Familial Clustering of Ruptured Intracranial Aneurysms in Autosomal Dominant Polycystic Kidney Disease

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• **Ruptured intracranial aneurysm (RICA) is a life-threatening complication of autosomal dominant polycystic kidney disease (ADPKD). A family history of RICA may be a risk factor for RICA. Six hundred eight adult members of 199 ADPKD families were interviewed, and family pedigrees were constructed. Individuals were classified as having definite, probable, or possible RICAs from evidence and history obtained in interviews. Central nervous system (CNS) events not consistent with RICA were classified as other CNS events. Seventy-seven CNS events occurred in 906 subjects with ADPKD (8.5%) versus 13 events in 823 subjects without ADPKD (1.6%; *P* < 0.0001). No event in subjects without ADPKD was consistent with an RICA. Twenty-seven other (non-RICA) CNS events occurred in subjects with ADPKD (3%) versus 13 events in subjects without ADPKD (1.6%; *P* = 0.05). The frequency of RICA was increased in subjects with ADPKD: 21 definite RICAs in subjects with ADPKD (2%) versus none in subjects without ADPKD (*P* < 0.001); 28 definite and probable RICAs in subjects with ADPKD (3%) versus none in subjects without ADPKD (*P* < 0.001); and 50 definite, probable, and possible RICAs in subjects with ADPKD (5.5%) versus none in subjects without ADPKD (*P* < 0.001). The null hypothesis that RICAs are randomly distributed among subjects with ADPKD was tested for definite RICAs (n = 21), definite and probable RICAs (n = 28), and definite, probable, and possible RICAs (n = 50). In the three categories, the null hypothesis was rejected at *P* less than 0.05, *P* less than 0.05, and *P* less than 0.005, respectively. Vascular CNS events occurred more frequently in ADPKD than non-ADPKD family members, and clustering of RICAs occurred in families with ADPKD.**

INDEX WORDS: Autosomal dominant polycystic kidney disease (ADPKD); intracranial aneurysms (ICAs); ruptured intracranial aneurysms (RICAs).

AUTOSOMAL DOMINANT polycystic kidney disease (ADPKD) is a systemic disease with both cystic and noncystic manifestations. Perhaps the most devastating noncystic manifestation is intracranial aneurysm (ICA). Individuals with ADPKD worldwide have an increased frequency of ICAs compared with the general population, with estimates of prevalence among individuals with ADPKD ranging from 4% to 41%.[1-4] Large prospective studies in North American populations have found rates of ICAs in individuals with ADPKD of 4% to 11.7% in contrast to the 1% prevalence in the general population.[1-3,5]

This increased ICA frequency is of concern because of the risk for rupture (RICA) and its devastating consequences. Although the rupture rate of ICAs per year is not known in ADPKD, 4% to 7% of individuals with ADPKD have subarachnoid hemorrhage (SAH) as the cause of death.[6-9] The frequency of ICAs and their role in mortality in ADPKD raise the question of screening all patients with ADPKD for this manifestation. Two decision analyses reached contradictory conclusions regarding screening of asymptomatic individuals with ADPKD.[10-12] Therefore, identifying subsets of individuals with ADPKD at high risk for RICA would simplify decisions about screening.

In the general population, several studies have shown an increased prevalence of ICAs in first-degree relatives of individuals who have had an ICA or SAH.[13-19] A prospective study of individuals with ADPKD using magnetic resonance angiography (MRA) found that 22% of 27 subjects with a family history of ICA or SAH had an asymptomatic ICA compared with 5% of 56 subjects who lacked such a family history.[2] Eigh-

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teen percent to 22% of individuals with ADPKD with an ICA have a family history of ICA or one highly suggestive of ICA.[20,21] These findings logically generate the important clinical question: Does the frequency of RICA show this familial clustering? This has been suggested by several investigators.[21,22] A retrospective study of RICAs in families in the ADPKD database at the University of Colorado (Denver, CO) was conducted.

METHODS

During the period from June 1, 1985, through January 30, 1990, a total of 608 consecutive adult (aged ≥18 years) members of 199 families with ADPKD who participated in the ongoing natural history study of ADPKD at the University of Colorado were interviewed by a single nurse practitioner, genetic counselor, or physician in the Clinical Research Center at the University of Colorado Health Sciences Center. The study protocol was approved by the Colorado Multiple Institutional Review Board. Informed consent was obtained from each subject participating in this study.

A formalized interview of each subject was conducted, and detailed family pedigrees were constructed. Questions were asked about personal or family occurrence of acute neurological events, strokes, intracranial hemorrhages, and RICAs in subjects with and without ADPKD in the pedigrees. Subjects with ADPKD were not selected for a personal or family history of ICA. The diagnosis of ADPKD for those subjects studied at the University of Colorado Health Sciences Center was based on detection by ultrasonography of a total of five or more cysts in both kidneys and usually a family history of polycystic kidney disease. ADPKD was diagnosed in 384 subjects by these criteria. In 224 subjects, the diagnosis of ADPKD was excluded by these criteria. Five hundred twenty-two additional individuals were considered to have ADPKD based on historical data obtained from relatives who were interviewed as described.

Additional information about all subjects said to have had acute central nervous system (CNS) events was obtained by reviewing autopsy reports, surgical reports, radiological reports and films, hospital records, and physician records. If these were unavailable, physicians, subjects, and other family members were interviewed to substantiate the history. Relatives in the pedigrees with and without ADPKD for whom little personal and no medical information were available were not included in the study.

Only subjects with or without ADPKD who were aged 18 years or older and identified by name and age in interviews or documents in the database were included. No subject aged younger than 18 years had a nontraumatic acute vascular CNS event. Nontraumatic acute vascular CNS events were classified as definite RICA, probable RICA, possible RICA, and other vascular CNS event. Categorization was performed by examination of case histories by two staff neurologists (R.L.H. and M.P.E.) blinded to the ADPKD status of each subject. Definite RICA required a clinical episode of SAH, with documentation of SAH and RICA by neuroimaging, surgery, or autopsy. Probable RICA included patients with medical records that described a clinical presentation and course likely to be from an RICA and not consistent with an alternative diagnosis, such as migraine, trauma, arteriovenous malformation, or ischemic stroke. Typically, either neuroimaging or spinal fluid testing (especially in the pre–computed tomographic scan era) confirmed SAH. Patients with possible RICA met the same clinical criteria, but supporting medical records were not available and medical information was relayed verbally by the patient or family. This information had to be quite compelling and typically was very detailed (eg, "According to my mother, my grandfather had a right middle cerebral artery aneurysm that ruptured and killed him. He grabbed his head, fell over, and died."). Intraparenchymal hemorrhages, cerebral infarction, and nonspecific cerebrovascular accident or stroke were not included as possible RICAs. Subjects with these events were placed into the "other vascular CNS event" category.

Frequencies of vascular CNS events, RICAs, and other vascular CNS events were compared between ADPKD and non-ADPKD family members by means of chi-square analysis. Because there was a large number of families with small numbers of affected members, Fisher's exact test using Monte Carlo sampling was used to test the null hypothesis that ICAs are randomly distributed among family members with ADPKD (StatXact software; Cytel Software Corp, Cambridge, MA). Using this method, more than 10,000 computer trials were performed in which the total number of RICAs was randomly distributed among ADPKD members of families of the same configuration as the families in our data set. It was recorded how often the test families showed the same or greater degree of clustering of RICAs seen in actual families. P less than 0.05 using this method would indicate that this degree of clustering occurred in less than 5% of trials.

RESULTS

Classification of patient groups is shown in Fig 1. Nine hundred six family members with ADPKD were identified, along with 823 family members without ADPKD. Three hundred eighty-four subjects with ADPKD were studied, and the diagnosis was confirmed at the University of Colorado Health Sciences Center, defined previously. Two hundred twenty-four subjects without ADPKD were also studied at the University of Colorado Health Sciences Center. A total of 77 vascular CNS events occurred in the 906 subjects with ADPKD (8.5%) compared with 13 vascular CNS events in 823 subjects without ADPKD (1.6%; $P < 0.0001$). None of the vascular CNS events in subjects without ADPKD was consistent with RICA. When definite, probable, and possible RICAs are excluded, there were 27 other vascular CNS events in 906 subjects with ADPKD (3%) in comparison to 13 vascular CNS

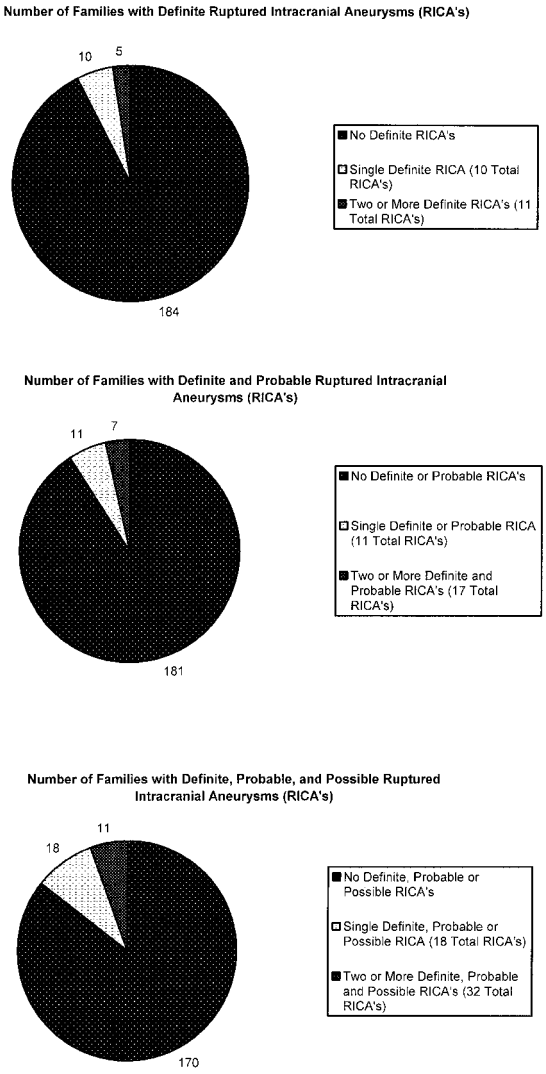

Fig 1. Distribution and classification of subjects and events among the 199 families with ADPKD. Vascular CNS events were classified as definite, probable, or possible RICA or other vascular CNS events depending on history and documentation obtained.

events in 823 subjects without ADPKD (1.6%; $P = 0.05$).

The distribution of RICAs among the 199 families is listed in Table 1. There were 21 definite RICAs in the 906 subjects with ADPKD (2%) and none among the 823 subjects without ADPKD ($P < 0.001$). If definite and probable RICAs are included, there were 28 RICAs in the 906 subjects with ADPKD (3%) and none among the 823 subjects without ADPKD ($P < 0.001$). If the three categories of definite, probable, and possible RICAs are included, there were 50

Table 1. Distribution and Classification of RICA Among 906 Subjects With ADPKD From 199 Families

No. of Family Members with ADPKD	Definite RICA	Probable RICA	Possible RICA	Total No. of Families
No family member with an RICA				
1	0	0	0	36
2	0	0	0	37
3	0	0	0	21
4	0	0	0	23
5	0	0	0	16
6	0	0	0	15
7	0	0	0	3
8	0	0	0	7
9	0	0	0	2
10	0	0	0	3
12	0	0	0	3
14	0	0	0	1
15	0	0	0	2
25	0	0	0	1
Total:				
665	0	0	0	170
Single family member with an RICA				
1	0	0	**1**	1
2	0	**1**	0	1
2	**1**	0	0	2
3	**1**	0	0	1
4	0	**1**	0	1
4	**1**	0	0	2
5	0	0	**1**	2
6	0	0	**1**	1
7	0	0	**1**	1
7	**1**	0	0	1
10	**1**	0	0	1
11	0	0	**1**	2
12	0	0	**1**	1
33	**1**	0	0	1
Total:				
129	8	2	8	18
Multiple family members with an RICA				
3	**3**	0	0	1
5	**1**	0	**1**	1
5	**2**	0	**3**	1
6	**2**	0	0	1
9	**1**	**2**	0	1
11	0	0	**2**	1
11	0	**3**	**2**	1
11	**2**	0	0	1
13	0	0	**2**	1
13	0	0	**4**	1
25	**2**	0	0	1
Total:				
112	13	5	14	11

Table 2. Occurrence of RICA in Subjects With Versus Without ADPKD for Categories of Definite, Definite and Probable, and Definite, Probable, and Possible RICA

	Subjects with ADPKD (n = 906)	Subjects Without ADPKD (n = 823)	*P* Value
Definite RICA (%)	21 (2)	0(0)	<0.001
Definite and probable RICA (%)	28 (3)	0(0)	<0.001
Definite, probable, and possible RICA (%)	50 (5.5)	0(0)	<0.001

NOTE. Values expressed as number (percent).

RICAs in the 906 subjects with ADPKD (5.5%) and none among the 823 subjects without ADPKD ($P < 0.001$; Table 2).

Figure 2 shows the distribution of RICAs among families for each category. When definite RICAs are included, 5 of the 199 families (2.5%) with two or more RICAs accounted for 52% of RICAs, and only 15 families (7.5%) accounted for all RICAs. When definite and probable RICAs are included, 7 of the 199 families (3.5%) with two or more RICAs accounted for 61% of RICAs, and only 18 families (9.0%) accounted for all RICAs. When definite, probable, and possible RICAs are included, 11 of 199 families (5.5%) with two or more RICAs accounted for 64% of RICAs, and 29 families (14.6%) accounted for all RICAs. This suggests a nonrandom familial distribution of RICAs.

The null hypothesis that RICAs are randomly distributed among subjects with ADPKD in the 199 families studied was tested for the following categories: definite RICAs (n = 21), definite and probable RICAs (n = 28), and definite, probable, and possible RICAs (n = 50). In the three categories, the null hypothesis was rejected at *P* less than 0.05, *P* less than 0.05, and *P* less than 0.005, respectively, indicating a nonrandom distribution of RICAs among the families. Thus, clustering of RICAs occurs in ADPKD families to a greater degree than expected by chance alone.

DISCUSSION

This study examined a large population of well-studied ADPKD families to assess the occurrence of RICAs and other vascular CNS events. This provides important information to clinicians caring for these patients. This study showed an increased risk for all types of vascular CNS events in subjects with ADPKD. The total percentage (frequency) of vascular CNS events in subjects with ADPKD (8.5%) exceeded the total percentage (frequency) of vascular CNS events in subjects without ADPKD (1.6%; $P < 0.0001$). When definite, probable, and possible RICAs are excluded, the total percentage (frequency) of

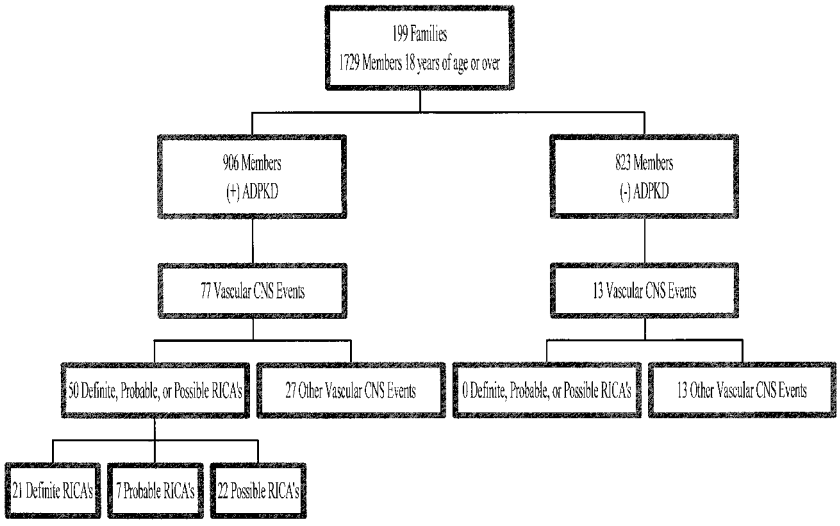

Fig 2. Distribution of RICAs among the 199 families with ADPKD. Vascular CNS events were classified as definite, probable, or possible RICA or other vascular CNS events depending on history and documentation obtained.

nonaneurysmal vascular CNS events in subjects with ADPKD (3%) was greater than the percentage (frequency) of nonaneurysmal vascular CNS events in subjects without ADPKD (1.6%; $P = 0.05$). However, given the possibility that some of the events in subjects with ADPKD labeled as possible and probable RICAs were nonaneurysmal, the greater incidence of other CNS events is likely significant and clinically important. This increase in the occurrence of vascular CNS events may be a consequence of the early onset of hypertension or abnormal CNS vasculature in individuals with ADPKD.

The percentage (frequency) of RICAs in subjects with ADPKD exceeded the percentage (frequency) of RICAs in subjects without ADPKD (none) by a statistically significant amount when definite, definite and probable, and definite, probable, and possible RICAs were compared ($P < 0.001$ in all three cases). Thus, this very large study confirmed a significantly increased risk for RICA in individuals with ADPKD compared with unaffected family members, strongly suggesting that this is a manifestation of the genetic defect. In this regard, it is important to note that polycystin-1 and polycystin-2 have been shown to be present in human arterial smooth muscle of cerebral arteries[23,24]; thus, abnormalities in these proteins could alter the structural integrity of the cerebral vasculature.

Results of the Monte Carlo analysis show that RICAs cluster in certain families with ADPKD. Reasons for this are not clear, but may relate to specific ADPKD mutations or so-called modifying genes, which may alter the expression of the underlying gene mutation. Familial clustering of RICAs has also been reported in the general population. Recent studies of the general population estimated the relative risk for SAH in a first-degree relative of a patient with SAH to range from 1.8 to 6.6.[15-18] Results of this current study support the notion that such clustering of RICAs also occurs in the ADPKD population.

Limitations to this study exist. In subjects not participating in the natural history study of ADPKD at the University of Colorado, the diagnosis of ADPKD was based on historical data obtained from relatives. However, individuals would tend to be more likely to call an affected family member unaffected than affected in the absence of clear information regarding ADPKD status. This would tend to make our findings of familial clustering more robust because no subject labeled unaffected was known to have experienced an RICA. The classification system of acute CNS events was not optimal. Although in each case, a reasonable attempt was made to confirm the diagnosis of RICA by reviewing angiograms, surgical reports, or autopsy results, such evidence was available for only 21 of 50 suspected cases in this population. Thus, events were classified as probable as well as possible by two blinded staff neurologists (R.L.H. and M.P.E.). However, the finding of increased incidence of RICAs in subjects with ADPKD compared with controls and the statistically significant finding of familial clustering using only those subjects with definite RICAs makes both these observations compelling, particularly when this is supported by the inclusion of probable and possible RICAs. Furthermore, the inclusion of probable and possible RICAs makes the possibility of bias in favor of inclusion of only those cases resulting in familial clustering less likely. The impact of individuals excluded from data analysis because of lack of information also is unclear. In addition, correlations of vascular CNS events with other clinical parameters were not possible because in 58% of subjects with ADPKD and 74% of subjects with RICA, baseline clinical data, including hypertension, smoking history, and presence of end-stage renal disease, were not available. Despite these shortcomings, this study indicates that clustering of RICAs likely occurs in families with ADPKD.

Noninvasive screening with MRA or computed tomographic angiography for ICAs in asymptomatic individuals with ADPKD may be of benefit. One decision analysis suggested that MRA screening for asymptomatic ICAs in young individuals with ADPKD would increase life expectancy and reduce the financial impact of ADPKD on society.[12] Another study suggested that screening for ICAs with MRA would increase the life expectancy of an asymptomatic 48-year-old individual with ADPKD by only 2 weeks; when the probability of impending ICA rupture was 50%, screening the same individual would increase life expectancy by more than 5 years.[25] Thus, investigators have reached different conclusions regarding screening for ICA with MRA. The benefit of screening for nonruptured

ICAs in individuals with ADPKD depends in part on their natural history, which is incompletely understood; morbidity and mortality rates associated with repair; and mortality rate of RICA.

In 1998, in a retrospective study of the general population, yearly risk for rupture was found to be less than 0.05% per year in ICAs less than 10 mm in diameter and 0.5% per year in ICAs 10 mm or more in diameter.[26] Whether these findings apply to individuals with ADPKD is unknown, but the majority of ICAs detected by screening asymptomatic individuals with ADPKD are less than 6 mm.[1-3] In a follow-up study of such ICAs in 10 individuals with ADPKD, no change or rupture was observed over a period of 14 to 54 months.[27] When considering surgical morbidity and mortality after repair of asymptomatic ICAs, there may be a bias toward reporting more favorable results. One meta-analysis of repair of ICAs indicated that surgical mortality may be as high as 2.6%, with a surgical morbidity of 10.9%. Approximately 50% of those with postoperative morbidity were dependent on others for help in daily activities of living.[28] Individuals with ADPKD may experience greater mortality from RICAs.[29] Thus, although there likely is no benefit in screening all individuals with ADPKD for ICA, the benefit of screening individuals with ADPKD from families in which RICAs appear to cluster remains to be fully clarified. Clearly, a family history of RICA was a risk factor for rupture in this study. This may help define which population of asymptomatic individuals with ADPKD would benefit most from screening for ICAs.

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