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CASE REPORT

Chronic kidney disease in a 7-year-old boy with an ultra-rare *REN* gene mutation. A case report and the literature review

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ABSTRACT

Chronic kidney disease (CKD) is a global health concern, particularly challenging in the pediatric population. The role of genetic factors, especially monogenic diseases that may account for up to 20% of progressive CKD cases, is often underestimated. This article presents the case of a 7-year-old boy with an ultra-rare REN gene mutation leading to autosomal dominant tubulointerstitial kidney disease (ADTKD). The child exhibited early-onset symptoms, including anemia resistant to conventional treatment, renal acidosis, hyperkalemia, growth impairment, and progressive renal dysfunction. The absence of characteristic findings on renal ultrasound and bland urine sediment raised the suspicion of ADTKD. Genetic testing confirmed a c. 77C > T mutation in the REN gene in both the patient and his 35-year-old mother, being currently in the initial phase of stage 4 CKD. Early diagnosis of ADTKD-REN is crucial for clinical management, prevention of serious complications, and targeted family counseling.

KEY WORDS:
chronic kidney disease, renin, autosomal dominant tubulointerstitial kidney disease, ultra-rare disease.

INTRODUCTION

Chronic kidney disease (CKD), defined as a progressive loss of renal function and assessed by a decline in glomerular filtration rate (GFR), is a major cause of morbidity worldwide. In the pediatric population, the etiology of CKD in early childhood is primarily attributed to congenital structural anomalies of the kidney and urinary tract, such as vesicoureteral reflux, renal dysplasia, and obstructive uropathy [1]. As children age, the role of immunological factors becomes more pronounced, and glomerulopathies emerge as the leading cause of CKD. In recent years, advancements in genetic research have greatly expanded our understanding of the genetic underpinnings of CKD. Notably, monogenic diseases may account for up to 20% of progressive CKD diagnoses. One such underrecognized disorder is autosomal dominant tubulointerstitial kidney disease (ADTKD) [2]. Autosomal dominant tubulointerstitial kidney disease is characterized by a slow, progressive decline in renal function caused by tubular atrophy and interstitial fibrosis, with bland urinary sediment and autosomal dominant inheritance. Pathogenic variants in the *MUC1* and *UMOD* genes are the most common causes of ADTKD. However, rarer (*REN, SEC61A1, DNAJB1*) and heterogeneous (*HNF1B*) subtypes have also been reported [3, 4]. This article presents the case of a 7-year-old boy with an ultra-rare *REN* gene mutation.

CASE REPORT

A boy of Polish descent, the first child of nonconsanguineous parents born naturally at the 39th week of gestation. The pregnancy was complicated by the mother's chronic renal failure and severe anemia, which required three blood transfusions. At birth, the APGAR score was 10,

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with a body weight and length of 2700 g (3rd–10th percentile) and 51 cm (75th percentile), respectively. A neonatal period was uneventful. However, since infancy, normocytic anemia poorly responsive to iron supplementation has been observed. Moreover, the patient presented with a hemodynamically insignificant patent ductus arteriosus.

At the age of 3 months, the patient was admitted to the hospital with a diagnosis of pneumonia and the following results: normal urea (33 mg/dl) and uric acid (4.8 mg/dl) concentrations, borderline creatinine (0.41 mg/dl), and hemoglobin values (9.8 g/dl). Although the pH and bicarbonate levels were decreased (7.28 and 19.4 mmol/l, respectively), they were not subsequently monitored.

Over time, additional symptoms were observed, including supraventricular arrhythmia, short stature (3rd percentile), primary nocturnal enuresis, adenoid hypertrophy, and delayed speech.

At the age of 5, the patient was admitted to a local hospital for evaluation of anemia. Surprisingly, in addition to normocytic anemia, elevated levels of creatinine (0.68 mg/dl) and urea (67.27 mg/dl) were found. Consequently, kidney disease was suspected, and the boy was referred to our Department of Pediatric Nephrology.

Upon admission, the patient presented with pallor, a faint systolic heart murmur, and arrhythmia. His weight and height were both in the 3rd percentile. Blood pressure (BP) was 87/40 mm Hg. The patient exhibited moderate normocytic anemia (hemoglobin 9.2 g/dl, with normal reticulocytosis – 11.7%, iron, transferrin, ferritin, folic acid, and vitamin B_{12} levels), borderline erythropoietin (EPO) – 5.84 mU/ml, creatinine (0.63 mg/dl, estimated GFR [eGFR] of 89.92 ml/min/1.73 m^2), uric acid (5.8 mg/dl), bicarbonates (20.8 mmol/l), and potassium (5.06 mmol/l) serum levels. Notably, elevated serum urea (58.9 mg/dl), cystatin C (1.68 mg/l), bland urine sediment, normal renal ultrasound, and extreme hypocalciuria with low fractional urinary calcium excretion of 0.12% and uricosuria at the upper limit of reference range (12 mg/kg/24 h) were stated (Table 1).

Darbepoetin treatment was started at an initial dose of 10 mcg monthly. Soon after, bicarbonates at a daily dose of 1.5 g were introduced due to the progression of metabolic acidosis (pH 7.28, bicarbonates 17.9 mmol/l). Renin and aldosterone levels were normal (23.6 uIU/ml and 159.30 pg/ml, respectively). Interestingly, the patient's 35-year-old mother, currently in the initial phase of 4-stage CKD (eGFR 30 ml/min/1.73 m^2), presented a similar clinical phenotype. Other family members, including the mother's 3 siblings and parents, had a negative history of kidney diseases.

Consequently, ADTKD was suspected, and the patient and his parents were genetically tested.

TABLE 1. Follow-up of selected laboratory results in the presented patient

Laboratory parameters	Reference range	First admission	Follow-up (month 6)	Follow-up (month 13)	Follow-up (month 18)	Follow-up (month 25)
Blood						
Creatinine [mg/dl]	0.32–0.59	0.63	0.74	0.84	0.91	0.98
Uric acid [mg/dl]	1.8–5.5	5.8	6.3	6.4	6.98	4.5
Urea [mg/dl]	15–36	58.9	51.8	70	66	74
Sodium [mmol/l]	132–145	135	137	135	135	138
Potassium [mmol/l]	3.5–5.1	5.06	5.77	5.57	5.63	5.8
Total calcium [mmol/l]	2.2–2.7	2.56	2.62	2.63	2.63	2.58
Phosphates [mmol/l]	1.05–1.8	1.48	1.73	1.43	1.5	1.47
Magnesium [mmol/l]	0.7–0.95	0.77	–	0.87	0.94	0.78
pH	7.32–7.38	7.322	7.4	7.39	7.326	7.33
Bicarbonates [mmol/l]	22.5–30	20.8	24.2	21.3	25.6	23.4
Hematocrit (%)	35–42.4	28.1	36.7	34.1	32.9	34.7
Hemoglobin [g/dl]	12–14	9.2	12	11.3	10.8	11.2
MCV [fl]	76.5–90.6	81	79.3	83.2	84.1	82.4
MCH [pg]	25–31	26.5	25.9	27.6	27.6	26.6
Parathormone [pg/ml]	10–65	55.75	83.52	86.86	129.9	52.85
Renin [ulU/ml]	4.4–46.1	23.6	–	37.1	–	–
Aldosterone [pg/ml]	13.37–233.55	159.3	–	153	–	–
Urine						
Calcium excretion [mg/kg/24 h]	1–4	< limit of detection	–	0.65	–	< limit of detection
Uric acid excretion [mg/kg/24 h]	5–12	12	–	–	–	5.77

Sanger sequencing of the coding exons of the *HNF1β* and *REN* genes, along with quantitative MLPA analysis of the *HNF1β* gene, was performed. Sequence analysis identified the heterozygous missense sequence variant c. 77C > T in exon 1 of the *REN* gene in the patient and his mother – genotype c. [77C > T]; [77 =]. Analysis of the *HNF1β* gene did not reveal any pathological findings. Thus, ADTKD-REN was diagnosed in both the patient and his mother.

On follow-up, a tendency to hypotension, hyperkaliemia, severe hypocalciuria, hyperuricemia, hyperparathyroidism, and progression of CKD has been observed. Figure 1 presents the decline in the patient's eGFR over a 2-year follow-up.

Intensification of darbepoetin treatment (20 mcg monthly) and bicarbonates (4 g daily) supplementation were necessary. Due to hypertrophy of the pharyngeal tonsil at nearly 6 years of age, an adenoidectomy was performed. Subsequently, the bedwetting evolved into nocturia.

At the age of 6.5, due to hyperparathyroidism (129.9 pg/ml), the active metabolite of vitamin D_3 (alfacalcidol at a daily dose of 0.25 mcg) was introduced. Calcemia (2.63 mmol/l) and phosphatemia (1.5 mmol/l) were normal. Due to slowly increasing uricemia (6.98 mg/dl), allopurinol at a daily dose of 50 mg was started. Simultaneously, uric acid 24-hour urine excretion decreased to 5.77 mg/kg. Currently, at the age of 7, the patient is in stage 2 CKD with a serum creatinine of 0.98 mg/dl (eGFR of 65 ml/min/1.73 m^2), urea 74 mg/dl, uric acid 4.5 mg/dl, hemoglobin 11.2 g/dl, bicarbonates 23.4 mmol/l, potassium 5.8 mmol/l, 25-hydroxy vitamin D 39.1 ng/ml, and parathormone 52.85 pg/ml (Table 1). Follow-up ultrasound showed slightly increased renal cortex echogenicity with preserved corticomedullary differentiation and normal kidney size (Figure 2), whereas Holter ECG improved with a significant reduction of supraventricular ectopic impulses.

Both the patient's height and weight are still at the 3rd percentile. Mental development is normal. Although bedwetting has not been observed since the adenoidectomy, nocturia persisted due to impaired renal concentrating ability. His BP values range 66/38–92/43 mm Hg, with a median of 80/44 mm Hg. To date, despite the tendency towards hypotension, no episodes of symptomatic hypotonia have been observed.

The patient is on a restricted low-potassium diet, with regular fluid intake and avoidance of non-steroidal anti-inflammatory drugs (NSAIDs).

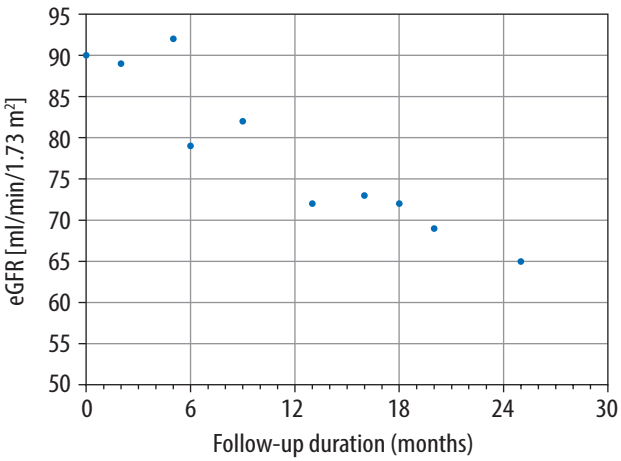

FIGURE 1. The decline in the presented patient's estimated glomerular filtration rate in a 2-year follow-up (using the Schwartz formula, Jaffe creatinine assay method)

eGFR – estimated glomerular filtration rate

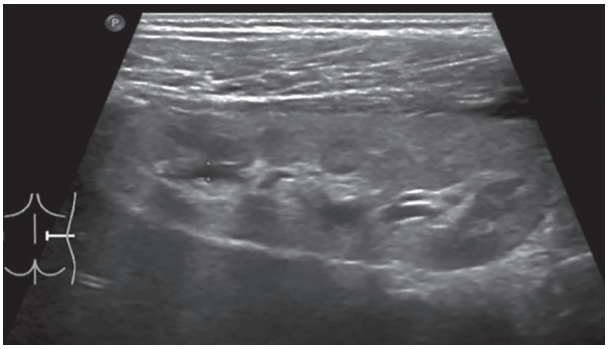

FIGURE 2. Ultrasound of the right kidney in the presented patient at the age of seven

Note slightly increased echogenicity of the renal cortex (Department of Pediatric Radiology, Medical University of Lublin).

DISCUSSION

Autosomal dominant tubulointerstitial kidney disease is a rare, genetically heterogeneous group of disorders that have been increasingly diagnosed as a cause of familial CKD. A definitive diagnosis can be established through genetic testing, particularly by using next-generation sequencing, and a kidney biopsy is generally not required as it typically reveals non-specific interstitial fibrosis and tubular atrophy [3, 5]. In the presented patient, ADTKD-REN (OMIM 613092) results from a heterozygous missense sequence variant c. 77C > T in exon 1 of the *REN* gene on chromosome 1. It is classified as potentially pathogenic in the ClinVar database and as pathogenic in the HGMD database and leads to an amino acid exchange from threonine to isoleucine in position 26 (p.Thr26Ile). Notably, the diagnosis of ADTKD-REN in the patient enabled the identification of the underlying cause of CKD in his previously undiagnosed 35-year-old mother.

The *REN* gene codes preprorenin, the precursor of human renin, which is predominantly expressed in the granular cells of the juxtaglomerular apparatus of the kidney. It is a 406-amino acid protein composed of a 23-amino acid N-terminal signal peptide, a 43-amino acid prosegment, and a 340-amino acid mature renin peptide [6]. Preprorenin is converted to prorenin by the cleavage of its N-terminal signal peptide. Prorenin can then be secreted *via* a constitutive pathway, or the N-terminal prosegment may be cut off to produce renin, which is subsequently stored in dense-core vesicles. Renin, an aspartic protease,

catalyzes the first step of the renin-angiotensin-aldosterone system (RAAS) [3], which is involved in a range of essential physiological processes, including nephrogenesis, regulation of renal sodium and potassium balance, modulation of vascular tone, erythropoiesis, and the development of cardiac hypertrophy [6].

The position of the pathogenic variant within one of 3 regions of the *REN* gene-encoding the mature renin peptide, the signal peptide region, or the prosegment – affects the phenotypic manifestations of affected individuals. Recently Živná *et al.* [7] characterized the genetic and clinical spectrum of ADTKD-REN in an international cohort of 111 individuals from 30 families. They identified genotype-phenotype correlations and significant variations in the disease course.

Heterogenous variant c. 77C > T detected in the presented case falls within the prosegment group. Notably, despite the early onset of renal impairment, GFR in the prosegment subgroup generally remains relatively stable during childhood and adolescence. Median renal survival in these patients is approximately 60 years [3, 7]. However, some individuals may progress to end-stage kidney disease (ESKD) in their fourth decade of life [8].

Živná *et al*. in their study described 19 patients from 2 families with the same, as in the presented patient, *REN* gene nucleotide change c. 77C > T. The mean ages of presentation and progression to ESKD in their cohort were 21.4 ±11.7 and 56 ±13 years, respectively. Notably, no one initially exhibited CKD [7]. Interestingly, in the presented case, eGFR declined by nearly 25 ml/min/1.73 m² over a relatively short two-year period, suggesting a more aggressive course of ADTKD-REN. However, the long-term course of the disease remains uncertain, particularly since the progression of CKD has slowed significantly over the second year of observation (Figure 1).

In contrast, mutations affecting the region encoding the mature renin peptide, are typically associated with gout and adult-onset CKD, which frequently progresses to ESKD by the late 60s [3].

In the prosegment form of ADTKD-REN, accumulation of renin and prorenin in the endoplasmic reticulum and Golgi apparatus, and decreased prorenin secretion are usually observed. Furthermore, affected individuals typically exhibit low or low-normal plasma renin concentrations [4, 7]. However, in ADTKD-REN neither renin nor aldosterone levels provide diagnostic value as they do not correlate with disease progression or severity [9]. Nevertheless, patients often exhibit a predisposition to hypotension, as well as an increased risk of acute kidney injury. Consequently, a salt-restricted diet, diuretics or other volume-depleting agents, NSAIDs, or treatment influencing the RAAS should be strictly avoided [10]. Although the presented patient's renin and aldosterone levels were normal, the tendency to low BP was observed. However, to date, no symptomatic hypotensive episodes have occurred.

Another hallmark of ADTKD-REN is renal tubular acidosis. Typically, serum bicarbonate levels range 15–22 mEq/l [11] and it usually manifests early in the disease course. Remarkably patients with the *REN* gene nucleotide change c. 77C > T, described by Živná *et al.* [7], did not have acidosis at the time of presentation. In the presented patient acidosis occurred in the third month of life, but it was not subsequently monitored, and only re-diagnosed at the age of 5. So, it remains unclear whether the condition persisted or reappeared later but unquestionably it manifested much earlier than in the cohort of patients with the same mutation described by Živná *et al.* [7].

A further indication of ADTKD-REN is hyperuricemia. Although its molecular mechanisms remain poorly defined, it is suggested to result from proximal tubular adaptations to plasma volume depletion, caused by anemia and hypotension. A compensatory response in the proximal tubule may cause increased uric acid reabsorption, thereby leading to hyperuricemia and hypouricosuria [5]. Typically, ADTKD-REN patients present early-onset gout with the first episode usually manifesting around the age of 30 [3]. 75% of patients described by Živná *et al*. [7], who had the same *REN* gene mutation as the presented patient, exhibited gout at the time of diagnosis. In the presented patient uricemia was slowly increasing. Simultaneously, urine uric acid excretion decreased by more than 50% from 12–5.77 mg/kg/24 h throughout a 2-year follow-up.

Remarkably, early-onset hypoproliferative anemia is a hallmark of ADTKD-REN. It is regarded as secondary to decreased production and low levels of EPO [6]. Furthermore, RAAS, except for body fluid and electrolyte balance regulation, directly influences the synthesis of EPO. Angiotensin II stimulates EPO mRNA and protein expression in renal proximal tubules with collecting ducts, particularly in intercalated cells [12]. The presented case involves moderate normocytic anemia, resistant to conventional treatment, observed since infancy before an eGFR decline. Notably, despite the anemia the EPO level remained within the lower norm. A favorable response to darbepoetin supports the role of the *REN* gene mutation in its pathogenesis [3].

The onset and severity of anemia notably depend on the type of the *REN* gene mutation. In the cohort study by Živná *et al*., anemia was present during childhood in 69% of patients in the prosegment group and 91% from the signal group, while it was not observed in the mature group [7]. Nevertheless, the mean hemoglobin level in children with ADTKD-REN is about 10 g/dl [3]. In the presented patient, hemoglobin was 9.2 g/dl before initiation of darbepoetin therapy. Interestingly, in ADTKD-REN patients, anemia typically improves during puberty, likely due to the production of sex hormones that stimulate EPO synthesis [6].

Another common feature of ADTKD-REN is a tendency to hyperkalemia [3, 7]. The presented patient's kalemia ranged 5.06–6.23 mmol/l, and consequently, a restrictive low-potassium diet was recommended. Since, in ADTKD-REN, impaired RAAS function results in aldosterone deficiency, mineralocorticoid supplementation may offer therapeutic benefits. Fludrocortisone, a synthetic corticosteroid with predominantly mineralocorticoid activity, increases sodium retention and potassium excretion, contributing to electrolyte balance and BP regulation. Some studies suggest that fludrocortisone may be an effective treatment for managing mild hyperkalemia and hypotension [3, 4, 7]. Although improvement in kidney function was observed in younger patients, its benefits may be limited in those with advanced CKD due to its possible risk of aggravating interstitial fibrosis. Thus, the KDIGO consensus report does not recommend fludrocortisone in patients with declining kidney function, hypokalemia, edema, and hypertension [9, 13].

While there is considerable evidence regarding the risk of hypotension in ADTKD-REN [3, 4, 7], to our best knowledge, no data regarding arrhythmias in the course of this disease is currently available. Certainly, CKD by itself predisposes to cardiac arrhythmias due to electrolyte imbalances, proarrhythmic properties of uremic toxins, metabolic acidosis, and autonomic nervous system activation. Moreover, anemia increases cardiac output, and left atrial strain may promote arrhythmia [14]. Furthermore, hypotension and RAAS dysfunction may additionally contribute to arrhythmogenesis in ADTKD-REN. In the presented patient, arrhythmia occurred early, and significant improvement was observed following the correction of anemia and acidosis.

Consequently, we suggest that ADTKD-REN patients may be at an increased risk of cardiac arrhythmias. Therefore, we propose Holter electrocardiogram monitoring as a part of the care guidelines for these patients.

A potential therapeutic option for the future management of ADTKD may involve the recently identified molecule BRD4780. Potentially, it may slow the progression of ADTKD-MUC1, ADTKD-UMOD, and ADTKD-REN by mitigating the accumulation of toxic proteins and fibrosis in the kidneys. However, further studies are necessary to confirm its efficacy [13].

The diagnostic challenges in ADTKD-REN are particularly significant due to the absence of distinctive abnormalities in both urinalysis and imaging studies, making accurate diagnosis more difficult. Typically, patients with ADTKD-REN present with bland urinary sediment, absence of proteinuria, and specific abnormalities on renal ultrasound, with initially normal kidney size, as observed in our patient. As the disease progresses, nonspecific signs of CKD, such as increased echogenicity, loss of corticomedullary differentiation, and cysts, may develop [4].

Autosomal dominant tubulointerstitial kidney disease REN leads to renal tubulointerstitial injury, which may result in the development of tubulopathy-related symptoms. So far, only hypouricosuria has been documented in the literature [5]. Therefore, the previously unreported severe hypocalciuria observed in the presented case may hypothetically serve as an additional diagnostic marker for the disease. However, this finding requires further investigation in a larger patient cohort to validate its significance.

CONCLUSIONS

Autosomal dominant tubulointerstitial kidney disease REN is an ultra-rare genetic cause of CKD in childhood. In the presence of a constellation of early-onset anemia, hyperkaliemia, hyperuricemia, acidosis, and renal failure with a non-characteristic renal ultrasound and normal urinary sediment, this diagnosis should be considered. Proper identification with early specialistic care improves the prognosis and is essential for longer preservation of kidney function, enables prevention of serious complications, and genetic counseling of family members.

DISCLOSURES

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4. Conflicts of interest: None.

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