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Review

Characteristics of Intracranial Aneurysms in the Else Kröner-Fresenius Registry of Autosomal Dominant Polycystic Kidney Disease

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Key Words

Intracranial aneurysms · Autosomal dominant polycystic kidney disease · Preventive medicine

Abstract

Background: Patients who harbor intracranial aneurysms (IAs) run a risk for aneurysm rupture and subsequent subarachnoid hemorrhage which frequently results in permanent deficits or death. Prophylactic treatment of unruptured aneurysms is possible and recommended depending on the size and location of the aneurysm as well as patient age and condition. IAs are major manifestations of autosomal dominant polycystic kidney disease (ADPKD). Current guidelines do not suggest surveillance of IAs in ADPKD except in the setting of family history if IA was known in any relative with ADPKD. Management of IAs in ADPKD is problematic because limited data exist from large studies. ***Methods:*** We established the Else Kröner-Fresenius Registry for ADPKD in Germany. Clinical data were assessed for age at diagnosis of IAs, stage of renal insufficiency, and number, location and size of IAs as well as family history of cerebral events. Patients with symptomatic or asymptomatic IAs were included. All patients with ADPKD-related

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IAs were offered mutation scanning of the susceptibility genes for ADPKD, the *PKD1* and *PKD2* genes. ***Results:*** Of 463 eligible ADPKD patients from the population base of Germany, 32 (7%) were found to have IAs, diagnosed at the age of 2–71 years, 19 females and 13 males. Twenty (63%) of these 32 patients were symptomatic, whereas IAs were detected in an asymptomatic stage in 12 patients. IAs were multifocal in 12 and unifocal in 20 patients. In 26 patients (81%), IAs were diagnosed before end-stage renal failure. Twenty-five out of 27 unrelated index cases (93%) had no IAs or cerebral events documented in their relatives with ADPKD. In 16 unrelated index patients and 3 relatives, we detected germline mutations. The mutations were randomly distributed across the *PKD1* gene in 14 and the *PKD2* gene in 2 index cases. Questionnaires answered for 320/441 ADPKD patients without IAs revealed that only 45/320 (14%) had MR angiography. ***Conclusion:*** In ADPKD, rupture of IAs occurs frequently before the start of dialysis, is only infrequently associated with a family history of IAs or subarachnoid hemorrhage, and is associated with mutations either of the *PKD1* or the *PKD2* gene of any type. Screening for IAs is widely insufficiently performed, should not be restricted to families with a history of cerebral events and should be started before end-stage renal failure.

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Introduction

A number of inherited disorders predispose to intracranial aneurysms (IAs). Hereditary IAs are most frequently observed in patients with autosomal dominant polycystic kidney disease (ADPKD) [1], but can also occur in autosomal recessive PKD [2]. Several groups have reported a 5–10% prevalence of IAs in ADPKD [3–5]. In ADPKD, IAs may occur in several family members affected by PKD [4].

IAs are associated with a risk for rupture [6, 7]. Subsequent subarachnoid hemorrhage frequently causes death or permanent neurological symptoms and deficits. The classic Hunt and Hess grading scale is commonly utilized for classification of the severity of subarachnoid hemorrhage [8]. Thus, if risk of aneurysmal rupture can be predicted beforehand, prevention of high-risk cases should be the strategy. The development of microneurosurgery and endovascular therapy provides excellent possibilities of such preventive treatment of unruptured aneurysms. Treatment of asymptomatic aneurysms is recommended depending on the size and location of the aneurysm as well as patient age and condition [9, 10]. However, prophylactic treatment cannot be administered in most cases of innocent IAs, since asymptomatic carriers of unruptured IAs are usually not diagnosed. Therefore, a potential but paramount approach is the identification of subsets of high-risk patients, such as those with hereditary disorders associated with IAs. Despite the belief that the prevalence of IAs is high in ADPKD, screening for IAs in individuals without a family history of IAs is not recommended [11, 12]. Since studies on ADPKD-associated IAs are limited, we analyzed IAs in a large population-based ADPKD registry for adequate management.

Material and Methods

We have established the Else Kröner-Fresenius Registry for ADPKD, with prospective accrual from 2005 onwards. For purposes of this study, registrants accrued between 2005 and the end of 2011 were considered. Patients were initially registered from the population base of southwestern Germany, and subsequently also from nephrology centers throughout Germany. All patients with ADPKD who were willing to provide clinical data were registered. Registrants were asked by questionnaire for information on age, gender, race, serum

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creatinine, results of abdominal ultrasonography, blood pressure values, and data from affected family members. We re-evaluated all diagnoses of ADPKD to ensure diagnoses were in accordance with internationally accepted criteria [12]. For patients with IA and ADPKD, a subsequent supplementary questionnaire was sent to the patients' and their healthy relatives' healthcare providers asking for the date of diagnosis of IA, location, number and size of IAs, symptoms, treatment, and outcome. The clinics where the patients were diagnosed and treated were contacted and asked for the neuroradiological documents and the clinical data of the patients. Another supplementary questionnaire was sent to the patients without IAs and their providers asked for neuroradiological imaging used for exclusion of IAs.

All patients were asked for 10 ml EDTA-anticoagulated blood for molecular genetic analyses. From these samples, genomic DNA was extracted using standard methods. Subsequently, the genes *PKD1* and *PKD2* were analyzed using techniques reported by us [13]. In brief, we analyzed all exons of the *PKD1* and *PKD2* genes primarily using denaturing high-performance liquid chromatography (DHPLC) as shown by Rossetti et al. [14]. If DHPLC revealed an abnormal chromatography, sequencing of the affected exon was performed. In order to exclude analyses of pseudogenes, we performed long-range PCR with 5 overlapping amplicons for the analysis of *PKD1* exons 1–32.

We compared all identified germline variants to those listed in the PKD foundation database at http://pkdb.mayo.edu/cgi-bin/mutations.cgi. In particular, we used in silico analysis for all detected missense DNA variants for potential pathogenicity using the programs SIFT, PolyPhen, SNAP, and Mutation Taster [15–19]. In addition, we checked whether the sequences containing the variant were highly conserved using the website http://www.ensembl.org. Finally, we sequenced the affected exons in 100 control blood samples from volunteers of the Freiburg blood bank.

All patients provided written informed consent. The Ethical Committee of the University Medical Center of the Albert Ludwig University Freiburg, Germany, approved the study.

Results

As of December 31, 2011, the Else Kröner-Fresenius Registry for ADPKD comprised 463 unrelated individuals for whom information regarding IAs was available. Of the 463 patients, 32 (6.9%; 19 females, 13 males) had IAs. Age at diagnosis of IAs was 2–71 (mean 42.9) years, and only 4 patients were younger than 30 years. Clinical characteristics are shown in table 1. IAs were symptomatic in 20/32 patients (63%) because of subarachnoid hemorrhage and asymptomatic in 12 patients. A history of IAs and ADPKD initiated neuroimaging in 2 members of one family who showed such lesions. Other asymptomatic IAs were detected in 10 patients who had ADPKD but no relatives affected by IAs.

Radiological documentation of IAs was available from 29 of the 32 patients reported to have IAs, i.e. radiologic documentation of 48 IAs was available from a total of 51 IAs. Twelve patients had >1 IA. Of the 48 documented IAs, the location and distribution were as follows: along the middle cerebral artery (n = 19), anterior communicating artery (n = 10), ophthalmic artery (n = 6), internal carotid artery (n = 3), pericallosal artery (n = 3), the callosomarginal artery (n = 2), posterior communicating artery (n = 1), posterior inferior cerebellar artery (n = 1), vertebral artery (n = 1), proximal anterior cerebral artery (n = 1) and basilar artery (n = 1).

In 26 patients (81%), IAs were diagnosed before end-stage renal failure. Twenty-five out of 27 index cases (93%) had a family history without IAs when the IAs were detected.

Treatment included neurosurgical procedures with clipping of the IAs in 19 patients. Endovascular treatment with coiling of the aneurysms was performed in 7 patients. Two ad-

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Table 1. Clinical characteristics of patients with IAs and mutations in the *PKD1* or *PKD2* gene

Case No.	Sex	Age at diagnosis of IA years	Symptoms, HH scale	Location of IAs	IAs, n	Size of IA, mm	Therapy	Diagnosis of IA before ESRF	Family history of IAs
1	M	49	sy	right and left middle cerebral artery	2	8 × 8 × 8, 10 × 10 × 10	clip	no	no
2	F	32	asy	left posterior inferior cerebellar artery	1	4.8 × 3.4	clip	yes	no; relative of case 22
3	M	46	asy	left internal carotid artery	multiple	n.a.	no	yes	no
4	M	36	asy	2 × anterior communicating artery	2	n.a.	coil 2 ×	yes	no
5	M	50	asy	right middle cerebral artery	1	4 × 4	clip	yes	relative of cases 6 and 29
6	M	46	asy	right middle cerebral artery	1	n.a.	no	yes	relative of cases 5 and 29
7	M	43	asy	right middle cerebral artery	1	5.1 × 4.7 × 4.6	clip	yes	yes; relative of cases 12 and 20
8	F	71	asy	right middle cerebral artery	1	n.a.	no	no	no
9	F	43	asy	right middle cerebral artery, callosomarginal artery, ophthalmic artery, left middle cerebral artery	4	ophthalmic left 7.5 × 5; right middle cerebral artery 4 × 6	clip media right	no	no
10	F	47	asy	middle cerebral artery, anterior communicating artery	2	n.a.	clip	yes	no
11	F	50	asy	internal carotid artery	1	2 × 3 × 3	no treatment	yes	no
12	M	41	asy	basilar artery	1	9.5 × 5.5 × 4	coil	yes	yes; relative of cases 7 and 20
13	F	34	asy	left middle cerebral artery, left pericallosal artery, left ophthalmic artery	3	n.a.	clip 1 ×, coil 1 ×, 1 not treated	no	no
14	M	47	headache	right middle cerebral artery and ophthalmic artery	2	n.a.	clip 1 ×	yes	no
15	F	49	HH1	right middle cerebral artery	1	4.2 × 4.5	clip	yes	mother with cerebral aneurysm
16	F	55	HH4	right pericallosal artery	1	3.7 × 3 × 4.5	coil	yes	no
17	F	45	HH4	right middle cerebral artery	1	6 × 6	coil	yes	no
18	F	38	SAB	n.a.	1	n.a.	clip	yes	no
19	F	31	SAB	anterior cerebral artery, anterior communicating artery	2	n.a.	coil 1 ×, 1 not treated	yes	no
20	M	43	SAB, HH1	left posterior communicating artery	1	2.9 × 2.2 × 2.8	clip	yes	yes; relative of cases 7 and 12
21	M	37	SAB, HH1	right middle cerebral artery	1	2.5 i.D.	clip	yes	no
22	M	29	SAB, HH1	anterior communicating artery	1	3 i.D	clip	yes	later*; relative of case 2

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Table 1 (continued)

Case No.	Sex	Age at diagnosis of IA years	Symptoms, HH scale	Location of IAs	IAs, n	Size of IA, mm	Therapy	Diagnosis of IA before ESRF	Family history of IAs
23	F	49	SAB, HH1, Fisher 2	ophthalmic artery 3×	3	1.5 i.D, 2.2 i.D., 2.5 i.D.	coil, clip 2×	yes	no
24	F	29/50	SAB/ SAB, HH2–3	anterior communicating artery, right internal carotid artery	2	2 i.D.	clip 2× in 21 years	yes	no
25	F	33	SDB, HH2	left vertebral artery	1	n.a.	coil	yes	no
26	M	42	sy	anterior communicating artery	1	n.a.	clip	yes	no
27	F	50	sy	left middle cerebral artery	1	n.a.	clip	yes	no
28	M	42	sy	anterior communicating artery	1	n.a.	clip	yes	relative of cases 5 and 6
29	F	27	sy	n.a.	1	9.5 × 7.9 × 10.6	n.a.	yes	father with cerebral hemorrhage
30	F	57	sy	2 × right middle cerebral artery and anterior communicating artery	3	n.a.	middle right cerebral artery clip, others not treated	no	no
31	F	2	sy	n.a.	1	n.a.	clip	yes	no
32	F	48	sy	2 × left middle cerebral artery, left pericallosal artery and left callosomarginal artery	4	n.a.	3 × coil 1 × clip	no	no

Cases 5, 6, and 29 are members of the same family, cases 2 and 22 are from another family, and cases 7, 12, and 20 from a 3rd family. HH = Cerebral dysfunction according to the Hunt and Hess grading scale; ESRD = end-stage renal disease; sy = symptomatic; asy = asymptomatic; SAB = subarachnoid hemorrhage; n.a. = data not available; i.D. = in diameter. * The family history of IAs for this case was clarified by our study and was not known to the patient.

ditional patients had clipping in one and coiling in another session for multiple IAs. Four patients with asymptomatic aneurysms were not treated, and for 1 patient treatment data were not available.

The questionnaire regarding exclusion of IAs were answered by the patients or their providers for a total of 320 patients. MRI was performed in 59, CT in 12 and MR angiography in only 14% (45/320) of the patients. 69 patients had no neuroradiological imaging.

Of 463 registrants with ADPKD who had clinical data regarding presence or absence of IAs, 228 were found to have germline mutations in *PKD1* or *PKD2*. Of these 228, 16 unrelated mutation-positive ADPKD patients also had IAs, yielding a prevalence of 7% of IAs in our series of mutation-positive ADPKD patients. These 16 patients comprised 11 females and 5 males with age at diagnosis of IA 2–57 (mean 41.5) years. Fourteen of the patients had mutations in the *PKD1* gene and 2 in the *PKD2* gene (tables 2, 3). The *PKD1* mutations were of the following types: 4 missense, 1 splice site, 1 small insertion, and 8 small deletions. The 2 *PKD2* mutations were of missense type. Of the mutations described here, 7 have never been described (http://pkdb.mayo.edu/cgi-bin/mutations.cgi). In particular, the mutations are spread over the exons of the *PKD1* gene involving exons 7, 10, 11, 15, 19, 24, 27, 38, 42, and 43.

Mutation testing was particularly useful in a girl (case 31; table 1) who was diagnosed and operated on an IA at age 2 years and reached end-stage renal failure by age 21 years. The initial assumption was that she had autosomal recessive PKD. However, clinical signs of liver involvement by cholangiodysplasia and liver fibrosis were absent. A *PKD1* germline muta-

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Table 2. Mutations of the *PKD1* gene in 17 patients with IAs

Case No.	Exon	Kind of mutation	Mutation	Amino acid	Established
3	7	frameshift	1602 del C	p. Gly 535 Glu fs × 23	no*
27	10	frameshift	2054_2055 del AG	p. Glu 685 Val fs × 28	definitely pathogenic
5, 6, 29	19	frameshift	7575_7576 del CT	p. Phe 2525 Leu fs × 69	no*
30	19	missense	7601 G/C	S 2534 T	no*
13	23	missense	8279 C/T	M 2760 T	no*
			8282 G/C	0R 2761 P	
			8291 T/C	M 2764 T	
31	24	splice	8792-2 A/C	Splice	likely pathogenic
32	27	missense	9398 G/A	G 3133 D	no*
8	37	frameshift	10840 del T	p. Tyr 3614 Thr fs × 18	no*
18	38	frameshift	11134 del C	p. Arg 3712 Gly fs × 114	no*
2, 23	42	frameshift	11554 del C	p. Leu 3852 Trp fs × 93	no*
16	43	missense	11717 G/T	C 3906 F	no*
17	11b	frameshift	2644_2645 dup GT	p. Pro 883 Cys fs × 16	no*
4	15d	frameshift	5014_5015 del AG	p. Arg 1672 Gly fs × 98	definitely pathogenic
28	15f	frameshift	5997_6004 del 8 bp	p. Ser 2000 Arg fs × 47	likely pathogenic

* These mutations have so far not been reported.

Table 3. Mutations of the *PKD2* gene in 2 patients with IAs

Case No.	Exon	Kind of mutation	Mutation	Amino acid	Established
14	4	missense	964 C/T	R 322 W	highly likely pathogenic
15	13	missense	2420 G/A	R 807 Q	undetermined

tion of missense type was identified in this patient, which was not seen in >200 control chromosomes and affecting a highly conserved DNA sequence, thus revealing the diagnosis of ADPKD by molecular means.

Discussion

While the consequences of unrecognized IAs are deadly, multiple studies have shown that the risk-benefit ratio is disadvantageous in indiscriminate surveillance of IAs and prophylactic treatment. However, it is suggested that surveillance and prophylactic treatment of individuals at high risk of IAs may yield a good risk-benefit profile [20]. IAs can occur sporadically or individuals can be genetically predisposed. Individuals who are genetically predisposed to IAs can be viewed as the subset of high-risk individuals who may benefit from routine surveillance and management. Heritable disorders with IAs as a component include Marfan syndrome [21], Ehlers-Danlos syndrome [22], Alport syndrome [23], and fibromuscular dysplasia [24, 25]. In addition, we have described IAs in autosomal recessive PKD-associated multiple cerebral aneurysms [2]. The majority of hereditary IAs, however, occur in ADPKD [3]; yet, IA surveillance without a family history of IA is not currently recommended [4, 9, 11].

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Thus, we aimed to determine the frequency and characteristics of IAs in ADPKD and were looking for demographic and clinical clues to guide surveillance and timing of surveillance.

Here, we present demographic, clinical, and molecular genetic data of 32 patients with IAs out of a total of 463 patients (7%) from the population-based Else Kröner-Fresenius Registry for ADPKD for whom central nervous system imaging data were available. The prevalence of unruptured IAs in the general population is about 3%, but in ADPKD it is about 7% according to a meta-analysis [26]. In our current population-based series, 12 of 32 ADPKD patients (38%) with IAs presented with asymptomatic IAs, representing 2.4% (12/491) of all ADPKD patients.

The clinical data from these ADPKD-related IA patients were revealing in 3 ways. First, >90% (29/32) of ADPKD patients detected with IAs were older than 30 years of age. This contrasts with other observations which report that IAs are only occasionally the presenting manifestation of ADPKD [4]. Second, most patients (26/32, 81%) showed IAs before reaching end-stage renal failure. Thus, these patients are far less frequently seen by physicians compared to those on dialysis who have three renal replacement treatments on hemodialysis per week or are regularly seen by nephrologists if on chronic ambulatory peritoneal dialysis. Consequently, the majority of patients with IAs run a high risk of being diagnosed late. The third and most important result of this study is the frequent absence of hints of IAs in the given ADPKD families. A history of IAs was initially present in only 2 families (1st family: cases 7, 12, and 20; 2nd family: case 15; table 1), whereas in a third family (case 28; table 1), cerebral hemorrhage indicated that an aneurysm might have been present. In two additional families, relatives with ADPKD proved to have IAs after IAs had been detected in the index cases (relatives of case 28: cases 5 and 6; relative of case 2: case 22; table 1). Thus, only a maximum of 5 of 27 families (19%) including patients with IAs had familial clustering of IAs, but the overwhelming majority of index cases had no clearly documented IAs in relatives at the time when the IA was diagnosed in the index case (25/27 index cases, 93%). In contrast to the expectation of multifocal involvement in a hereditary disorder, only 12 out of 321 patients (38%) had multiple aneurysms.

From the molecular genetic viewpoint, IAs occurred in patients with mutations in both the *PKD1* gene and the *PKD2* gene. The mutations in both genes comprise missense, splice site, small deletions, and small insertions. The mutations identified in this study do not show a clustering within certain areas of the genes, i.e. in the 5′ region of *PKD1* as reported by others [4]. Thus, the molecular genetic results may not add substantial predictive value to identify risk for IAs in ADPKD patients.

Our study is particularly timely in the context of an ongoing debate on whether general surveillance of IAs in ADPKD is warranted [11]. Two studies did not suggest an increased risk for growth and rupture in initially unruptured IAs in ADPKD compared to IAs in the general population; therefore, a widespread screening for unruptured IAs in ADPKD was not recommended [11, 27]. Our current data, however, raise doubts. Based on our data, we suggest that all patients with ADPKD older than 30 years of age should undergo a baseline screen for IAs. The state of the art technique is magnetic resonance angiography, which can be easily performed without contrast medium and appears to be cost-effective [20]. It is astonishing that despite the known risk for IAs in ADPKD, only 14% of 320 patients of this series classified as not having IAs had been sufficiently investigated by MR angiography.

In conclusion, IAs occurring in ADPKD are associated with germline mutations of the *PKD1* and *PKD2* genes. Virtually all IAs occur after the age of 30 years, before onset of end-stage renal failure, and rarely in a setting of families with known cerebral events. We also showed a risk of rupture with sequelae. Our data support that screening for IAs should not be restricted to individuals whose families have a history of cerebral events and should be started before end stage renal failure.

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