Clinical Factors Associated with the Risk of Intracranial Aneurysm Rupture in Autosomal Dominant Polycystic Kidney Disease

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**Keywords**
Aneurysmal rupture · Autosomal dominant polycystic kidney disease · Dolichoectasia · Hypercholesterolemia · Intracranial aneurysm · Mitral inflow deceleration time

**Abstract**

**Background:** The occurrence of intracranial aneurysms is higher in patients with autosomal dominant polycystic kidney disease (ADPKD) than in the healthy population. However, research concerning the factors related to the risk of intracranial aneurysm rupture in patients with ADPKD is still insufficient. **Objectives:** The aim of the study was to investigate the prevalence of intracranial aneurysms and aneurysmal subarachnoid hemorrhage (SAH) and to analyze the systemic factors associated with high-risk aneurysms in patients with ADPKD. **Methods:** We screened patients who underwent cerebral angiography between January 2007 and May 2017 in the ADPKD registry. Patients were examined for the presence of intracranial aneurysms and subsequently reclassified into 3 groups based on the risk of aneurysmal rupture: the aneurysm-negative (group 1), low-risk aneurysm (group 2), or high-risk aneurysm (group 3). Various systemic factors were compared, and independent factors associated with high-risk aneurysms were analyzed. **Results:** Among the 926 patients, 148 (16.0%) had intracranial aneurysms and 11 (1.2%) had previous aneurysmal SAH. Patients with intracranial aneurysms were further classified into group 2 (low-risk aneurysms, 15.5%) or group 3 (high-risk aneurysms, 84.5%). Age (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.01–1.05, \( p = 0.004 \)), female sex (OR 3.13, 95% CI 1.94–5.06, \( p < 0.001 \)), dolichoectasia (OR 8.57, 95% CI 1.53–48.17, \( p = 0.015 \)), and mitral inflow deceleration time (DT) (OR 1.01, 95% CI 1.00–1.01, \( p = 0.046 \)) were independently associated with high-risk aneurysms, whereas hypercholesterolemia (OR 0.46, 95% CI 0.29–0.72, \( p = 0.001 \)) was negatively associated. **Conclusion:** In the present study among patients with ADPKD, the prevalence of intracranial aneurysms and aneurysmal SAH was 16 and 1.2%, respectively. Age, female sex, dolichoectasia, and mitral inflow DT were positively associated with high-risk aneurysms, whereas hypercholesterolemia was negatively associated. A subsequent large-scaled longitudinal study is needed to define the plausibility of the clinical parameters.
Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder, in which multiple cysts invade the renal parenchyma [1]. Mutations of the PKD1 gene on chromosome 16 and PKD2 gene on chromosome 4 are known to cause ADPKD; PKD1 abnormalities are more common than PKD2 abnormalities, exhibiting nearly 100% penetrance [2]. Both PKD1 and PKD2 genes are essential in maintaining the integrity of the vascular wall to endure endothelial shear stress. ADPKD has the highest prevalence among single autosomal genetic diseases with 1 in 1,000 of the global population having been diagnosed with ADPKD.

The size and number of renal cysts gradually increase as the disease progresses, with a corresponding increase in the frequency of kidney-related comorbidities such as renal dysfunction, hematuria, and renal hypertension. It generally progresses to ESRD at a median age of 60 years. In addition to the renal complications, patients exhibit several extrarenal complications, including multiple liver and pancreatic cysts, bile duct dilatation, and cardiac valve and vascular insufficiency [3].

Vascular insufficiency includes aneurysms, dissecting, and dilatation. Although the prevalence of intracranial aneurysms in patients with ADPKD varies, it is approximately 3–4 times more than in a healthy population, [4] while the incidence of aneurysmal rupture in these patients is >5 times that of healthy controls [5]. Aneurysmal rupture accounts for 85% of subarachnoid hemorrhage (SAH), and half of the patients with untreated SAH die within a month. Due to the high incidence and probability of aneurysmal rupture in ADPKD, early diagnosis prior to rupture is an essential aspect of patient care [6].

Previous studies have rarely attempted to identify the factors related to the presence of aneurysms and aneurysmal SAH in patients with ADPKD [7]. Herein, we aimed to identify ADPKD-related systemic markers associated with the development and high-risk phenotype of intracranial aneurysms.

Methods

Study Population

All the patients who visited a single tertiary hospital were diagnosed with ADPKD between January 1, 2007, and May 31, 2017, and were enrolled in the present study. The diagnostic criteria, as reported by Pei et al. [8], were as follows: patients aged between 15 and 39 years with 3 or more cysts found on 1 or both sides of the renal parenchyma, patients aged between 40 and 59 years with 2 or more cysts found in each kidney, and patients aged 60 years or older with 4 or more cysts in each kidney. The study protocol was approved by the institutional review board of Seoul National University Hospital (No. 1804-054-936). Additionally, the committee waived the requirement for informed consent.

Data Acquisition

The ADPKD registry primarily aims to assess the target organ damage related to ADPKD. Starting in 2007, we screened newly enrolled patients for demographic and cardiovascular risk factors, and collected their laboratory and echocardiographic data. Patients were classified as hypertensive if they had been diagnosed with hypertension prior to visiting the hospital, were taking antihypertensive drugs, or had at least 2 consecutive blood pressure readings of 140/90 mm Hg. Patients were classified as having diabetes mellitus when they presented with a fasting blood glucose reading of ≥126 mg/dL, glycated hemoglobin reading of ≥6.5, and random glucose reading of ≥200 mg/dL together with symptoms of hypoglycemia; or when their blood glucose was ≥200 mg/dL following a 75-g oral glucose tolerance test. Patients were classified as having hypercholesterolemia if they had been diagnosed with hypercholesterolemia prior to their visit to our hospital, or if they were diagnosed after fasting for longer than 8 h post admission. The diagnostic criteria for hypercholesterolemia during hospitalization were as follows: (a) low-density lipoprotein cholesterol (LDL-C) ≥100 mg/dL with coronary artery disease (CAD) or a CAD equivalent, (b) LDL-C ≥130 mg/dL with 2 or more risk factors, and (c) LDL-C ≥160 mg/dL with 1 risk factor-risk factors included smoking, hypertension, high-density lipoprotein cholesterol <40 mg/dL, and a family history of premature CAD. Patients were classified as having atrial fibrillation if they had been diagnosed prior to admission or when it was observed by means of electrocardiogram or 24-h Holter monitoring during hospitalization. Coronary heart disease was diagnosed when patients had a history of acute myocardial infarction, evidence of asymptomatic myocardial infarction, or myocardial ischemia on an electro- or echocardiogram, or a history of angina pectoris or coronary artery bypass graft. A patient was classified as having a family history of ADPKD if their first-degree relatives had previously been diagnosed with ADPKD.

Subgroup Classification

First, the patients were classified into 2 groups based on the presence or absence of intracranial aneurysm. Intracranial aneurysms often have a heterogeneous etiology, and certain types of aneurysms (e.g., paraceloid aneurysm) have a very low risk of rupture [9]. Based on the above, the patients were further classified into 1 of 3 groups: the aneurysm-negative (group 1), low-risk aneurysm (group 2), or high-risk aneurysm (group 3). Patients with intracranial aneurysms were classified into group 3, provided they met at least 1 of the following 4 criteria, which were developed and first used by the authors: (1) one or more intracranial aneurysms located distally to the paraophthalmic segment of the internal carotid artery, (2) one or more intracranial aneurysms with a minimum diameter of 5 mm or more, (3) two or more intracranial aneurysms identified in the same patient, or (4) a history of aneurysmal SAH. Patients who did not meet any of the above criteria were categorized into group 2.

Classification of Imaging Data

Dolichoectasia of the basilar artery (BA) was determined based on a cutoff diameter of 4.5 mm [10]. Blood vessels other than the
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Results

In total, 1,666 patients diagnosed with ADPKD from January 2007 to May 2017 were screened in this study, from which 740 (44.4%) were excluded because their cerebrovascular images were not available. Thereupon, 926 patients were included in the final analysis. Among them, 148 (16.0%) presented with a total of 195 intracranial aneurysms. Intracranial aneurysms were most frequently observed in the middle cerebral artery (45.6%), and the proportion of aneurysms with a diameter ≥5 mm was 16.0%, as shown in Table 1. Approximately, 11 patients (1.2% of the total number of patients and 7.4% of patients with intracranial aneurysms) had a previous history of aneurysmal SAH.

The aneurysm-positive group comprised older patients and a higher proportion of women than the aneurysm-negative group (Table 2). Additionally, the aneurysm-positive group had a higher prevalence of hypertension and intracranial dolichoectasia, higher grade of hepatic cysts, larger total kidney volume, and a more prolonged mitral inflow DT than the aneurysm-negative group. Hypercholesterolemia was observed less frequently in the aneurysm-positive group than the aneurysm-negative group.

Patients with intracranial aneurysms were further classified into subgroups according to the risk of rupture (as described in methods section): 23 (15.5%) patients were assigned to the low-risk aneurysm group (group 2), and 125 (84.5%) to the high-risk aneurysm group (group 3; Table 3). Group 3 comprised older patients and a higher proportion of women, along with a higher prevalence of dolichoectasia, larger total kidney volume, higher LVMI and mitral inflow DT, and a lower glomerular filtration rate than the aneurysm-negative group. The aneurysm-negative group had a higher proportion of patients with hypercholesterolemia than the other 2 groups.

Multinomial logistic regression analysis (Table 4) identified age (OR 1.03, 95% confidence interval (CI) 1.01–1.05, p = 0.004), female sex (OR 3.13, 95% CI 1.94–5.06, p < 0.001), hypercholesterolemia (OR 1.05, 95% CI 0.29–0.72, p = 0.001), dolichoectasia (OR 8.57, 95% CI 1.53–

| Table 1. Location and size of intracranial aneurysms in ADPKD patients |
|-----------------------------------------------|
| Location* | Intracranial aneurysms, n (%) |
|----------|-------------------------------|
| Anterior communicating artery                | 17 (8.7) |
| Anterior cerebral artery                      | 10 (5.1) |
| Middle cerebral artery                        | 89 (45.6) |
| Posterior communicating artery                | 13 (6.7) |
| Internal cerebral artery                      | 47 (24.1) |
| Posterior arteries†                           | 19 (9.7) |
| Size in largest dimension, mm†                 |
| <2.0                                            | 14 (7.5) |
| 2.0–2.9                                         | 69 (36.9) |
| 3.0–3.9                                         | 52 (27.8) |
| 4.0–4.9                                         | 22 (11.8) |
| 5.0–6.9                                         | 16 (8.6) |
| 7.0–9.9                                         | 10 (5.3) |
| 10.0–12.9                                      | 3 (1.6) |
| >13.0                                           | 1 (0.5) |

ADPKD, autosomal dominant polycystic kidney disease; BA, basilar artery; MRA, magnetic resonance angiography. * The total number of IAs is 195 in 148 patients. † Posterior arteries include posterior cerebral artery and BA. ‡ Among the total IAs, 187 aneurysms in 142 patients were measured for the dimension, but 8 aneurysms in 6 patients were not because the aneurysms were obscured in MRA.
48.17, \( p = 0.015 \), and mitral inflow DT (OR 1.01, 95% CI 1.00–1.01, \( p = 0.046 \)) as the factors significantly associated with high-risk aneurysms. In contrast, none of the factors were associated with low-risk aneurysms when compared to the aneurysm-negative group. Logistic regression analysis according to aneurysmal rupture (group 1 and 2 vs. group 3) showed similar results to multinomial logistic regression analysis (group 1 vs. group 2 vs. group 3; online suppl. Table; for all online suppl. material, see www.karger.com/doi/10.1159/000513709).
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**Table 3. Characteristics according to the presence and risk of intracranial aneurysms in ADPKD patients**

| Variables                        | Intracranial aneurysm | p value          |
|----------------------------------|------------------------|------------------|
|                                  | negative (N = 778)    | low risk (N = 23) | high risk (N = 125) |
| Demographics                     |                        |                  |
| Age, years                       | 50.8±13.5              | 52.0±14.3        | 57.9±11.6             | <0.001*          |
| Male, n (%)                      | 389 (50.0)             | 15 (65.2)        | 30 (24.0)             | <0.001**         |
| CVD risk factors                 |                        |                  |
| Hypertension                     | 568 (73.0)             | 17 (73.9)        | 104 (83.2)            | 0.053            |
| Diabetes mellitus                | 51 (6.6)               | 1 (4.3)          | 7 (5.6)               | 0.850            |
| Hypercholesterolemia             | 305 (39.2)             | 6 (26.1)         | 36 (28.8)             | 0.043            |
| Atrial fibrillation              | 14 (1.8)               | 0 (0.0)          | 2 (1.6)               | 0.803            |
| Smoking                          | 75 (9.6)               | 3 (13.0)         | 6 (4.8)               | 0.173            |
| Alcohol consumption              | 91 (11.7)              | 4 (17.4)         | 14 (11.2)             | 0.690            |
| Ischemic heart disease           | 46 (5.9)               | 0 (0.0)          | 3 (2.4)               | 0.138            |
| BMI                              | 23.1±3.1               | 23.3±2.1         | 22.8±2.6              | 0.643            |
| Family history                   | 374 (48.1)             | 11 (47.8)        | 53 (42.4)             | 0.498            |
| Echocardiography                 |                        |                  |
| Aortic insufficiency             | 32 (4.1)               | 1 (4.3)          | 6 (4.8)               | 0.939            |
| Valvular heart disease           | 150 (19.3)             | 4 (17.4)         | 28 (22.4)             | 0.691            |
| Aortic diameter, mm              | 33.9±3.2               | 35.0±3.0         | 33.5±2.6              | 0.075            |
| Mitral inflow E, m/s             | 0.6±2.5                | 0.5±0.2          | 0.5±0.1               | 0.093            |
| Mitral inflow A, m/s             | 0.6±0.2                | 0.6±0.1          | 0.7±0.2               | 0.104            |
| Mitral inflow DT, ms             | 198.7±38.7             | 211.6±31.6       | 210.7±47.3            | 0.003*           |
| Mitral inflow E/A                | 0.9±0.4                | 1.0±0.3          | 0.9±0.3               | 0.110            |
| Mitral annulus medial E', cm/s   | 6.5±1.6                | 6.9±1.8          | 6.0±1.4               | 0.001**          |
| MV E/E'                          | 8.6±2.4                | 8.2±2.2          | 9.5±3.2               | 0.001**          |
| LV mass, g                       | 150.3±32.9             | 158.8±25.6       | 153.6±45.8            | 0.328            |
| LVMI, g/m²                       | 86.9±17.9              | 89.8±12.1        | 91.7±29.0             | 0.037*           |
| Dolichoectasia                   | 2 (0.3)                | 0 (0.0)          | 5 (4.0)               | <0.001*          |
| Disease severity                 |                        |                  |
| Total KV, L                      | 1.8±1.6                | 1.6±1.2          | 2.4±1.9               | <0.001*          |
| Liver cysts                      | 2.4±1.2                | 2.2±1.3          | 3.0±0.9               | <0.001**         |
| Laboratory                       |                        |                  |
| WBC, ×10³/μL                    | 6.2±2.1                | 6.2±1.5          | 5.8±2.7               | 0.200            |
| Neutrophil, %                    | 58.8±9.9               | 58.8±9.6         | 61.0±11.2             | 0.079            |
| Lymphocyte, %                    | 30.7±9.2               | 30.7±8.8         | 29.1±10.2             | 0.217            |
| AST, IU/L                        | 21.0±17.2              | 18.4±4.7         | 22.0±13.7             | 0.616            |
| ALT, IU/L                        | 18.2±13.5              | 14.3±7.0         | 16.6±10.1             | 0.175            |
| Total bilirubin, mg/dL           | 0.8±1.0                | 0.9±0.6          | 0.8±1.3               | 0.877            |
| Cr, mg/dL                        | 2.2±4.9                | 1.8±1.8          | 2.5±2.6               | 0.654            |
| GFR, mL/min/1.73 m²              | 62.2±33.3              | 58.9±30.4        | 46.2±32.6             | <0.001*          |
| ESR, mm/h                        | 16.4±14.6              | 21.0±30.0        | 18.9±16.2             | 0.112            |

ADPKD, autosomal dominant polycystic kidney disease; CVD, cardiovascular disease; DT, deceleration time; LV, left ventricular; LVMI, left ventricular mass index; KV, kidney volume; WBC, white blood cell; AST, aspartate aminotransferase; ALT, amino alanine transferase; GFR, glomerular filtration rate; ESR, erythrocyte sedimentation rate. * Significant difference between the negative and high-risk groups. ** Significant difference between the high-risk group and others.

**Discussion**

The prevalence of intracranial aneurysms in patients with ADPKD is reported to be approximately 10–12%, [16] ranging from 1.2% (Finnish) to 20% (Japanese), which is around 3 times higher than in the general population. In the present study, the prevalence was 16% in patients with ADPKD, which is 3 times higher than in the general population from the Republic of Korea.
Approximately, 80% of spontaneous SAHs are caused by aneurysmal rupture [17]. A meta-analysis of 18 studies showed that the annual incidence of spontaneous SAH in the general population was 0.01%. In contrast, aneurysmal SAH in patients with ADPKD was reported to be 4 times higher than in controls, occurring at a younger age and comprising relatively small-sized aneurysms. Among patients undergoing kidney transplantation, patients with ADPKD had a prevalence of SAH that was 4 times higher than patients without ADPKD [6]. In the present study, the prevalence of previous aneurysmal SAH in patients with ADPKD was 1.2%, which is notably higher than in the general population (0.02%) of Korea. However, there was no difference in the outcome of aneurysmal SAH between the patients with ADPKD and age- and sex-matched controls [18].

Intracranial arterial dolichoectasia occurs when the diameter of at least 1 major cerebrovascular artery is extended beyond its normal range. A previous study showed that intracranial dolichoectasia was present in 4.7% of patients with ADPKD, approximately 80 times higher than in the control group (0.06%). In another study of patients with ADPKD who underwent cerebral angiography, dolichoectasia was reported in 2.3% of patients, but not in patients without ADPKD [19]. In the present study, 7 patients (0.76%) presented with intracranial dolichoectasia, which is lower than in previous studies. Moreover, intracranial dolichoectasia was mainly found in patients with aneurysm (3.4%), particularly those with a high-risk phenotype (4.0%). Vascular abnormalities of intracranial aneurysms and dolichoectasia originate from the loss of wall integrity as a result of weakened connective tissue. The manifesting features of abnormal vascular wall integrity differ depending on the vascular geometry: dolichoectasia occurs in a long cylindrical artery such as the BA, and aneurysms occur at sites of bifurcation or branching. However, whether the distribution of intracranial dolichoectasia or aneurysms differs according to vascular geometry or ethnicity requires further investigation.

Patients with ADPKD have a higher incidence of heart disease than healthy individuals, which is one of the leading causes of death in these patients [20]. One in 4 patients with ADPKD present with mitral valve prolapse, and aortic root dilatation has been reported in 8%. Additionally, patients with ADPKD have a high incidence rate of LV hypertrophy. Mitral inflow DT refers to the time interval between the early diastolic stage of the left ventricle and the final deceleration [21]. In grade 1 LV diastolic dysfunction, initial filling of the ventricle is limited. Therefore, mitral inflow DT tends to extend, while in grade 2 or higher, the pressure in the left atrium becomes greater than in the left ventricle, and the mitral inflow DT decreases more than normal. The variable pattern of mitral inflow DT partly reflects the LV diastolic dysfunction. Further research is warranted to determine whether patients with aneurysms and a long mitral inflow DT progress to severe LV dysfunction [22].

In the present study, patients with hypercholesterolemia had a lower prevalence of intracranial and high-risk aneurysms. Low serum cholesterol or LDL-C is associated with increased hemorrhagic stroke [23]. In a meta-analysis of intracranial aneurysms, a high serum cholesterol was associated with a low risk of SAH. Meanwhile in other studies, a high total cholesterol concentration increased the risk of intracerebral hemorrhage and SAH [24]. Large-scale prospective studies are needed to establish whether hypercholesterolemia has a protective effect on intracranial aneurysms and aneurysmal SAH in patients with ADPKD.

The categorization of the patients with ADPKD according to the 4 criteria seems to be arbitrary in the present study. However, it deserves mentioning that the low-risk aneurysm group (group 2) showed numerically intermediate (such as LVMI and GFR) or relatively healthy characteristics (such as dolichoectasia, kidney volume, and hepatic cysts). Although further studies are needed, a simple set of 4 criteria (location, maximal width, multiplicity, and a history of SAH) may be helpful to screen for high-risk intracranial aneurysms in patients with ADPKD.
This study has a few limitations. First, it is a retrospective cross-sectional study. Over 40% of the initially screened patients were excluded due to the unavailability of their cerebrovascular images. A longitudinal prospective study is needed in the future to define whether intracranial aneurysms evolve into high-risk aneurysms or aneurysmal SAH. Second, the present study was performed in a single center; therefore, the generalizability of the findings cannot be guaranteed. A multicenter study is needed to enhance the applicability of the findings to a larger population. Last, magnetic resonance angiography (MRA) was used to detect aneurysms and dolichoectasia. MRA is known to underestimate the arterial diameter, and this may have affected the reported prevalence of dolichoectasia.

Conclusion

In the present study among patients with ADPKD, the prevalence of intracranial aneurysms and aneurysmal SAH was 16 and 1.2%, respectively. Age, female sex, dolichoectasia, and mitral inflow DT were significantly and positively associated with high-risk aneurysms, whereas hypercholesterolemia was negatively associated. Metabolic parameters have to be carefully examined and considered for the suitable care of patients with ADPKD.

Statement of Ethics

The study has been approved by the research institute’s committee on human research, and the committee waived the requirement for informed consent. (Seoul National University Hospital; No. 1804-054-936).

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

K.H.J. and C.H.L. contributed to study design and conception. S.K.J. and C.H.L. performed the statistical analysis and interpreted the data. C.H.L. wrote the first draft of the manuscript. C.A. and H.J.R. revised the manuscript for intellectual content. H.S.K. provided critical advice and comments for the manuscript. All authors read and approved the final manuscript.

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