/38 ± 4 [Pejovic et al., 2007]) that was poorly responsive to IV fluids. She was started on vasopressin (up to 0.0007 mcg/kg/min) and dobutamine (up to 10 mcg/kg/min) to support blood pressure. Fludrocortisone at 0.1 mg twice daily was started on her second day of life. Abdominal ultrasound revealed bilateral normal-sized kidneys (48 and 50 mm in length) with increased cortical echogenicity. Weaning dobutamine was prioritized over vasopressin and successfully completed on DOL three. She had spontaneous but minimal urine output and was successfully extubated on DOL four. As well, vasopressin was weaned off on DOL four without any issues. Her laboratory markers peaked at her ninth day of life: her sCr peaked at 539 μmol/L (normal range: 21–46 μmol/L), her urea rose to 10.6 mmol/L, her sodium rose to 147 mmol/L (normal range: 135–145 mmol/L), and her potassium dropped to 2.9 mmol/L (normal range: 3.5–5.0 mmol/L). Due to her electrolyte changes, her fludrocortisone was decreased to 0.1 mg daily. She experienced gradual but continuous improvements in spontaneous diuresis. Fludrocortisone required further dose adjustments to optimize electrolytes. Kayexelate and sodium supplementation were started when she was 2 months of age.

She encountered multiple additional medical issues during her prolonged hospital stay. Specifically, she developed two courses of necrotizing enterocolitis (NEC) at 1 month of age (corrected gestational age 37 weeks and 1 day, Stage 2A NEC) and 1 month and 2 weeks of age (corrected gestational age 39 weeks and 2 days of age, suspected Stage 1B). She was noted to have a patent ductus arteriosus (PDA) and small apical ventricular septal defect (VSD). In an attempt to optimize her gastrointestinal perfusion in the context of a hemodynamically significant PDA and recurrent episodes of NEC, her PDA was surgically ligated at 6 weeks of age. She became anemic, and required multiple transfusions as well as the initiation of Darbepoetin at 2 months of age. She developed cow's milk

protein intolerance that led to a change of formula to an amino acid-based formula. She was discharged from hospital at 2 months and 10 days of age.

Patient 2 was admitted at 4.5 months of age with significant hypernatremia (Na 174 mmol/L) and hypertension, despite no changes to her fludrocortisone dosing. Fludrocortisone was discontinued and her sodium level normalized over the course of a few weeks. In addition, she required gastrostomy tube (G-tube) insertion at 8 months of age for failure to thrive and poor oral feeding skills. Post-G-tube insertion, she has been gaining weight appropriately, albeit with ongoing difficulties with emesis. At 9 months of age, she was noted to have new intermittent horizontal nystagmus. She subsequently underwent MRI head imaging that demonstrated abnormal symmetric T2 signal intensities in the globi pallidi, optic radiations, and central tegmental tracts, for which she is currently being worked up for a possible concurrent metabolic/mitochondrial disease. Additionally, she has been admitted to hospital for pneumonia at 9 months of age, and vomiting with dehydration at 11 months of age.

At present, patient 2 is 11 months of age and her sCr appears to be stabilizing at 110 μmol/L (normal range: 15–32 μmol/L) with an estimated glomerular filtration rate (eGFR) of 22 ml/min per 1.73 m^2 (Cystatin C method), and 22 ml/min per 1.73 m^2 (Schwartz method). Therefore, she has chronic kidney disease stage IV like her sibling. Her latest renal ultrasound demonstrated large kidneys (58 and 58 mm in length; $Z = +2.83$ based on Scholbach and Weitzel (2012) and body surface area calculations), though it should be noted that this may be confounded by her failure to thrive. Kidneys bilaterally had markedly increased echogenicity and preserved corticomedullary differentiation. She has not required renal replacement therapy. Her serum sodium levels have been stable, and her blood pressures have trended down to the low range, in keeping with her diagnosis and clinically like her sister. She is being treated with Darbopoeitin for her renal anemia, kayexalate for the hyperkalemia, and alfacalcidol. With time, she will also likely require further CKD medications (such as bicarbonate therapy), as this was the case with her sibling. She was confirmed to carry the same *ACE* variants as her sibling.

Clinical data of these two siblings, as well as 18 previously published AR-RTD patients with survival past the neonatal period, are described in Tables 1 and S1. Our two siblings represent the first *ACE*-related AR-RTD family to have more than one affected infant survive the neonatal period, albeit with different clinical courses. In this cohort, 11 patients did not receive renal replacement therapy (including our two patients), 9 of whom have variants in the *ACE* gene. Three of these nine patients received vasopressin during the neonatal period.

3 | DISCUSSION

Autosomal-recessive renal tubular dysgenesis is a rare genetic disorder that was previously thought to be an almost universally lethal disease. However, there have been several case reports that describe patients with survival past the neonatal period (Bacchetta et al., 2007; Danilov et al., 2010; de Oliveira et al., 2011; Gribouval et al., 2005, 2012; Hibino et al., 2015; Kim et al., 2012; Richer et al., 2015; Ruf et al., 2018; Schreiber et al., 2010; Uematsu et al., 2006, 2009; Zingg-Schenk et al., 2008). To our knowledge, this is the first family with two affected siblings with *ACE* mutations that have survived the critical neonatal period, and we have summarized the previously reported 18 cases with long-term survival. We also describe the first patient to have received both fludrocortisone and vasopressin (sibling 2 herein) in the neonatal period, with successful onset of diuresis on day of life four. Though the genotypes and clinical courses have been variable among the cases with long-term survival, a more thorough understanding of the commonalities between them may help inform medical prognostication as well as medical decision making.

Currently, the treatments for AR-RTD in the neonatal period are not well defined and have historically been mainly supportive with renal replacement therapy as required. However, there are unique challenges for renal replacement therapy in neonates that often make it an undesirable option. Additionally, patients with AR-RTD have been shown to be largely refractory to usual supportive measures for hypotension and anuria, including IV fluid boluses, furosemide, catecholamines, and hydrocortisone. Infusions of fresh frozen plasma (FFP) to provide exogenous angiotensinogen have been described to normalize blood pressure in two neonates with *AGT* mutations (Hibino et al., 2015; Uematsu et al., 2006). It would not be expected that FFP would have similar benefits in AR-RTD caused by mutations in other components of the RAS, given that they are predicted to have normal angiotensinogen but are lacking an enzyme downstream in the pathway.

Variants in the *ACE* gene are the most common cause of AR-RTD (Gribouval et al., 2012). The *ACE* gene encodes angiotensin-converting enzyme, which is a key component of the renin-angiotensin system (reviewed in: [Bernstein et al., 2012; Lavoie & Sigmund, 2003]). Renin (*REN*) converts angiotensinogen (*AGT*) to angiotensin I, and then ACE converts angiotensin I into biologically active angiotensin II (ATII). Angiotensin II regulates blood pressure by increasing renal sodium reabsorption at the proximal tubule, by stimulating the production of aldosterone by the adrenal cortex, and by stimulating the release of vasopressin in the posterior pituitary (reviewed

in: [Lavoie & Sigmund, 2003]). In turn, vasopressin has two primary functions: to increase the amount of free water reabsorbed by the kidney, and to constrict arterioles; therefore it also plays a role in maintaining blood pressure (Treschan & Peters, 2006). Presumably, the treatment of neonates with AR-RTD neonates with vasopressin thus circumvents the defective component of RAS to provide vasopressin, thereby providing a component of the system that would be lacking in patients with AR-RTD. Three of the nine patients in this series that did not need renal replacement therapy received vasopressin in the neonatal period with normalization of blood pressures in all three patients and almost immediate diuresis in two of the patients.

Of note, treating with vasopressin does not correct the concomitant low aldosterone, which is also a result of ATII absence. Aldosterone acts to increase blood pressure by increasing renal sodium and water reabsorption, as well as promoting renal secretion of potassium (Briet & Schiffrin, 2010). Fludrocortisone is often eventually used in AR-RTD patients to replace the missing aldosterone, though there have not been any published reports of using fludrocortisone in the neonatal period. Patient two described in this study was the first to receive fludrocortisone in the neonatal period: it was started at 0.1 mg twice daily on her second day of life. She remained on it until 4.5 months of age, though dose adjustments to optimize electrolytes were necessary. Of the three patients to receive vasopressin, our patient was the only to receive both fludrocortisone and vasopressin the neonatal period, and was the only one that did not require a prolonged wean of vasopressin due to recalcitrant hypotension and oliguria. She was weaned off vasopressin on day of life four, whereas both previously reported patients had rapid deteriorations of blood pressure and urine output with weaning attempts (weans successfully completed over the course of 3 weeks and 9 weeks in previous patients) (Richer et al., 2015; Ruf et al., 2018). We postulate that replacing aldosterone at this earlier time may have supported blood pressure enough to enable a more rapid and successful wean of the vasopressin, though further cases are needed to corroborate this hypothesis.

The minority of patients with AR-RTD survive the neonatal period, which raises the questions of what drives the severity of the phenotype. While no correlation has been observed between the mutated gene and the specific phenotype, one group has recently postulated that, similar to other genetic renal diseases, there may be more severe phenotype when the affected protein is located more distally along the RAS pathway (Rotem-Grunbaum & Landau, 2020). They noted that at the time there were no documented cases of patients with *AGT1R* mutations and survival past the neonatal period. However, shortly thereafter there has been a publication describing two siblings with AR-RTD and homozygous nonsense mutations in *AGT1R* (Demirgan et al., 2021). We suspect that the original lack of surviving patients with *AGT1R* variants is more reflective of the lower incidence of *AGT1R*-related AR-RTD in general. When we conduct a chi-squared test on survival by gene using the 78 cases of AR-RTD in the literature with genotype information available; the survival of AR-RTD patients did not differ by causative gene ($p = .27$). However, this may change as more cases are described and treatment options change for the specific gene involved (e.g., treatment with FFP for patients with *AGT* mutations).

An alternative hypothesis was put forward by Gribouval et al. (2012). This group correlated non-truncating mutations with superior survival outcomes. Indeed, 14 of the 18 families described in this study have at least one non-truncating mutation, compared to only nine of the 39 in a previously published cohort of AR-RTD families without any surviving affected family members. This difference is statistically significant ($p = .016$, chi-squared test), and indicates that the presence of at least one non-truncating variant may allow survival. We hypothesize that survival may be influenced by residual function of the protein, with missense variants retaining at least some native function.

However, the type of mutation does not appear to be the sole factor associated with patient survival: eight of the families described herein additionally had at least one affected or presumed affected siblings that died in utero or neonatally. In fact, the family characterized in this report is only the second family described that has had two affected siblings survive the neonatal period, and both families affected siblings had different phenotypes and neonatal courses. This would suggest that modifier genes and/or the neonatal treatment may alter their trajectory. There remains the question as to whether less severe variants in the RAS genes can be responsible for the milder autosomal recessive nephropathies. A recent report by Fila et al. identified three patients with biallelic non-truncating *ACE* variants that were identified between 4 and19 years of age during genetic investigations for progressive kidney disease (Fila et al., 2020). These three patients were only retrospectively recognized to have had mild AR-RTD neonatal courses. This suggests that RAS mutations may present as a spectrum of phenotypes, with the interaction between the type of variant, modifier genes, and neonatal treatment that may determine patient outcomes.

In summary, AR-RTD is a rare genetic disorder that most often results in neonatal death secondary to pulmonary hypoplasia and anuric renal failure. We describe a family with two affected siblings that survived the neonatal

TABLE 1 Summary of patients with AR-RTD with survival past the neonatal period

Patient	Variants	Consanguinity	Sex	Oligohydramnios	Gestational age at birth	Duration of post-natal anuria
ACE mutations						
Uematsu et al. (2009)	(1) c.13_22del10, p.S5Gfs*136 (2) c.3508_3543del36, p.1172_1183del12	–	Female	26 weeks	33 weeks	16 days
Schreiber et al. (2010)	(1) c.38_49del12, p.13_16del4 (2) c.38_49del12, p.13_16del4	–	Male	22 weeks	33 weeks	15 days
Danilov et al. (2010); de Oliveira et al. (2011)	(1) c.3293A > G, p.Q1069R (2) c.3293A > G, p.Q1069R	–	Female	None	35 weeks	NR
Kim et al. (2012)	(1) c.776G > A, p.R259H (2) c.1454delC, p.P485Lfs	–	Male	29 weeks	32 weeks and 4 days	6 h
Gribouval et al. (2012)	(1) c. 47_70del24, p.16_23del (2) c. 47_70del24, p.16_23del	NR	Female	NR	NR	NR
Gribouval et al. (2012)	(1) c.776G > A, p.R259H (2) Not detected	NR	Male	+	33 weeks	NR
Gribouval et al. (2012)	(1) c.1803delG, p.K601Nfs*40 (2) c.3626G > C, p.R1209P	NR	Male	+	40 weeks	NR
Richer et al. (2015)	(1) c.820_821delAG, p.R274Gfs*117 (2) c.3521delG, p.G1174Afs*12	NR	Male	26 weeks and 5 days post-PPROM	27 weeks and 3 days	1 day but then became anuric for 4 days.
Ruf et al. (2018)	(1) c.5303 + 1G > A (aberrant splicing) (2) c.1487G > A, p.R496Q (aberrant splicing)	NR	Male	32 weeks	34 weeks	37 h
Fila et al. (2020): Patient 1	(1) c.38_43 del, p.13_14del (2) c.38_43 del, p.13_14del	+	Female	None	36 weeks	2 days
Fila et al. (2020): Patient 2	(1) c.38_49del, p.13_16del (2) c.1698G > T, p.G566=	NR	Female	Late oligohydramnios	Term	NR
Fila et al. (2020): Patient 3	(1) c.38_43del, p.13_14del (2) c.38_43del, p.13_14del	NR	Male	None	Term	NR

Hypocalvaria	Lung hypoplasia	Dialysis	Renal outcome	Age at last follow-up	Additional features
+	+	+	Ongoing PD dialysis for CKD V	3 years	
+	−	+	CKD IV at 3 months of age. Started on oral fludrocortisone at 18 months with stabilization of K levels. GFR 19 ml/min/1.73 m^2 at 3 years of age with standard conservative therapy for CKD. Low-normal blood pressure	3 years	
+	+	+	Continuous PD for first 6 months of life and cycling PD thereafter. Cadaveric renal transplantation at 4 years of age	4 years	Persistent PDA, FTT
+	−	−	At 1 month of age, oral fludrocortisone was started. Currently 2 years of age with normal BP and CKD II	2 years	Pneumoperitoneum from ileal perforations at 7 h after birth and underwent emergency ileostomy.
NR	NR	NR	Renal transplant at 3 years of age	NR	NR
NR	NR	+	CRD at 6 years	NR	NR
NR	NR	−	Normal renal function at 8 years of age	NR	NR
−	−	−	Deterioration to CKD III at 12 months of age. Fludrocortisone started at 13 months of age	14 months	PDA requiring ligation, anemia, necrotizing enterocolitis
+	−	−	At 17 months of age has CKD II and is on fludrocortisone and sodium bicarbonate supplementation. Normal blood pressure	17 months	Spontaneous gastric perforation on DOL 4, which was surgically treated without complications
NR	−	−	At age 4 months, eGFR was 27 ml/min/1.73m^2. At age 19 years, eGFR was 60 ml/min/1.73m^2	19 years	Anemia requiring RBC transfusions and erythropoietin; gout attack at 16 years
NR	−	−	Chronic renal failure discovered at age of 16 after episode of pyelonephritis. eGFR 40 ml/min/1.73m^2 at age of 19. Normal blood pressure	19 years	Anemia requiring erythropoietin
Large anterior fontanelle	NR		Initial spontaneous improvement in renal function with eGFR at age 4 years of 55 ml/min/1.73 m^2. Normal blood pressure.		Anemia requiring erythropoietin, mild developmental delay

TABLE 1 (Continued)

Patient	Variants	Consanguinity	Sex	Oligohydramnios	Gestational age at birth	Duration of post-natal anuria
This study: Patient 1	(1) c.38_43del, p.13_14del (2) c.1487G > A, p.R496Q	–	Female	33 weeks	33 weeks and 2 days	10 days
This study: Patient 2	(1) c.38_43del, p.13_14del (2) c.1487G > A, p.R496Q	–	Female	28 weeks and 4 days	33 weeks and 3 days	4 days
REN mutations						
Zingg-Schenk et al. (2008); Bacchetta et al. (2007)	(1) NR, p.S135Y (2) NR, p.S135Y	+	Female	Detected shortly before birth	35 weeks	2 days with anuria thereafter and resumption of diuresis at 2 months
AGT mutations						
Uematsu et al. (2006)	(1) c.604C > T, p.Q202X (2) c.1290delT, p.F397Lfs*25	–	Female	24 weeks, recurrent infusions of saline solutions in amniotic cavity	35 weeks	29 days
Gribouval et al. (2005) and Zingg-Schenk et al. (2008)	(1) c.1124G > A, p.R375Q (2) c.1124G > A, p.R375Q	+	Female	32 weeks	38 weeks	3 days
Hibino et al. (2015)	(1) c.1355delT, p.L452Cfs*2 (2) NR	–	Female	Prior to delivery	32 weeks	10 days
AGT1R mutations						
Demirgan et al. (2021): II-1	(1) c.376C > T, p.Arg126X (2) c.376C > T, p.Arg126X	+	Male	NR	39 weeks	NR
Demirgan et al. (2021): II–2	(1) c.376C > T, p.Arg126X (2) c.376C > T, p.Arg126X	+	Female	20 weeks	32 weeks	24 days

Abbreviations: NR, not reported; PD, peritoneal dialysis; sCr, serum creatinine; TOP, termination of pregnancy.

Hypocalvaria	Lung hypoplasia	Dialysis	Renal outcome	Age at last follow-up	Additional features
Large anterior fontanelle	–	–	At 2 months of age, sCr nadir of 52 μmol/L. Renal function thereafter slowly deteriorated to stage III-IV CKD at 8 months of age. Her renal function has remained stable since on conservative renal therapy	3 years 5 months	PDA, bicuspid aortic valve, anemia required erythropoietin
+	+	–	CKD stage IV at 2 months of age with sCr appearing to stabilize at 110 μmol/L. Kayexelate and sodium supplementation started at 2 months of age and fludrocortisone stopped at 4.5 months of age	11 months	PPHN, PDA requiring ligation, small apical VSD, recurrent NEC, anemia requiring erythropoietin, cow's milk protein intolerance; intermittent nystagmus with abnormal signal intensity in globi pallidi, optic radiations, central tegmental tracts currently being investigated for metabolic/ mitochondrial disease
+	–	+	PD stopped at 5 months of age. Renal cadaveric transplantation at 4.3 years of age with removal of native kidneys 20 days posttransplantation due to massive polyuria. Blood pressure in the low range of normal	10 years	Poor growth requiring GH therapy with some recovery
+	+	+	Chronic renal failure. Blood pressure in normal range	18 months	PDA
+	+	+	CKD III. At 2 years of age, sCr nadir of 62 μmol/L with increase thereafter to 188 μmol/L. Blood pressure in the low range of normal	15 years	Anemia requiring erythropoietin
+	+	+	At 2 years and 4 months, her creatinine clearance rate (CCr) had decreased to 72–88 ml/min/1.73 m^2	4 years	
+	–	–	Admitted to hospital at 5 months with noted impaired renal function (sCr 176 μmol/L). With medical management, sCr came down to 88 μmol/L. Between ages 1 and 22 years, sCr increased from 88 to 161 μmol/L. Requires sustained potassium-lowering therapy, oral phosphorus solution, and bicarbonate	22 years	Joint contractures at wrists and ankles. Central hypotonia. Failure to thrive. Hypophosphatemia.
Large fontanelle	–	+	sCr nadir of 35 μmol/L with slow progression up to 67 μmol/L at 6 years of age. Requires sustained potassium-lowering therapy, and bicarbonate	6 years	PDA. Centra hypotonia.

period. Though they had different clinical courses and received different treatments, neither required renal replacement therapy. Early treatment with both fludrocortisone and vasopressin in the neonatal period may be the treatments of choice for hypotension and anuria in this often refractory condition, though further studies are needed to clarify this. Characterization of all patients surviving the critical neonatal period suggests that key determinants of outcome appear to be: the presence of a non-truncating mutation, as well as contributions by modifier genes and/or neonatal treatment. A more thorough understanding of the factors affecting survival will help to guide prognostication and medical decision-making in this often lethal disease.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Planned and supervised this study: Gabrielle Weiler and Christine M. Armour. *Analyzed imaging and clinical reports*: Afrah Alrajhi and Brigitte Bonin. *Interpreted genetic data*: Joanna Lazier. *Performed clinical work*: Joanna Lazier and Sarah Lawrence. *Drafted the manuscript and all authors worked on the final version of the manuscript*: Krista M. Vincent. All the co-authors read and approved the final version of the manuscript.

ETHICAL STATEMENT

Informed patient consent was obtained. Institutional ethics permission was not required.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

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