Renal Tubular Dysgenesis Associated with Compound Heterozygous ACE Mutations

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Abstract: Inherited renal tubular dysgenesis (RTD), a rare, autosomal recessive disorder is caused by mutations in the genes encoding components of the renin-angiotensin pathway: angiotensinogen (AGT), renin (REN), angiotensin-converting enzyme (ACE), and angiotensin II receptor type 1 (AGTR1). It characterized by the absence or poor development of renal tubules, and associated with oligohydramnios, Potter sequence and neonatal death due to renal or respiratory failure. We report a family with two mutations in the coding region of the ACE gene: a nonsense mutation in exon 4 (c.538C>T) and a frameshift deletion at nucleotide 3073 and nucleotide 3074 in exon 20 (c.3073_3074delTC). The mutations were in the compound heterozygous state causing disease, because each parent had their own mutation.

Keywords: Genetic counseling; Oligohydramnios; Prenatal diagnosis

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1 Introduction

Renal tubular dysgenesis (RTD) is a severe disorder of renal tubular development characterized by fetal anuria, oligohydramnios, and severe postnatal hypotension. Genetic forms have an autosomal recessive inheritance and are caused by mutations in genes encoding key components of renin-angiotensin system (RAS): angiotensinogen (AGT), rennin (REN), angiotensin-converting enzyme (ACE), and angiotensin II receptor type 1 (AGTR1)[1]. Except for a few cases, the prognosis has been thought to be universally poor, with patients dying either in utero or shortly after birth[2-4].

Autosomal recessive RTD, usually regarded as a rare disorder, may be more frequent than previously thought. It might be easily over-looked in the absence of detailed pathological examination of the renal parenchyma[5]. Antenatal ultrasounds generally show normal kidney structure, but anuria. Early identification or consideration of this severe disease through sonography is essential to allow for genetic counseling and early prenatal diagnosis[6].

The RAS mutations of this disease are genetically heterogeneous. There are different types of mutations which have been observed distributed in four genes of the RAS. Angiotensin II (ANG II) is the final product of the activation of the RAS cascade. However, all these mutations affect the production (AGT, REN, ACE mutations) or the efficacy (AGTR1 mutations) of ANG II[6][7]. Most mutations (64.6%) affect the ACE gene, the largest gene of the RAS. Whatever the type of ACE mutation, renal renin expression was strongly increased. It’s probably the result of the absence of functional ACE, which lead to the ANG II production and the negative control on renin production[8]. This paper introduced a family, which carried ACE mutations in the compound heterozygous state.

2 Case report

The first affected pregnancy happened in 2012, and the mother almost had no prenatal tests. Though fetal kidneys and bladder appeared normal on ultrasonographic examination, oligohydramnios without premature rupture of the membranes (PROM) was discovered at 32 weeks gestation. A few
days later, the mother had a spontaneous preterm delivery, and the baby died just a day after birth due to respiratory failure (no autopsy was performed). A year later, she conceived a second pregnancy. At 20 weeks gestation, the fetus was diagnosed with oligohydramnios by ultrasound scan. The couple accepted the amniocentesis, and the chromosomes of the fetus were normal (46, XX or XY). However, in view of the fetal poor prognosis, this young couple decided to terminate the second pregnancy. The termination of pregnancy was performed with Ethacridine lactate, but autopsy wasn’t carried out. After induced labor, the parents tested their own chromosomes, and both of them were normal. In their third pregnancy in 2015, fetal ultrasound at 20 weeks gestation showed severe oligohydramnios, and suspected adelomorphic polycystic kidney. Given the possible poor prognosis of fetus, the couple once again chose pregnancy termination with Ethacridine lactate. Nevertheless, the fetal monogenic test of polycystic kidney and hepatic disease 1 (PKHD1) gene had no special finds.

During the fourth pregnancy, the couple accepted regular antenatal care. At 23 weeks gestation, when ultrasound detected oligohydramnios without PROM, the pregnant mother was transferred to our hospital. Because of a gradual and repeat decrease in amniotic fluid, the supplementary infusions of saline solution into the amniotic cavity were performed several times during the hospitalization. Unfortunately, when 28 weeks gestation, the fetal ultrasound showed no more amniotic fluid, neither image of bladder. The family requested termination of pregnancy with double-balloon catheters. A 1090 g girl was born. Her Apgar scores were 8 at 1 min, 9 at 5 min and 10 at 10 min. The neonate was admitted to an intensive care unit due to severe dyspnea, cyanosis and premature. However, she had anuria from beginning to end, and died on the second day caused by respiratory failure. Autopsy was carried up within 4 hours of the infant’s death, and the histopathological examination of her renal tissue sample confirmed dysplasia of renal tubule and collecting duct (Figure 1). The histologic findings were consistent with RTD. The couple wished to help determine the molecular cause of the disease. After obtaining written informed consent from the couple, we performed a gene analysis of inherited kidney disease. Blood samples from the proband and both parents were obtained for next generation sequencing of a targeted panel of genes. No chromosomal abnormalities were detected. Subsequently, the sequencing analysis revealed two suspected pathogenic mutations in the coding region of ACE gene on chromosome 17 that included exon4: c.538C>T (p.Arg180*) and exon20: c.3073_3074delITC (p.Ser1027Tyrfs*14) (Figure 2). c.538C>T (p.Arg180*) is a nonsense mutation which results in the early termination of the protein encoded by this gene at the 180th position of amino acid. The normal protein is compose of 1306 amino acids. c.3073_3074delITC (p.Ser1027Tyrfs*14) is a frameshift mutation which leads to the mutation of serine at the 1027th position of the protein encoded by this gene into tyrosine and the early termination at the 1040th position of amino acid. Therefore, it may result in truncated protein or degradation. The two above mutations haven’t been recorded in the normal population genome sequencing database, and neither of them has been reported in other literatures. However, after these protein termination sites, there are some pathogenic mutations which have been reported. Therefore, the two mutations of ACE gene may work together in the compound heterozygous state to cause RTD in offspring. The parents are both heterozygous carriers of one of this two ACE mutations. The mother carries c.538C>T (p.Arg180*), and the father carries c.3073_3074delITC (p.Ser1027Tyrfs*14). The couple had no history of consanguinity, and the mother didn’t exposure to angiotensin converting enzyme inhibitor or non-steroidal anti-inflammatory drugs. Nevertheless, given the lack of DNA samples, we couldn’t prove that previous miscarriages in this family were also due to compound heterozygous ACE mutations in the affected fetuses. In 2018, after finding the disease gene, the couple decided to accept in vitro fertilization (IVF). Through the preimplantation genetic testing (PGT), the couple got eight embryos screened for ACE gene. One of them was absolutely normal, three of them had the same mutation with the mother, and the rest four had the same mutation with the father. The absolute normal embryo was given priority in first IVF cycle, however, it failed in implantation. Then, in the second IVF cycle, one embryo with the same nonsense mutation of the mother was chosen. In February 2019, a baby girl was born at 38 weeks and 5 days of gestation by a normal spontaneous delivery.
Birth weight was 3000 g, birth height was 50 cm, and Apgar scores were 10 at 1 min, 10 at 5 min and 10 at 10 min. The neonate carried the same mutation with her mother, and her clinical phenotype was also absolutely normal like her mother. During the most recent follow-up, she was growing well. The couple planned to have their second child under IVF in the next two years.

3 Discussion

Recognition of RTD is very important. However, it’s challenging to diagnose RTD by prenatal ultrasound. Therefore, the diagnosis is usually only established at carrying out an autopsy in fetus or infants dying with the features of oligohydramnios\(^9\). The affected kidneys are usually of normal size, but may be enlarged. The characteristic microscopic finding in RTD is the absence or incomplete differentiation of the proximal convoluted tubules. The glomeruli appear crowded because of the deficient tubular development\(^10\). The etiology of this altered renal morphogenesis has been divided into primary and secondary causes. Primary RTD is due to inherited autosomal recessive genetic mutations in a sporadic or familial form affecting the RAS gene. The final result of these mutations is the absence of ANG II, which is necessary for normal renal growth and development, especially the proximal renal tubules\(^8\)\(^11\). Secondary RTD is caused by the use of an angiotensin-converting enzyme inhibitor to treat hypertension in pregnant women, which may result in a similar clinical picture\(^12\).

The proposed causal mechanism of RTD is chronic renal hypoperfusion or incomplete ischemia commonly leading to renin upregulation, exacerbating the decreased glomerular perfusion, and subsequently resulting in poor development of the proximal renal tubules\(^13\). Without the development of proximal renal tubules, there is a persistent reduction of amniotic fluid volume, and eventually, a lack of urine production. Afterwards, the symptoms caused by oligohydramnios may present gradually, such as Potter sequence with compressed faces (low-set ears, flattened nose), limb deformities (clubfeet), pulmonary hypoplasia, and skull ossification defects\(^9\). The prognosis of RTD is generally poor and characterized by either intrauterine fetal demise or neonatal death caused by anuria, refractory hypotension, and respiratory failure. There were cases reported that few survivors were alive, but almost required frequently dialysis for their chronic or end-stage renal disease\(^11\).

The production and disposal of amniotic fluid is a dynamic process. Alteration in specific fetal, maternal, and placental factors may affect the amniotic fluid volume. Unexplained oligohydramnios, found on prenatal ultrasound examination, is probably the single most important diagnostic marker for intrauterine detection\(^14\). Once oligohydramnios is diagnosed, a careful assessment of both patients (mother and fetus) is necessary\(^11\). In RTD cases, oligohydramnios is detected by ultrasound typically around or before 20 weeks gestation. After the more common reasons for second trimester oligohydramnios, like drug or PROM, have been excluded, fetal disease states that may affect renal function should be considered\(^10\). Associated congenital malformations are depended on the presence and duration of oligohydramnios. If the in utero exposure to oligohydramnios is relatively short, pulmonary hypoplasia may not occur\(^15\).

In primary RTD cases, the ACE mutations are the most frequent of the mutations in the RAS genes\(^8\). Most of ACE mutations are presented in the homozygous state, but some are presented in the compound heterozygous state, like in our case. The autosomal recessive inheritance form of RTD has important implications for subsequent prenatal counseling. In our case, although we paid a lot of attentions and active treatments to the proband, we still couldn’t help her to be alive at the end. Her kidney autopsy suggested RTD, and we found the suspected pathogenic mutations of RTD by the sequencing analysis. There were two mutations in the coding region of ACE on her chromosome 17, one was exon4: c.538C>T (p.Arg180*), the other was exon20: c.3073_3074delTC (p.Ser1027Tyrfs*14). The two mutations of ACE gene leaded to RTD in the form of compound heterozygotes, which respectively came from her parents. Both the parents were heterozygote genotype of one of the two mutations. The mother carries c.538C>T (p.Arg180*), and the father carries c.3073_3074delTC (p.Ser1027Tyrfs*14). At last, we used the PGT to screen out the inherited mutations and help the parents get a healthy baby.

Based on the role of the RAS during kidney
development and the RAS gene expression in the RTD phenotype, we may find that more different forms of genetic defects in the RAS could be the cause of the RTD disease. However, in fact, it’s not easy to find out the definite cause and treat it. In our case, the couple took almost 7 years to get a healthy baby. During their long and difficult diagnosis and treatment process, we summarize three important clinical steps. First is to find out the disease. The proband is the key. Before the couple came to our hospital, they already had three times of adverse pregnancy with oligohydramnios. They took amniocentesis, tested their own chromosomes, suspected polycystic kidney, and had the PKHD1 monogenic test. However, they found out nothing. Until the fourth pregnancy, the diagnosis was finally confirmed as RDT through the proband’s autopsy. The recognition of RTD is helpful to clear the next steps in genetic counseling and help find the way to avoid it happening again. Second is to find out the definite cause of the disease. The phenotypes of genetic and secondary RTD are similar, and all components of the RAS are expressed in kidney development\(^8\). So, the molecular confirmation of RTD is important to enable accurate prenatal diagnosis. Through the genetic testing for hereditary kidney disease, we found out that two ACE mutations expressed in the compound heterozygous state and leaded to RTD. One of them is a nonsense mutation from mother, and the other is a frameshift mutation from father. Third is to screen out the disease causing genes. Due to the PGD technique, we could know the exact carrying mutation(s) of each embryo, and chose the better one for IVF to prevent the disease from presenting in offsprings.

Until now, there are no effective intrauterine interventions for RTD. Therefore, the accurate genetic counseling and prenatal diagnosis are important in clinic, which are based on recognizing the RTD disease, clearing the cause, and avoiding the pathogenic factor expression. In our case, we found a new form of compound heterozygous ACE mutations resulting in RDT, but we don’t know its specific pathogenic mechanism. However, we still hope that our case could be helpful to provide an efficient clinical thought for RTD prenatal counseling.

Further research should be oriented more toward the relationship between the different RAS gene mutation forms and the RAS protein expressions, and the pathogenic mode analyses of compound heterozygous mutations in RAS.

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We express our appreciation to the parents who accepted the publication of their medical history in the hope that they might get another healthy child soon.

5 Disclosure

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Figure 1. Renal pathology staining of the proband. Glomeruli crowded together because of the reduced number of tubular sections. Absence of recognizable proximal tubules.

Figure 2. (A) The proband has a nonsense mutation in ACE (c.538C>T (p.Arg180*)) which present heterozygously in mother’s DNA.
Figure 2. (B) The proband has a frameshift mutation in ACE (c.3073_3074delTC (p.Ser1027Tyrfs*14)) which present heterozygously in father’s DNA.

References


