Cerebral Aneurysms and Polycystic Kidney Disease: A Critical Review

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ABSTRACT: The pathogenic basis of the association between adult polycystic kidney disease (APKD) and cerebral aneurysms is unknown. We have compared cerebral aneurysms in 79 patients with APKD gleaned from the literature to the sporadic aneurysm cases reported by the Cooperative Study to determine if there are significant biological differences between these two groups. Sixty-eight patients had a single aneurysm and 11 (14%) had multiple aneurysms. In APKD patients with subarachnoid hemorrhage from a single aneurysm there was a significant over-representation of males (72%, p < 0.01); and the APKD group had more aneurysms of the middle cerebral artery (37%, p < 0.05). The peak decennial incidence and mean age of rupture of APKD-associated aneurysms was younger (mean age 39.7 years, p < 0.01) and over 77% of APKD-associated aneurysms had ruptured by age 50 versus 42% for sporadic aneurysms (p < 0.001). Cerebral aneurysms co-existed with APKD in the absence of hypertension in 25% of 45 cases where the presence or absence of hypertension was recorded. These biological differences and the occurrence of aneurysms in normotensive APKD patients suggests an etiology which may be independent of hypertension and that APKD-associated aneurysms may be genetically determined. It is hypothesized that cases of inherited, familial cerebral aneurysms could be linked to a genetic defect resembling that which occurs on chromosome 16 in APKD.

The etiology of cerebral aneurysms remains unknown. They may result from incomplete involution of fetal cerebral arteries as the brain expands and alters its vascular pattern, from the hemodynamic stresses at branching points as the jet of arterial blood strikes the far wall, or may result from the weakening effects of atherosclerosis and arterial hypertension on the cerebral vessel wall. A possible genetically-determined etiology for cerebral aneurysms, producing a structural weakness in the arterial wall, is suggested by 1) the occurrence of cerebral aneurysms in families, where they rupture at an earlier age and at a smaller size, and frequently occur at the same or at mirror sites in affected individuals; 2) from their occurrence in identical twins in whom they frequently occur at same or mirror sites and frequently rupture within two to five years of each other; 3) and by their occurrence in genetically-determined conditions such as adult polycystic kidney disease (APKD).1
Adult polycystic kidney disease is an autosomal, dominantly inherited disorder arising from a defect which maps to chromosome 16. This disorder has extrarenal manifestations resulting from hepatic, pancreatic and cardiovascular involvement. Of interest to neurosurgeons is the occurrence of cerebral aneurysms in up to 40% of APKD patients.

The pathogenesis of cerebral aneurysms in APKD is unknown. Developmental and congenital hypotheses can be invoked to explain this association. As the majority of APKD patients will become hypertensive during their illness it is possible that aneurysms develop as a result of the effects of arterial hypertension on the cerebrovascular wall. However, not all APKD patients with cerebral aneurysms are hypertensive, and it is unclear whether hypertension in itself is sufficient to produce cerebral arterial aneurysms. The occurrence of cerebral aneurysms in patients with APKD, therefore, may simply reflect the inheritance of a disorder that affects the cerebral vasculature as well as other tissues of mesenchymal origin. If this were the case hypertension could be considered a factor aggravating a congenital predisposition to aneurysm formation.

We have compared biological features of cerebral aneurysms in APKD patients derived from the literature with those of the sporadic aneurysms reported by the Cooperative Study to determine if there are differences between these two groups which might support a role for genetic factors in the formation of cerebral aneurysms.

**METHODS**

A review of the published literature was performed using APKD and cerebral aneurysms as key words. Of the reports thus gleaned, those written in English, French and Spanish, and those written in other languages where an adequate translation was available were analyzed. Those reports stating sex, age, at the time of rupture and the site of the ruptured aneurysm were considered. These data were then compared, by Chi² and student’s t tests, to data from ruptured sporadic aneurysms reported by the Cooperative Study. The mean age of rupture of sporadic aneurysms was obtained from Andrews’ study of the aneurysms diagnosed at the Dartmouth-Hitchcock Medical Center, 1964-1975 (R.J. Andrews, personal communication, 1986). A total of 100 reports of cerebral aneurysms associated with APKD, from 1901 to 1989, were reviewed (references available on request). The age, sex, and site of aneurysme were reported in 79 instances. Sixty-eight of these patients had a single aneurysm and 11 had 2 or more aneurysms. As some data on sporadic aneurysms are only available for patients with a single ruptured aneurysm, APKD patients are grouped into those with a single ruptured aneurysm or into a group containing all single and multiple ruptured aneurysms where appropriate for comparison.

**OBSERVATIONS**

**Sex** There were more males (n = 49, 72%) than females (n = 19, 28%) with a single ruptured aneurysm in the APKD group than in the sporadic aneurysm group (43% male, 57% female, both p < 0.01) (Figure 1). Of the 11 APKD patients with multiple aneurysms, 5 were female and 6 were male.

**Age** The peak decennial incidence of aneurysm rupture in APKD patients with single and multiple aneurysms was 40-49 years versus 50-59 years for the sporadic aneurysm patients (Figure 2); and the mean age of rupture in APKD patients with a single aneurysm was younger (39.8 years ± 1.4 S.E.M.) than for the sporadic aneurysm patients (51.4 ± 1.2, p < 0.0001, Figure 3). Male APKD patients presented with subarachnoid hemorrhage (SAH) at a mean age of 37.9 ± 1.7 years and females at 44.2 ± 2 years. Seventy-seven percent of all APKD-associated aneurysms had ruptured by age 50 compared to only 42% of sporadic aneurysms (p < 0.0001, Figure 4).

**Aneurysm site** There was an over-representation of aneurysms of the middle cerebral artery (MCA; 37% vs 21%, p < 0.05), and an under-representation of aneurysms of the internal carotid artery (ICA; 18% vs 30%, p < 0.05) in APKD patients with a single rupture aneurysm when compared to patients with sporadic aneurysms (Figure 5). No statistically significant difference was noted in the distribution of aneurysms on the anterior cerebral artery complex or on the vertebrobasilar system.

**Multiplicity of Aneurysms** There was no significant difference in the incidence of multiple aneurysms in APKD patients and in sporadic aneurysms (14% vs 19%).

**Arterial hypertension** The presence or absence of arterial hypertension was stated in 45 reports of single APKD-associated aneurysms: 11 (25%) APKD patients were normotensive and 33 (75%) were hypertensive. Of the 11 APKD patients with multiple aneurysms, 6 were hypertensive, 1 was normotensive, and in 4 patients the state of the blood pressure is unknown.

**DISCUSSION**

Aneurysms in adult polycystic kidney disease

The hypothesis that a genetically-determined defect of the cerebral arterial wall may play a role in the pathogenesis of
cerebral aneurysms is supported by their occurrence in identical twins, in individuals within the same family, and in association with genetically-determined conditions, such as APKD.\(^1\) Despite these observations, there is no firm correlation between a biochemical lesion and the formation of cerebral aneurysms, and there is no reliable laboratory test which can identify individuals who have a cerebral aneurysm.\(^7\) A study of the biological features of cerebral aneurysms arising in the context of APKD may provide some insight into the putative genetic mechanisms which may operate in their pathogenesis.

Patients with APKD have numerous associated lesions in addition to cerebral aneurysms. Among the most frequent are cardiac valve abnormalities which may be present in up to 29% of APKD patients.\(^9\) Other disorders include thoracic aortic aneurysms, inguinal and umbilical hernias and cysts in the liver and kidney.\(^9\) This pattern of abnormalities suggests that the APKD gene is responsible for the normal structure and function of connective tissues. In this respect, the association of cerebral aneurysms in APKD patients mirrors the occurrence of cerebral aneurysm in disorders of connective tissues including Marfan’s syndrome, pseudoxanthoma elasticum, fibromuscular dysplasia and Ehlers-Danlos syndrome type IV.\(^1\)

Our data suggest that cerebral aneurysms occurring in association with APKD differ from sporadic aneurysms in several biological features. Aneurysms in APKD patients appear to predominantly affect males and to rupture at a younger age. They involve the MCA more often than expected and are seen less frequently on the supraclinoid ICA than in sporadic cases. It is possible that these differences result from an inherited cerebrovascular defect rather than from arterial hypertension. As our study is based on a literature review we cannot eliminate the possibility of reporting bias as a factor in these observations.

**Hypertension and aneurysm formation**

The relationship of cerebral aneurysms and arterial hypertension is ill-defined and a causal role of arterial hypertension in the genesis of cerebral aneurysms remains unproven. Epidemiological studies assessing the association of arterial
Figure 4 — Cumulative age group at time of rupture. Seventy-seven percent of APKD aneurysms have ruptured by age 50 compared to 42% of sporadic aneurysms ($p < 0.001$). (Numbers at the base or immediately above each column represent the number of patients in each group.)

Figure 5 — Site distribution of single ruptured cerebral aneurysms. There is a significant over-representation of MCA aneurysms (37%) in the APKD group compared to the sporadic aneurysm group ($p < 0.05$), and an under-representation (18%) of ICA aneurysm ($p < 0.05$). ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; VBS = vertebro-basilar system. (Numbers at the base of each column indicate the number of patients in each group.)

Hypertension and cerebral aneurysms have produced equivocal and conflicting results. Some have demonstrated an over-representation of arterial hypertension in patients with cerebral aneurysms while others have not.

A history of arterial hypertension has been noted in up to 47% of patients with cerebral aneurysms and cardiac enlargement has been noted in up to 69%; and arterial hypertension may be up to three times as frequent in patients with aneurysms than in unselected autopsy material. Similarly, the Framingham study found that arterial hypertension was significantly more frequent in patients with a ruptured cerebral aneurysm than in age and sex matched controls. Nonetheless a significant number of patients with a cerebral aneurysm do not have a history of hypertension, nor is cardiac hypertrophy present at autopsy. These observations have led Black and Hicks to conclude that arterial hypertension is therefore not an essential, absolute prerequisite for the formation of cerebral aneurysms. They suggest that arterial hypertension may act on primarily diseased cerebral arteries with deficient elastica; or that the association between hypertension and aneurysms reflects the presence of a common vascular disorder and that the two are without a cause and effect relationship. Further, the Framingham study is based on a small number of patients whose mean systolic and diastolic blood pressures overlap with the mean control values and whose average systolic and diastolic values differ from controls by only 10 and 6 mm Hg respectively. Atheromatous lesions are common at the site of aneurysm formation, and Crompton was unable to separate the effect of arterial hypertension from those of atheroma in patients with cerebral aneurysms. He suggested that aneurysms can arise from an inherent abnormality of the internal elastica; and that atheroma can promote aneurysm formation by decreasing the elasticity of cerebral arteries, widening arterial bifurcations, and enlarging medial defects. Moreover, it has been demonstrated that the rupture of cerebral aneurysms carries a higher mortality when complicated by arterial hypertension and autopsy studies may therefore be biased towards a falsely elevated association of aneurysms and hypertension. Using non-lethal SAH as a marker for cerebral aneurysms is not informative of the total number of aneurysms in a population as the unruptured ones remain undiagnosed both in hypertensive and normotensive subjects.

Other studies have failed to demonstrate an over-representation of hypertension in patients with ruptured cerebral aneurysms compared to age and sex-matched controls, suggesting that the latter can arise and rupture independent of the former. Andrews and Spiegel, while not demonstrating an...
association between arterial hypertension and a single aneurysm, have demonstrated an association between arterial hypertension and multiple cerebral aneurysm. This is seen almost exclusively in females with more than two aneurysms. Ostergaard has interpreted the latter as supporting the hypothesis that arterial hypertension is important for the formation of multiple cerebral aneurysms. However, it has been demonstrated that atherosclerosis, especially at sites of arterial branching where aneurysms often arise, is also more frequent in cases of multiple aneurysms and therefore a causal relationship between multiplicity and arterial hypertension is not clearly defined. The association between multiplicity and hypertension may therefore suggest that both conditions result from a common disease, atherosclerosis, as suggested by Black and Hicks. Further, in Ostergaard and Hog's study only approximately 25% of patients with 2 or 3 aneurysms were hypertensive by history or on the basis of cardiac enlargement (only 10% with a single aneurysm). These data can be interpreted to indicate that multiple and single aneurysms are more likely not be associated with arterial hypertension, casting doubt on the role of hypertension in aneurysm formation rather than supporting it. In this regard it is noteworthy that the APKD patient group in our study did not have an over-representation of multiple cerebral aneurysms when compared to the number of patients with multiple aneurysms identified in the Cooperative Study (14 versus 19%).

Hypertension and aneurysm rupture

The role of pre-existing hypertension as a risk factor for the rupture of a pre-existing cerebral aneurysm is also open to question. McCormick and Schmalstieg did not identify an association between systemic arterial hypertension and aneurysm rupture when compared to age and sex-matched controls; and multivariate outcome analyses of initially unruptured aneurysms did not identify hypertension as an increased risk of eventual rupture. A biochemical model analysis of cerebral aneurysms predicts that blood pressure is not as important a factor for eventual aneurysm rupture as are wall thickness and wall composition. However, many studies indicate that hypertension aggravates the effects of SAH from a ruptured aneurysm and is associated with a higher mortality. It is unlikely that epidemiological studies will unequivocally support or refute a causal association of arterial hypertension and cerebral aneurysms. The critical epidemiological study, one that would screen a large population for the presence and absence of aneurysms and hypertension has not been done as it would require cerebral angiography of large asymptomatic populations. The experimental laboratory offers little support for the concept of a hypertensive etiology in the formation of cerebral aneurysms; those aneurysms being produced in animals rendered hypertensive resembling more the Charcot-Bouchard aneurysms seen in hypertensive hemorrhage rather than the “berry” aneurysms germane to our discussion.

Hypertension and adult polycystic kidney disease

The role of hypertension in the genesis of aneurysms in patients with APKD also remains unproven. The data reported here and data from a previous study suggest that arterial hypertension is not necessary for the development of cerebral aneurysms in APKD patients: a systematic, angiographic study of 17 asymptomatic APKD patients from 10 families identified 7 patients with an unruptured aneurysm: 2 were hypertensive, 5 were not. In our study the presence or absence of arterial hypertension was reported in only 45 of the 68 APKD cases with a single aneurysm. If all the remaining patients were hypertensive then in only 16% of the reported APKD patients with a single aneurysm would hypertension not be a possible factor in their etiology.

We feel that the weight of evidence suggests that arterial hypertension may not be a determining factor in the development of cerebral aneurysm in APKD: the role of hypertension in the formation of cerebral aneurysms is unclear; cerebral aneurysms were present in the absence of hypertension in 25% of APKD patients in whom this parameter was recorded; cerebral aneurysms have been documented in asymptomatic normotensive carriers of APKD who were screened by cerebral angiography; and while there may be a correlation between arterial hypertension and an increased incidence of multiple aneurysms, only 14% of APKD patients in our study had multiple aneurysms versus 19% in the sporadic aneurysm population. Because of these considerations, we believe that, although hypertension may contribute to the earlier rupture seen in the APKD group, arterial hypertension is not the primordial mechanism accounting for aneurysm formation in APKD patients.

Conclusions

Adult polycystic kidney disease results from a defect mapped to chromosome 16 which is inherited in an autosomal dominant fashion and which may lead to abnormalities in tissues of mesenchymal origin. It is possible, therefore, that cerebral aneurysms seen in this condition reflect a genetically-determined lesion in the mesenchymal component of the cerebral blood vessel wall, albeit one on which other acquired factors, such as arterial hypertension, may act. In this regard a systematic study of the cerebral blood vessels in patients with APKD may reveal important clues in the pathogenesis of cerebral aneurysms. An interesting question to be addressed is whether patients with familial, or even with sporadic, aneurysms could be carriers of inborn errors affecting cerebral blood vessels such as those which are implicated in APKD. This constitutes a hypothesis which can be tested with currently available techniques.

References