A series of unlikely genetic events: clinical expression in a late onset ARPKD case

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BACKGROUND

Renal cystic diseases include a heterogeneous group of inherited kidney disorders including Polycystic Kidney Disease (PKD). According to the mechanism of inheritance, two conditions can be distinguished: the autosomal dominant form, ADPKD, is characterized by nephromegaly, bilateral renal cysts and chronic renal failure (CKD) starting from the 3rd-4th decade of life, caused for the most part from pathogenic variants in the *PKD1* and *PKD2* genes; the autosomal recessive form, ARPKD (MIM # 263200) is characterized by the development of cysts in ducts collectors and congenital hepatic fibrosis, caused by biallelic pathogenic variants in the ***PKHD1*** gene (chromosome 6p12.3-p12.2). Recent studies indicate also the presence of a second gene, *DZIP1L*, associated with cases of "moderate ARPKD". ARPKD was once referred to polycystic infant kidney. Today, however, the variable age of onset, with one third of patients onset after 20 years of age, no longer makes it a pathology with paediatric onset only, but also in adults.

CLINICAL CASE

This is a 55 years old female, currently with an eGFR <15mL / min / 1.73 $m^{2,}$ on the liver-kidney pre-emptive kidney transplant.

At the age of 40 she came to our attention with CKD (3b) attributed to nephritis which occurred at the age of 4. At 16 years old, she was hospitalized and the diagnosis of CKD was confirmed. The family history showed that the firstborn had died after 21 days from birth and the second child had enlarged kidneys at birth, hyperechoic echo structure as from polycystic kidneys. The genetic analysis conducted in the second child highlighted the presence of two pathogenetic variants in compound heterozygosity in the ***PKHD1* gene** (NM_138694.4): c.4870C>T, p. Arg1624Trp (*maternal origin*) and c.10444C>T, p. Arg3482Cys (*paternal origin*), confirming the diagnosis of ARPKD.

In addition, the patient had pre-pregnancy creatinine 1.6mg/dL which reached 2.42 mg/dL after 21 months from the last birth, with no other alterations in the bio-humoral tests. Renal ultrasound showed kidneys in place, reduced in volume, the left one with a bipolar diameter of 10 cm, the right one with a bipolar diameter of 9.3 cm. Accentuated parenchymal echogenicity with discreet subversion of the echostrusture by microcystic dissemination. Calcific hyperechoic spots scattered bilaterally more numerous on the left. After the genetic test of the second child, the patient was classified by previous nephrology center as unaffected and a “healthy carrier” of a variant in the ***PKHD1* gene**. This conclusive genetic framework, however, could not fully explain her renal clinical history, which in a few years had reached eGFR<15 ml/min/1,73m^2.

It was therefore considered useful to repeat the genetic analysis for a better classification of the cystic kidney disease that has determined the clinical picture of CKD. The second genetic analysis conducted in the genes involved in PKD revealed two variants in the ***PKHD1* gene**: the presence of the missense variant identified in her son (c.4870C>T, p. Arg1624Trp) and a second frameshift variant c.9523_9524delinsG, p. Asn3175Valfs*8, classified according to the *American College of Medical Genetics and Genomics* (ACMG) standards as *likely pathogenic*. The association of the two variants in compound heterozygosity in the *PKHD1* gene allowed us to conclude that she had recessive polycystic kidney disease, ARPKD as well.

CONCLUSION

The recognition of phenotypic variability in the expression of ARPKD is a potentially important consideration both in the paediatric finding and in the evaluation of adult cystic pathology. More and more late onset ARPKD cases present a non-typical clinical picture. For this reason, genetic evaluation with the analysis of the genes involved in PKD remains an important resource in achieving proper diagnosis.

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