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Screening and Management for Intracranial Aneurysms in Japanese Patients With ADPKD

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is often complicated with extrarenal abnormalities including intracranial aneurysm (ICA) and subarachnoid hemorrhage (SAH), which leads to poor outcome-high mortality and neurological sequelae with a negative impact on patient quality of life.[1] Therefore, because prevention of aneurysmal SAH has the highest potential to prevent poor outcome, appropriate screening and management of aneurysm is important for improving patient prognosis and quality of life. However, the timing of screening and follow-up for ICA is controversial.[2]

Japanese, as well as ADPKD, are risk factors for incidence of intracerebral aneurysm according to the previous meta-analysis,[3] which leads to the hypothesis that ICA is more prevalent in Japanese ADPKD patients. However, there is no published data on the prevalence of ICA in Japanese ADPKD patients. In addition, although the guideline recommends annual follow-up for unruptured ICA with low risk of rupture and consultation to neurosurgeon for that with high risk of rupture,[4] it remains unknown whether the management is effective for ICA in ADPKD patients to prevent ICA rupture.

In this study, we retrospectively investigated the prevalence, clinical course and management of ICA in Japanese ADPKD patients admitted to a single university hospital and the result could help physicians to manage ICA in ADPKD patients.

RESULTS

Baseline Characteristics

Study design was described in Supplementary Method. Of all 136 ADPKD patients who admitted to our hospital (age, 50.7 ± 15.3 years old; female 71 (47.8%); eGFR 60.2 ± 26.9 ml/min/1.73 m^2; Total kidney volume, 1281.1 ± 1009.4 ml), 24 patients (17.6%) had ICA at first admission (Figure 1). Seventy percent of patients with ICA were female. Five patients with ICA (20.8%) already had history of SAH while 2 patients without ICA (1.8%) had. All patients with history of SAH were under 50 years old. Smoking status, low density lipoprotein cholesterol, statin use and the proportions of family history of SAH or ICA in patients with and without ICA were not different. Baseline kidney function and kidney size were similar in both groups (Table 1). All patients with ICA did not have neurological symptoms.

Characteristics of Aneurysm

At first admission, 29 ICAs in 24 patients were detected. Of these ICAs, 26 (89.7%) were less than 5 mm, and 3 ICAs (10.3%) were 5 mm. All but 1 aneurysm was saccular, and 24 (82.8%) were located in anterior circulation (Table S1). Although the prevalence of ICAs were higher in older patients, a certain proportion of younger patients had ICAs (Figure 1). In addition, 5 patients (20.8%) had multiple ICAs.

When we investigated factors associated with aneurysm using univariate logistic models, female was

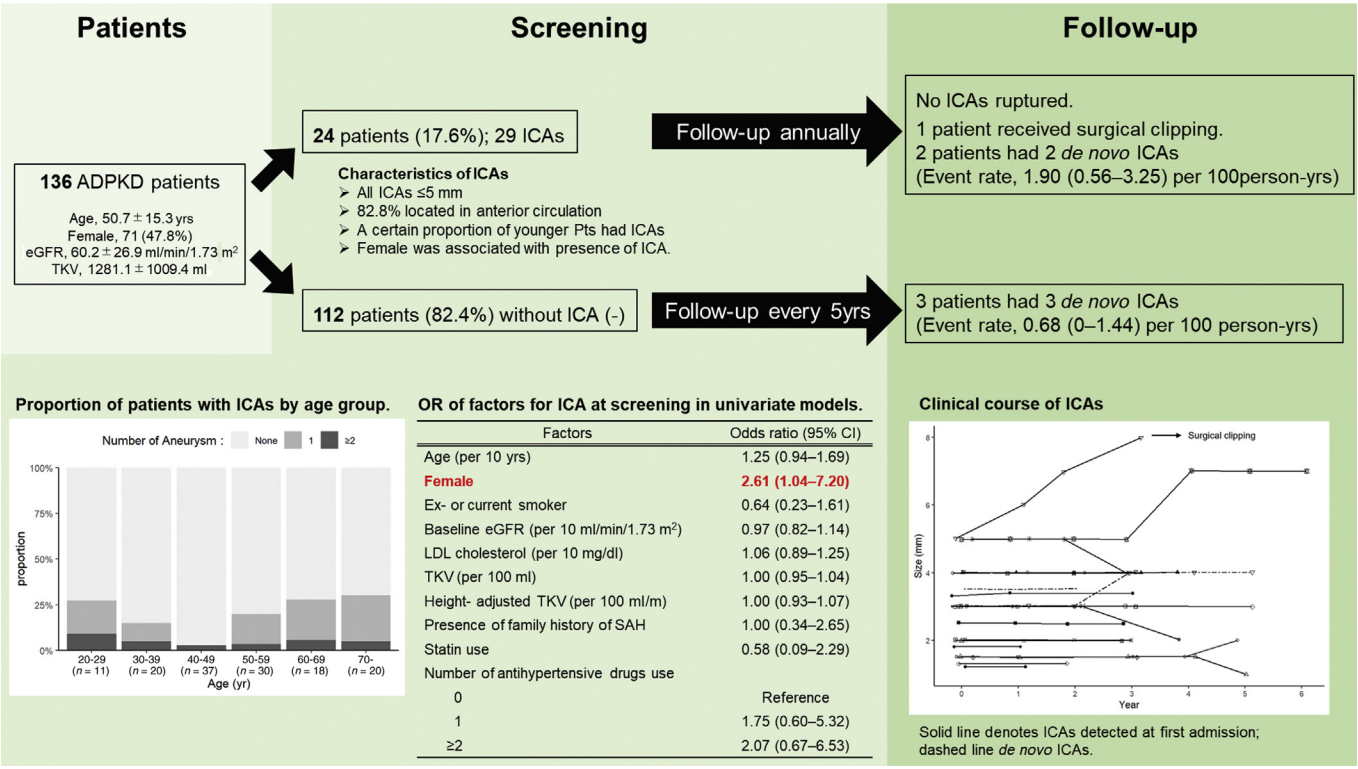

Figure 1. Study results overview. ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; ICA, intracranial aneurysm; LDL, low density lipoprotein; SAH, subarachnoid hemorrhage; TKV, total kidney volume.

Table 1. Baseline characteristics of patients with ADPKD with and without ICA

Factors	ICA (+) (n = 24)	ICA (−) (n = 112)
Age (yr)	55.0 ± 18.1	49.8 ± 14.6
Male, *n* (%)	7 (29.2)	58 (51.8)
Smoking status, *n* (%)		
Nonsmoker	17 (70.8)	68 (60.7)
Ex-smoker	4 (16.7)	26 (23.2)
Current smoker	3 (12.5)	18 (16.1)
Hypertension	17 (70.8)	63 (56.2)
History of SAH	5 (20.8)	2 (1.8)
Medication, *n* (%)		
Calcium blocker	11 (45.8)	36 (32.1)
Angiotensin receptor blocker	13 (54.2)	49 (43.8)
Alpha blocker	2 (8.3)	4 (3.6)
Diuretics other than Tolvaptan	2 (8.3)	4 (3.6)
Family history of ADPKD	18 (75.0)	80 (71.4)
Family history of SAH or ICA	6 (25.0)	25 (22.3)
Baseline eGFR (ml/min per 1.73 m^2)	58.3 ± 30.8	60.6 ± 26.1
LDL cholesterol (mg/dl)	110.2 ± 22.6	106.0 ± 28.4
Statin use, *n* (%)	2 (8.3)	12 (13.4)
TKV (ml)	1276.2 ± 904.3	1282.2 ± 1034.3
htTKV (ml/m)	785.5 ± 533.4	772.4 ± 614.8
Mayo class, *n* (%)		
A	3 (12.5)	17 (15.2)
B	12 (50.0)	48 (42.9)
C	5 (20.8)	30 (26.8)
D	3 (12.5)	13 (11.6)
E	1 (4.2)	4 (3.6)

ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; htTKV, height adjusted total kidney volume; ICA, intracranial aneurysm; LDL, low density lipoprotein; SAH, subarachnoid hemorrhage; TKV, total kidney volume.

associated with presence of ICA at admission (Odds ratio, 2.61; 95% confidence interval, 1.04–7.20) while any other factors including smoking status, low density lipoprotein cholesterol, the presence of hypertension, family history of SAH, kidney function, and kidney size were not (Figure 1).

Follow-up of ICA

During 105.2 person-years follow-up of patients with ICA at first admission, no aneurysms were ruptured, and almost all ICAs did not change (Figure 1). One patient received surgical clipping because of rapid growth and increasing risk of rupture. Two ICAs in 2 patients were newly detected (1.90 per 100 person-years; 95% confidence interval, 0.56–3.25).

On the other hand, during 442.9 person-years follow-up of patients without ICA at first admission, 3 ICAs in 3 patients without ICAs were newly found (0.68 per 100 person-years; 95% confidence interval, 0–1.44). These *de novo* ICAs were less than 5 mm and did not change.

DISCUSSION

This study is the first to evaluate the incidence and clinical course of ICA in Japanese ADPKD patients. The findings in the study are as below: (1) higher incidence of ICA than that of Japanese patients non-ADPKD and ADPKD patients in other countries, (2) possible higher

rate of *de novo* aneurysm, and (3) female patients were associated with the presence of ICA. This study also could propose the appropriate management of ICA because no aneurysms were ruptured during the observation.

The incidence of ICA in Japanese ADPKD patients was higher than that in Japanese non-ADPDK patients (4%)[S1] and that in non-Japanese patients with ADPKD (9%).[S2] This finding is consistent with the recent study from Japan.[S3] Many previous clinical and basic studies show that 2 independent factors–Japanese and ADPKD–are risk factors for incidence of ICA.[3,5,S4,S5] Therefore, it is assumed that Japanese patients with ADPKD have high risk of ICA multiplied by the 2 factors, and the finding is consistent with the hypothesis.

Three characteristics should be taken care. First, a large part of ICAs was located in anterior circulation. This characteristic is known as a high risk of rupture regardless of ICA size according to the large observational studies in Japan.[5,S6] Second, about 20% of ADPKD patients with ICA had multiple aneurysms, which is a risk factor for rupture in the previous Japanese observational study.[6] Third, it is of note that the prevalence of ICA in young patients at age of 30s and 40s were high. These results tell us physicians that we should recognize younger as well as older ADPKD patients have the risk of ICA. These characteristics indicates that ADPKD patients have not only high prevalence of unruptured ICA but also possible high risk of rupture, and all patients should be screened at first admission.

Screening for ICA in all ADPKD patients is controversial. According to previous reports from the United States and Denmark, the prevalence of ICA is 3-fold to 4-fold higher in patients with family history of SAH or ICA than those without.[S7,S8,S9] The Kidney Disease: improving global outcomes guideline does not recommend systemic screening in all ADPKD patients.[7] On the other hand, this study found that no factors including family history of SAH or ICA were not associated with the prevalence of ICA, except female patients. In addition, the prevalence of ICA was higher in Japanese patients than those in other countries. Therefore, we consider that screening for ICA should be routinely done in all ADPKD patients. Routine screening is also justified in the aspect of cost on the basis of the previous report.[8]

Follow-up of patients without ICA is another issue. It is no consensus about whether ADPKD patients without ICA at screening should be followed and about which ADPKD patients without ICA should be targeted. This study found that *de novo* ICAs were detected during follow-up with the rate of 0.68 per 100 person-years (95% confidence interval, 0–1.44). This rate was potentially higher than the previous report.[9] This finding in this study suggests that magnetic resonance angiography should be repeated for all patients with ADPKD without ICA at regular intervals.

This study elucidated that female patient was associated with the presence of ICA in ADPKD. This finding is consistent with previous multicenter studies,[3,4,S7] which reported that around 70% of all patients non-ADPKD with unruptured ICA was female. In addition, it is recently reported that female was associated with ICA rupture though the pathophysiology remains unclear.[9] Although no ICA had not been ruptured in all female ADPKD patients during follow-up in our study probably because the study size was small and regular follow-up of magnetic resonance angiography prevented and detected ICA at high risk of rupture, physicians should take more care over female patients.

The size of aneurysms observed in this study were mostly small and unchanged during the follow-up. This result might cast doubt on the need of annual follow-up for patients with small ICA. However, according to a previous study[S7] in Japan, small aneurysms had a considerable risk of rupture with the cumulative incidence of 0.91% at 2 years and 30% of small aneurysms were treated before rupture. The previous findings may suggest the need of regular follow-up even for patients with small ICA and support our management.

This study was limited by its small sample size, referral bias and retrospective nature. Especially, screening protocol should be validated in a large multicenter randomized trial because this study had a small number of patients requiring interventions so that it remains difficult to detect patients at high risk of ICA rupture or requiring interventions.

In summary, we found high prevalence of ICA in ADPKD patients and that our protocol of ICA management may prevent ICA rupture and detect de novo ICA appropriately.

DISCLOSURE

RM received payment for speakers' bureaus from Otsuka pharmaceutical Co. MN received grants from Astellas, Bayer, Boehringer Ingelheim, JT, Kyowa Kirin, Torii, Mitsubishi Tanabe, Ono, Chugai, Daiichi Sankyo, Takeda, consulting fee from Akebia, Astellas, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Kyowa Kirin, honoraria from AstraZeneca, JT, Kyowa Kirin, Torii, Mitsubishi Tanabe, Ono, Chugai, Daiichi Sankyo. All the other authors declared no competing interests.

AUTHOR CONTRIBUTIONS

RM conceived of the study, participated in its design and coordination, collected samples, analyzed the data. KH and RO collected and analyzed the data. YH, KD and MN provided critical advice for the analysis. RM wrote the manuscript, with contributions from all authors.

SUPPLEMENTARY MATERIAL

Supplementary file (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Location of all ICAs.

STROBE Statement.

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