Screening for intracranial aneurysms in autosomal dominant polycystic kidney disease is cost-effective

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Intracranial aneurysm rupture is a dramatic complication of autosomal dominant polycystic kidney disease (ADPKD). It remains uncertain whether screening should be widespread or only target patients with risk factors (personal or familial history of intracranial aneurysm), with an at-risk profession, or those who request screening. We evaluated this in a single-center cohort of 495 consecutive patients with ADPKD submitted to targeted intracranial aneurysm screening. Cerebral magnetic resonance angiography was proposed to 110 patients with a familial history of intracranial aneurysm (group 1), whereas it was not our intention to propose it to 385 patients without familial risk (group 2). Magnetic resonance angiography results, intracranial aneurysm prophylactic repair, rupture events, and cost-effectiveness of intracranial aneurysm screening strategies were retrospectively analyzed. During a median follow up of 5.9 years, five non-fatal intracranial aneurysm ruptures occurred (incidence rate 2.0 (0.87–4.6)/1000 patients-year). In group 1, 90% of patients were screened and an intracranial aneurysm was detected in 14, treated preventively in five, and ruptured in one patient despite surveillance. In group 2, 21% of patients were screened and an intracranial aneurysm was detected in five, and treated preventively in one. Intracranial aneurysm rupture occurred in four patients in group 2. Systematic screening was deemed cost-effective and provides a gain of 0.68 quality-adjusted life years compared to targeted screening. Thus, the intracranial aneurysm rupture rate is high in ADPKD despite targeted screening, and involves mostly patients without familial risk factors. Hence, cost-utility analysis suggests that intracranial aneurysm screening could be proposed to all ADPKD patients.

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Autosomal dominant polycystic kidney disease (ADPKD), the most common hereditary kidney disease,[1,2] frequently leads to end-stage renal disease, (~4.7% of the renal replacement therapy population in the United States[3] and 10% in Europe[4]) and is associated with several extrarenal complications.[5]

The most frequent vascular anomaly in ADPKD is an intracranial aneurysm (ICA). ICA prevalence in ADPKD is estimated at between 9% and 12%,[6,7] higher than in the general population (2%–3%).[8,9] The only identified risk factor for ICA in ADPKD is a familial history of unruptured or ruptured ICA. In patients with a familial risk of ICA, the prevalence of ICAs is higher than in the absence of family history (22% vs. 6%–8%).[7] However, ICAs in ADPKD have not been linked to a specific mutation or genetic anomaly.[10]

The main complication of ICAs is subarachnoid hemorrhage (SAH) following rupture. The mean age at rupture is lower in ADPKD (41 years) than in the general population (51 years).[11] Despite significant progress, mortality and morbidity remain high after SAH.[12]

Noninvasive screening for unruptured ICAs is possible. Computed tomography angiography and time-of-flight magnetic resonance angiography (MRA) have a similar sensitivity and specificity to detect ICAs as small as 2 to 3 mm.[13] The use of a contrast agent is necessary for computed tomography angiography but not for MRA. In addition, MRA screening does not use radiation. MRA is recommended to screen for ICAs in ADPKD.[14–16]

When an unruptured ICA is identified, decisions made take into account its size, location, and morphology.[17] Small aneurysms can be managed conservatively but should be reevaluated regularly because aneurysms may grow in size.[14,18] Prophylactic repair is performed by endovascular coiling or, more rarely currently, by neurosurgical clipping.

In ADPKD, a panel of international experts recently recommended a targeted ICA screening, whereas others propose screening to all ADPKD patients (systematic screening).[19] In a targeted screening policy, only patients with a family history of ICA or SAH, patients with a high-risk profession, and patients who demand screening despite adequate information are proposed ICA screening.[14] We recently conducted a large survey to describe the attitudes of French-speaking European nephrologists toward screening for ICA. Although most nephrologists followed the current recommendations for the initial screening of ICAs, 28% of the panel was in favor of systematic ICA screening.[20]

The objective of this study was to evaluate the targeted screening policy that was conducted between 2008 and 2015 in our center in a large ADPKD cohort. We report and analyze MRA results, neurologic intervention, neurologic events, and ICA rupture events. Using the results obtained from the current cohort and previously published studies, we then conducted a cost-utility study to compare the currently recommended targeted screening approach with a systematic screening policy.

RESULTS

Population characteristics

Records for a total of 508 patients were reviewed. One patient was lost to follow-up (moved to a foreign country with no available contact information), 10 patients had a history of ICA rupture (including 9 with no known familial history of ICA at the time of rupture), and 2 patients had ICA prophylactic treatment before inclusion. These 13 patients were excluded from the analysis. The study population consisted of 495 patients with a median follow-up time of 5.9 years (interquartile range, 3.3–7.1). The clinical characteristics of the study population are shown in Table 1. Two patients died during follow-up of causes unrelated to ICA.

ICA screening

The population was divided in 2 groups (Figure 1). Group 1 was formed by 110 patients (22%) with a familial risk of ICA, including 3 patients in whom the familial risk of ICA was identified during the follow-up period. In accordance with our policy, most patients in this group ($N = 100$, 90%) had cerebral MRA. Seven patients refused to undergo ICA screening despite adequate information, and 3 patients did not undergo ICA screening for unknown reasons. When performed, MRA detected an unruptured ICA in 14 patients (14% of performed MRAs).

Group 2 was composed of 385 patients (76%) with no risk factors for ICA. Eighty-one (21%) underwent magnetic resonance imaging screening. An unruptured ICA was detected in 5 patients (6%). The reasons for ICA screening in these patients are summarized in Supplementary Table S1.

In 3 patients, 2 ICAs were found at screening. There was no other patient with multiple ICAs. Nineteen patients underwent a control screening following an initial negative screening. No incident ICA was found in these control imaging studies. Baseline characteristics of patients in each group are shown in Table 1.

Characteristics, management, and outcomes of unruptured ICAs

ICA screening led to the diagnosis of 19 patients with unruptured ICAs (Table 2). Six (32%) underwent prophylactic treatment due to ICA size, location, and/or evolution in time (Table 3), according to the decision flowchart (Supplementary Figure S1). One patient (case 10) refused to receive endovascular treatment. Another patient (case 6) had a surgical repair for an ICA that was small but irregular in shape and located on the bifurcation of the left middle cerebral artery, with a fronto-opercular branch that emerged at

Table 1 | Baseline characteristics of patients included in the study

Parameter	All patients	Group 1: familial risk	Group 2: no familial risk	*P* value[a]	NA, *N* (%)
N (%) of patients	495 (100)	110 (22)	385 (78)		
Age at inclusion, yr, median (IQR)	39 (30–49)	40 (33–49)	39 (29–48)	0.4	0 (0)
Female sex, *N* (%)	287 (58)	66 (60)	221 (57)	0.7	0 (0)
Age at ADPKD diagnosis, yr, median (IQR)	28 (20–37)	28 (20–35)	28 (19–37)	0.8	180 (36)
No family history of ADPKD, *N* (%)	74 (17)	11 (10)	63 (19)	0.05	66 (13)
Follow-up duration, median (IQR)	5.9 (3.3–7.1)	4.9 (2.8–6.9)	6.1 (3.6–7.1)	0.03	0 (0)
sBP, mm Hg, median (IQR)	128 (120–136)	131 (121–138)	128 (119–136)	0.1	8 (2)
dBP, mm Hg, median (IQR)	80 (71–86)	81 (70–87)	79 (71–85)	0.5	8 (2)
Controlled BP, *N* (%) (sBP ≤140 mm Hg and dBP ≤90 mm Hg)	378 (78)	80 (74)	298 (79)	0.4	8 (2)
BMI, kg/m^2, median (IQR)	24 (22–26)	25 (22–27)	24 (22–26)	0.4	68 (14)
mGFR, ml/min, median (IQR)	81 (62–99)	84 (67–96)	80 (60–101)	0.8	33 (7)
Patients receiving the following medications, *N* (%)					
Antihypertensive agents	255 (53)	57 (53)	198 (53)	1	11 (2)
Anticoagulants and antiplatelet agents	8 (2)	1 (1)	7 (2)	0.8	11 (2)
Statins	28 (6)	4 (4)	24 (6)	0.4	11 (2)
Antidepressants (including sertraline)	17 (3)	5 (5)	12 (3)	0.7	11 (2)

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; dBP, diastolic blood pressure; IQR, interquartile range; mGFR, measured glomerular filtration rate; NA, not available; sBP, systolic blood pressure.
[a]*P* values of the comparison between group 1 and group 2 using the Mann-Whitney *U* test or the χ^2 test, when appropriate.