The Association between Polycystic Kidney Disease and Cerebral Aneurysms

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ABSTRACT: Rupture of cerebral aneurysms is an important cause of morbidity and mortality in patients with adult polycystic kidney disease (PKD). In the present paper, we review the literature regarding the association of cerebral aneurysms and PKD and emphasize, by means of a case report, the importance of familial clustering of aneurysms in patients with PKD. We conclude that the prevalence of intracranial aneurysms in patients with PKD approaches 40% and is likely significantly higher in patients with PKD and a positive family history for cerebral aneurysm. We recommend that screening cerebral angiography be strongly considered in all patients with PKD and a family history of cerebral aneurysm or subarachnoid hemorrhage.

RÉSUMÉ: Association entre la maladie polykystique du rein et les anévrysmes cérébraux La rupture d'anévrysmes cérébraux est une cause importante de morbidité et de mortalité chez les patients atteints de la forme adulte de la maladie polykystique du rein (MPR). Dans cet article, nous revoyons la littérature concernant l'association d'anévrysmes cérébraux et de MPR, et nous soulignons au moyen d'une histoire de cas, l'importance de l'agrégation familiale d'anévrysmes chez les patients atteints de MPR. Nous concluons que la prévalence d'anévrysmes intracrâniens chez les patients atteints de MPR approche 40% et est vraisemblablement significativement plus élevée chez les patients avec MPR et une histoire familiale positive d'anévrysme cérébral. Nous recommandons qu'une angiographie cérébrale de dépistage soit sérieusement considérée chez tous les patients avec une MPR et une histoire familiale d'anévrysme cérébral ou d'hémorragie sous-arachnoïdienne.

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Rupture of cerebral aneurysms is an important cause of morbidity and mortality in patients with adult polycystic kidney disease (PKD).[1,2,3] The prevalence of occult cerebral aneurysms in association with PKD has been estimated to be between 10-30%.[2] However, the indications for screening cerebral angiography in patients with PKD remain controversial.[2,3] Recently, Saifuddin and Dathan[4] described a family whose three members all had PKD and intracranial aneurysms. These authors suggested that a positive family history of cerebral aneurysm in patients with PKD should prompt radiological investigation. In the present paper we report an additional case of familial clustering of cerebral aneurysms in PKD and review the literature regarding the association of cerebral aneurysms and PKD.

Case Report

The patient, a 48-year-old woman, was noted in 1971 to be hypertensive and have an abdominal mass. Subsequent investigations showed evidence of polycystic kidney and liver disease. Between 1971 and 1989 there was evidence of progressively worsening ascites and hepatic function. In May 1989, the patient was admitted to a hospital in her home province with a ruptured hepatic cyst. In June 1989, the patient was transferred to the Toronto Hospital for evaluation regarding renal and hepatic transplantation. Although there was no history to suggest previous subarachnoid hemorrhage, the family history (Figure 1) revealed that the patient's mother and brother died at the ages of 34 and 28 respectively of a subarachnoid hemorrhage proven at autopsy. The patient has two children, aged 19 and 24 respectively in good health. The patient's medications included enalapril, furosemide, nifedipine, atenolol, and amiloride.

Physical examination revealed a blood pressure of 130/90 mm Hg. The patient was mildly icteric with a sallow complexion. There was marked hepatomegaly, massive ascites and bilateral pitting edema of the legs. The neurological examination was normal.

Investigations

The serum creatinine was 343 μmol/l (N: 53-150) and the creatinine clearance 0.22 ml/s/1.73 m^2 (N: 1.58-2.16). The total bilirubin was 21 μmol/l (N: < 17) and the alanine amino transaminase 179 IU/1 (N: 5-35). A computerized tomographic (CT) scan of the abdomen disclosed severe polycystic kidney and liver disease (Figure 2). An enhanced CT scan of the brain was normal. A neurosurgical opinion was sought by the transplantation team as to the advisability of proceeding with organ transplantation. Because of the history of PKD and the family history of subarachnoid hemorrhage, a screening cerebral angiogram was recommended to rule out an occult cerebral aneurysm. In view of the impaired renal function, a digital sub-

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traction angiogram was performed to minimize the dose of iodinated contrast materal injected. Angiography (Figures 3, 4) revealed multiple aneurysms including: 1. a 1 cm multilobed aneurysm of the proximal (M1) segment of the right middle cerebral artery (MCA); 2. a 2 cm multilobed aneurysm of the right MCA bifurcation; 3. a 2 cm multilobed M1 aneurysm of the left MCA bifurcation; 4. a 7 mm left pericallosal aneurysm.

Operations and Postoperative Course

The timing of aneurysm surgery in relationship to organ transplantation was discussed. In view of the anticipated difficulty in maintaining a stable blood pressure during a prolonged transplantation procedure, it was concluded that the cerebral aneurysms should be repaired as an initial procedure.

In July 1989, the patient underwent a right frontotemporal craniotomy allowing for both a pterional and interhemisheric exposure. The proximal M1 and M1 bifurcation aneurysms and the left pericallosal aneurysm were clipped. During dissection of the anterior cerebral complex, a small 3 mm diameter aneurysm of the anterior communicating artery was found. This lesion was too small to be clipped and thus was coagulated and wrapped with gauze. The postoperative course was unremarkable. Two weeks later, the patient underwent a left pterional craniotomy and clipping of the left M1 bifurcation aneurysm. A small 4 mm aneurysm involving a superior temporal M2 branch of the left MCA was discovered during the dissection and treated by coagulation and wrapping.

The patient again made a smooth recovery from the second craniotomy. In November 1989 a donor became available and the patient underwent combined hepatic and renal transplantation from which she again made an excellent recovery. The patient was discharged from hospital in December 1989 with normal renal and hepatic function, normal neurological status and on significantly reduced antihypertensive medication.

Discussion

Three disorders have been associated with intracranial aneuryms: aortic coarctation, Ehlers-Danlos syndrome, and adult onset (Potter Type 3) PKD.[5,6] It is noteworthy that patients with the infantile (Potter Type 1) or childhood (Potter Type 2) forms of PKD are not at increased risk for developing cerebral aneurysms.[1] The association between PKD and cerebral aneurysm was first reported by Borelius in 1901.[8] Dunger[9] subsequently discussed the frequent association of aneurysmal subarachnoid hemorrhage and PKD.

While it has been estimated that 10% of patients with PKD will die of aneurysmal subarachnoid hemorrhage[1,2,3] estimates of the prevalence of intracranial aneurysms in patients with PKD vary considerably.[2] Table 1 summarizes the results of eight clinical and autopsy series which have examined this question.[3,7,10-15] Only those series providing statistically valid data

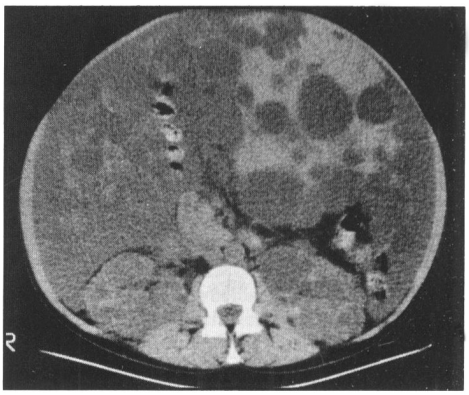

Figure 2 — A computed tomographic (CT) image of the abdomen disclosing marked polycystic renal and hepatic disease.

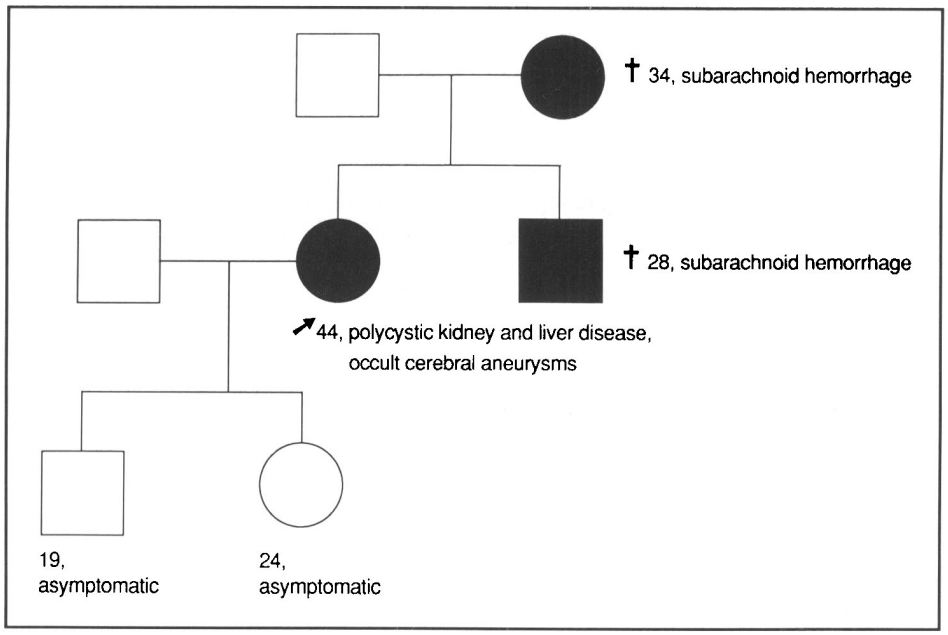

Figure 1 — The family history disclosed that the patient's brother and mother died at ages 28 and 34, respectively of a subarachnoid hemorrhage.

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were analysed. If one includes series in which the cerebral vasculature was not systematically examined,[10-13] the incidence of subarachnoid hemorrhage or intracranial aneurysm in PKD is approximately 10%. This figure thus reflects the incidence of symptomatic (i.e. ruptured) cerebral aneurysms in patients with PKD, since asymptomatic patients did not undergo examination of the cerebral vasculature in these studies. However, by limiting the analysis to series in which the brain was examined at autopsy or by cerebral angiography, a figure of approximately 38% is obtained (Table 1). This number reflects more accurately the prevalence of ruptured and unruptured cerebral aneurysms in patients with PKD.

Recently, Saifuddin and Dathan[4] and Kaehny et al.[16] have described familial clustering of intracranial aneurysms in PKD.

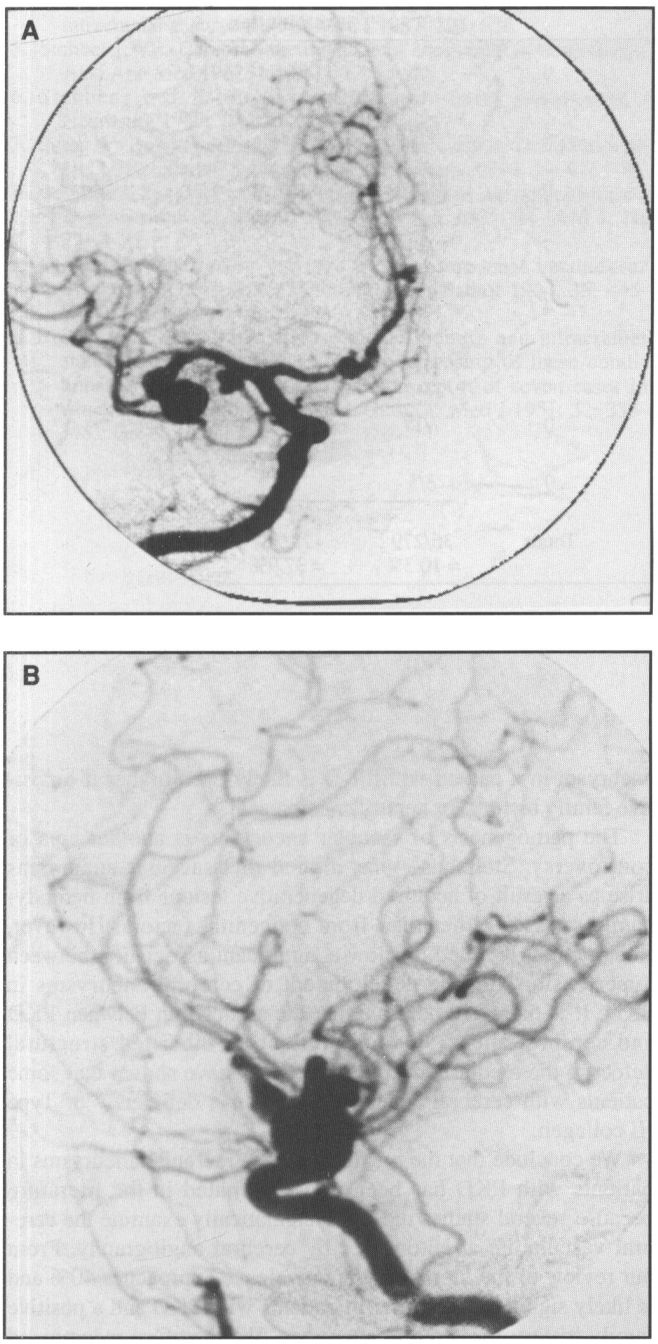

*Figure 3 — Digital subtraction angiogram; right internal carotid injection; anteroposterior (**A**) and lateral (**B**) projections. These images demonstrate: a 1 cm multilobed aneurysm of the proximal (M1) segment of the right middle cerebral artery (MCA) and a 2 cm multilobed aneurysm of the right MCA bifurcation. At operation, a 3 mm aneurysm of the anterior communicating artery was found. This lesion was not appreciated preoperatively, but may be seen on close inspection of the anteroposterior image.*

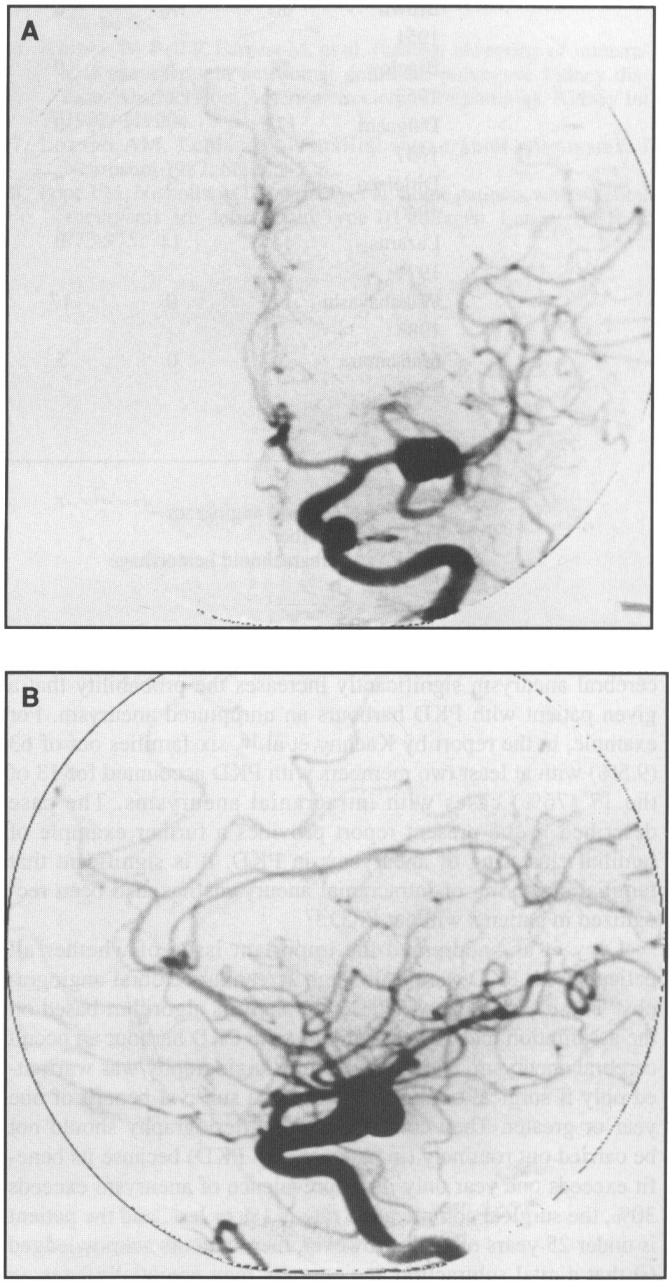

*Figure 4 — Digital subtraction angiogram; left internal carotid injection; anteroposterior (**A**) and lateral (**B**) projections. These images demonstrate: a 2 cm multilobed M1 aneurysm of the left middle cerebral artery (MCA) bifurcation and a 7 mm left pericallosal aneurysm.*

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Table 1: Association between polycystic kidney and cerebral aneurysms

Reference	No. of cases	Autopsies with brain examination	Angio	Aneurysm	SAH/ no aneurysm	No. of cases SAH or aneurysm	
						all cases	cases with angio/brain examination
Suter 1949	5	5	0	2	0	2/5	2/5
Brown 1951	36	16	0	6	2	8/36	8/16
Bigelow 1953	14	6	0	3	0	3/14	3/6
Dalgaard 1957	173	?	0	1	7	8/173	–
Dirlefsen 1960	15	3	2	2	4	6/15	–
Lazarus 1971	14	14	0	0	1	1/14	1/14
Wakabayashi 1983	17	0	17	7	0	7/17	7/17
Matsumura 1986	5	0	5	3	0	3/5	3/5
					Totals	36/279 = 10.3%	22/58 = 37.9%

Abbreviations:
Angio : cerebral angiogram
No. : number
SAH : subarachnoid hemorrhage

These authors have suggested that a positive family history for cerebral aneurysm significantly increases the probability that a given patient with PKD harbours an unruptured aneurysm. For example, in the report by Kaehny et al.[16], six families out of 63 (9.5%) with at least two members with PKD accounted for 13 of the 17 (76%) cases with intracranial aneurysms. The case described in the present report provides a further example of familial clustering of aneurysms in PKD. It is significant that familial clustering of intracranial aneurysms has also been recognized in patients without PKD.[17]

Levy et al.[2] addressed the important issue of whether all patients with PKD should undergo screening cerebral angiography. These authors used a decision analysis algorithm based on the assumption that 30% of patients with PKD harbour an occult cerebral aneurysm, and that screening angiography was warranted only if surgical treatment conferred a survival benefit of one year or greater. They concluded "that arteriography should not be carried out routinely (in patients with PKD) because its benefit exceeds one year only if the prevalence of aneurysm exceeds 30%, the surgical complication rate is 1% or less, and the patient is under 25 years of age". However, these authors acknowledged (i) that digital subtraction angiography may potentially have an important role in screening for aneurysms and that (ii) angiography should be carried out if the expected prevalence or aneurysms exceeded 30%. It is therefore significant that the prevalence of aneurysms in PKD may be as high as 40% (Table 1). Indeed the expected prevalence of an occult cerebral aneurysm in a patient with PKD is likely even higher if a positive family history for aneurysm is present.

The pathogenesis of saccular aneurysms is another area of controversy. Stehbens[5,6] has argued that saccular aneurysms arise as a result of acquired degenerative lesions from hemodynamic stresses rather than from congenital factors. However, Kaehny et al.[16] failed to show a significant association between hypertension and the development of cerebral aneurysms in PKD. It is therefore possible that the association between PKD and cerebral aneurysms may reflect an inherited structural defect in the media. Indeed, Pope et al.[18] have shown that some patients with cerebral aneurysms harbour a deficiency of Type III collagen.

We conclude that the prevalence of intracranial aneurysms in patients with PKD has been underestimated in the literature because several studies did not systematically examine the cerebral vasculature at autopsy or by cerebral angiography. From our review of the literature, the prevalence approaches 40% and is likely significantly higher in patients with PKD and a positive family history for cerebral aneurysm. We therefore recommend that screening cerebral angiography be strongly considered in all patients with PKD and a family history of cerebral aneurysm or subarachnoid hemorrhage.

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