Saccular Intracranial Aneurysms in Autosomal Dominant Polycystic Kidney Disease

Wouter I. Schievink, Vicente E. Torres, David G. Piepgras, and David O. Wiebers

ABSTRACT
The literature on the association of intracranial aneurysms in autosomal dominant polycystic kidney disease (ADPKD) consists mainly of case reports and small series of patients. To provide a more-detailed description of this association and its frequency, the records of all ADPKD patients with saccular intracranial aneurysms, all ADPKD autopsy cases including brain examination, and sex- and age-matched autopsy cases without ADPKD seen at the Mayo Clinic between 1945 and 1984 were reviewed. The presentation of the 41 patients (22 men and 19 women; mean age, 46.4 yr) with this association was subarachnoid hemorrhage, or intracranial hemor- rhage in 33, transient ischemic attacks in 2, incidental angiographic or autopsy finding in 5, and discovery during angiographic screening in 1. Thirty-one, seven, and three patients harbored one, two, and three aneurysms, respectively, arising from the middle cerebral artery (N = 23), anterior communicating artery (N = 16), internal carotid artery (N = 11), and vertebral or basilar artery (N = 4). A family history of intracranial aneurysm, subarachnoid hemorrhage, or intracranial hemorrhage at an early age was present in 22% of the patients. Small aneurysms (<5 mm) were less likely to have ruptured or caused symptoms (P < 0.04). There was a trend for hypertension to be associated with the severity of the subarachnoid hemorrhage. Aneurysmal rupture occurred before age 50 in 64% of patients. Of the 89 ADPKD autopsy cases with brain examination, 22.5% had intracranial aneurysms. Intact aneurysms, however, were found in only 4.2% of patients who died from causes other than aneurysmal rupture, which was not different from 2.1% in the control group. No clinical features useful in the identification of patients at risk for developing an intracranial aneurysm were detected. ADPKD was diagnosed in 1.7% of the 120 cases of verified aneurysmal subarachnoid hemorrhage in Rochester residents. The findings suggest that (1) intact intracranial aneurysms in ADPKD are less common than appears from the literature, (2) aneurysmal size correlates with the presence of symptoms and the risk of bleeding, and (3) aneurysms may rupture more often and at a younger age as compared with sporadic aneurysms.

Key Words: Cerebral aneurysm, polycystic kidney disease, subarachnoid hemorrhage

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disorder characterized by bilateral multiple renal cysts. With a prevalence rate of approximately 1 in 400 to 1,000 population, ADPKD is one of the most common genetic diseases (1–3). The gene responsible for the majority of cases of ADPKD (>90%) has been identified by linkage analysis on the short arm of chromosome 16 (16p13.3) (4–6). The manifestations of ADPKD are not limited to the kidneys. Cysts may also be found in the liver, pancreas, spleen, pineal gland, and subarachnoid space (7–11). Additionally, various cardiac valvular, vascular, and other connective tissue abnormalities have been described. Mitral valve prolapse is the most common cardiac valve abnormality (12). Vascular abnormalities described in patients with ADPKD include intracranial aneurysms (ICA) (12–19), cerebral arteriovenous malformations (20,21), persistent fetal carotid-basilar communications (22–23), moyamoya disease (24), intracranial dissection (25), aortic dissection (3,26), aortic aneurysms (3,26), aortic coarctation (26), aortic root dilatation (3,26), and visceral arteriovenous malformations (26). Colonic diverticulosis, spontaneous colonic rupture, and inguinal herniae appear to be relatively common features of ADPKD (2,3,7,8,27).

The literature on ICA associated with ADPKD consists mainly of case reports and small series of patients. Population-based epidemiological studies con-
cerning the occurrence of ADPKD in patients with aneurysmal subarachnoid hemorrhage have not been reported. In this article, we report on all patients with ICA associated with ADPKD seen at the Mayo Clinic during a 40-yr period to identify the clinical, radiographic, and pathological characteristics of this group of patients. In addition, the epidemiology of ICA associated with ADPKD in Rochester, Minnesota, is studied.

PATIENTS AND METHODS

Descriptive Study

The clinical, laboratory, and radiographic data of all patients with a diagnosis of ICA associated with ADPKD who were seen at the Mayo Clinic between 1950 and 1989 and the records of all autopsies performed on patients with ADPKD at the Mayo Clinic during the same time period were reviewed.

Clinical diagnoses of ADPKD were based on excretory urography, angiography, ultrasonography, computed tomography, or surgery. The criteria for clinical diagnosis included bilateral renal cystic disease with a family history of ADPKD or bilaterally enlarged and diffusely cystic kidneys with exclusion of other renal cystic diseases (28). Autopsy findings meeting the criteria of ADPKD included bilateral renal cysts with diffuse and homogeneous involvement of the renal cortex and medulla with exclusion of other renal cystic diseases. The diagnosis of ICA was based on angiography, surgery, or autopsy. Fusiform aneurysms were excluded from the study. Subarachnoid hemorrhage (SAH) was diagnosed by cerebrospinal fluid examination, CT, surgery, or autopsy. The clinical conditions of patients with aneurysmal SAH was graded according to the Hunt and Hess classification (29) at the time of first medical attention. Hypertension was defined as a history of treatment of elevated blood pressure or the continuing presence of a blood pressure greater than 160/95 mm Hg before the time of SAH or diagnosis of the ICA. Renal function at the time of diagnosis of the ICA was rated as "normal" when serum creatinine and urea were within normal limits (<1.0 and <45 mg/dL for women, and <1.2 and <50 mg/dL for men, respectively), as "impaired" when these levels were above normal, and as "failure" when the patients were on dialysis or had received a renal transplant.

To compare the frequency of unruptured ICA at autopsy in patients with and without ADPKD, two cases without polycystic kidneys were matched by sex, age, and year of the autopsy to each of the ADPKD autopsy cases. Only autopsies that included examination of the brain were used for this comparison. Patients who had a clinical diagnosis of ICA or who had died as a result of ICA rupture were excluded.

Epidemiological Study

The unique features of the database system employed for epidemiological studies in Rochester have been described extensively (30). All Rochester residents with a diagnosis of ADPKD who suffered a SAH due to a ruptured ICA between 1945 and 1984 were identified. The diagnostic criteria as outlined above were employed.

Statistical Analysis

The two-sample t test, the $\chi^2$ test, and the Fisher's exact test were used for statistical analysis.

RESULTS

Descriptive Study

The age and sex distribution of the 41 patients with ICA associated with ADPKD are shown in Figure 1. There were 19 women (46%) and 22 men (54%) with a mean age of 46.4 yr (range, 20 to 72 yr). A clinical diagnosis of ICA was made in 26 patients, and ADPKD was diagnosed clinically in 30 patients. Twenty-four patients were known to have ADPKD at the time of the diagnosis of their aneurysm. Twenty-six (63%) of the 41 patients had a known family history of ADPKD.

Presenting signs and symptoms of the aneurysms included SAH in 33 patients and transient ischemic attacks in 2 patients. In three patients, the aneurysm was an incidental autopsy finding, in two patients it was discovered incidentally during investigations for neurological disease unrelated to the aneurysm, and in one patient with a strong family history of cerebral hemorrhage, the aneurysm was detected during screening with angiography. Two patients suffered a recurrent SAH from a second ICA at intervals of 8 and 16 yr, respectively, from their initial hemorrhage. In addition to 21 patients with SAH in whom the aneurysm was diagnosed by angiography, 2 patients with ADPKD who suffered a SAH had a nega-
tive angiogram; these 2 patients are not included in this study but were seen at our institution during the same time period as the study patients.

In total, 54 ICA were found in the 41 patients. Multiple aneurysms were found in 10 patients (24%); 7 patients harbored two aneurysms, and 3 patients had three aneurysms each. The size and location of the ICA is shown in Table 1. Giant ICA (>25 mm) were relatively common and constituted 15% of all aneurysms. There were twice as many aneurysms arising from the middle cerebral artery than from the internal carotid artery (Table 1). Of the 23 middle cerebral artery aneurysms, approximately two thirds were found in men. The remainder of the ICA were divided equally among the sexes.

Aneurysms 5 mm in diameter or larger were more likely to have ruptured or caused other symptoms (5 of 12 versus 24 of 32; \( P = 0.04 \)) than smaller aneurysms (Table 1). Forty-two percent of ICA smaller than 5 mm in diameter had ruptured compared with 69% of those 5 mm in size and larger. The two unruptured giant ICA had caused cerebral ischemic symptoms due to distal embolization. The sizes of the intact ICA are shown in Table 2. The majority (five of seven; 71%) of intact ICA discovered at autopsy were smaller than 5 mm in diameter.

Twenty-eight patients (68%) had arterial hypertension, 10 (24%) did not, and in 3 patients, previous blood pressure status could not be ascertained (7%). Renal function was normal in 21 patients (51%) and impaired in 7 patients (17%), and chronic renal failure was present in 6 patients (15%). In seven patients, renal function tests had not been performed (17%).

Of the 33 patients presenting with SAH, 9 were in grade I, 8 were in grade II, 4 were in grade III, and 12 were in grades IV and V. The mean age of these 16 women and 17 men at the time of the initial SAH was 46.5 yr. There was a trend for previous hypertension (Table 3), but not renal function, to be associated with the severity of the hemorrhage, although this did not reach statistical significance \( P = 0.06; \) one tail). Of the 17 grade I and II patients, 8 were hypertensive (47%) and seven were normotensive (41%) (information on hypertension was unavailable in 2 patients). In contrast, of the 16 grades III through V patients, 12 were hypertensive (75%) and 3 were normotensive (19%) (blood pressure status was unknown in the remaining patient).

The outcome of SAH at 6 months follow-up was excellent or good in 13 patients (39%) and poor or fair in 2 patients (6%); 18 patients had died (55%). Limiting the outcome analysis to the 23 patients with SAH who had been diagnosed with ADPKD during life, the overall results were less dismal. Outcome was excellent or good in 13 patients (57%) and poor or fair in 2 patients (9%), and 8 patients had died (35%).

Nine patients had a family history of ICA \((N = 4)\), SAH \((N = 2)\), or "intracranial hemorrhage" occurring

<table>
<thead>
<tr>
<th>Mode of Detection</th>
<th>Size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autopsy</td>
<td>2</td>
</tr>
<tr>
<td>Angiography</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
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<td></td>
<td>5</td>
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<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
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</tr>
</tbody>
</table>

*Symptomatic.

TABLE 2. Size of Intact ICA

<table>
<thead>
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</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>5-9</td>
<td>Angiography</td>
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<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td></td>
</tr>
<tr>
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</tbody>
</table>

TABLE 3. Severity and outcome of SAH related to previous blood pressure status

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Grades I and II</th>
<th>Grades III through V</th>
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<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>8</td>
<td>12</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Normal</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Grade according to the Hunt and Hess classification (28).
Epidemiological Study

During the 40-yr period from 1945 to 1984, 181 cases of primary SAH were diagnosed in residents of Rochester, Minnesota. In 120 of the 181 patients, the presence of a ruptured ICA was confirmed. In the remaining 61 patients, the cause of the SAH was arteriovenous malformation, disorder of coagulation, vasculitis, or amyloid angiopathy, or remained unknown. In 2 (1.7%) of the 120 patients with aneurysmal SAH, a diagnosis of ADPKD was established: clinically in 1 patient and at postmortem examination in 1 patient. In a third patient with ADPKD from Rochester, an intact ICA was incidentally found at autopsy. Additionally, bilateral unruptured fusiform aneurysms of the middle cerebral artery were found incidentally in a 85-yr-old woman with ADPKD from Rochester who was not included in the study.

DISCUSSION

Epidemiology

An ICA is one of the best-known extrarenal manifestations of ADPKD. Nevertheless, the frequencies of ICA observed at autopsy in patients with ADPKD are variable, ranging from 0 to 50% (13,14,16,31,32), compared with 0 to 10% in the general population (33). This variability may in fact reflect differences in diagnostic criteria and thoroughness of examination, which cannot be controlled in retrospective studies. In our autopsy material, ICA were detected in 22.5% of patients with brain examination. However, intact ICA were found incidentally in only 4.2% of the cases, which is not significantly different from a frequency of 2.1% observed in a control population matched by sex, age, and year of examination. In previous smaller series of autopsies in ADPKD (13,14,16,32), ICA were detected in 26.8% (11 of 41) and intact ICA were found incidentally in only 6.7% (2 of 30) of patients. Our failure to detect a significant difference in the frequency of incidental ICA between the ADPKD and control groups may indicate that an increased risk of ICA rupture is more important than an increased frequency of ICA in ADPKD. It could also be due to familial clustering (see references 42-44) and small sample size.

Conventional arteriography in three groups of patients with ADPKD from Japan and one from Finland has demonstrated ICA in 7 of 19 patients (37%) (34), 7 of 17 patients (41%) (35), 3 of 5 patients (36), and 3 of 5 patients (37), respectively; this compares with an angiographic frequency of ICA in the general population of 0.5 to 1% (38,39). Using a combination of conventional arteriography, CT, and magnetic resonance imaging (MRI), Kaehny et al. (40) could demonstrate ICA in 6 of 60 North American patients with ADPKD (10%). Employing MRI and high-resolution CT, Torres et al. (9) were unable to detect any definite ICA in 96 consecutive patients with ADPKD. In a subsequent group of 40 ADPKD patients studied with the use of MRI angiography, an ICA was demonstrated in 1 patient (2.5%) (41). Discrepancies between the arteriographic studies (34,35), the imaging study by Kaehny et al. (40), and the CT and MRI studies by Torres et al. (9,41) may at least partly be explained by the observed clustering of ICA in certain families with ADPKD (42-44), the bias to report small studies only when they provide positive results, racial differences, and differences in the resolution of the imaging techniques used.

The frequency of ADPKD among patients with ICA has been investigated as well. In three autopsy series, prevalence rates of 4.0 (14), 6.4 (16), and 7.4% (13), respectively, were recorded. Employing abdominal CT, Wakabayashi et al. (35) screened 36 patients with aneurysmal SAH and found ADPKD in 2 patients (5.6%), 1 of whom had a parent with ADPKD. In the study presented here, with strict diagnostic criteria, ADPKD was present in 1.7% of all patients in Rochester who had suffered an aneurysmal SAH during a 40-yr time period. The true prevalence may be higher because ADPKD is not diagnosed until...
postmortem examination in nearly one third of patients in our community (2) and only a fraction of the patients with aneurysmal SAH underwent postmortem examination.

The risk of harboring an ICA and suffering a SAH in ADPKD patients is not well defined. We have used the population data of Rochester per age groups and 5-yr calendar periods between 1945 and 1984 and the estimated survival adjusted prevalence of ADPKD for this community and time period (2,3) to calculate the ADPKD person years at risk for ICA rupture. On the basis of these data, the frequency of ICA rupture in the ADPKD population of Rochester was found to be \( \frac{1}{2,000} \) person yr overall and \( \frac{1}{5,000} \) person yr when only patients over 30 yr of age are considered to be at risk. This figure may underestimate the true frequency, because a diagnosis of ADPKD could have been missed in one or more patients with aneurysmal SAH. Nevertheless, the low prevalence rates of ADPKD among patients with ICA discussed above (13,14,16) and the lack of a family history of ADPKD in these patients with aneurysmal SAH in a community-based study suggest that a gross underestimation is unlikely.

Clinical and Pathological Characteristics

In contrast to the female predominance found in patients with ICA in general (45,46), the male-to-female ratio in our patients was approximately equal with a slight male predominance (1.2:1). In their reviews of the literature, Lozano and LeBlanc (47) and Levey (48) found a more pronounced male predominance (2.6:1 in ADPKD patients with rupture from a single ICA only and 1.6:1, respectively). It has been reported that ICA associated with ADPKD rupture at a significantly younger age than in sporadic ICA (47,49), and the study presented here supports this. The mean age (46.5 yr) of our patients with aneurysmal SAH was lower than that of patients with ruptured ICA in general (45,46), with few patients 60 yr of age and older. Aneurysmal rupture occurred before age 50 yr in 64% of our patients, in 77% of the patients with ADPKD reviewed by Lozano and LeBlanc (47), and in 80% of those in the study of Chauveau et al. (49), as compared with 40 to 45% of sporadic cases (45,46). Aneurysms arising from the middle cerebral artery were more common, and those arising from the internal carotid artery were less common, in our patients than in sporadic cases, confirming the findings of previous investigators (46-48). Middle cerebral artery aneurysms were particularly common in our male patients with ADPKD. Giant ICA have rarely been reported in patients with ADPKD. In our patients, 15% harbored aneurysms 25 mm in diameter or larger. This large number of giant aneurysms probably reflects a referral bias in our neurosurgical practice. Of 23 patients with ADPKD and SAH who had undergone cerebral angiography, ICA were detected in 21 (91%). The frequency of a negative angiogram (9%), therefore, does not appear to be significantly different from that in sporadic cases of SAH (50).

In their review of the literature, Lozano and LeBlanc noted that 80% of patients with ADPKD and aneurysmal SAH died from the initial hemorrhage (47). This is likely because of the fact that there were a large number of patients in whom ADPKD was diagnosed at autopsy. The mortality rate of SAH in our patients was 55%. Excluding the patients with SAH in whom ADPKD was diagnosed at autopsy, however, the mortality rate decreased to 35%. Thus, the mortality rate of aneurysmal SAH associated with ADPKD was comparable to that expected in the general population.

Several investigators have stressed the importance of arterial hypertension in the development of ICA (51). Hypertension was found more frequently in our patients (68%) than in patients with ICA in general (45). However, hypertension is unlikely to be of primary importance in the cause of aneurysms in general (52,53) or those associated with ADPKD. Approximately one fourth of our patients were known to be normotensive before the diagnosis of the aneurysm, a figure similar to that reported in the literature for patients with ADPKD and ICA (47-49). Wakabayashi et al. (35) found that 71% of their patients with ADPKD and unruptured ICA were not hypertensive. On the other hand, hypertension may aggravate the severity of the SAH, as was reflected by a trend for previous hypertension to be associated with a worse clinical condition at initial medical evaluation.

In approximately one fifth of our patients, there was a familial history of SAH or one suggestive of aneurysmal SAH. It has been shown that familial ICA in general rupture at a smaller size and when the patient is younger in comparison with sporadic ICA (54). Within our group of patients, the clinical characteristics of those with a familial history of ICA, SAH, or cerebral hemorrhage occurring at an early age were not significantly different from those of patients without such a history, including aneurysm size and patient age. However, the number of patients is small and ICA were documented to be the cause of intracranial hemorrhage in the family members of only about one half of the patients with a positive family history.

The frequency of extracranial cysts, diverticular disease, and aortic aneurysms in the 20 ADPKD patients with an ICA coming to autopsy was similar to that found in the 69 patients with ADPKD who did not harbor an ICA at postmortem examination. Although the numbers are small, it would appear that the occurrence of ICA in patients with ADPKD is not
associated with a significantly different prevalence at autopsy of at least some of the extrarenal manifestations of the disease. However, the average age in the patients with an ICA (49.7 yr) was lower than that of the patients without an ICA (56.8 yr) and hepatic cysts as well as colonic diverticula are known to be acquired lesions, even in the setting of an underlying hereditary disorder.

Screening for ICA

The management of unruptured asymptomatic ICA in general (52,55–61), and the screening for ICA in patients with ADPKD (9,55,56,61) or those with a family history of ICA (58), in particular, remains a subject of considerable controversy. Some authors have recommended angiographic screening of all patients with ADPKD (19,35). Hatfield and Pfister advocated angiography in young hypertensive patients with ADPKD (62). In 1983, Levey et al. (56), using a decision-analytical approach, could not recommend routine angiography in patients with ADPKD. Preliminary data have since suggested that ICA tend to cluster in certain families with ADPKD (42–44). In 1990, Levey proposed screening with high-resolution CT of patients with ADPKD and a family history of ICA who do not yet have renal failure (55).

Our study provided no evidence for any clinical characteristics, e.g., the presence of other extrarenal manifestations, that may be useful in the identification of the ADPKD patient at risk for developing an ICA. To detect intact asymptomatic ICA, we suggest screening of the following ADPKD patient groups (9): those with a family history (suggestive) of ICA or SAH; those with atypical neurological findings that could constitute aneurysmal symptoms other than rupture; those with high-risk occupations; those who will undergo major elective surgery likely to be accompanied by major changes in cerebral hemodynamics; and those who request screening for the purpose of reassurance. It is likely that the majority of aneurysms that rupture probably do so at the time of or shortly after their formation, and screening is therefore unlikely to be of benefit to all patients (52).

Preliminary data suggest that the most effective currently available noninvasive technique to screen for ICA is MRI angiography (63–65). Additionally, because no intravascular contrast medium is required, MRI angiography is particularly suitable for ADPKD patients with impairment of renal function. Conventional arteriography, however, remains the "gold standard" in the detection of ICA and may be considered in selected cases, e.g., concerned patients with a strong family history of ICA. Patients with signs or symptoms suggestive of aneurysmal expansion, leak, or hemorrhage, or distal embolization should undergo prompt evaluation with conventional arteriography.

REFERENCES

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