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Case Report

A Case of Renal Tubular Dysgenesis with a Novel Mutation of *AGT* Gene

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Abstract Renal tubular dysgenesis is an autosomal recessive disorder caused by pathogenic variants in *REN, ACE, AGT* or *AGTR1* genes which encode components of the renin-angiotensin system. Clinical features included neonatal renal failure, pulmonary hypoplasia and refractory systemic hypotension. We report a premature neonate with typical clinical features of renal tubular dysgenesis resulting in early neonatal death. Molecular testing showed he has novel biallelic pathogenic variants in *AGT* gene. We performed literature review on this rare disease entity and summarised its clinical features and current management.

Key words *Arterial hypotension; Neonatal renal failure; Oligohydramnios sequence; Potter sequence; Renaltubular dysgenesis*

Introduction

Renal tubular dysgenesis (RTD) is a rare severe disorder of renal tubular development. Anuria in the fetal period would lead to oligohydramnios, Potter sequence, pulmonary hypoplasia, refractory hypotension and skull ossification defects. It is caused by pathogenic variants of genes that encoding different components of the renin-angiotensin system. We here reported a case of RTD in a preterm neonate presenting with multi-organ failure and typical phenotypic manifestations.

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Case

A premature neonate was born at 32 weeks by emergency Caesarean section for pre-labour, prolonged rupture of membrane and thick meconium stained liquor. Antenatal ultrasonography examination showed severe oligohydramnios. The birth weight was 1890 gram (50th centile), body length and head circumference were at 50th centile and 25th centile respectively. He had multiple craniofacial dysmorphic features including large anterior fontanelle (sized 65 mm x 35 mm), widened sutures, squashed facial profile, hypertelorism, anteverted nostrils, epicanthic fold, low-set ears and redundant skin fold at posterior neck (Figure 1). He had generalised hypotonia with edematous extremities, adducted and dorsiflexed wrists. Features were suggestive of Potter sequence. He was the mother's first pregnancy from non-consanguineous Chinese couple. The family history was non-contributory that there was no family history of any renal or syndromal diseases.

He had respiratory distress syndrome immediately after birth that was refractory to surfactant treatment and high frequency oscillatory ventilation. His severe pulmonary hypoplasia and pulmonary hypertension did not respond to inhaled nitric oxide at maximum concentration of 20 parts per million. His respiratory condition was in downhill course despite maximal intensive care supports. He was anuric since birth. Renal ultrasound on day two of life was

normal with no focal abnormal parenchymal echogenicity. His renal function and electrolytes continued to deteriorate with maximum creatinine of 205 umol/L and hyperkalemia of 6.7 mmol/L that was not corrected by dextrose-insulin infusion and sodium resonium. After discussion with paediatric nephrologists, renal replacement therapy was not recommended due to prematurity and grave prognosis with multi-organ failure. Because of grave prognosis, redirection to palliative care was agreed by parents. He succumbed at 61.5 hours of life. His Potter's facies and early signs of renal failure with anuria led to the suspicion of RTD. With consent by parents, post mortem examination and potential genetic studies were performed afterwards.

Post-mortem Findings

External examination concurred with clinical findings. On internal examination, the left lung weighed 14 g and the right lung weighed 17 g. Combined lung weight to body weight ratio was compatible with lung hypoplasia. The genitourinary system showed no gross abnormality. Histologically, the lung tissue showed mean radial alveolar count less than 4 (decreased) and the renal cortex showed crowded glomeruli. Immunohistochemically, the renal tubules only expressed epithelial membrane antigen and were negative for CD 10, indicative of lacking in proximal tubular differentiation (Figure 2). The muscle walls of the interlobular arteries and arterioles were thickened and the vessels were disorganised. Overall features were consistent with renal tubular dysgenesis and possible pulmonary hypoplasia.

Mutation Analysis

Whole exome sequencing was performed. Compound heterozygous pathogenic variants in *AGT* gene was detected in the patient. Each of the variant was inherited from each parent.

Discussion

RTD is a severe disease affecting renal tubular development in-utero. The pathology is the absence or low numbers of differentiated proximal tubules, leading to a histological appearance of closely packed glomeruli.[1] The amniotic fluid volume could be normal prior to the 22nd week of gestation. Oligohydramnios typically occurs by late second trimester.[2,3]

Currently at least four genes are found to be associated with RTD. From a case review on mutation spectrum in 48 unrelated families with autosomal recessive renal tubular dysgenesis, pathogenic variants were identified as *ACE* (64.4%), *REN* (20%), *AGTR1* (8.3%) and *AGT* (7.3%).[4] All are inherited in autosomal recessive (AR) manner. The variant c.1087C>T (p.Gln363*) in this case has been reported in ClinVar database [RCV000492929.1] but whole *AGT* gene deletion has not been reported in Human Gene Mutation Database professional (BiobaseQIAGEN),

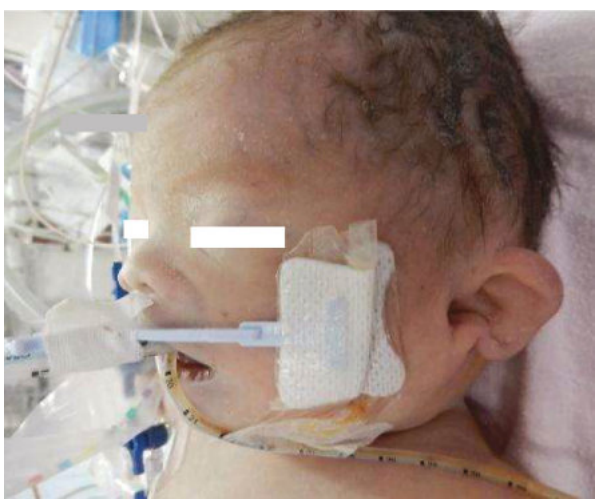

Figure 1 Low nasal bridge, receding chin, posteriorly rotated and low set ears, redundant skin fold at posterior neck.

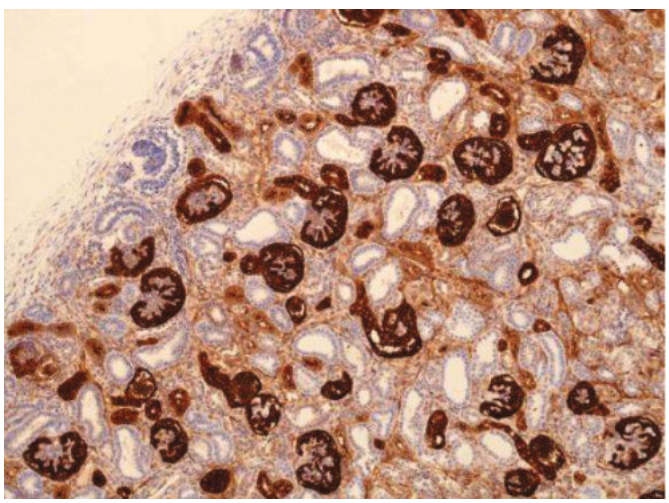

Figure 2 Staining with CD10 - showing absence of proximal tubules, only glomeruli are highlighted (10x magnification power).

ClinVar ExAC and gnomAD database. So it is the first case of whole *AGT* gene deletion related RTD case in the literature. RTD is a rare condition with unknown prevalence. It was first described by Allanson[5] in 1983. Since then over 100 cases of RTD with or without molecular genetic diagnosis had been reported. Previous reports described AR-RTD as a lethal disease, but there were a few cases reported in the literature with survival beyond neonatal period.[6,7] Factors associated with survival remain unknown.

There is no known genotype and phenotype correlation.[4] From literature search, the six cases (two with *AGT* gene mutation, three with *ACE* gene mutation, one with *REN* gene mutation) who survived through neonatal period suffered from chronic renal failure requiring long term dialysis.[6] The comparison of two survival cases in literature with our case is summarised in Table 1.

The main diagnostic features of RTD are from renal histology. The morphological hallmark is the poorly differentiated tubules in renal cortex with absence or low number of proximal renal tubules. Normal renal proximal tubules have brush border and are stained with antibodies to proteins (CD10, CD15 or ACE). In RTD, there is absence of staining of proximal renal tubules. Instead, most tubular sections are labeled with anti-epithelial membrane antigen antibodies, normally a marker of distal tubules and collecting ducts. Glomeruli are normal, slightly retracted, or enlarged as a result of mesangial expansion. They appear to be closely packed because of the reduced number of tubular sections. A constant feature of the disease, demonstrated by a smooth muscle actin labeling, is the marked thickening and disorganisation of the muscular wall of interlobular and preglomerular arteries, also focally present in arcuate arteries.[8]

No major kidney malformations can be seen by renal ultrasonography. Kidneys are usually normal or slightly enlarged, with or without discrete hyperechogenicity or loss of corticomedullary differentiation.

Conclusion

Autosomal recessive RTD is a severe disease of renal tubular development. The diagnosis should be considered if there is late second trimester oligohydramnios, postnatal anuria with early renal failure, respiratory failure with difficult ventilation, Potter sequence features, unexplained refractory systemic hypotension and/or normal ultrasonography findings of urinary system. Most cases had intrauterine death or died shortly after birth. The diagnosis can be confirmed by analysis of renal histology and exclusion of other possible causes of secondary renal tubular dysgenesis. Genetic counseling and genetic studies should be done. Early recognition of the disease is important, as this aids with genetic and histology tests, also with identification of genetic defect, it may be beneficial for prenatal diagnosis or preimplantation genetic diagnosis in subsequent pregnancy.

Declaration of Interest

There are no conflicts of interest to declare.

Table 1 Comparison of index case with survival cases[7] of RTD with *AGT* gene variants

Reference	Uematsu et al[9]	Zingg-Schenk et al[10]	Present case
Gender	Female	Female	Female
Gestation (weeks)	35	38	32
Gene	*AGT*	*AGT*	*AGT*
Pathogenic variant 1	p.Gln202*	p.Arg375Gln	p.GIn363*
Pathogenic variant 2	p.Phe397Leufs*25	p.Arg375Gln	whole AGT gene deletion
Renal outcomes	CKD	CKD III	Death
Age at last follow-up	18 months	15 years	N/A

CKD: chronic kidney disease; N/A: not available.

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