

Intracranial Arterial Dolichoectasia in Autosomal Dominant Polycystic Kidney Disease

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Abstract. Autosomal dominant polycystic kidney disease (ADPKD) is a systemic disorder with a variety of cardiovascular manifestations. This study presents a group of patients with ADPKD who had intracranial arterial dolichoectasia. One hundred seventy-eight ADPKD patients were screened with magnetic resonance angiography, 40 ADPKD patients had conventional angiography, and 98 ADPKD patients underwent a brain autopsy. For comparison, 360 patients without ADPKD who had magnetic resonance angiography and conventional angiography or brain autopsy were also studied. The prevalence of asymptomatic intracranial arterial dolichoectasia was 2.2% (4 of 178), 2.5% (1 of 40), and 2.0% (2 of 98) in the three ADPKD groups, respectively. None of the patients without ADPKD had intracranial arterial dolichoectasia. In addition to the seven patients with asymptomatic disease, two ADPKD patients with vertebrobasilar dolichoectasia had posterior cir-

ulation ischemic symptoms. The mean age of the nine patients (five men and four women) was 56.6 yr (range, 41 to 67 yr). The posterior circulation was involved in five patients, the anterior circulation was involved in two patients, and both were involved in two patients. Arterial dissection was believed to have caused middle cerebral artery dolichoectasia in one patient, and intracranial arterial dissections were strongly suspected in two other patients. Six of the nine patients with intracranial arterial dolichoectasia had additional vascular manifestations of ADPKD. Some patients with ADPKD are at an increased risk of developing intracranial arterial dolichoectasia and dissections. Recognizing this association is important because (1) it may be a cause of stroke; (2) it may mimic a saccular aneurysm on radiographic studies; and (3) it suggests that the arteriopathy of ADPKD may be more generalized than previously believed. (*J Am Soc Nephrol* 8: 1298–1303, 1997)

Intracranial arterial dolichoectasia is defined as elongation (Greek: *δολιχος*) and dilatation (Greek: *εκτασια*) of a segment of cerebral artery. The terms intracranial fusiform aneurysm and dolichoectasia are often used interchangeably, and the distinction between these two entities may be marginal, although a true fusiform aneurysm is not associated with elongation of the artery.

The pathogenesis of arterial dolichoectasia is unclear, but both congenital and acquired factors are probably involved. Dolichoectasia of cervicocephalic vessels has been reported previously in heritable connective tissue disorders such as Marfan's syndrome, Ehlers-Danlos syndrome, and neurofibromatosis (1). In this article, we report an association of intracranial arterial dolichoectasia with autosomal dominant polycystic kidney disease (ADPKD), another heritable disorder affecting a variety of connective tissues, including the cardiovascular system (1–4). Recognizing this association may be important because (1) it may be a cause of stroke; (2) it may mimic a saccular intracranial aneurysm on radiographic stud-

ies; and (3) it suggests that the arteriopathy of ADPKD may be more generalized than previously believed.

Materials and Methods

Patients

Three groups of patients with ADPKD were studied to estimate the prevalence of intracranial arterial dolichoectasia in ADPKD. Group I consisted of all patients with ADPKD who were screened for the presence of an intracranial aneurysm with magnetic resonance angiography (MRA) between 1988 and 1995, group II consisted of all patients with ADPKD who underwent conventional angiography between 1950 and 1995, and group III consisted of all patients with ADPKD who underwent postmortem examination of the central nervous system between 1950 and 1995. For comparison, we determined the prevalence of intracranial arterial dolichoectasia in 50 patients who underwent MRA and conventional angiography in a study of carotid artery stenosis during 1995 and in 310 consecutive brain autopsies of patients between 30 and 75 yr of age who had a non-neurological cause of death between January 1993 and May 1995. The medical records, radiographic studies, and autopsy reports of these patients were reviewed.

Clinical diagnoses of ADPKD were based on excretory urography, angiography, ultrasonography, computed tomography, or surgery. The criteria for a 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. 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 criteria for

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the diagnosis of dolichoectasia included elongation and dilation of an intracranial artery exceeding twice the diameter of the parent artery. Hypertension was defined as a history of treatment of elevated BP or the continuing presence of a BP greater than 160/95 mmHg. Renal function 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 patient was on dialysis or had received a renal transplant.

Statistical Analysis

Fisher's exact test was used to compare the frequencies of intracranial arterial dolichoectasias in the ADPKD and control groups.

Results

Asymptomatic intracranial arterial dolichoectasia was found in 4 (2.2%) of 178 patients in group I (age, 44 ± 13 yr), in 1 (2.5%) of 40 patients in group II (age, 52 ± 12 yr), and in 2 (2.0%) of 98 patients in group III (age, 56 ± 14 yr) (Figures 1 and 2). Three patients studied with MRA also had conventional angiography. Six patients studied with conventional angiography also underwent postmortem examination. Therefore, the total number of patients studied was 307. The prevalence of asymptomatic intracranial arterial dolichoectasia among these 307 patients with ADPKD was 2.3% (95% confidence interval, 0.9 to 4.8%). None of the 360 patients without ADPKD (age, 59 ± 13 yr) who had MRA and conventional angiography or brain autopsy had intracranial arterial dolichoectasia. The prevalence of intracranial arterial dolichoectasia in the ADPKD patients was significantly higher than in the patients without ADPKD (Table 1).

In addition to these seven patients with asymptomatic intracranial arterial dolichoectasia, there were two ADPKD patients with posterior circulation cerebral ischemic symptoms or



Figure 1. Magnetic resonance (MR) angiogram showing vertebrobasilar dolichoectasia with dilation of the proximal basilar artery to 10 mm (arrow) in a 41-yr-old man.



Figure 2. MR angiograms showing dolichoectasia of the middle cerebral artery (arrows) in a 57-yr-old woman. These changes are most consistent with arterial dissection. Note how the dolichoectatic vessel in Panel B resembles a saccular aneurysm in Panel A.

Table 1. Prevalence of asymptomatic intracranial arterial dolichoectasia in autosomal dominant polycystic kidney disease (ADPKD)

Group	No. of Patients	With Dolichoectasia	
		Number	Percentage
ADPKD	307	7	2.3 ^a
Without ADPKD	360	0	0

^a P = 0.004.

brainstem compression due to vertebrobasilar dolichoectasia diagnosed with conventional angiography (Figure 3).

The clinical and radiographic characteristics of the nine patients with intracranial arterial dolichoectasia are summarized in Table 2. The mean age of these five men and four women was 56.6 yr (range, 41 to 67 yr). They were all from different families. The posterior circulation was affected in five

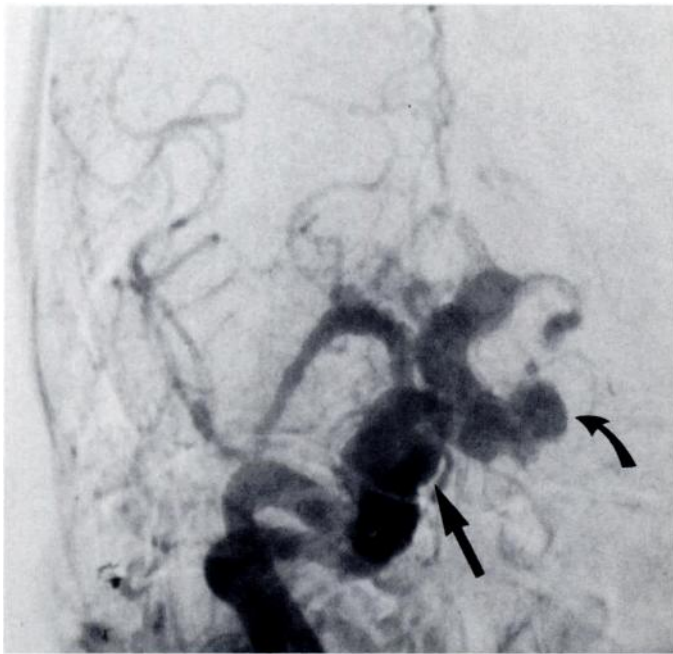


Figure 3. Anteroposterior arteriogram showing vertebrasilar (curved arrow) and carotid (straight arrow) dolichoectasia in a 54-yr-old man.

patients, the anterior circulation was affected in two patients, and both arterial distributions were affected in two patients. All patients had a family history of ADPKD. In addition, the father of patient 1 underwent surgical clipping of an intracranial aneurysm when he was 43 yr old and died of a ruptured abdominal aortic aneurysm 16 yr later. The father of patient 5 died at 42 yr of age from a cerebral hemorrhage, and the mother of patient 6 died at 52 yr of age from a cerebrovascular accident.

Tissue sections and blocks were available for review in only one of the two patients diagnosed at autopsy. Microscopic examination of the dolichoectatic basilar artery in this patient revealed extensive defects of the internal elastic lamina (Figure 4).

One patient with symptomatic vertebrasilar dolichoectasia was treated with aspirin, one patient with symptomatic vertebrasilar dolichoectasia died in a motor vehicle accident before surgical intervention, and the patients with asymptomatic dolichoectasia were not treated.

On the basis of its radiographic appearance, the localized dolichoectasia of the middle cerebral artery in case 4 was believed to be due to a spontaneous arterial dissection (Figure 2). Intracranial arterial dissections were strongly suspected in two other patients. In addition to the vertebrasilar dolichoectasia in case 7, angiography also demonstrated an area of dilation and stenosis of the carotid siphon most consistent with arterial dissection (Figure 5). One of the 178 patients screened for an intracranial aneurysm with MRA had suffered an ischemic stroke after a severe unilateral headache at age 15, and angiography had shown a middle cerebral artery occlusion. At age 35, however, MRA showed the middle cerebral artery to be

patent, suggesting that the arterial occlusion had been caused by a dissection.

Discussion

Intracranial arterial dolichoectasia is not commonly considered to be a feature of ADPKD, although the presence of intracranial fusiform aneurysms and a megadolichobasilar artery has occasionally been mentioned in patients with ADPKD (5–7). The prevalence of asymptomatic intracranial arterial dolichoectasia in our study was remarkably similar among the three groups of patients with ADPKD (2.0 to 2.5%) and significantly higher than that observed in patients without ADPKD. Intracranial arterial dolichoectasia is an uncommon vascular lesion that is found in only 0.06% of cerebral arteriograms (8) and in less than 0.2% of routine brain autopsies (9). The posterior circulation is more commonly involved than the anterior circulation, and in some patients both carotid and vertebrasilar circulations are affected (8–12). Although intracranial arterial dolichoectasia has been reported in childhood and adolescence (10,13–17), the majority of patients are in their sixth or seventh decade of life (8–12,18). Most dolichoectatic cerebral arteries probably remain asymptomatic throughout life, but they may also be the cause of cerebral ischemic symptoms, brainstem compression, cranial nerve dysfunction, and hydrocephalus (8–18). Although the natural history of intracranial arterial dolichoectasia is not well-defined, rupture of dolichoectatic arteries is probably uncommon and, in contrast to saccular intracranial aneurysms, prophylactic surgical intervention for asymptomatic intracranial arterial dolichoectasia to prevent subarachnoid hemorrhage is generally not recommended.

The pathogenesis of intracranial arterial dolichoectasia is controversial, and some investigators have proposed the presence of an underlying arteriopathy, whereas others have stressed the importance of arterial hypertension, with or without superimposed atherosclerosis (8–19). Recently, it has been suggested that in some cases arterial dolichoectasia may be a sequela of arterial dissection (17,20). In patients with ADPKD, all of these factors may play a role. The possible inter-relationship of the ADPKD arteriopathy, hypertension, intracranial arterial dolichoectasia, intracranial arterial dissections, and saccular intracranial aneurysms is shown in Figure 6.

An underlying arteriopathy has become well-established as a prominent extrarenal component of ADPKD (1–6). Patients with ADPKD are at an increased risk not only of developing saccular intracranial aneurysms (1–6,21), but also of dissections of the thoracic aorta (22,23), cervicocephalic arteries (24,25), and possibly coronary artery aneurysms (26). In addition, interruption of the internal elastic lamina, a consistent finding in intracranial arterial aneurysms and dolichoectasias, has been described in otherwise normal intracranial arteries of patients with ADPKD (27).

Polycystin, the protein encoded by the gene responsible for the most common form of ADPKD (PKD1), may be an integral membrane protein containing multiple extracellular domains that could play a role in maintaining the structural integrity of extracellular matrices (28–30). It is strongly expressed in the

Table 2. Clinical data on nine patients with ADPKD and intracranial arterial dolichoectasia^a

Case No.	Age/Sex	Site of Dolichoectasia	Symptoms	HTN	Renal Function	HC	History of Smoking	Other Vascular Manifestations
1	41/M	VBA		+	Impaired	+	-	Coronary or systemic-pulmonary artery fistula
2	52/M	VBA		+	Failure	-	+	Abdominal aortic aneurysm; aortic root dilatation
3	57/F	VBA		-	Impaired	-	-	-
4	57/F	Left MCA		+	Failure	-	-	-
5	54/M	VBA, Bilateral ICA	VBA distribution, stroke	+	Failure	-	+	Ectasia/dissection thoracic aorta; BA tip aneurysm
6	63/F	Bilateral ACA		+	Impaired	-	-	ACoA aneurysm; persistent trigeminal artery
7	67/M	VBA	VBA distribution, TIA, and brainstem compression	+	Impaired	NA	+	Dissection right ICA
8	55/M	VBA, Bilateral ICA		+	Failure	-	-	Ectasia thoracic aorta
9	64/F	VBA		+	Impaired	-	-	-

^a HTN, hypertension; HC, hypercholesterolemia (total cholesterol exceeding upper 75th percentile for gender and age); M, male; VBA, vertebrobasilar artery; F, female; MCA, middle cerebral artery; ICA, internal carotid artery; BA, basilar artery; ACA, anterior cerebral artery; ACoA, anterior communicating artery; NA, not available; TIA, transient ischemic attack.

vascular smooth muscle of large elastic and distributive arteries (31). It seems likely that mutations in the PKD1 gene contribute directly to the development of the arteriopathy. Certain

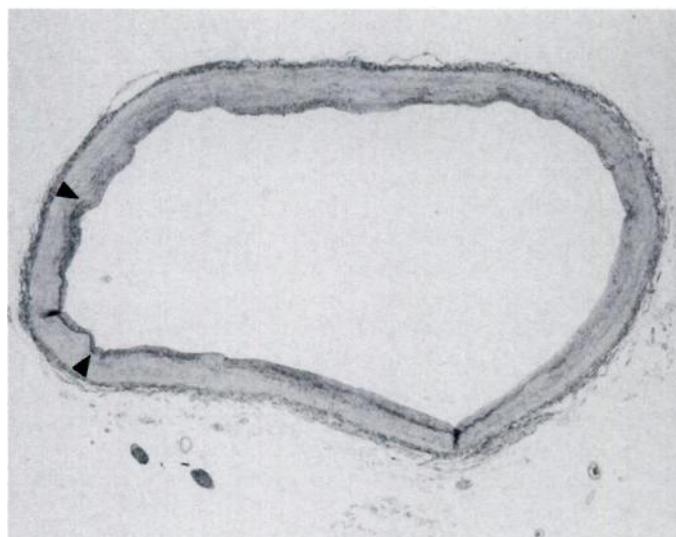


Figure 4. Dolichoectatic basilar artery found at autopsy in a 55-yr-old man. Note the interruption of the internal elastic lamina (arrowheads). Movat stain.

mutations may be particularly associated with vascular lesions, as suggested by the familial clustering of intracranial aneurysms (21) and by the cosegregation of ADPKD1 and an overlap connective tissue disorder, with dilation of the aortic root and dissecting aneurysms of the thoracic aorta and vertebral arteries in certain families (24). This possibility is also supported by our observation that most patients with intracranial arterial dolichoectasia had additional vascular manifestations of ADPKD.

The most common extrarenal complication of ADPKD is arterial hypertension. Hypertension is found in approximately one-fourth of children with ADPKD, in one-half to three-fourths of adults with normal renal function, and in more than 80% of adults with end-stage renal disease (3–4). Ninety-one percent of the presently reported patients with ADPKD and intracranial arterial dolichoectasia were hypertensive. It is uncertain to what extent hypertension contributed to the development of the dolichoectasia. Nevertheless, the low prevalence of intracranial arterial dolichoectasia in the general population suggests that hypertension alone, without other contributing factors, is not a likely cause of this lesion.

In one of our patients, the dolichoectatic middle cerebral artery appeared radiographically to be the result of a spontaneous arterial dissection, and in two other patients with AD-



Figure 5. Lateral carotid arteriogram showing stenoses and dilation of the carotid siphon (arrow), consistent with arterial dissection, in a 67-yr-old man.

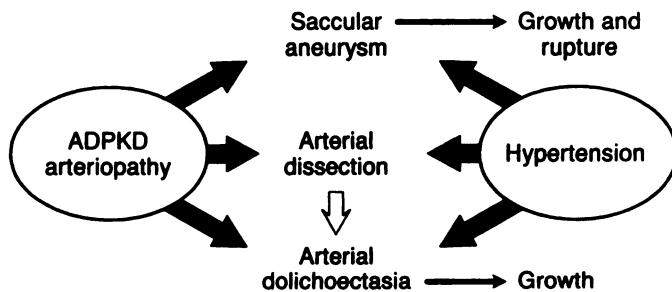


Figure 6. Diagram of the possible inter-relationship of the ADPKD arteriopathy, hypertension, intracranial arterial dolichoectasia, intracranial arterial dissections, and intracranial saccular aneurysms.

PKD a spontaneous intracranial arterial dissection was strongly suspected. Spontaneous intracranial arterial dissection has been reported previously in a patient with ADPKD (25), and our study suggests that this may not be an exceptional occurrence.

The association of intracranial arterial dolichoectasia and ADPKD may have some clinical implications. In patients with ADPKD who present with cerebral ischemic symptoms, the clinical index of suspicion should be increased not only for saccular intracranial aneurysms or premature (hypertension-induced) atherosclerotic disease, but also for intracranial arterial dolichoectasia and arterial dissection. In addition, it is important to recognize the possibility of intracranial arterial dolichoectasia mimicking a saccular aneurysm (Figure 2), particularly if only routine angiographic projections are used (32).

In conclusion, patients with ADPKD are at an increased risk not only of developing saccular intracranial aneurysms but also intracranial arterial dolichoectasia and dissections.

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