Intracranial Aneurysms in Autosomal Dominant Polycystic Kidney Disease

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ABSTRACT

BACKGROUND AND PURPOSE: ADPKD correlates with an increased frequency of ICANs, but universal screening for ICANs in patients with ADPKD is not currently recommended. The aim of our study was to determine which groups might benefit from screening by determining the prevalence of ICANs in the Polish ADPKD population and identifying any subgroups with an increased risk for ICANs.

MATERIALS AND METHODS: Eighty-three adult, predialysis-phase patients with ADPKD underwent screening for ICANs with MRA of the brain.

RESULTS: The prevalence of ICANs in the studied population was 16.9%, with 6% of the screened group requiring neurosurgical intervention. We also found that the frequency of ICANs increases with age, reaching 22.4% in patients older than 45 years. All diagnosed ICANs were small (< 9 mm) and were localized in the anterior circulation. In addition, MR imaging revealed arachnoid cysts in 4.8% of patients with ADPKD.

CONCLUSIONS: We suggest that patients older than 45 years with ADPKD be considered as candidates for screening for ICANs, and we propose a clinical algorithm for this subgroup. However, we could not find risk factors for ICANs in younger patients with ADPKD.

ABBREVIATIONS: ADPKD = autosomal dominant polycystic kidney disease; AH = arterial hypertension; CKD = chronic kidney disease; ICAN = intracranial aneurysm; CI, confidence interval

ADPKD is the most common monogenic disease, affecting 1 of every 1000 people. However, although ADPKD leads to end-stage renal disease in a large proportion of patients, its symptoms are not limited to the kidney. Extrarenal manifestations include, among others, cysts in other organs (eg, liver and pancreas); arterial hypertension; and ICANs,[1] which are more likely to occur in patients with ADPKD than in the general population.[2] There is also a higher incidence of ICAN rupture in younger patients than is seen in the general population,[3,4] which correlates with a high risk for serious complications or death.[5,6]

According to the analysis of Butler et al,[7] universal screening for ICANs in the ADPKD population may positively influence patient outcome and is cost-effective. On the other hand, ICANs detected by screening are usually small, with a very low expected rupture rate.[8] Therefore, in clinical practice, the indications for screening are limited to subgroups of patients with either a family history of ICAN or previous aneurysm rupture, those undergoing major elective surgery, or those in a high-risk occupation.[9] Furthermore, universal screening is thought to be of low cost-effectiveness, and risks have been associated with treatment of diagnosed ICANs.[10] Unfortunately, except for a positive family history of subarachnoid hemorrhage, no risk factors for ICANs in patients with ADPKD have been defined,[3] which means that we are not able to identify all patients with a risk for subarachnoid hemorrhage from ICAN rupture. However, as some authors support systematic screening for ICANs in patients with ADPKD,[11,12] our study was designed to determine the prevalence of ICANs in the Polish ADPKD population to identify subgroups with an increased risk for ICANs who might benefit from screening.

MATERIALS AND METHODS

Eighty-three patients diagnosed with ADPKD according to the unified ultrasonographic criteria[13] were included in our study (Table 1). All included patients were white and were in the predialysis period of ADPKD. Twenty-three of the patients in this study were related to other patients, comprising 10 families. A detailed

Table 1: Characteristics of study group

Characteristic	Values
Men/Women (%)	32 (38.6)/51 (61.4)
Mean age (range; SD)	46 (19–75; 15)
Stage of chronic kidney disease (%)[a]	
1	23 (27.7)
2	20 (24.1)
3	25 (30.1)
4	14 (16.9)
5	1 (1.2)
Body mass index (%)	
Underweight (BMI ≤18.5 kg/m^2)	4 (4.8)
Normal (BMI 18.6–24.9 kg/m^2)	41 (49.4)
Overweight (BMI 25.0–29.9 kg/m^2)	28 (33.7)
Obese (BMI ≥30.0 kg/m^2)	10 (12.1)
Arterial hypertension (%)	80 (96.4)
Insufficient control of blood pressure	62 (74.7)

Note:—BMI indicates body mass index.
[a] Estimated glomerular filtration rate is calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula.

Table 2: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Diagnosis of ADPKD	Pregnancy
Age ≥18 years	Contraindications for MR imaging
Written informed consent	Dialysis or post-kidney transplantation

list of the inclusion and exclusion criteria are presented in Table 2. A 3D time-of-flight MRA study of the brain was performed to screen for ICANs in patients included between May 2009 and June 2012 at the Medical University of Warsaw Department of Radiology. The MR scanners used in the study were a Magnetom Avanto 1.5T (Siemens, Erlangen, Germany) and an Ingenia 1.5T HP (Philips Healthcare, Best, the Netherlands). For the Magnetom Avanto, examinations were made between 2009 and 2011; for the Ingenia, examinations were conducted in 2012. Details of the imaging parameters are presented in Table 3. For patients with a suspected ICAN, MR results were verified by use of CT angiography and were then referred to a specialist in neurosurgery. The criteria used for intervention in patients with intact aneurysms were an aneurysmal diameter of more than 5 mm, irregular shape with blebs or domes on the aneurysm, or progression in size or change in shape on CT angiography. In addition, established high-risk factors for aneurysmal rupture—including a history of tobacco use, hypertension, and a family history of intracranial aneurysm ruptures—were considered in the assessment of treatment options.

This study was conducted in accordance to 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.

We performed statistical analysis by using Statistica software, version 10 (StatSoft, Tulsa, Oklahoma). χ^2 tests and Fisher exact tests were used when appropriate. A P value of $< .05$ was considered statistically significant.

RESULTS

On the basis of MRA, 18 ICANs in 14 patients were suspected. Of those, CT angiography confirmed 16 ICANs in 12 patients. Aneurysms were not proven in 2 patients with an MR imaging suspicion of very small (≤2 mm) ICAN. In 2 male patients with previous ICAN rupture (both occurring before age 40 years), new aneurysms were not diagnosed. As a result, we determined that the prevalence of ICANs in the studied population was 16.9% (14/83; 95% CI, 8.6%–25.1%). Furthermore, in 4 patients (28.6%) 2 ICANs were diagnosed, with the remainder (10/14; 71.4%) found to have a single ICAN. All ICANs were localized in the anterior circulation, including 12 (66.7%) in the middle cerebral artery, 5 (27.8%) in the anterior communicating artery, and 1 (5.6%) in the internal carotid artery. Among 16 newly diagnosed ICANs, 9 were smaller than 5 mm, and the remaining 7 were between 5 and 9 mm in diameter. After neurosurgical consultation, 5 patients with ICANs ≥5 mm in diameter were treated, and the remaining 7 were not. In total, 6% (95% CI, 0.8%–11.3%) of screened patients with ADPKD required treatment of ICANs. In addition, there was no significant difference in the prevalence of ICANs across sex (women: 9/51 [17.6%]; 95% CI, 6.8%–28.5%; men: 5/32 [15.6%]; 95% CI, 2.3%–28.9%) in patients with ADPKD.

The rates of newly diagnosed ICANs were recorded in the second (0/1; 0%), third (0/15; 0%), fourth (1/14; 7.1%), fifth (1/11; 7.1%), sixth (7/27; 25.9%), seventh (3/9; 33.3%), and eighth (0/6; 0%) decades of life ($P < .05$ for differences between the third and sixth and the third and seventh decades of life), that is, newly diagnosed ICANs were detected in 1 (2.9%) of 34 patients ≤45 years old and in 11 (22.4%) of 49 patients > 45 years old ($P < .05$). In addition, the only patient younger than 45 years diagnosed with ICAN did not need treatment, whereas in patients older than 45 years in which ICANs were detected, 5 (45.4%) of 11 did. New ICANs were diagnosed in 0 (0%) of 4 patients, 5 (12.2%) of 41 patients, 4 (14.3%) of 28 patients, and 3 (30%) of 10 patients who were underweight, normal weight, overweight, and obese, respectively. However, these differences did not reach statistical significance. Furthermore, new ICANs were diagnosed in patients with first (3/23; 13%), second (1/20; 5%), third (3/25; 12%), fourth

Table 3: Imaging parameters used for 3D TOF MRA

	MR Imaging Scanner	
	Siemens Magnetom Avanto 1.5T	Philips Ingenia 1.5T HP
Years of use	2009–2011	2012
Sequence type	T1WI 3D GRE	T1WI 3D FFE
TOF sequence parameters	TE: 7.15 ms; TR: 22 ms; NSA: 1	TE: 6.91 (outphase) ms; TR: 25 ms; NSA: 1
Pixel size (mm) MPS	0.7/0.7/0.7	0.4/0.7/1.0
Matrix RECON	320	512
Flip angle (°)	25	20
Total scan duration (min/sec)	7/13	4/50

FFE indicates fast-field echo; GRE, gradient-recalled echo; MPS, measurement phase and section direction; NSA, number of sampling averages.

(5/14; 35.7%), and fifth (0/1; 0%) stage CKD ($P < .05$ for the difference between second and fourth stage CKD).

New ICANs were detected in 7 (11.3%) of 62 patients with insufficiently controlled AH, 4 (22.2%) of 18 patients with well-controlled AH, and 1 (33.3%) of 3 patients without AH, though these differences were not statistically significant. Among the 23 patients with family members in the studied population, ICANs were detected in 2 patients from different families. In addition, MR imaging results revealed arachnoid cysts in 4 patients (2 men, 2 women; 4.8%; 95% CI, 0.1–9.5%), though no patient with an arachnoid cyst was found to have an ICAN. From an anatomic standpoint, 3 cysts were localized in the posterior cranial fossa and 1 in the middle cranial fossa; the latter was the largest cyst (50 × 48 × 90 mm). None were determined to be symptomatic or require treatment.

DISCUSSION

In our study, the prevalence of ICANs in the ADPKD population was 16.9% (95% CI, 8.6%–25.1%), with equal distribution between male and female patients, which is consistent with what is found in the literature (4%[14]–22.5%[15]). However, our findings are slightly higher compared with the large study of Xu et al,[11] in which the prevalence of ICANs in ADPKD was 12.4%, with equal distribution between the sexes. This feature may be able to distinguish between ICANs in patients with ADPKD and ICANs in the general population, where a higher prevalence has been reported in women.[2] Of note, only 6% (95% CI, 0.8–11.3%) of screened patients with ADPKD required treatment of ICANs. However, when the prevalence of ADPKD is considered, the number of patients who need treatment becomes substantial, accounting for 60 patients for each 1 million people in the general population.

All ICANs detected in our study were small, which is in accordance with the study of Xu et al.[11] However, because 50% of ICANs that rupture are < 10 mm,[4,5] small diameter is not a consideration against screening. All ICANs detected in our study were localized in the anterior circulation, in accordance with a previous study.[11] The most common site of ICAN in ADPKD is the middle cerebral artery, another feature that distinguishes ICANs in patients with ADPKD from ICANs in the general population, where the internal carotid artery is the most common location.[3] Although no case of ICAN in the posterior circulation was detected in our study, some authors have reported this location as being rare[4,5,8,15] and therefore it should be expected in some cases. In addition, we found multiple ICANs in 28.6% of patients, which is more than what has been previously reported.[4,5,11]

According to our data, the prevalence of ICANs increases with age. We only found a single ICAN in patients younger than 45 years, whereas in patients older than 45 years, the frequency of ICANs increased to 22.4%. Because almost half of them required treatment, in our opinion, screening for ICANs should be considered in all patients older than 45 years with ADPKD. An additional reason is that a large proportion of such patients in this age group go on to have end-stage renal disease[1] and become candidates for kidney transplantation or other surgical procedures, such as nephrectomy. Because ICAN is often seen together with uncontrolled blood pressure (occurring in nearly three-quarters of patients in our group), which may increase the risk for periop-

erative complications, we suggest screening for ICANs with MRA as an obligatory procedure during pretransplant evaluation in patients with ADPKD. Other authors have also reported increases in ICAN frequency with age and have suggested systematic screening in patients with ADPKD, but they recommend that screenings start at age 30 years.[11] However, we believe that screening at this young age is not supported by our results. We also did not find a connection between the prevalence of ICANs and body mass index. In addition, although we tried to assess the connection between the prevalence of ICANs and renal function, we only found statistically significant differences between second and fourth stage CKD. This finding is similar to a previous study,[11] which found the frequency of ICANs to be unrelated to renal function.

AH is a risk factor for subarachnoid hemorrhage in the general population,[16] but hypertension is not considered a risk factor for the formation of ICANs in ADPKD.[3,11] In our study, we found that insufficient control of AH did not correlate with an increased frequency of ICANs. However, the limitations of our analysis were that the number of "well-controlled AH" and "no-AH" subgroups was insufficient and that only qualitative data on hypertension were considered. The prevalence of ICANs has been previously reported to be associated with the duration of hypertension.[11] However, in our experience it is a difficult factor to assess, as many patients with ADPKD also live with unrecognized AH. Additional risk factors for subarachnoid hemorrhage in the general population are tobacco smoking and heavy alcohol consumption,[16] but we omitted these factors in our analysis because of incomplete data.

According to published data, subarachnoid hemorrhage from rupture of ICAN in ADPKD often occurs at a young age,[5,15,17] with 64% occurring before age 50 years.[4] Also, patients with a previous stroke from a ruptured ICAN are at risk for new ICANs and should be examined for them.[18] We only detected 2 patients with previous rupture of ICAN in our study, and we did not detect new ICANs in these patients. Although we believe that the number of patients in our subgroup was too low to make valuable conclusions, we agree that this group should be periodically screened for new ICANs. Still the question remains of how to predict an ICAN rupture in younger patients; unfortunately, we failed to identify any risk factors for ICAN and rupture in younger patients with ADPKD.

A positive family history for ICAN is considered a risk factor for ICAN,[5,11,19] and ICAN rupture tends to cluster in some families.[11,19] In our study, we did not find an increased prevalence in family members of involved patients. Again, we believe that this finding is probably the result of a low number of patients in this particular subgroup.

MRA revealed false-positive results in 2 of our patients. Although MRA is a method of choice in the detection of ICANs in patients with ADPKD because there is no x-ray exposure or need for contrast media administration, it has limited specificity, especially in the detection of very small ICANs. Although such ICANs usually do not need treatment, false-positive results may lead to redundant CTA. Therefore, the suspicion of very small ICANs should not be verified with CTA but may only require periodic follow-ups with MRA and should only be verified in case of en-

largement. Additional findings included the discovery of arachnoid cysts in 4.8% of patients. Previous reports have found that arachnoid cysts in ADPKD occur at a rate of 7.1%–8.1%.[20,21] Although these cysts increase the risk for chronic subdural hematoma,[22] none of the discovered cysts resulted in neurologic symptoms or complications.

We propose a clinical algorithm for ICANs in ADPKD, in which all patients older than 45 years with ADPKD undergo screening with MRA, after which the suspicion of an ICAN > 2 mm in diameter should be followed by CTA, and if verified positively, the patient should be referred to a specialist in neurosurgery. In patients with suspected ICAN ≤2 mm in diameter, follow-up with MRA should be considered. Although we do not propose any specific intervals between MR imaging, we believe that that once a year seems reasonable. The obvious limitation of our algorithm is that at-risk patients younger than 45 years are not included, so indications for screening in that group still need to be established.

CONCLUSIONS

The prevalence of ICANs in a sample of Polish patients with ADPKD amounts to 16.9%. Furthermore, 6% of the screened population required neurosurgical treatment of ICANs. We also found that the frequency of ICANs increases with age, reaching 22.4% in patients older than 45 years. Therefore, we suggest that this subgroup of patients be considered as candidates for ICAN screening, especially before elective surgery such as nephrectomy or kidney transplantation. Unfortunately, we could not determine any significant risk factors for ICANs in patients younger than 45 years with ADPKD.

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