Secondary Cardiomyopathy in Polycystic Kidney Disease Syndrome

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In clinical settings, secondary cardiomyopathy, which arises from a systemic disorder or is caused by a detectable cause, should be distinguished from idiopathic cardiomyopathy. Suwa, et al reported the occurrence of elderly-onset cardiomyopathy in a patient diagnosed as having polycystic kidney disease (PKD).1 In the genetic screening of 404 cardiovascular disease-related genes, only a PKD1 frameshift variant was detected, in which genetic testing could successfully contribute to the diagnosis. According to the ACMG (The American College of Medical Genetics and Genomics) criteria of 2015,5 in order to judge the pathogenicity of previously-unreported novel variants, genetic testing of the relatives is needed; when inherited, co-segregation of genotype with the disease can be used as strong evidence, whereas when de novo, both maternity and paternity should be confirmed. The variant in this case happened to be listed as the causative mutation in the PKD mutation database,3 therefore, genetic testing of the relatives was not necessary for elucidating the pathogenicity of this PKD1 variant. In addition, the authors demonstrated that there was no other causing-variant within a wide range of cardiovascular genes, which could straightforwardly lead to the genetic diagnosis of secondary cardiomyopathy as a cardiac manifestation of systemic “PKD syndrome” in this PKD patient.

If only an idiopathic cardiomyopathy-related variant (e.g., TTN truncating variant) had been detected in the genetic screening, is it reasonable to diagnose the patient as having a co-occurrence of idiopathic cardiomyopathy by chance in a PKD patient? I do not think so. In some PKD patients, no causing-variant in PKD1 or PKD2 can be detected. And, basically, there is little likelihood of co-occurrence of PKD and idiopathic DCM by chance without any mutual relationship. When cardiomyopathy is observed in a PKD patient, we should first suspect this cardiomyopathy is a secondary cardiomyopathy as a cardiac manifestation of systemic “PKD syndrome” independently of the genetic screening results (Figure). Therefore, we can think of the cardiomyopathy as being the same as that in patients with muscular dystrophy or classic Fabry disease. An idiopathic cardiomyopathy-related variant detected in a PKD patient could function as a second-hit variant or a genetic modifier rather than cause an idiopathic cardiomyopathy. Such a variant may affect the presence or absence of secondary cardiomyopathy, or which kind of cardiomyopathy (e.g., dilated cardiomyopathy, hypertrophic cardiomyopathy, or left ventricular non-compaction3) occurs.

Taken together, periodic cardiovascular evaluation should be performed in PKD patients considering that secondary cardiomyopathy could occur as one of the systemic disorders in “PKD syndrome”. Medical knowledge of the cardiac findings in PKD patients should be accumulated. Genetic screening is also recommended to clarify the genetic background as well as the genotype-phenotype correlation.

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Mutations in two genes PKD1 and PKD2 are known to account for PKD. Basic research has clearly shown that a molecular abnormality causing PKD could directly induce the cardiomyopathy independently of advanced renal failure or hypertension. Polycystin-1 encoded by Pkd1 is a transmembrane protein in the cell membrane and functions as a cardiomyocyte mechanosensor that governs L-type Ca\(^{2+}\) channel protein stability. Polycystin-2 encoded by Pkd2 is an intracellular calcium channel that regulates intracellular calcium signaling. Although cardiac abnormalities and renal cysts can be recapitulated in Pkd1-overexpressing mice, in Pkd2 knockout mice, cardiomyopathy was observed, whereas renal lesion was not. In humans, PKD2 mutation was reported to cause isolated cardiomyopathy without renal disease. Here, we must mention the possibility that such a “cardiac PKD” could occur. In some of the PKD patients, clinical manifestation is limited to the heart or cardiomyopathy precedes the renal disease, which is consistent with those with cardiac Fabry disease. In this context, it is of clinical importance to distinguish this “cardiac PKD” from idiopathic cardiomyopathy. At present, however, genetic evidence concerning the genetic background of “cardiac PKD” is lacking. Family history of PKD can contribute to a diagnosis of “cardiac PKD”. In addition, the gene panel for genetic screening should contain PKD1 and PKD2, which might help us distinguish “cardiac PKD” from idiopathic cardiomyopathy.

In conclusion, the case report by Suwa, et al will raise awareness of the occurrence of secondary cardiomyopathy in patients with PKD, directing our attention to the functional and genetic relationships between polycystins and cardiomyopathy. Further studies on PKD-related cardiomyopathy are warranted.

Disclosures

Conflicts of interest: None.

References