Intracranial aneurysms in renal transplant recipients with autosomal dominant polycystic kidney disease

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Introduction Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic renal disorder. Its prevalence is estimated at 1:1000. In a substantial number of adult patients, ADPKD leads to end-stage kidney disease (ESKD).[1] The median age of onset of ESKD is between 58 and 79 years, depending on the type of disease.[2] The clinical picture of ADPKD is not limited to the kidneys; there are numerous extrarenal manifestations of the disease, and the most dangerous are intracranial aneurysms (IAs). The prevalence of IAs in ADPKD is estimated at 11.5%,[3] compared with approximately 2% in the general population.[4] However, these data apply to the pre-ESKD population, while studies on the prevalence of IAs in patients with ADPKD and ESKD are limited in the literature. To date, the results of a single study on a Korean population are available.[5] According to previous studies, the incidence of IAs in ADPKD increases with age and correlates with kidney enlargement,[6] which is recognized as a prognostic marker of progression to ESKD in ADPKD.[7] Additionally, patients with ESKD are at a very high risk of cardiovascular complications, and ADPKD is a significant risk factor for intracranial hemorrhage among patients on dialysis[8] and after renal transplantation.[9] These findings led to the hypothesis that the prevalence of IAs in patients with ADPKD and ESKD is further increased. To test it, we conducted a cross-sectional study on the prevalence of IAs in renal transplant recipients with ADPKD.

Patients and methods Over 2500 renal transplant recipients were managed at the outpatient department of the Department of Immunology, Transplant Medicine, and Internal Diseases of the Medical University of Warsaw, Poland during the period of the study (2015–2019). Within this group, 88 patients with ADPKD were identified, and 66 of these patients accepted to participate in our study. The inclusion criteria were: the diagnosis of ADPKD, being a renal transplant recipient, age older than 18 years, lack of contraindications for magnetic resonance imaging, and signed informed consent. We decided not to exclude patients with a history of IA from our study because we sought to investigate the prevalence of IA in the entire group of renal transplant recipients with ADPKD. After inclusion to the study, 3-dimensional time-of-flight magnetic resonance angiography of the brain was performed. All imaging studies were performed between January 2015, and November 2019, using the Ingenia 1.5T HP scanner (Philips Healthcare, Best, the Netherlands). Demographic and clinical parameters were obtained from medical records. All patients with suspected or diagnosed IA were referred to a neurosurgeon.

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the ethics committee of the Medical University of Warsaw approved the protocol. All patients gave written informed consent for inclusion into the study.

Statistical analysis We performed statistical analysis with the Statistica software, version 12.5 (StatSoft, Tulsa, Oklahoma, United States). The Pearson χ^2 test, the Fisher exact test, and the Mann–Whitney test were used as appropriate. The strength of the relationship between tested nominal features was determined with the Yule phi contingency coefficient. A P value of less than 0.05 was considered statistically significant.

TABLE 1 Characteristics of the study group (n = 66)

Characteristic		Values
Men/women, n (%)		33 (50)/33 (50)
Age, y, median (range; IQR)		60.94 (37.5–78.2; 54.2–64.9)
Time after renal transplantation, mo, median (range; IQR)		34.97 (0.6–236; 8.51–85.72)
eGFR, ml/min/1.73 m² [CKD-EPI formula], median (range; IQR)		47.5 (7–97.3; 33.7–67.5)
Tacrolimus/cyclosporine A, n (%)		46 (69.69)/20 (30.31)
Mycophenolate mofetil/azathioprine, n (%)		51 (77.27)/6 (9.1)
Past acute rejection, n (%)		4 (6.1)
Cold ischemia time, min, median (range; IQR)		1290 (555–3875; 897–1870.8)[a]
Warm ischemia time, min, median (range; IQR)		32 (17–45; 22–35)[b]
Time on dialysis before transplantation, mo, median (range; IQR)		22 (0–84; 12–32)
Height, cm, median (range; IQR)		170 (155–196; 165–178)
Body mass, kg, median (range; IQR)		70 (52–110; 63–82)
BMI, kg/m², median (range; IQR)		24.23 (18.40–31.25; 22.51–26.41)
BMI, n (%)	≤18.5 kg/m² (underweight)	1 (1.5)
	18.6–24.9 kg/m² (normal)	39 (59.1)
	25–29.9 kg/m² (overweight)	22 (33.3)
	≥30 kg/m² (obese)	4 (6.1)
Arterial hypertension, n (%)		63 (95.5)
Ischemic heart disease, n (%)		12 (18.2)
Dyslipidemia, n (%)		18 (27.3)
Diabetes, n (%)		20 (30.3)
Intracranial aneurysm in a family history, n (%)		28 (42.4)
Intracranial aneurysm treatment or SAH before transplantation, n (%)		14 (21)
Past sepsis, n (%)		16 (24.2)

a Data available for 45 patients

b Data available for 42 patients

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SAH, subarachnoid hemorrhage

Results A total of 66 patients were included in the study. All included patients were Caucasians. All patients were recipients of their first renal transplant. The characteristics of the study group are presented in **TABLE 1**.

Based on the imaging results, 18 IAs were diagnosed in 15 patients. All patients presented with a single IA, except for 1 patient who had 4 aneurysms. IAs were localized mainly in the anterior circulation (82%). The localization of 1 IA was impossible to establish, as its presence was manifested by a spontaneous subarachnoid hemorrhage (SAH) in the posttransplant period. Of note, this particular patient had not undergone brain imaging in the past, and the hemorrhage occurred 13 years after the transplantation. This patient was not excluded from the analysis, considering that more than half of the other participants were also not examined in the pretransplantation period. The mean diameter of IAs was 4.6 mm. The largest IA was 14 mm in diameter and 18 mm in length, and the smallest was only 1 mm in diameter. Most of the diagnosed IAs were small; 14 (82%) with a diameter less than 7 mm. Eight of the patients diagnosed with IA were qualified

for surgical clipping or endovascular coiling due to the risk of rupture. In the group of patients with IA, 8 (53%) had a positive family history of IA, and 5 (33%) had neurosurgical treatment due to an aneurysm or had SAH before the kidney transplantation.

Significant associations were found between IA presence and body mass index (median in IA-positive group, 28.03; median in IA-negative group, 24.03; $P = 0.01$), headaches ($P < 0.001$; Yule phi = 0.51), dyslipidemia ($P = 0.02$; Yule phi = 0.29), and time after transplantation (median in IA positive group: 7.07; median in IA negative group: 46.03; $P = 0.03$) as well as cold ischemia time (median in IA positive group, 823.5; median in IA negative group, 1361.5; $P = 0.02$).

Discussion The results of our cross-sectional study in renal transplant recipients with ADPKD suggest that the prevalence of IAs in this population is increased (22.7%). This may be linked to an increased risk of SAH in this cohort. As ADPKD is the fourth leading cause of ESKD, responsible for approximately 10% of cases,[10] the number of patients at risk is substantial. The prevalence of IAs in our study was even higher compared

with the results of Kim et al,[5] which may be explained by ethnic differences (that study included Korean patients). The majority of IAs in our study were localized to the anterior cerebral circulation, which corresponds with the results of the previous study.[11]

We expected the prevalence of IA to increase with age, as was suggested previously.[6] Such a trend was not shown by our analysis; however, it is important to consider that younger subjects were underrepresented due to the fact that renal transplantation is required in the older group. We therefore believe that a high prevalence of IAs in our group is linked to the age of included patients.

As reported previously, IAs were equally distributed between men and women,[11] which is a characteristic feature in ADPKD, but in contrast to what is typically seen in the general population. Height and body mass did not impact IA occurrence in our study, but an increased body mass index was observed among patients with IAs compared to those without IAs.

In our group, patients with IAs reported having a headache significantly more frequently compared to non-IA cases. The presence of a headache was not thought to be a manifestation of IA in ADPKD[12]; however, according to our results, headache should be considered an indication for IA screening in patients with ADPKD.

Intracranial aneurysm in a pretransplant medical history and a positive family history for IA were not risk factors for IA in our population. However, in the literature, a positive family history for IA is considered a risk factor for IA in the ADPKD population,[11] and we believe that our findings result from the low number of patients in our group.

Renal function did not impact the occurrence of IA in our analysis, which is in line with previous findings.[11] Time after renal transplantation negatively correlated with the frequency of IAs. Also, cold ischemia time was found to be negatively associated with the risk for IAs. That was quite unexpected, and these results should be verified in a larger study. We failed to demonstrate an association between IA and ischemic heart disease as well as cardiovascular risk factors except for dyslipidemia.

Our study has several limitations. Due to the characteristics of the Polish population, only Caucasians were included in our study. The group was relatively small, and only selected factors were analyzed as potential risk factors for IA. Moreover, a relatively large number of patients in our group had a positive family history or medical history of IA, which may lead to a bias towards an increased prevalence of IAs in the study group. Finally, in a large proportion of our patients, data on IA presence prior to transplantation was lacking.

We believe that our results may reflect the natural history of ADPKD, and our observations are applicable to all post-ESKD patients with ADPKD, including both renal transplant recipients and those on dialysis. As 1 in 5 patients with ADPKD after renal transplantation has IA and is at risk of SAH, efforts should be made to identify the possible risk factors for IA occurrence in this group. Until they are known, we suggest that all renal transplant recipients with ADPKD, and most probably, patients with ADPKD on dialysis, should undergo imaging for IAs, and in the case of suspicion or diagnosis of IA, should be referred to a neurosurgeon. Screening for IA may be of special importance in patients with overweight or obesity, headache, and dyslipidemia.

Conclusions   The prevalence of IAs in our group of patients with ADPKD after renal transplantation was 22.7%. Until specific risk factors for IA occurrence in this group are known, we recommend that all renal transplant recipients with ADPKD should undergo screening for IAs with magnetic resonance angiography.

ARTICLE INFORMATION

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