Intracranial Aneurysms in ADPKD
How Far Have We Come?

Ivana Y. Kuo[1] *and Arlene Chapman*[2]

CJASN 14: 1119–1121, 2019. doi: https://doi.org/10.2215/CJN.07570719

Autosomal dominant polycystic kidney disease (ADPKD), the most common hereditary kidney disease, is relatively uncommon, occurring in approximately one in every 1000 people, with fewer than 300,000 diagnosed in the United States. Intracranial aneurysms are one of numerous types of vascular manifestations in ADPKD and occurs infrequently (5%–9%), but three- to five-fold more often than among the general population. Proper identification of risk factors for intracranial aneurysm formation in ADPKD is important and can allow for targeted patient screening and risk factor reduction. These data are critical given the significant morbidity and mortality (between 40% and 60%) associated with intracranial aneurysm rupture in ADPKD. Before prospective observational studies in patients with asymptomatic ADPKD determined the frequency of intracranial aneurysms accurately, it was thought that intracranial aneurysm frequency was as high as 40%, because of case selection bias. Given these issues, it is critical that adequate numbers of patients have follow-up for an extended duration in an unbiased, prospective fashion to determine the risk for intracranial aneurysm formation and rupture in ADPKD. Similar to intracranial aneurysms in the general population, large studies typically include >10,000 participants. These studies have identified smoking exposure, hypertension, and family history as important risk factors for intracranial aneurysm formation.

In this edition of CJASN, Sanchez Munoz (1) provide an updated analysis of 812 individuals with ADPKD, which is an expanded population from previous reports. Compared with other smaller reports from the same institution (Table 1) (2,3), the positive family history of intracranial aneurysm has reduced from 67% (2) to 50% (3) to 37%. In addition, the frequency of a positive family history of a ruptured intracranial hemorrhage remains higher, 39% (3) and 23% in the current paper. Work by Sanchez-Munoz more accurately reflects other cohorts with regard to the frequency of a family history of a ruptured intracranial aneurysm due to the larger number of subjects available for study and a reduction but not complete absence of referral bias. Overall, the new data confirm the three- to five-fold higher intracranial aneurysm frequency (8%–9%) than the general population (2%–3%), and a rate of new intracranial aneurysm formation and growth rate similar to that found in the general population are reported. Genotype data are incomplete, which precludes determination of genetic contributions to intracranial aneurysm formation. Smoking exposure among intracranial aneurysm cases is consistently high throughout all reports (rates three times greater than the current general population), a similar risk factor for individuals with intracranial aneurysm in the general population. Frequency of intracranial aneurysm in the anterior circulation of the circle of Willis is high (85%), but again similar to the general population. Hypertension frequency is noted to be high, consistent with the presence of ADPKD. Intriguingly, and new in this report, a more advanced stage of CKD is associated with intracranial aneurysm. The opportunity to evaluate this larger population with a broad range of kidney function has allowed for this association to be detected.

Included in this report, outside ADPKD cohorts from randomized, clinical trials were included to increase the number of participants available for evaluation. However, caution in interpretation is suggested given specific exclusion criteria (evidence of an intact and unruptured intracranial aneurysm), restricted inclusion criteria (relatively intact kidney function), short duration of follow-up (despite the high number of patient-years calculated because of large numbers of individuals), low frequency of smoking exposure, single patients participating in multiple cohorts not accounted for, and rigorous BP control (dictated by clinical trial design). These cohorts are perhaps not appropriate to draw conclusions regarding intracranial aneurysm in the general ADPKD patient population. On the basis of the single-center data provided by Sanchez Munos (1), it can be said that the indications for screening for intracranial aneurysm in ADPKD and risk factor reduction remain largely unchanged. Importantly, difficulties in determining a unique biologic basis for the increased rate of intracranial aneurysm formation in ADPKD still remain.

Vascular abnormalities, including endothelial dysfunction, left ventricular hypertrophy, abnormal ventricular relaxation, dilated cardiomyopathy, and intracranial aneurysm, occur in patients with ADPKD. As the polycystin proteins (polycystin 1 and 2) are present in both smooth muscle and endothelial cells, it is tempting to speculate that reduced protein expression and

[1]Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois; and [2]Department of Medicine, University of Chicago, Chicago, Illinois

Correspondence: Dr. Arlene Chapman, Department of Medicine, University of Chicago, 5841 S Maryland Ave MC5100, Chicago, IL 60637. Email: achapman1@medicine.bsd.uchicago.edu

Table 1. Clinical and aneurysm characteristics in patients with ADPKD between 1989 and 2019 at a single center

Variable	1989–2002[a]	1989–2009[b]	1989–2017[c]
No. screened		407	812
Intracranial aneurysms/patients/%	23/21/NA	45/38/9	94/75/9
Family History of intracranial aneurysm or sub-arachnoid hemorrhage, in patients with intracranial aneursym (%)	67	50	37
Smokers (%)	50	42	43
Hypertension, in patients with intracranial aneurysms (%)	91	97	90
Anterior circulation (%)	77	84	88
Genotyping Available (%)	38	68	55
Overall intracranial aneurysm rupture (%/patient-years)	NA	0	0.04
New intracranial aneurysm after initial MRI (%/patient-years)	NA	0.40	0.33

NA, not available; MRI, magnetic resonance imaging.
[a]Gibbs et al. (2).
[b]Irazabal et al. (3).
[c]Sanchis et al. (1).

function in either of the two vessel layers, or their primary cilia, coupled with the additional traditional inflammatory insults of reduced kidney function, hypertension, and smoking exposure, could lead to an increased frequency of intracranial aneurysm formation.

Patients with ADPKD, even in those with preserved kidney function, have endothelial dysfunction typified by decreased availability of the vasodilator nitric oxide and an increase in circulating reactive oxidative stress markers (4,5). Moreover, inflammatory markers are elevated in patients with ADPKD, which can also contribute to vascular remodeling. Based on this report by Sanchez Munoz (1), the sequelae of mutations in the ADPKD genes and the loss of polycystin protein from the vasculature may enhance intracranial aneurysm formation in the setting of traditional risk factors (hypertension, smoking, and CKD), rather than inciting a novel mechanism of intracranial aneurysm formation. It remains to be determined if the ADPKD genes and their proteins participate in a unique signaling mechanism that is independent of reactive oxidative stress or nitric oxide production, resulting in intracranial aneurysm formation.

Detailed mechanistic studies using knockout murine models have focused on the smooth muscle cell layer, where polycystin 1 and polycystin 2 regulate different vascular responses. Loss of polycystin 1 from smooth muscle cells diminishes the myogenic response in the mesenteric circulation without alterations in systemic BP (6). In contrast, loss of polycystin 2 from smooth muscle cells results in hypotension, with no change to mesenteric myogenic tone, but decreases evoked a-adrenergic contraction (7). Similar detailed studies examining the endothelium are yet to be conducted and may indicate a primary role for ADPKD genetic defects in intracranial aneurysm formation. Therefore, it may be that the specific genotype (either *PKD1* or *PKD2*) is a unique confounder to the overall vascular formation. In summary, this report provides some incremental confirmatory information regarding the increased frequency of intracranial aneurysm, the traditional characteristics of intracranial aneurysm in ADPKD similar to the general population, and a significant need for more mechanistic studies to determine how central a role the ADPKD proteins polycystin 1 and 2 play in intracranial aneurysm formation.

It is highly unlikely that a large, prospective, longitudinal study to specifically examine intracranial aneurysms in ADPKD will add new information to what has now been established. The hereditary contribution to intracranial aneurysm formation is strongest with first-degree relatives, suggesting that years of shared environment or nurture are also a component of the familial contribution to aneurysm formation. In-depth phenotyping of appropriately selected patients not necessarily large in number may provide the most informative study for intracranial aneurysms in ADPKD. Currently, accurate measures of endothelial function, alterations in vascular reactivity, and measures of arterial stiffness and precise measures of cardiac function are available. These studies could be performed in those with and without intracranial aneurysm from the same family and in families with no prior intracranial aneurysm. Response to acute hydrocarbon exposure mimicking smoke inhalation could also be performed in these same individuals, with direct measurement of endothelial and vascular smooth muscle function. These types of measurements most likely will shed light on to the mechanistic contributions of the polycystins to intracranial aneurysm formation in ADPKD.

Disclosures

Dr. Chapman and Dr. Kuo have nothing to disclose.

Funding

Dr. Kuo is supported by a grant from National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (R00DK101585) during the conduct of the study.

References

1. Sanchis IM, Shukoor S, Irazabal MV, Madsen CD, Chebib FT, Hogan MC, El-Zoghby Z, Harris PC, Huston J, Brown RD, Torres VE: Presymptomatic screening for intracranial aneurysms in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 14: 1151–1160, 2019
2. Gibbs GF, Huston J 3rd, Qian Q, Kubly V, Harris PC, Brown RD Jr., Torres VE: Follow-up of intracranial aneurysms in autosomal-dominant polycystic kidney disease. *Kidney Int* 65: 1621–1627, 2004

3. Irazabal MV, Huston J 3rd, Kubly V, Rossetti S, Sundsbak JL, Hogan MC, Harris PC, Brown RD Jr., Torres VE: Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 6: 1274–1285, 2011
4. Raptis V, Loutradis C, Sarafidis PA: Renal injury progression in autosomal dominant polycystic kidney disease: A look beyond the cysts. *Nephrol Dial Transplant* 33: 1887–1895, 2018
5. Klawitter J, Reed-Gitomer BY, McFann K, Pennington A, Klawitter J, Abebe KZ, Klepacki J, Cadnapaphornchai MA, Brosnahan G, Chonchol M, Christians U, Schrier RW: Endothelial dysfunction and oxidative stress in polycystic kidney disease. *Am J Physiol Renal Physiol* 307: F1198–F1206, 2014
6. Bulley S, Fernández-Peña C, Hasan R, Leo MD, Muralidharan P, Mackay CE, Evanson KW, Moreira-Junior L, Mata-Daboin A, Burris SK, Wang Q, Kuruvilla KP, Jaggar JH: Arterial smooth muscle cell PKD2 (TRPP1) channels regulate systemic blood pressure. *ELife* 7, 2018
7. Sharif-Naeini R, Folgering JH, Bichet D, Duprat F, Lauritzen I, Arhatte M, Jodar M, Dedman A, Chatelain FC, Schulte U, Retailleau K, Loufrani L, Patel A, Sachs F, Delmas P, Peters DJ, Honoré E: Polycystin-1 and -2 dosage regulates pressure sensing. *Cell* 139: 587–596, 2009

Published online ahead of print. Publication date available at www.cjasn.org.

See related Patient Voice, "An ADPKD Patient's View on Screening for Intracranial Aneurysms," and article, "Presymptomatic Screening for Intracranial Aneurysms in Patients with Autosomal Dominant Polycystic Kidney Disease," on pages 1117–1118 and 1151–1160, respectively.