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Case Report

Coexistence of Autosomal Dominant Polycystic Kidney Disease and Hereditary Distal Renal Tubular Acidosis in a Child: A Very Rare Case Report and Literature Review

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited cystic kidney disease that exhibits a variety of clinical manifestations due to multiple mutation types and a variety of penetration powers.

Renal tubular acidosis (RTA) is a group of transport defects secondary to reduced proximal tubular reabsorption of bicarbonate (HCO3-), the distal secretion of protons (hydrogen ion, H+), or both, resulting in impaired capacity for net acid excretion and persistent hyperchloremic metabolic acidosis with a normal anion gap (AG) 12±2 mmol/L. The above conditions are either secondary to other causes or primary, with or without known genetic defects.

ADPKD rarely can cause RTA, however, the potential heritage interactions of ADPKD and distal renal tubular acidosis (dRTA) mutations have not yet been identified. As far as we know, dRTA and ADPKD have not been reported in the same patient. Here we present a 4-year-old patient who was diagnosed with ADPKD with *PKD1* (NM_001009944.3): c.11014C>T (p.Arg3672Trp) heterozygous and type1 RTA (dRTA) with *SLC4A1* (NM_00342.4): c.1765C>T (p.Arg589Cys) heterozygous mutation, but no sign of cystic kidney disease in his mother despite having the same *PKD1* mutation. His father had an incomplete form of dRTA presented with a SLC4A1 mutation (with no metabolic acidosis, a urinary pH of 7, and a history of recurrent kidney stones). The child is being treated with 5–8 mEq/kg of citrate, and cyst growth seems to have stopped following a 2-year follow-up. The case highlights the importance of "two hits" or the coexistence of different abnormalities in the development of cystic formation in ADPKD.

Keywords: Polycystic kidney disease, *PKD1*, *PKD2*, *SLC4A1*, renal tubular acidosis, mutation

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is mainly caused by mutations in *PKD1* (80–85%) and *PKD2* (15–20%), which encode Polycystin 1 (PC1) and Polycystin 2 (PC2), respectively (1-3). The incidence of de novo ADPKD sequence variants is about 10% in affected cases (4). It affects around 1 in 1,000 live births (5-6). The disease is characterized by the formation of cysts in various locations in the kidneys, occurs in only a portion of the tubules in the nephrons, but mostly in the distal regions. Cysts development and growth usually start in utero and progress, but kidney function is typically conserved until the age of 30–40 years (1-6). The progressive development and growth of numerous bilateral kidney cysts, result in urine concentration defects, hypertension, acute and chronic pain, kidney stones, hematuria, urinary tract infections, and, most importantly, kidney function loss (7). ADPKD is usually an adult-onset disease in which approximately 70% of patients progress to kidney failure. Up to now, no interventions were shown to slow the rate of disease progression in ADPKD. The treatment of ADPKD has therefore been symptomatic, with the aim of reducing

morbidity and mortality associated with disease manifestations.

Renal tubular acidosis (RTA) is hyperchloremic metabolic acidosis with a normal anion gap (AG):12±2 mmol/L. Distal RTA (dRTA) can be secondary related to the causes such as obstructive uropathy, reflux nephropathy and chronic tubulointerstitial nephritis or primary with or without known genetic defects. Hereditary dRTA is a rare genetic disorder (8). The genetic cause is determined in only 70%–80% of patients (8-10). Three different transport proteins have been found as causes of dRTA; the B1/ATP6V1B1, a4/ATP6V0A4 subunits of the vacuolar-type H+-ATPase (H+-ATPase), and chloride–bicarbonate exchanger AE1/SLC4A1 band 3 (11,12). While the autosomal dominant form of dRTA is related to AE1 mutation, the autosomal recessive form is associated with mutations in genes *ATP6V1B1*, *ATP6V0A4*, and *SLC4A1*, which encode subunits a4 and B1 of V-ATPase, and the AE1 bicarbonate/chloride exchanger respectively (13).

In AE1 protein; the gene that encodes the Cl−/HCO3− exchanger, mutations usually present as dominant dRTA, but a recessive pattern has been recently described (13-16). Several studies have shown trafficking defects in the mutant protein rather than the lack of function as the major mechanism underlying the pathogenesis of dRTA from AE1 mutations. Hereditary dRTA typically presents in infancy, however, especially the appearance of dRTA, in individuals with autosomal dominant and recessive form of *SLC4A1* can be later according to other types of genetic defects (*ATP6V1B1* and *ATP6V0A4*) (11-15).

Dominant AE1 mutation can exhibit a complete or incomplete dRTA clinical transmission (14,15). The clinical variant of dRTA that presents with inadequate urinary acidification without spontaneous metabolic acidosis is termed incomplete dRTA (idRTA). Failure to acidify urinary pH <5.3 in the NH4Cl load was considered diagnostic for idRTA. These conditions significantly impact the quality of life in untreated individuals and can lead to growth failure, osteoporosis, rickets, and even kidney failure. Moreover, 8.33% of the patients presented with tubular proteinuria (urine protein <1 g/day) and low-molecular-weight proteinuria on urine protein electrophoresis. Metabolic acidosis is mild in *SLC4A1* mutations, and all cases with hereditary dRTA can develop nephrocalcinosis. Children with dRTA should be followed-up long-term for hearing ability, kidney function, and growth (17).

The primary objectives of dRTA treatment are correction of the metabolic acidosis and the avoidance of disease-related complications. Alkali in the form of a mixture of sodium and potassium citrate salts is recommended to be administered to maintain normal serum bicarbonate. The amount of alkali needed usually decreases with age. Infants require as much as 5–8 mEq/kg of citrate or HCO3-, whereas adults require only about 0.5–1 mEq/kg. Potassium supplementation is needed in the majority of patients with hypokalemic hereditary distal RTA.

CASE

TA 50-month male child suffering from dysuria, fever, and suprapubic pain was bought to the pediatric nephrology polyclinic. He was born from unrelated parents and on healthy until he had the urinary tract infection episodes onset 1 year ago. The patient's laboratory findings demonstrated mild proteinuria, leukocyturia, and a slightly increased CRP level. The whole blood count and the remaining biochemical parameters were found in normal ranges. However, urine pH was 5.5 and in an arterial blood gas analysis, pH; 7.26, K+; 2.42 mEq/L, HCO3-; 15 mmol/L were found. 24 hours urine collection revealed 7 mg/kg/day (>4 mg/kg/day) hypercalciuria, proteinuria and beta2 microglobulinuria in normal ranges. The anion gap (AG) was calculated as 13 mmol/L (AG:12±2 mmol/L). Considering all clinical and laboratory findings, the patient was diagnosed with dRTA and he was evaluated in terms of primary and secondary dRTA.

The kidney USG indicated anechoic corticopelvic cystic lesions in both kidneys, which cannot be clearly distinguished from the focal sequelae of caliectatic appearances. The abdominal and brain computed tomography (CT) also showed bilateral multiple kidney

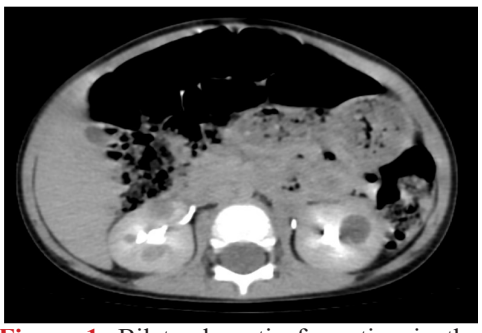

Figure 1. Bilateral cystic formation in the kidneys axial computed tomography image (no kidney stone)

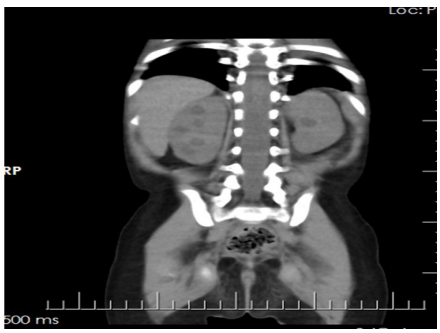

Figure 2. Bilateral cystic formation in the kidneys coronal computed tomography image (no kidney stone)

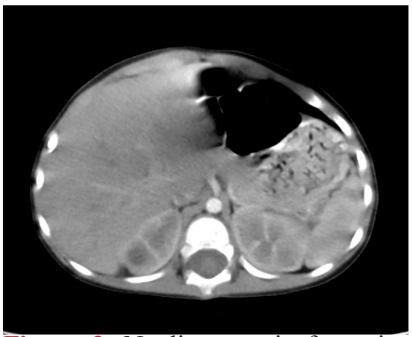

Figure 3. No liver cystic formation in the child's computed tomography images

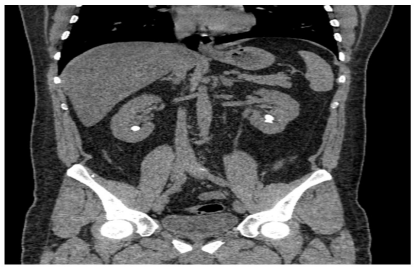

Figure 4. Bilateral kidney stones (Father's computed tomography image)

cystic formations with no intrinsic and peripheral contrast enhancement (the maximum sized cyst was in 12X8.5 mm in the right kidney lower pole) (**Figure 1-3**), but there was no sign of liver, brain, or pancreatic ductal cysts. The child has large cortical and corticomedullary cysts, considering the clinical view and the findings are suggestive of *PKD1* as the cause of cystic formation.

The patient was evaluated for PKD and primary known genetic defects of dRTA with whole genome sequencing analyzes. Both dRTA and ADPKD, genetically mutant have been reported in the child; with a Polycystin-1 (*PKD1*) pArg3672Trp heterozygous and type 1 RTA (dRTA) *SLC4A1* pArg 589Cys heterozygous mutation. The clinical features and the result of genetic analysis suggest that the child has a hereditary dRTA and ADPKD1.

The child was evaluated for hearing abilities, growth deficiency, rickets, and hereditary hemolytic anemia (a very rare complication), and was found negative for those. The patient was diagnosed that he has ADPKD and dRTA with no extra renal manifestations. The patient was put on potassium citrate salts treatment to correction of hypokalemia and metabolic acidosis, monitoring with blood $HCO3^-$ and urinary PH, and calcium level.

Meanwhile, the parents were evaluated for cystic kidney disease and RTA. Mother had no clinical signs of ADPKD and RTA, however, the father had a history of recurrent kidney stones without kidney cysts and metabolic acidosis (**Figure 4**). The genetic analysis panel of mother and father show that mother has *PKD1* (NM_001009944.3): c.11014C>T (p.Arg3672Trp) heterozygous and father has *SLC4A1* (NM_00342.4): c.1765C>T (p.Arg589Cys) heterozygous mutation.

Genotypic and phenotypic characteristics of patient, mother and father

- The child: The child has ADPKD with *PKD1* heterozygous mutations, and exhibits diffuse cystic formation in both kidneys. The child also has a hereditary dRTA related to the *SLC4A1* gene mutation.
- The mother (40 years old): Despite carrying the same mutations of the patient, she has no clinical sign of the ADPKD. She had no history of kidney stones and also the *SLC4A1* gene mutation is negative.
- The father (45 years old): The father has *SLC4A1* gene heterozygous mutation as the same of patient has, related to the hereditary dRTA. He has a history of kidney stones without metabolic acidosis, but with a failure to maximally lower urine pH (urinary pH was 7) (**Figure 4**). The father presentation reflects the variant of type of dRTA that is termed idRTA.

DISCUSSION

Although ADPDK is considered an adult disease, the phenotypic spectrum of ADPKD ranges from in utero onset to adequate kidney function at old age. About 2% of ADPKD cases occur in early childhood, and the severity of the disease makes it difficult to distinguish from autosomal recessive polycystic kidney disease. ADPKD has various presentation types due to concomitant different penetration poverty of the mutations. Similar genetically mutations may express varying severity of disease in members of the same family. The mechanism by which a heterozygous mutation results in cyst development is controversial. The pathogenesis underlying the polycystic kidney disease phenotypes is still unclear. All these variability's suggest that PKD mutations alone may not be sufficient for cyst development and support a two hit hypothesis, due to possible complex interaction of the affected gene with other factors (18,19). In addition to primary cilia defects, PKD cells exhibit many other cellular aberrations (dedifferentiation, increased proliferation and apoptosis, polarity defects, and altered gene expression) proposed to be associated with cystogenesis and/or cyst progression (20,21).

The "two hit' has been reported which they thought to be effective in cyst formation in ADPKD (18,19). Schlevogt et al. reported that the mutant *SEC61A1* results in enhanced proteasomal degradation and impairs biosynthesis of PC2 (22). Similarly, in our case, the coexistence of dRTA may promote the early and diffuse cystic formation.

To date, whole genome sequencing or next-generation sequencing of long polychain reaction products, and somatic mutations of PKD genes can be detected in >90% of kidney cysts (23). Studies reported that the cyst formations of disease is dosage of functional *PKD1* protein dependent, where incompletely penetrant alleles influence disease severity (24,25). Additionally, a dose of functional polycystin-1 that falls below a critical threshold may be important to promote cyst formation (24,25). In this case, the mother has the same heterozygous PKD mutation (NM_001009944.3): c.11014C>T (p.Arg3672Trp), however, in contrast to the child, she had no cystic formation in her kidneys at the age of 40 years. It supports the previous data arguing that *PKD1* and *PKD2* gene mutations are not solely enough to develop cyst formation. We could not study

the RNA expression of PC1, in the mother's urine, or the expression of RNA of mutant *PKD1*, in immortalized urine sediment cells. So it can be speculated that the mother functional PC1 level expected to be normal or high than critical threshold.

AE1 mutations causing dRTA were initially described by Bruce et al., and later by Karet et al. (13-16,26). AE1 mutations are classified as autosomal dominant and recessive dRTA (26,27). AE1 protein is encoded by the *SLC4A1* gene in humans and present in the basolateral face of α-intercalated cells of the collecting ducts of the nephron. Since AE1 is abundantly present on erythrocytes and helps maintain cytoskeleton structure as well as ion transport, hemolytic anemia (HA) may be seen in some types of hereditary dRTA associated with AE1 mutations. In cases with dominant AE1 mutations, erythrocytes are capable to maintain chloride/bicarbonate traffic (in contrast to α-intercalated cells), thus membrane functions remain intact and this explains the absence of HA. The only AD AE1 mutation causing HA with dRTA has been reported with A858D mutation from Malaysia and India (28,29). Most autosomal recessive AE1 mutations reported so far have been seen associated with HA as a result of Southeast Asia ovalocytosis or hemolytic spherocytosis (30,31). HA however, is not always present in autosomal recessive AE1 mutations. In this report, the child has dRTA with *SLC4A1* (NM_00342.4): c.1765C>T (p.Arg589Cys) heterozygous mutation but no other extra renal manifestation such as hemolytic anemia.

Heterozygous AE1 mutation can exhibit a complete or idRTA clinical transmission (18). Bruce et al. reported idRTA in 8 of 18 patients and over the follow-ups of 10 years, and 2 of 8 developed acidosis (26). Incomplete dRTA was also described in the father of 2 affected children from Brazil (32). Then after, *AD A888L* mutation was found in this family. The incomplete form of dRTA, like complete dRTA, presents with failure to maximally lower urine pH, but blood pH and plasma bicarbonate remain normal. In our case, *SLC4A1* heterozygous mutation has been described in the father; with low urine acidification capacity and kidney stones, and no metabolic acidosis. Given all of this, the father has idRTA and according to our knowledge, this is the first case from Turkey.

Genetic mutations responsible for inherited diseases often alter the structure of transcribed mRNA and the resulting protein, inducing instability in both. However, in our patient, we could not measure the mRNA activities.

CONCLUSION

This case underscores the diverse phenotypic manifestations of genetic mutations, as demonstrated by the child's presentation of both ADPKD and dRTA, while the mother carries the same *PKD1* mutation without exhibiting symptoms of ADPKD. The genetic analysis also revealed the father's heterozygous mutation in *SLC4A1*, leading to idRTA, further highlighting the variability in disease expression within families. The pathogenesis of ADPKD and dRTA involves intricate molecular mechanisms, including potential interactions between mutated genes and other cellular factors. The "two-hit" hypothesis, where secondary mutations or environmental factors exacerbate disease progression, may contribute to the early and diffuse cystic formation observed in this case. Moreover, in adults, even in the absence of metabolic acidosis, genetic testing should be considered if there is insufficient urine acidification capacity along with a history of kidney stones.

Treatment strategies for these conditions focus on managing symptoms and complications, such as metabolic acidosis and electrolyte imbalances, to improve patient outcomes and quality of life. The utilization of alkali therapy for correcting metabolic acidosis in dRTA and close monitoring of kidney function are crucial aspects of patient management.

DECLARATIONS

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