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Atypical clinical presentation of Autosomal Recessive Polycystic Kidney Mimicking Medullary Sponge Kidney disease

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INTRODUCTION

Medullary sponge kidney disease (MSK) is a nephropathy characterized by the association of tubular ectasia of precalyceal ducts with sporadic cystic development, multiple renal stones and/or nephrocalcinosis (calcification of renal parenchyma) and frequently tubular acidification defect. In most cases, both kidneys are affected. The prevalence of MSK in the general population is still unknown. In particular some patients may develop tubular ectasia without recurrent kidney stone formation, thus they can remain undiagnosed. Among kidney stone formers, a condition reaching up to 10% of the general population, MSK prevalence is more than 8 %.¹

Patients affected by MSK are at risk to form recurrent renal stones, responsible for renal colic and multiple urological interventions. Nevertheless chronic kidney disease (CKD) is rarely reported. Many patients affected by MSK complain about chronic flank pain, even in the absence of patent renal colic.²

It has been hypothesized that MSK could have a genetic basis. Currently, only a few cases clustering in family have been reported, suggestive of incomplete penetrance. MSK has been associated with various malformations such as those observed in Beckwith-Wiedemann syndrome with renal developmental defects. Hepatic disease such as Caroli disease, responsible for biliary duct dilation, have been described.³

The Glial cell-derived neurotrophic factor (GDNF), a ligand of RET, allows ureteric bud branching and invasion of the metanephric blastema with collecting ducts and upstream kidney formation. Recently, GDNF variants have been identified in MSK patients, supporting the idea that MSK might result from precalyceal and collecting ducts development defects.⁴

Considering the potential genetic origin of MSK, a whole-exome sequencing was proposed in two adult patients affected by MSK with CKD, an uncommon condition of MSK.

CASES PRESENTATION

Medical history

Case 1. A young woman had a bilateral MSK diagnosed in 2010 when she was 20-yrs old (Figure 1). There was no familial case of MSK. She experienced several renal colics but no stone was analyzed. She had a mild CKD diagnosed in 2012 (serum creatinine 130 $\mu\text{mol/l}$), without urine sediment abnormality, that worsened during a first pregnancy in 2015. A reno-ureteroscopy was performed, showing papilla with typical MSK lesions. Renal function rapidly declined with a progression toward end-stage renal failure, and she received a kidney allograft, in 2019. Urine calcium excretion was normal in 2012 but the patient was already affected by CKD at this time.

Case 2. A man was affected by renal colics due to recurrent kidney stones since he was 28-yrs old, in 1996. His brother was affected by Caroli disease. MSK was diagnosed in 1996 by intravenous urography and confirmed by CT-scan in 2019. Kidneys contained multiple kidney stones and tissue calcifications. He progressively developed a CKD: serum creatinine level was 189 $\mu\text{mol/l}$ in 2019 and measured GFR (DTPA-technetium renal clearance) was 35 ml/min/1.73m². He had a mild tubular proteinuria (0.16 g/L) and urine sediment was normal. Urine biochemistry did not reveal hypercalciuria (urine calcium excretion: 2.25 mmol/day) but were performed after the onset of CKD. He had low urine citrate excretion (1.38 mmol/day) and increased urine oxalate excretion (0.61 mmol/day). No stone was analyzed.

Genetic analyses

As renal function worsened rapidly, without other renal disease than MSK, a whole-exome sequencing was proposed to both patients. The whole-exome analysis in case 1 revealed two

mutations of *PKHD1*. The first mutation was nonsense: c.7514T>A, p.Leu2505* with paternal origin and the second one was missense: c.4870C>T, p.Arg1624Trp inherited from the mother and affecting the IPT/TIG 11 domain (Figure 2).

In case 2, the whole-exome analysis revealed also two mutations in *PKHD1*: a frameshift mutation: c.5895dup, p.Leu1966ThrfsTer4 and a missense pathogenic variant: c.5134G>A; p.Gly1712Arg in the IPT/TIG 12 domain of *PKHD1* (Figure 2). No segregation analyses were performed to confirm the paternal or maternal origin of the alleles.

These mutations were reported to be pathogenic in patients affected by autosomal recessive polycystic kidney disease (ARPKD).

DISCUSSION

More than 300 *PKHD1* pathogenic mutations have been recorded, which are responsible for autosomal recessive polycystic kidney disease (ARPKD). *PKHD1* is a 500kb gene located on chromosome 6 (6p21.1-p12) coding for polycystin.⁵ Polycystin is expressed in the kidney, in the distal part of the nephron especially in the collecting duct, and also in the bile duct epithelium and in the pancreas. Polycystin associates with primary cilia and basal bodies, suggesting a role in cilia-related functions of the cells (development and maintenance of renal tubule architecture).⁶ Most patients are compound heterozygous, carrying 2 different alleles. ARPKD is one of the most frequent causes of genetic renal diseases, with a prevalence estimated at 1/20,000 births. A presentation occurring in utero or at birth is classic in ARPKD, associating oligohydramnios, pulmonary hypoplasia and enlarged echogenic kidney. Kidneys are affected by cystic dilatation and ectasia of renal collecting tubules, and congenital hepatic fibrosis. The disease is extremely severe with a high mortality. For patients surviving the

neonatal period, 50% will have an end-stage renal failure during the first decade. However, the diagnosis may also be considered in young adults with polycystic hepatorenal disease as some patients affected by ARPKD develop a less severe disease with delayed CKD.⁷

A link between *PKHD1* mutations and MSK has been hypothesized by Gunay-Aygun et al. They performed ultrasound evaluation in 110 parents of patients affected by ARPKD.⁸ These parents carried a single mutation transmitted to the proband but were not affected by ARPKD. Six of them had increased medullary echogenicity and 10 had small liver cysts. Medullary echogenicity was identified as nephrocalcinosis and considering the common features between MSK and ARPKD, the authors hypothesized that MSK could be the consequence of heterozygous *PKHD1* mutations. More recently, Shan et al. reported that heterozygous *Pkhd1* mutant mice develop cystic liver disease and tubule ectasia mimicking MSK.⁹

In the two patients affected by *PKHD1* compound heterozygous mutations, the diagnosis of MSK was made early but the absence of (large) renal cysts did not suggest that these patients could carry *PKHD1* mutations. Some *PKHD1* mutations may therefore lead to an “intermediate” disease, between MSK and ARPKD, affecting young adults. Both patients were affected by CKD. Of note, the diagnosis of MSK is not easy because it is still based on imaging, and CT-scan may not perform like urography in subtle MSK cases, and, as clearly shown by these 2 cases, a similar phenotype occurs in other conditions (ARPKD, but also potentially other forms of nephrocalcinosis). These observations deserve further studies in larger cohorts of MSK patients, to assess the prevalence of *PKHD1* mutations and whether heterozygous carriers are at risk to develop MSK or whether 2 mutations are required.

Conclusion

We describe herein that *PKHD1* biallelic mutations may lead to a “hybrid” disease, between MSK and ARPKD, without multicystic phenotype and affecting adults (Table 1). Both patients were affected by CKD, with a rapid and severe progression, and clinicians should be aware that the presence of CKD in a patient diagnosed as MSK could result from *PKHD1* mutations. Moreover, these observations suggest that the development of MSK could be related to impaired cilia-related functions of tubular cells.

Table 1-Teaching Points

- Medullary sponge kidney disease (MSK) prevalence is more than 8 % among kidney stone formers (a condition affecting 10% of the general population)
- MSK may have a monogenic origin: a familial segregation was observed in some cases and mutations of *GDNF* were associated with MSK
- *PKHD1* biallelic mutations may be diagnosed as an atypical MSK leading to CKD in adulthood
- *PKHD1* biallelic mutations may therefore be causative for autosomal recessive polycystic kidney disease (ARPKD) and/or for MSK-like disease
- The role and prevalence of mono- or bi-allelic mutations of *PKHD1* in patients affected by MSK need to be addressed

Disclosure

All the authors declared no competing interests.

Patient Consent

The authors declare that they have obtained consent from the patients discussed in the report, including written consent for whole-exome sequencing.

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Figure Legends

Figure 1. Representative CT-scan (case 1) revealing kidney tissue calcifications (arrows).

Figure 2. Mutations discovered in case 1 and case 2.

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