Intracranial Aneurysms in Polycystic Kidney Disease Linked to Chromosome 4

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ABSTRACT
Autosomal dominant polycystic kidney disease is genetically heterogeneous, with at least two chromosomal loci accounting for the disease. When the mutation is located on chromosome 16 (PKD1), extrarenal manifestations such as the rupture of intracranial aneurysms are well known. In the case of localization on chromosome 4 (PKD2), in which the renal disease runs a milder course, not much is known about the incidence of extrarenal manifestations. A PKD2 family is reported in which two members had subarachnoidal bleeding due to intracranial aneurysms; there was strong clinical evidence of subarachnoidal bleeding in a third family member. This indicates that the familial clustering of intracranial aneurysms may also occur in PKD2 families. Because of the considerable mortality and morbidity of intracranial aneurysms, screening with magnetic resonance angiography in PKD2 patients with a positive family history of intracranial aneurysms is recommended.

Key Words: Chromosome 4, extrarenal manifestations, subarachnoidal bleeding

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder that can be caused by mutations on at least two different chromosomes (1–3). In about 86% of ADPKD cases, the responsible gene is located on the short arm of chromosome 16 (PKD1), with the second gene located on the long arm of chromosome 4 (PKD2) (1). Clinical variability both in the symptoms of the disease and in the progression to renal failure has repeatedly been related to this genetic heterogeneity (4,5). For instance, in PKD2, the disease tends to run a milder course, with longer patient survival and slower progression toward end-stage renal failure. A lower prevalence of hypertension has been reported, whereas the age at the time of diagnosis is higher with fewer renal cysts present at that time than in PKD1. However, the clinical picture in ADPKD is dependent not only on renal but also on extrarenal manifestations (6).

One of the most impressive and alarming extrarenal manifestations of ADPKD is the sudden rupture of an intracranial aneurysm. The frequency of intracranial aneurysms in PKD1 families is about 10%, ranging from 0 to 40%, probably reflecting selection bias to some extent (7). The estimated prevalence of aneurysms in patients with ADPKD and a positive family history is 26% (with a 95% confidence interval of 9% to 42%) (8). Both of these prevalences are significantly higher than the 1.2% prevalence in the general population (9). A single case of an intracranial aneurysm in a PKD2 patient has been described (4).

It is unclear if extrarenal complications of the disease in PKD2 are, in analogy to the more favorable renal outcome, less severe than in PKD1. Not much is known about the presence of other extrarenal manifestations, such as hypertension, cardiovascular abnormalities, left ventricular hypertrophy, and the presence of cysts in liver and pancreas in PKD2. Hypertension seems to be less prevalent in PKD2; liver cysts seem to occur to the same extent as in PKD1 (4,5).

Recent studies have suggested that the PKD1 gene encodes for a protein, polycystin, that is involved in cell-cell and cell-matrix interactions (10–12). These interactions may be important in the development of intracranial aneurysms and some of the other extrarenal manifestations. It is conceivable that the PKD2 gene encodes for a similar protein, or a protein interacting with polycystin, and might therefore also lead to the same extrarenal manifestations as PKD1.

Because linkage analysis to determine PKD2 is available (2), these families can now be recognized reliably and their clinical course can be established. With these aspects in mind, we report a large family with PKD2, where three members exhibited characteristic clinical signs and symptoms as a result of intracranial aneurysms.

PATIENTS AND METHODS
Linkage to chromosome 4 was demonstrated as described elsewhere (2). In short, linkage between ADPKD2 and the DNA markers D4S423 and D4S231 located on the long arm of the chromosome, in the region 4q13-q23, was assessed. Multipoint analysis of a part of the family showed a lod score of 4.19 (linkage is more than 10,000 more likely than non-linkage), which is highly suggestive for linkage to chromosome 4. In the meantime, linkage to chromosome 16 was...
excluded, with DNA markers surrounding the 16p13.3 region (1). A multipoint linkage analysis showed a lod score of less than -2 (nonlinkage is 100 times more likely than linkage).

**Patient 1**

A 50-yr-old man was diagnosed as ADPKD in 1992 by renal sonography because of a positive family history. Sonography also revealed numerous small cysts in the liver. He had normal renal function without hypertension (no antihypertensive drugs). In 1993, he was referred with clinical symptoms compatible with a subarachnoid hemorrhage. At admission, he was somnolent with a blood pressure of 155/85 mm Hg and a systolic murmur, Grade 2/6 located at the apex. There were no focal neurologic deficits. Cerebral arteriography showed an aneurysm of the basilar artery (Figure 1), as well as two very small aneurysms located at the left medial artery and at the right ophthalmic artery. At operation, the ruptured aneurysm located at the basilar artery was clipped; the others could not be treated during this operation. Recovery was uneventful: only a paresis of the right nervus oculomotorius was observed. Cerebral arteriography 6 months after the operation showed clips at the basilar artery without a recurrence of the aneurysm. At the place of the aneurysm of the left medial artery a local stenosis was observed, although the aneurysm was undetectable, suggesting that the aneurysm had thrombosed. The aneurysm of the ophthalmic artery had not increased in size. Elective clipping did not seem necessary. In view of the stenosis at the left medial artery, acetylsalicylic acid was prescribed. One year later, his blood pressure was 160/100 mm Hg, for which he was treated with enalapril, 10 mg daily. On follow-up, his blood pressure was 135/80 mm Hg with stable renal function.

**Patient 2**

In 1984, a 34-yr-old woman was referred with clinical symptoms compatible with a subarachnoid hemorrhage. She complained of severe headache with nausea; her blood pressure was 150/90 mm Hg. There were no focal neurologic deficits. Electrocardiography showed signs of an old anterior infarction. Cerebral arteriography showed a moderate-sized saccular aneurysm of the anterior communicating artery, which was clipped. Recovery was uneventful: cerebral arteriography during follow-up showed no aneurysms. In 1988, she underwent laparotomy because of a palpable mass in the left upper abdomen, which was found to be a cystic liver. Further investigation by computed tomographic scan and ultrasound revealed cystic kidneys and pancreatic cysts. The patient's mother was said to have had kidney and liver cysts, but exact data were not available.

**Patient 3**

The father of a female patient with polycystic kidney disease suddenly died at 49 yr of age. Before his death, he experienced severe headache with vomiting and loss of consciousness. His general practitioner found symptoms compatible with cerebral compression. The tentative diagnosis of polycystic kidney disease with subsequently subarachnoid hemorrhage could not be made with certainty, because an autopsy was not performed. Symptoms of polycystic kidney disease were lacking; the patient had never attended his general practitioner before because there were no complaints regarding his health. He was a moderate cigarette smoker and drank no alcohol. However, the clinical symptoms were very suggestive for subarachnoid hemorrhage, and through linkage analysis, it was proved that his daughter had inherited the disease through him (Figure 2).

**DISCUSSION**

In this family with PKD2, 34 individuals had proven ADPKD. 51 persons had a 50% chance of carrying the mutation, and 19 of those showed no cysts at ultrasound made over the age of 30 (Figure 2). Three members with PKD2 showed clinical evidence of intracranial aneurysms, which in two patients was confirmed by cerebral angiography. The prevalence of

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**Figure 1.** Cerebral angiography of Patient 1, showing a saccular aneurysm at the basilar artery top. This was the side on which the bleeding occurred. The aneurysm was clipped.

**Figure 2.** Partial pedigree for the PKD2 family with the occurrence of intracranial aneurysms. The black boxes indicate the members with PKD2; diagonal lines show deceased family members. The numbers in the diagonal boxes indicate the numbers of male or female persons. The numbers placed under the boxes correspond to the patients with intracranial aneurysms.
ruptured intracerebral aneurysms in affected members of this family with PKD2 is 8.8%. This prevalence is significantly higher than that in the general population (1.2%) (9) and is on the same order as in PKD1 (about 10%) (6). Kimberling et al. found, in a 250-member PKD2-family with 71 affected members, one case of rupture of a cerebral aneurysm (4). In two of our PKD2 patients presented here, hypertension was not present and renal function was within normal limits at the time of rupturing. In the first patient, multiple aneurysms were seen. This patient also developed hypertension, and at sonography, cysts were present in the liver. In the second patient, ultrasound imaging revealed a cystic liver and cysts in the pancreas; this patient’s mother was said to have had a cystic liver and cystic kidneys.

Our observations provide evidence that the rupture of intracranial aneurysms and familial clustering can also occur in PKD2 patients and suggest that the prevalence and severity of extrarenal complications, i.e., intracranial aneurysms, in ADPKD are not dependent of PKD1-gene or PKD2-gene involvement. With this report included, only three definite cases of cerebral aneurysms have been described in two PKD2 families. Therefore, it is not possible to state that the presence of cerebral aneurysms is associated with the presence of PKD2. However, these cases indicate that this connection may be more than coincidental. These data cannot yet provide a reliable estimate of the prevalence of intracranial aneurysms in PKD2, because the underlying diagnosis of ADPKD may be overlooked in PKD2 patients presenting with subarachnoid hemorrhage as a result of intracranial aneurysms, especially when less severe renal symptoms are present. Further investigations to establish the prevalence of intracranial aneurysms and other extrarenal manifestations in PKD2 are needed.

In PKD1, the rupture of intracranial aneurysms does not seem to be related to the presence of renal failure. An important role of hypertension in the pathogenesis of intracranial aneurysms is likely, but a substantial number of patients have no history of hypertension when struck with subarachnoid bleeding (13). Remarkably, PKD patients without a positive family history for intracranial aneurysms had a significantly higher systolic blood pressure ($P < 0.05$) than did patients with a positive family history (13). This suggests that, apart from hypertension, genetic factors play a role in the pathogenesis of intracranial aneurysms.

In 6.7% of patients with intracranial aneurysms, familial clustering has been described in the absence of ADPKD or connective tissue disorders (14). Autosomal dominant inheritance has been reported in some of these families (15,16). In PKD1 patients, familial clustering of intracranial aneurysms is present in 18 to 26% (7,8,13,17). Age at aneurysm rupture is similar in familial intracranial aneurysms without ADPKD (43.9 yrs) to that in ADPKD patients (39.5 yr) and lower compared with that for sporadic intracranial aneurysms (52.5 yr) (13,14). The presence of multiple aneurysms seems to occur more frequently in familial cases: 26% in ADPKD and 53% in familial intracranial aneurysms without ADPKD compared with 21% in sporadic cases (13,14).

Abnormalities in structural proteins or extracellular matrix abnormalities are probably responsible for the development of cysts. Recently, it has become clear that the protein that is produced by the PKD1 gene may be responsible for those effects (10–12). It is conceivable that this mutation also has a negative effect on the structure of vessel walls. An example of abnormalities of the extracellular matrix in ADPKD is the increased prevalence of mitral valve prolapse, other heart valve defects (18), annuloaortic ectasia (19), and (dissecting) aneurysms of the abdominal aorta (20–22). In support for changes in the extracellular matrix in relation to the development of intracranial aneurysms is a small study in which 50% of 14 patients who died of intracranial aneurysms had abnormalities in collagen Type III (23). Also, very interestingly, a family with six members has been described showing cosegregation of ADPKD and overlap connective tissue disorders, in which markers for PKD1 were tightly linked to both ADPKD and overlap connective tissue disorders (24). The question is whether the chance of developing aneurysms is equal in each family, e.g., does one mutation lead to a higher chance of the development of aneurysms than another mutation? Because the PKD1 gene has recently been identified (25), this question can now be addressed, at least for the chromosome 16–linked form.

The rupture of an intracranial aneurysm leads to considerable morbidity and mortality, whereas the surgical repair of an unruptured aneurysm results in low mortality and morbidity rates (26). The natural history of unruptured aneurysms is not well known, but the risk of rupture seems to increase with the size of the aneurysm (27). With magnetic resonance angiography, a reliable noninvasive technique of screening for intracranial aneurysms has become available. By this technique, one can establish intracranial aneurysms ≥5 mm with a sensitivity of 86% (28). Although this is based on limited data, we recommended the screening of PKD2 patients with a positive family history for intracranial aneurysms (at least one family member) with magnetic resonance angiography, as has been proposed for PKD1 patients (13).

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