KI REPORTS
KIReports.org
CLINICAL RESEARCH

Autosomal Dominant Polycystic Kidney Patients May Be Predisposed to Various Cardiomyopathies

Fouad T. Chebib[1], Marie C. Hogan[1], Ziad M. El-Zoghby[1], Maria V. Irazabal[1], Sarah R. Senum[1], Christina M. Heyer[1], Charles D. Madsen[1], Emilie Cornec-Le Gall[1], Atta Behfar[2], Peter C. Harris[1] and Vicente E. Torres[1]

[1]Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; and [2]Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Introduction: Mutations in *PKD1* and *PKD2* cause autosomal dominant polycystic kidney disease (ADPKD). Experimental evidence suggests an important role of the polycystins in cardiac development and myocardial function. To determine whether ADPKD may predispose to the development of cardiomyopathy, we have evaluated the coexistence of diagnoses of ADPKD and primary cardiomyopathy in our patients.

Methods: Clinical data were retrieved from medical records for patients with a coexisting diagnosis of ADPKD and cardiomyopathies evaluated at the Mayo Clinic (1984–2015).

Results: Among the 58 of 667 patients with available echocardiography data, 39 (5.8%) had idiopathic dilated cardiomyopathy (IDCM), 17 (2.5%) had hypertrophic obstructive cardiomyopathy, and 2 (0.3%) had left ventricular noncompaction. Genetic data were available for 19, 8, and 2 cases of IDCM, hypertrophic obstructive cardiomyopathy, and left ventricular noncompaction, respectively. *PKD1* mutations were detected in 42.1%, 62.5%, and 100% of IDCM, hypertrophic obstructive cardiomyopathy, and left ventricular noncompaction cases, respectively. *PKD2* mutations were detected only in IDCM cases and were overrepresented (36.8%) relative to the expected frequency in ADPKD (15%). In at least 1 patient from 3 IDMC families and 1 patient from a hypertrophic obstructive cardiomyopathy family, the cardiomyopathy did not segregate with ADPKD, suggesting that the *PKD* mutations may be predisposing factors rather than solely responsible for the development of cardiomyopathy.

Discussion: Coexistence of ADPKD and cardiomyopathy in our tertiary referral center cohort appears to be higher than expected by chance. We suggest that *PKD1* and *PKD2* mutations may predispose to primary cardiomyopathies and that genetic interactions may account for the observed coexistence of ADPKD and cardiomyopathies.

Kidney Int Rep (2017) **2,** 913–923; http://dx.doi.org/10.1016/j.ekir.2017.05.014
KEYWORDS: ADPKD; cardiomyopathies; hypertrophic cardiomyopathy; idiopathic dilated cardiomyopathy; left ventricular noncompaction; polycystic kidney

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by relentless formation of fluid-filled cysts in the kidney, leading eventually to end-stage renal disease. It is caused by mutations to *PKD1* encoding polycystin-1 or *PKD2* encoding polycystin-2 (PC2).[1–5] Polycystin-1 is a transmembrane protein in the cell membrane and primary cilia where it interacts with PC2.[6–13] PC2 is a member of the transient receptor potential channel family, found in the endoplasmic reticulum and in primary cilia. Polycystins, particularly PC2, contribute to the regulation of calcium release from intracellular stores.[11–14]

Polycystins are expressed in many tissues, including tubular epithelia, endothelial and vascular smooth muscle cells, and cardiomyocytes.[15–20] In fact, ADPKD is a systemic disease associated with several extrarenal manifestations, including multiple cardiovascular complications such as early development of hypertension, left ventricular hypertrophy, and diastolic dysfunction; cardiac valvular disease; aortic root dilatation; arterial aneurysms and dissections; and pericardial effusion.[21] Although the cardiovascular

Correspondence: Fouad T. Chebib, Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN, 55905. E-mail: chebib.fouad@mayo.edu
Received 17 April 2017; revised 11 May 2017; accepted 28 May 2017; published online 5 June 2017

manifestations of ADPKD have been thought to be due to compression of the renal vasculature by cysts, leading to hypertension and cardiac dysfunction, increasing evidence suggests that alterations in polycystin expression directly affect the function of the endothelium,[22] vascular smooth muscle,[23] and cardiomyocytes[24] and may be at least in part responsible for the cardiovascular manifestations of the disease.

Studies in experimental animal models strongly suggest that the polycystins play a role in cardiac development and myocardial function. We have previously suggested an association between ADPKD and IDCM.[25] A few cases of hypertrophic obstructive cardiomyopathy (HOCM) and ADPKD have also been reported.[26,27] Left ventricular noncompaction (LVNC) is being reported with increasing frequency in patients with ADPKD. Patients with ADPKD may also have an increased risk for the development of atrial fibrillation, a common manifestation of cardiomyopathy, after adjusting for other risk factors including hypertension, hyperlipidemia, and chronic kidney disease.[28] Therefore we reviewed our ADPKD database to comprehensively identify the cases of a diagnosis of IDCM, HOCM, or LVNC coexisting with ADPKD. We found that these diagnoses coexisted in this database with a frequency that appears to be higher than expected by chance association alone. However, they did not segregate together in some members of 3 IDMC families and 1 HOCM family. This suggests a possible genetic interaction between these diseases rather than the *PKD* mutations being a direct cause of the cardiomyopathies. The purpose of this report is to raise awareness of this possible association and genetic interaction.

SUBJECTS AND METHODS

Study Population

All adult patients with ADPKD who were evaluated at the Mayo Clinic in Rochester, Minnesota, from January 1984 to December 2015 were identified ($n = 3885$). The diagnosis of ADPKD was based on Ravine's criteria in the presence of a positive family history. In the absence of family history, the criteria for a diagnosis of ADPKD were the presence of at least 20 bilateral renal cysts and the absence of clinical findings suggesting the presence of a different cystic disease.

Patients with cardiomyopathies were identified by International Classification of Diseases, 9th Revision (ICD-9) codes and a keyword search of clinical notes through the Mayo Clinic database. The keywords included heart failure, idiopathic dilated cardiomyopathy, left ventricular noncompaction, and hypertrophic obstructive cardiomyopathy. Medical records of all patients with potential cardiomyopathies were reviewed thoroughly. A diagnosis of IDCM was made for patients with a left ventricular ejection fraction (LVEF) $\leq 40\%$ with exclusion of coronary artery disease (>50% obstruction of 1 or more coronary arteries or positive ischemia on stress test), exclusion of other secondary causes such as active myocarditis or primary or secondary form of heart muscle disease, and exclusion of advanced renal failure (estimated glomerular filtration rate $\leq$15 ml/min or the need for renal replacement therapy at time of the cardiomyopathy diagnosis). A diagnosis of HOCM was made for patients with increased left ventricular wall thickness ($\geq$15 mm) as determined by any imaging modality (transthoracic echocardiography, magnetic resonance imaging, or computerized tomography). LVNC was diagnosed by transthoracic echocardiography Jenni criteria (thickened left ventricular wall consisting of 2 layers, evidence of flow within the deep intertrabecular recesses on color Doppler echocardiography, prominent trabecular meshwork in the left ventricular apex or midventricular segments of the inferior and lateral wall).

Demographics and clinical data were retrieved from the patients' electronic records. Estimated glomerular filtration rate was calculated by using the Chronic Kidney Disease Epidemiology Collaboration formula.[29] The Mayo Clinic Institutional Review Board approved the study, and all patients provided research authorization.

Genetic Analysis

The entire coding and flanking intronic regions of *PKD1* and *PKD2* were screened for mutations by direct sequencing as previously described.[30,31] Pedigrees were completed for all families, and whenever possible, the family members with known ADPKD and/or cardiomyopathy were contacted.

Statistical Analysis

Data were reported as means $\pm$ SD for normally distributed data or median and interquartile range (IQR) for skewed data. Survival status was obtained for all patients using a vital records website (www.archives.com).[32] Patient survival was analyzed using the Kaplan-Meier method.

RESULTS

Among the 3885 patients with ADPKD, 159 were identified with a potential diagnosis of cardiomyopathy, but 101 of these were excluded because of evidence of cardiac ischemia, advanced renal failure, or other secondary causes leading to cardiomyopathy (Figure 1). Among the 58 patients included in this case series, 39 had IDCM, 17 had HOCM, and 2 had LVNC.