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Natural history of intracranial aneurysms in autosomal dominant polycystic kidney disease

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ABSTRACT

Autosomal-dominant polycystic kidney disease (ADPKD) is a relatively frequent genetic disorder that is associated with increased prevalence of intracranial aneurysms (IAs). However, evidence on the natural history of IAs in ADPKD is suboptimal. That leads to difficulties in development of recommendations on surveillance on patients with IAs in their medical history, or the need for repeat imaging for IAs in those with a negative result of the initial screening. The aim of the article is to present our experience on the natural history of IAs in ADPKD patients.

Material and methods: Thirty-four ADPKD patients, managed at our outpatient department, with imaging for intracranial aneurysms performed at least twice, were included into present retrospective analysis.

Results: Among 8 patients with an IA in their medical history, no new IA was observed during 93 patient-years of follow-up. In 6 patients with untreated, unruptured IAs, IA growth was observed in 2 cases during 32 patient-years of follow-up. Finally, among 20 patients with a negative result of initial screening, 2 new IAs were noticed during 115 patient-years of follow-up, including 1 patient with a positive family history for an IA, and 1 patient without a family history.

Conclusions: Our observations support repeat imaging for IAs in patients with ADPKD, positive family history of IA, and negative result of initial screening. Additionally, efforts should be made to develop clinical and/or laboratory risk factors for IAs development in ADPKD patients without family history of IA, which enable to identify patients who should undergo repeat imaging for IAs.

Autosomal-dominant polycystic kidney disease (ADPKD) is a relatively frequent genetic disorder, affecting one in 400–1000 live births [1], and leading to renal failure in a high proportion of involved subjects [2]. Among extra-renal manifestations of ADPKD, intracranial aneurysms (IAs) belong to the most important, due to the possible consequences of IA rupture, including persistent disability, and death. The prevalence of IAs in ADPKD patients is estimated at 9–12% [3,4], compared to

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approximately 2% in the general population [5]. Although some authors advocate for universal screening for IAs in ADPKD patients [6], the screening for IAs is quite costly, and the treatment of IAs uncovered by it is not free from the risk of peri-procedural complications [7,8]. That is why the screening for IAs is recommended only in selected subgroups including high-risk patients [1,2,9]. However, in general, these recommendations are not supported by large, high-quality studies. Also, evidence on the natural history of IAs in ADPKD is suboptimal; the knowledge on this subject is based only on a few studies, which included less than 200 participants [3,10–13]. That leads to difficulties in development of high-quality recommendations on (1) surveillance on patients with IA/IAs in their medical history, or (2) the need for repeat screening for IAs in those with a negative result of the initial examination.

According to the authors of the latest review [14], further studies on the natural history of IAs in ADPKD are needed. The aim of the article is to present our experience on the natural history of IAs in this group of patients.

1. Material and methods

All adult ADPKD patients, managed at our outpatient department, with imaging for intracranial aneurysms performed at least twice, were included into present retrospective analysis. Most of them (23/34, 68%) initially participated in our cross-sectional study on the prevalence of IAs in ADPKD patients; the design and results of that study were published previously [15]. The follow-up examinations were performed between July, 2009, and May, 2017. In all participants, the diagnosis of ADPKD was established according to current criteria [16].

In general, population of the current study may be divided into 3 categories: (1) patients with rupture, or treatment, of an IA in their medical history, who were screened for new IAs, according to current recommendations [1,2]; (2) patients with diagnosed IA, who were not qualified to surgical or intravascular intervention, and who were reevaluated for IA growth, according to current recommendations [2]; and (3) patients without IA on the initial imaging. In the latter category, imaging was made in patients with a family history of IAs, according to current standards [1,2,9]; and in those with symptoms suggesting the possibility of IA development (in most cases headache), what was also in line with recommendations [1,9]. Additionally, due to the previous observations [3,15] that the frequency of IAs development in ADPKD increases after 45 year-of-age, and according to the suggestion of Lee at al. [9] that repeat screening should be considered in patients with ADPKD who are at high risk of an IA 5–10 years after the initial examination, imaging was proposed to patients older than 45 year-of age with a negative result of initial screening. Finally, examination for IAs was proposed to those before renal transplantation, with uncontrolled hypertension, and tobacco smokers, what was also in line with guidelines [9].

In all cases, 3D time-of-flight magnetic resonance angiography (MRA) of the brain was performed. Demographic and clinical data were extracted from case records. Renal function was assessed according to the CKD-EPI formula.

The study was conducted in accordance to the principles of the Declaration of Helsinki. Due to the fact that examinations were made based on medical indications, and were in line with current guidelines, the approval of the ethics committee was not necessary.

Descriptive statistics was made using Statistica software. Quantitative data are expressed as mean ± standard deviation.

2. Results

Thirty-four patients were included into current study, including 8 patients with rupture ($n = 7$), or treatment ($n = 1$), of an IA in their medical history (subgroup 1); 6 patients with untreated, unruptured IAs, who were reevaluated for IA growth (subgroup 2); and 20 patients with a negative result of initial screening (subgroup 3). Characteristics of patients are presented in Table 1.

In subgroup 1, there were 4 men (50%), and 4 women (50%). The mean age of patients was 53.6 ± 13.1 years (range 30–70 years). The mean estimated glomerular filtration rate (eGFR) was 49 ± 34.5 mL/min/1.73 m^2 (range 17–122 mL/min/1.73 m^2). Mean time between IA rupture, or treatment, and the last imaging was 139 ± 66.2 months (range 36–252 months). In this subgroup, no new IA was noticed.

Subgroup 2 included 1 man (17%), and 5 women (83%). The mean age in this subgroup was 62.8 ± 2.6 years (range 60–67 years), and the mean eGFR was 45 ± 32.6 mL/min/1.73 m^2 (range 12–95 mL/min/1.73 m^2). Mean time between the diagnosis of IA and the last imaging was 64 ± 12.9 months (range 50–85 months). During the observation period, IAs in 4 patients (67%) were stable, while in 2 cases (33%) growth of IAs was noted.

Finally, in subgroup 3, there were 11 men (55%), and 9 women (45%). The mean age in this subgroup was 50.2 ± 13.5 years (range 29–79 years), and the mean eGFR was 56 ± 28.7 mL/min/1.73 m^2 (range 7–99 mL/min/1.73 m^2). The mean time between the first and the last imaging was 69 ± 15.5 months (range 36–110 months). In this subgroup, 2 new IAs in 2 patients (10%) were noted. The first patient with a new diagnosed IA was a 40 year-old male with a positive family history for IA, and no symptoms, while the second patient was a 64-year-old woman with a negative family history for an IA, with stage 3 chronic kidney disease (CKD), who was a tobacco smoker. She had labile values of blood pressure and reported periodical appearance of slight dizziness. In the former patient the interval between the first (negative) and the second (positive) examination was 71 months, while in the latter – 55 months.

3. Discussion

We attempted to analyze the natural history of IAs in ADPKD based on 34 patients, divided into 3 subgroups.

In subgroup 1, screening for new IAs in those with IA rupture, or treatment, in their medical history, was done. According to the literature [11,17], patients with IA in their medical history are at risk for development of new IAs. Therefore, screening for new IAs is recommended in this group

Table 1 – Characteristics of the patients included into the study.

Pt no.	Subgroup	Sex	Age at the last imaging (years)	Familial history of IA	Follow-up duration (months)	eGFR (CKD-EPI) at the last imaging (mL/min/1.73 m^2)	Intracranial aneurysm characteristics*
1	1	M	54	N	120	68	ACoA, ruptured
2	1	F	63	N	252	18	MCA, ruptured
3	1	F	30	P	36	122	ACoA, ruptured
4	1	F	70	N	156	50	ND, ruptured
5	1	F	53	P	168	51	MCA, ruptured
6	1	M	46	N	156	25	ACoA, ruptured
7	1	M	46	N	156	41	MCA, ruptured
8	1	M	67	N	67	17	ACoA, treated
9	2	F	61	N	67	60	MCA, 4 mm, stable
10	2	F	60	N	62	16	ICA, 2.5 mm → 4 mm
11	2	M	62	N	50	95	ACeA, 2 mm, stable; MCA, 2 mm, stable
12	2	F	65	N	52	24	ACeA, 5 mm, stable
13	2	F	67	N	70	12	MCA, 7 mm, stable
14	2	F	62	N	85	60	MCA, 2 mm → 4 mm; MCA, 2.5 mm → 4 mm
15	3[a]	F	56	N	69	27.2	
16	3[a]	F	62	N	79	60	
17	3[b]	M	40	P	71	93	MCA, 5.5 mm
18	3[c]	M	54	N	84	15	
19	3[a]	F	55	N	79	83	
20	3[c]	M	67	N	75	11	
21	3[d,e]	F	36	N	36	94	
22	3[c,f]	F	62	N	58	7	
23	3[e]	M	36	N	54	54	
24	3[a]	M	57	N	84	74	
25	3[e]	M	32	N	73	72	
26	3[d,f]	M	40	N	71	18	
27	3[a]	M	79	N	75	40	
28	3[b]	M	38	N	68	76	
29	3[a]	F	56	N	60	71	
30	3[e]	F	45	N	50	68	
31	3[a,e,f]	F	64	N	55	48	ICA, 3 mm
32	3[d,e]	F	29	N	61	99	
33	3[e]	M	39	N	110	68	
34	3[a,d,f]	M	56	N	67	50.9	

* In subgroup 1, aneurysm location and whether it ruptured, or was prophylactically treated have been presented; in subgroup 2, aneurysm location, and its maximum diameter have been presented in stable cases, while in those with progression aneurysm's maximum diameter have been presented both in the initial, and the last imaging; in subgroup 3, aneurysm location and its maximum diameter have been presented in those with positive result of the follow-up imaging.
Motive for repeat screening in patients with a negative result of the initial examination (subgroup 3): a: age >45 years; b: positive family history for intracranial aneurysm; c: before renal transplantation; d: uncontrolled arterial hypertension; e: symptoms; f: tobacco smokers.
Abbreviations: M: male; F: female; P: positive; N: negative; ACoA: anterior communicating artery; ACeA: anterior cerebral artery; MCA: middle cerebral artery; ICA: internal carotid artery; ND: no data.

[1,2,9]. Surprisingly, we did not observe a new IA in this subgroup despite 93 patient-years of follow-up. However, this fact may be attributed to the small number of cases in this subgroup, and the bias associated with study design.

Subgroup 2 consisted of patients, in whom observation of previously diagnosed IAs was conducted. Indications for repeat imaging are the least controversial in such patients, compared to other subgroups. In our series, 2 cases of IAs growth was observed during 32 patient-years of follow-up. The progression involved 33% (2/6) of our series. The incidence of IAs growth was higher in our study (6.25%) compared to the results of meta-analysis of Zhou et al. (1.84%) [14], and the review of Cagnazzo et al. (0.4%) [18]. We believe that our observation supports the need for reevaluation in ADPKD patients with untreated unruptured IAs. According to Chapman et al. [2], in this group imaging should be repeated every 6–24 months, and, based on our results, we agree with this statement.

The last subgroup included 20 patients with a negative result of the first screening for IAs. The indications for repeat examinations in such patients are relatively poorly supported by the literature except for those with a family history of IA rupture, or with symptoms suggestive of IA possibility. We observed development of 2 new IAs during 115 patient-years of follow-up. New IAs were observed in 10% (2/20) of our series, compared to 2.6% in the study of Schrier et al. [12]. Again, the

incidence of development of new IAs in those without IA at baseline was higher in our analysis (1.75%) compared to the meta-analysis of Zhou et al. (0.63%) [14]. It might be caused by the fact that patients with low risk for IAs (e.g. young, asymptomatic, non-smokers, with a negative family history) were not subjects for repeat screening in our center. In our analysis, in 1 patient, a family history of IA was positive, and this case is in line with the recommendation for repeat imaging in such patients [1,2,9]. However, in the second case, indications for repeat screening might be considered controversial. The family history for IAs in this patient was negative, and slight dizziness is not infrequent in this age group. She was a tobacco smoker; however, smoking is considered a risk factor for IAs development in the general population [19], but it is not known if it also applies to ADPKD. This case illustrates the need for further searching for risk factors for IAs development, using clinical, and laboratory approach. Until now, it is even not known whether risk factors for IAs development in the general population apply also to ADPKD patients. Similarly, molecular biology led to identification of factors that may contribute to IAs development, and may become laboratory markers of IAs in the general population [20]; there is a need to verify whether these factors may become markers of IAs in ADPKD.

In contrast to the general population, where the median age of IA rupture is around 50 years, in ADPKD the risk of IA rupture is maximal between 40 and 50 years, and decreases after 50 years-of age [21]. The median age of IA rupture in ADPKD is around 40 years [22]. However, due to the fact that the prevalence of IAs increases with age [3,14], and substantial frequency of IA progression in patients after 60 year-of-age observed in our study (subgroup 2), we believe that even patients older than 50 years-of-age require re-screening.

Having in mind obvious limitations of our analysis, including relatively low number of cases, and its design, we feel that until accurate clinical, and laboratory risk factors for IAs development in ADPKD population are available, indications for repeat screening in those with a negative result of the first study should not be narrowed.

4. Conclusions

Our observations support repeat imaging for IAs in patients with ADPKD, positive family history of IA, and negative result of initial screening. Additionally, efforts should be made to develop clinical and/or laboratory risk factors for IAs development in ADPKD patients without family history of IA, which enable to identify patients who should undergo repeat screening for IAs.

Conflict of interest

None declared.

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