Coronary Aneurysms in Patients with Autosomal Dominant Polycystic Kidney Disease

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Abstract. Patients with autosomal dominant polycystic kidney disease (ADPKD) have an increased risk of intracranial aneurysms. Reports on arterial aneurysms in other locations have not been conclusive. The present study was initiated to investigate the prevalence of coronary aneurysms. Thirty ADPKD patients who had undergone coronary angiography on clinical indication were identified, 15 after renal transplantation. For each ADPKD patient, a control patient was identified with end-stage renal disease, investigated by coronary angiography, and matched for age, sex, and time relation to transplantation.

Coronary Aneurysms in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) may present with a variety of extrarenal manifestations. Involvement of vascular walls may cause arterial aneurysms, most often diagnosed in the subarachnoid region where the prevalence is 5 to 10% (1,2). An increased incidence of aortic aneurysms has also been reported (3,4), but was not verified in a large screening study (5). Coronary aneurysms have been described in ADPKD patients in two separate case reports (6,7). A preliminary report on the prevalence of coronary aneurysms in an ADPKD population with end-stage renal failure has also been published; however, that study was conducted without comparable control subjects (8). Whether coronary aneurysms are a manifestation of ADPKD is therefore not known. The present investigation was initiated to provide such information.

Materials and Methods

Patients

We searched for ADPKD patients who had undergone coronary angiography. Thirty were identified. Demographic background data are presented in Table 1. Twenty-four were kidney transplant patients, seventeen of whom were members of a cohort of 115 ADPKD renal transplant patients (1985 to 1993) whose records have been extensively reviewed with respect to renal and extrarenal manifestations of the disease (9). Three more ADPKD patients received their first transplants in the period 1982 to 1983 and four other patients from the period 1993 to 1996. The angiographies had been performed a median of 1.2 yr before transplantation in nine patients (range, 0.2 to 3.5 yr) and a median of 4.8 yr after transplantation in fifteen patients (range, 0.4 to 14.4 yr). In addition to the 24 transplant patients, five patients had been evaluated for, but not yet undergone, transplantation, and one belonged to a population treated with peritoneal dialysis in the Sahlgrenska Universitetssjukhuset. As also shown in Table 1, there was a clinical indication for all angiographies.

The ADPKD diagnosis was obvious in all cases, based on a dominant mode of inheritance in 24 patients. Two others had parents who died young, the heredity was incompletely investigated in two, and two lacked a family history of the disease. In each of the six cases, the constellation of clinical findings made the diagnosis unequivocal: All had enlarged polycystic kidneys before they became uremic, four with very large kidneys. Three were reported to have liver cysts. Two had siblings with the disease.

In the same populations of patients with end-stage renal disease (ESRD), fifty-seven individuals were identified who had undergone coronary angiography and had renal diagnoses other than ADPKD or diabetic nephropathy. These patients, and the ADPKD patients, were separated into four groups according to sex and the time of coronary angiography in relation to transplantation. Within each group, patients with ADPKD were matched with the control who was closest in age at the time of investigation. The difference in age was less than 5 yr in all pairs and less than 3 yr in twenty-five pairs. Table 1 shows how the control population compares with the study population with respect to basic demographics. There was no significant difference between ADPKD patients and control subjects in the time interval between transplantation and angiography, as calculated separately for patients investigated before and after transplantation. One ADPKD patient and one control subject was of Finnish/Estonian origin and one in each group was from the Middle East. The other 56 patients were Swedish by origin.

The angiograms were requested and received in original from the eight radiology units where they had been performed. They were reevaluated by one experienced investigator (Dr. Lamm). A stenosis was considered significant if the vessel diameter was reduced by ≥50%. The number of vessels affected was determined by involvement of the right coronary artery (RCA), the circumflex left artery,
Table 1. Background data for 30 patients with autosomal dominant polycystic kidney disease (ADPKD) who underwent coronary angiography and 30 matched control subjects with end-stage renal disease of other origin

<table>
<thead>
<tr>
<th>Group</th>
<th>Age Median, Range (yr)</th>
<th>Gender (M/F)</th>
<th>Number Investigated after Transplantation</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPKD (n = 30)</td>
<td>56, 45 to 71</td>
<td>20/10</td>
<td>15</td>
<td>Angina/Silent Ischemia</td>
</tr>
<tr>
<td>Controls (n = 30)</td>
<td>56, 45 to 73</td>
<td>20/10</td>
<td>15</td>
<td>25</td>
</tr>
</tbody>
</table>

and the left anterior descending artery. An aneurysm was defined as an increase in the artery diameter by 50% or more, a definition used in several surveys of the prevalence of aneurysms or ectasias in coronary angiograms (10–13). Ectasias were also noted as "minor" when judged to be pathologic but not fulfilling the criterion of an aneurysm, either because the dilation was less pronounced or a normal reference vessel was not available.

Statistical Analyses

The Mann-Whitney U test was used to compare values, and the χ² test was used to compare frequencies in ADPKD patients and control subjects.

Results

Table 2 shows the angiography findings in ADPKD patients and control subjects. Coronary aneurysms were detected in angiograms of four ADPKD patients and two control subjects. The difference is not statistically significant. A distinctive saccular aneurysm, measuring 8 mm, was found in the left anterior descending artery of one ADPKD patient (Figure 1). This patient was also known to have a renal artery aneurysm. The angiogram of another ADPKD patient showed a similar but smaller aneurysm, whereas the other two aneurysms in ADPKD patients were elongated or fusiform ectasias. One of these is depicted in Figure 2. In both control subjects with aneurysms, these were seen in the RCA; one patient had two successive aneurysms each measuring approximately 8 mm, the other had one measuring 2 × 3 cm. The two patients had IgA nephritis and not biopsy-verified glomerulonephritis, respectively. The latter patient had three previously diagnosed aneurysms (of the abdominal aorta, the thoracic aorta, and a subclavian artery). This is the only patient in whom a coronary aneurysm was diagnosed in the clinic; all others were observed during the review. Five more ADPKD patients, but none of the control subjects, had segments with pathologic dilation not fulfilling the criteria of an aneurysm. An example is given in Figure 3. Including the minor ectasias, the prevalence of pathologic dilations was higher in patients with ADPKD (P = 0.01).

In addition to the aneurysms and ectasias, significant stenoses of main coronary arteries were found in most patients and control subjects. As shown in Table 2, they were more frequent

Table 2. Findings in coronary angiograms performed in 30 patients with ADPKD and 30 matched control subjects with end-stage renal disease of other origin: revascularization procedures in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Vessels with Significant Stenosis</th>
<th>Angiograms with Aneurysms</th>
<th>Minor Ectasias</th>
<th>Revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3</td>
<td></td>
<td></td>
<td>PTCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First Choice</td>
</tr>
<tr>
<td>ADPKD (n = 30)</td>
<td>4 2 2 18</td>
<td></td>
<td>4 5</td>
<td>6</td>
</tr>
<tr>
<td>Controls (n = 30)</td>
<td>8 12 5 5</td>
<td></td>
<td>2 0</td>
<td>9</td>
</tr>
</tbody>
</table>

* PTCA, percutaneous transluminal coronary angioplasty.

* Numbers higher than in control group, P ≤ 0.01.
Coronary Aneurysms in ADPKD

Posterolateral branch of the RCA. In the control group, no life-threatening complications occurred, but one of the patients (without aneurysm) developed a moderate peripheral dissection during PTCA.

As of June 1997, seven ADPKD patients and four control subjects have died. Among the ADPKD patients, the causes of death were ischemic heart disease (two), dissecting aneurysm of the thoracic aorta (two), dilated cardiomyopathy (one), and malignancy (two). One of the latter was the patient with a circumflex aneurysm. Seven of nine patients with aneurysms or minor dilatations of coronary arteries are alive. Two control patients died of ischemic heart disease, two of uremia. Both control patients with aneurysms are alive; the one with multiple aneurysms has undergone surgery to correct it.

Discussion

Coronary aneurysms have been reported in association with ADPKD in two case reports, which gives only a hint of a connection (6,7). Whether ESRD is significant in the pathogenesis of aneurysms is not known. A series similar to ours has been published, yet without control subjects, and in preliminary form (8). In that study, aneurysms or ectasias were found in 11 of 32 angiograms performed in ADPKD patients with ESRD (34%). The prevalence of definite aneurysms was much lower in our series (only four of 30, or 13%). However, this is still higher than in a general population of patients with suspected coronary heart disease (1.5%) (11).

There seems to be agreement on the definition of an aneurysm (10-13), but the evaluation is not always easy in the presence of atherosclerotic change. The discrepancy in numbers between the previous and present studies may be a result of that. Therefore, in the present study, matched control subjects with ESRD were used for comparison, and the evaluation of all angiograms was made by one observer.

Coronary artery aneurysms were found in two of the control subjects. The difference in numbers between ADPKD patients and control subjects was only statistically significant when ectasias not fulfilling the strict definition of an aneurysm were also considered. These were either less than 50% wider than the adjacent normal vessel or could not be classified, because, due to arteriosclerotic lesions, the normal reference diameter could not be assessed.

One of the control patients had the unique history of four arterial aneurysms. This suggests that, in addition to the presumed glomerulonephritis, he might have a general disorder of the extracellular matrix such as has been proposed in ADPKD. At the time of surgery for his abdominal aortic aneurysm, his kidneys were reported to be multicystic, as well as atrophic. He has no heredity for ADPKD, or for aneurysms, but one may speculate that he might be a representative of the large number of undetected ADPKD cases (14). There is a case for studying the prevalence of ADPKD genes in populations with aneurysms.

The control patients, although otherwise well matched, seem to have had less pronounced atherosclerosis than the ADPKD patients, at least with respect to number of major coronary arteries involved. What is the significance of that difference for
the outcome? In a population with atherosclerotic change, aneurysms may be overlooked because thrombosis, stenosis, or occlusion may have disrupted or hidden them. Thus, the true incidence of aneurysms may be higher than that observed, and more so in the ADPKD group. In addition, some of the minor ectasias might have been classified as aneurysms had not the occlusion may have disrupted or hidden them. Thus, the true incidence of aneurysms in ADPKD cases.

Because the minor ectasias were identified as pathologic, we consider them indicators of an increased tendency toward artery dilation in ADPKD patients, occurring either spontaneously or in connection with the atherosclerotic process. A connection between aneurysm formation in general and atherosclerosis has been suggested (10). Coronary ectasia, when demonstrated in patients not identified as having ADPKD, was often found to involve multiple segments. A diffuse abnormality of the vessel wall of these patients was therefore suggested (13).

Subarachnoid aneurysms are of great clinical significance due to their tendency to rupture and the serious consequences in such a case. The clinical consequences of the observed coronary aneurysms are not clear. The anatomical differences between the two locations may be of importance for symptoms and diagnosis. For instance, rupture of a coronary aneurysm might be misinterpreted as myocardial infarction with hemopericardium caused by rupture of the ventricular wall. Rupture of a coronary aneurysm with massive hemopericardium has in fact been reported (15).

Another aspect of aneurysms is the possibility of dissection (16,17). In the general population, dissection of coronary arteries has been described as a spontaneous phenomenon and as complicating PTCA (18). ADPKD has never been implicated as a predisposing factor, but may be one. Dissection has been reported in a vertebral artery of a patient with ADPKD (19) and was a major problem in one of our patients during PTCA. Dissection may cause myocardial ischemia (16,20). Most likely, such events could remain undiagnosed.

In our series of 115 renal transplant patients with ADPKD, one died of a ruptured abdominal aneurysm, another of a dissecting thoracic aneurysm (9). A new lethal case of dissecting thoracic aneurysm has now occurred in that population as a complication of coronary bypass surgery. The patient had a coronary aneurysm, possibly an indication of a predisposing abnormality of the arterial vessel walls. Prolonged follow-up of the identified cases will perhaps reveal further consequences.

The mechanism for aneurysmal formation in ADPKD is unknown. The PKDI gene codes for the protein polycystin, which is present in the cytoplasm of epithelial and other cells in various organs in adults with ADPKD (21,22). The possible link to a membrane defect remains unclear. Furthermore, aneurysms are found only in a minority of ADPKD patients and have been reported to be clustered in certain families (23–25). No such clustering was seen in this material, but the available family history was not complete. One patient with a coronary artery aneurysm had a renal artery aneurysm as well. It may be that patients with aneurysms share a defect not present in the majority of ADPKD patients; thus, they may have a separate form of the disease or a separate disease that is genetically linked (24). Continued molecular genetic studies may disclose such diversity.

References

18. Illa R, Bigham H, Brennan J, Cabin H, Cleman M, Remetz M:


