Follow-Up of Intracranial Aneurysms in Autosomal Dominant Polycystic Kidney Disease by Magnetic Resonance Angiography¹ ²

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ABSTRACT
The purpose of this study was to assess the value of magnetic resonance angiography (MRA) in the follow-up of patients with autosomal dominant polycystic kidney disease (ADPKD) and saccular intracranial aneurysms (ICA), the risk of MRA-defined growth of asymptomatic incidental ICA, and the rate of development of MRA-defined de novo ICA in these patients. Between 1989 and 1995, 15 asymptomatic incidental ICA measuring 1.5 to 6.5 mm in diameter, three symptomatic aneurysms, and one asymptomatic concurrent aneurysm were detected by MRA in this study in 18 patients from 15 families. Four-vessel cerebral angiography in the three patients with symptomatic ICA and autopsy in one patient with an asymptomatic incidental ICA did not reveal additional aneurysms undetected by MRA. Thirty MRA studies were obtained in 10 of the 15 patients with incidental ICA during a cumulative clinical follow-up of 500 months (mean, 33.3; range, 0 to 65 months). The cumulative interval between the initial and the last MRA was 306 months (mean, 30.6; range, 14 to 51 months). No change in aneurysmal size or development of de novo aneurysms was detected. Eight MRA studies were obtained in the three patients with symptomatic ICA during a cumulative clinical follow-up of 130 months (mean, 43.3; range, 23 to 64 months). The cumulative interval between the first and the last MRA was 95 months (mean, 31.7; range, 15 to 49 months). Development of de novo aneurysms was not detected. These results indicate that MRA is an appropriate technique to follow small asymptomatic incidental ICA in patients with ADPKD and that the risk for rapid growth of these aneurysms is low. Although the results of this study should be viewed as preliminary, they do not suggest a higher rate of development of de novo aneurysms or a higher frequency of multiple aneurysms in patients with ADPKD and ICA as compared with patients with sporadic ICA in the general population.

Key Words: ADPKD, Intracranial aneurysms, magnetic resonance angiography

Previous studies have shown that magnetic resonance angiography (MRA) is a useful method to screen appropriate patients with autosomal dominant polycystic kidney disease (ADPKD) for saccular intracranial aneurysms (ICA) and that high-resolution three-dimensional (3D) time-of-flight is the most sensitive MRA technique for their detection (1,2). Most ICA discovered by screening asymptomatic ADPKD patients are small and presumed to have a low risk of rupture (1–6). Multivariate analyses of unruptured aneurysms in the general population have shown that the only predictor for aneurysmal rupture is the size of the aneurysm, and follow-up studies of unruptured ICA have shown that their rupture is associated with aneurysmal growth (6–8). Therefore, the purpose of this study was to assess the value of MRA in the follow-up of patients with saccular ICA, the risk of MRA-defined growth of asymptomatic incidental ICA, and the rate of development of MRA-defined de novo ICA in patients with ADPKD and ICA.

MATERIALS AND METHODS

Patients

The patients with ADPKD who were seen by the authors during the period from 1989 to 1995 were given detailed information regarding the association of ICA and ADPKD and the possible indications for noninvasive presymptomatic evaluation for ICA in this disease. This information was based in part on the results of our previous studies (1,9–11). Of these patients, 178 asymptomatic ADPKD patients agreed to undergo MRA. Fifteen of these patients were found to have a single ICA. Because of the small size of these ICA, surgery was not recommended and yearly MRA evaluations were advised. Four additional patients were found to have dolichoectatic intracranial arteries and have been reported separately (12). During the same period of time, MRA detected three symptomatic ICA and one asymptomatic concurrent

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ICA in three ADPKD patients. These patients underwent successful clipping of the symptomatic aneurysms and MRA re-evaluations were recommended at 1- (when there was a concurrent asymptomatic aneurysm) or 3-yr intervals.

**Methods**

Patients were examined using a 1.5-T Superconducting Imaging System (Signa: GE Medical Systems, Milwaukee, WI). Standard magnetic resonance (MR) imaging of the head was performed with sagittal T1-weighted and transaxial T2-weighted sequences. In addition, high-resolution 3-mm transaxial T1-weighted imaging through the circle of Willis was obtained. Magnetic resonance angiographic imaging was performed using the Multisequence Vascular Package (GE Medical Systems). The MR examination included the use of both 3D time-of-flight (TF) and 3D phase-contrast imaging sequences. During the time of this study, significant improvements in MR angiographic techniques occurred. Currently, the most sensitive MR angiographic technique for detecting ICA is a high-resolution 3D TF technique (TR48; TE6.9; 1 excitation, 512x256 views, 20º flip angle, and 22x16-cm field-of-view, 1-S ramped pulse, and flow compensation).

Maximum intensity projection after processing was performed by isolating the right-carotid, left-carotid, and posterior communications. Care was taken to include the anterior communicating artery in both carotid volumes. This subvobume technique was necessary to display the arterial vasculature optimally as well as to eliminate overlapping vessels. Correlation between viewing the subvolumes in a cine loop on an independent workstation and with the source images facilitated identification and characterization of the aneurysms. A saccular ICA was diagnosed when a focal, asymmetric outpouching of an artery with a discrete base was detected.

**RESULTS**

Nineteen ICA in 18 patients from 15 families were detected by MRA: 15 asymptomatic incidental ICA in 15 patients and three symptomatic and one asymptomatic concurrent ICA in three patients. Ten of the 18 patients (55.5%) had a family history of ICA or nontraumatic subarachnoid hemorrhage as diagnosed by a neurologist or a pathologist at our center or elsewhere.

The age and gender of the 15 patients with asymptomatic incidental ICA and the location and size of these ICA at the time of initial detection, as well as the duration of the clinical follow-up, total number of MRA studies, interval from the first to the last MRA, and MRA findings, are summarized in Table 1. One patient was killed in a motor vehicle accident shortly after the initial evaluation. The cause of death was massive hemothorax. At autopsy, the presence of an unruptured left-carotid siphon aneurysm was confirmed and no additional aneurysms were found. One patient with a 5-mm left-carotid siphon ICA has declined re-evaluation with MRA. The three most recently diagnosed patients have not yet been restudied.

Thirty MRA studies were obtained in ten of the 15 patients with incidental ICA during a cumulative clinical follow-up of 500 months (mean, 33.3; range, 0 to 65 months). The cumulative interval between the initial and the last MRA in these ten patients was 306 months (mean, 30.6; range, 14 to 51 months). With improving MR angiographic techniques, the aneurysms had subtle differences in appearance, but overall there was no change in their size or configuration (Table 1, Figures 1 through 3). New aneurysms were not detected in any of these patients in the follow-up studies.

Symptomatic ICA were detected by MRA in three patients presenting with subarachnoid hemorrhage, sentinel headache, or homonymous hemianopsia. One of these patients, the only one in this series with

<table>
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<tr>
<th>Patient Numbers</th>
<th>Age and Gender</th>
<th>Location</th>
<th>Size (mm)</th>
<th>Number of MRA Studie</th>
<th>Interval from First to Last MRA (months)</th>
<th>Clinical Follow-Up (months)</th>
<th>Findings</th>
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<tr>
<td>1</td>
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<td>Basilar tip</td>
<td>1.5</td>
<td>5</td>
<td>51</td>
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<td>Right carotid siphon</td>
<td>4</td>
<td>4</td>
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<td>54</td>
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<td>3</td>
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<td>Right superior cerebellar</td>
<td>1.5</td>
<td>5</td>
<td>35</td>
<td>48</td>
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<td>3</td>
<td>3</td>
<td>25</td>
<td>43</td>
<td>No growth/de novo ICA</td>
</tr>
<tr>
<td>7</td>
<td>37 F</td>
<td>Left carotid siphon</td>
<td>3</td>
<td>3</td>
<td>24</td>
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<td>3</td>
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<tr>
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<td>Left carotid siphon</td>
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<td>1</td>
<td>2</td>
<td>14</td>
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<tr>
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<td>47 F</td>
<td>Left carotid siphon</td>
<td>5</td>
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<td>65</td>
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<tr>
<td>13</td>
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<td>4</td>
<td>1</td>
<td>11</td>
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<tr>
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<td>Right middle cerebral</td>
<td>3</td>
<td>1</td>
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<tr>
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<td>4.5</td>
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a MRA, magnetic resonance angiography.
Figure 1. Three-dimensional time-of-flight images illustrating the stability of a 1.5-mm basilar tip aneurysm in Patient 1.

Figure 2. Three-dimensional phase-contrast and 3D TF images illustrating the stability of a 4-mm right-carotid siphon aneurysm in Patient 2.

multiple aneurysms, had a second asymptomatic concurrent aneurysm. These three patients were subsequently studied with conventional angiography and there was a good correlation between MRA and conventional angiograms (Figure 4). The presentation, age, and gender of the patients, as well as the location and size of the ICA, duration of the clinical follow-up, total number of MRA studies, interval from the first to the last MRA, and MRA findings, are summarized in Table 2. Interestingly, the patient presenting with a
sentinel headache and a 5-mm aneurysm at the right middle cerebral artery had a negative high-resolution MR imaging study with 3-mm cuts through the circle of Willis 5 yr earlier, before undergoing combined segmental hepatectomy and cyst fenestration for severe polycystic liver disease. These three patients underwent successful clipping of the symptomatic aneurysms. Eight MRA studies were obtained in these three patients during a cumulative clinical follow-up of 130 months (mean, 43.3; range, 23 to 64 months). The cumulative interval between the initial and the last MRA in these three patients was 95 months (mean, 31.7; range, 15 to 49 months). New aneurysms were not detected in any of these patients. After the large left posterior communicating artery aneurysm in one of these patients was clipped, an attempt to evaluate the asymptomatic concurrent left-carotid siphon aneurysm with MRA proved unsuccessful because of the artifact from the adjacent aneurysmal clip.

DISCUSSION

The association of ICA with ADPKD (9) and the high mortality from aneurysmal rupture (13) have led physicians to consider the value of screening patients with ADPKD for unruptured ICA. The value and cost effectiveness of such screening depends upon the prevalence of ICA in ADPKD, the yield and risk of the screening procedure, and the likelihood of benefit from intervention (5). The latter is further dependent on the probability of rupture of asymptomatic ICA, the rate of development and rupture of de novo ICA, and the morbidity and mortality from rupture or from interventional therapy. In previous studies, we have shown that: (1) the prevalence of asymptomatic ICA in
TABLE 2. Autosomal dominant polycystic kidney disease patients with symptomatic intracranial aneurysms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>16</th>
<th>17</th>
<th>18</th>
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<tbody>
<tr>
<td>Presentation</td>
<td>Subarachnoid hemorrhage</td>
<td>Sentinel headache</td>
<td>Homonymous hemianopsia</td>
</tr>
<tr>
<td>Age and Gender</td>
<td>43 M</td>
<td>49 F</td>
<td>76 F</td>
</tr>
<tr>
<td>Location</td>
<td>Left anterior cerebral</td>
<td>Right middle cerebral</td>
<td>Left posterior communicating</td>
</tr>
<tr>
<td>Size (mm)</td>
<td>3</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Clinical Follow-Up from Clipping of Aneurysm (months)</td>
<td>64</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>Number of MRA Studies</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Interval from First to Last MRA (months)</td>
<td>49</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Findings</td>
<td>No de novo aneurysms</td>
<td>No de novo aneurysms</td>
<td>No de novo aneurysms</td>
</tr>
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</table>

* Concurrent asymptomatic aneurysm.
* MRA, magnetic resonance angiography.
* Concurrent aneurysm not visualized because of clip artifact.

Adult ADPKD patients is in the order of 4 to 10%, lower than initially thought; (2) this prevalence is higher in patients with a family history of ICA; (3) MRA, particularly high-resolution 3D TF MRA, is a sensitive technique for the detection of ICA; and (4) most ICA detected by presymptomatic MRA screening of ADPKD patients are small, measuring 5 mm or less in diameter (1,11). These conclusions are in agreement with the results of other recent studies (2-4).

Very little information is available on the natural history of unruptured ICA in ADPKD. Therefore, decisions regarding the management of patients with ADPKD who have unruptured ICA are currently based on the information available from the general population. The results of the study presented here, although preliminary, provide data specific to patients with ADPKD. In addition to this study, other prospective, long-term follow-up studies of unruptured ICA, such as the International Study of Unruptured Intracranial Aneurysms (ISUIA) (14), will eventually determine whether the risk of aneurysmal rupture and the morbidity associated with surgery for unruptured ICA in patients with ADPKD and ICA are similar to those of patients with sporadic ICA.

With regard to the risk of rupture, multivariate analyses of unruptured ICA in the general population have shown that the only predictor of aneurysmal rupture is the size of the aneurysm (6–8). In addition, rupture of previously diagnosed unruptured ICA may be preceded by aneurysmal growth (8). Furthermore, significant differences may exist between asymptomatic aneurysms diagnosed concurrently with ruptured aneurysms (concurrent ICA) and asymptomatic truly incidental aneurysms diagnosed by presymptomatic screening or during investigations unrelated to symptomatic aneurysms (incidental ICA) (5–7,15). The risk of rupture of asymptomatic concurrent ICA has been estimated at 1 to 2% per year (8,16–17), but the influence of aneurysmal size has not been well defined. On the other hand, a number of studies have looked into the risk of rupture of asymptomatic incidental ICA, with consistent results (6–8,18–19). In these studies, no incidental aneurysm measuring less than 10 mm in diameter ruptured. Reports of rupture of previously documented small asymptomatic ICA are very rare and, in most of these cases, the aneurysms were not incidental or there were associated procedures, such as a carotid endarterectomy, that might have precipitated the rupture of the aneurysm (20–21). Therefore, the annual rate of rupture of small incidental aneurysms is probably low, less than 1%, whereas aneurysms measuring more than 10 mm in diameter have a significant rupture rate, estimated at 3 to 4% a year (6–7). The low risk of rupture of incidental aneurysms less than 10 mm in diameter in these studies is at odds with the frequent observation at autopsy or angiography of ruptured aneurysms of this size (6–7). The most likely explanation for this discrepancy is that the critical size for rupture is smaller if rupture occurs at the time of or soon after aneurysm formation and that most aneurysms that rupture do so at this time (6–7). This discrepancy also could be explained in part by a higher frequency of small compared with large aneurysms or by a decrease in the size of some aneurysms after rupture (6–7).

The results of our study in regard to growth of small incidental ICA in ADPKD patients indicate that these aneurysms have remained stable over the period of the study. Although these findings are preliminary, they are consistent with the premise that follow-up of small asymptomatic incidental ICA in patients with ADPKD is an appropriate management decision. Additional investigation into the natural history of these aneurysms is necessary to determine whether a critical size mandates surgical clipping or another type of...
interventional therapy. As in the general population, the stability of these aneurysms contrasts with the small size (3 and 5 mm) of the aneurysms in two patients presenting with symptomatic ICA, one with subarachnoid hemorrhage and one with a sentinel headache. Whether these aneurysms had developed shortly before presentation cannot be determined from this study, but it is interesting to note that one of the two patients had a negative high-resolution MR imaging study 5 yr previously.

There is scant information available on the rate of de novo aneurysm formation after a previous diagnosis of ICA or aneurysmal rupture in the general population. Because of the high mortality and morbidity of aneurysmal rupture and the short-term follow-up in most studies of ICA, the rates of de novo aneurysm formation and rupture have probably been underestimated. In the only prospective angiographic study, the annual rate of de novo aneurysm formation was 2.2% (8). Miller et al. (22) and Rinne and Hernesniemi (23) have estimated an incidence of de novo aneurysmal rupture after a first subarachnoid hemorrhage of 60 and 63 per 100,000 per yr, respectively. In another large study, de novo aneurysmal subarachnoid hemorrhage was observed in 1% of 986 patients 4 to 7.5 yr after aneurysmal formation and rupture. These rates clearly exceed the incidence of aneurysmal subarachnoid hemorrhage in the general population of approximately 10 per 100,000 per yr. respectively. In another large study, the annual rate of de novo aneurysm formation was 2.2% (8).

The absence of de novo aneurysmal formation in our study may be a result of its prospective nature, duration of follow-up, and the composition of the study group (44.5% of the patients without a family history of ICA and 83% of the patients with incidental ICA). In the study by Chapman et al. (26), there was a family history of ICA in 71% of the patients with de novo ICA, compared with 33% of the patients without de novo ICA, and 50% of the patients had a history of subarachnoid hemorrhage. Additional studies will be needed to determine whether the risk of de novo aneurysm formation and rupture is higher in patients with a strong family history of ICA and a previous history of subarachnoid hemorrhage.

One of the three patients in our study with symptomatic ICA, but none of the 15 patients with incidental ICA, had multiple aneurysms. This is consistent with the reported frequencies of 14% (27), 24% (11), and 31% (4) in previous large autopsy or clinical studies, which primarily included ADPKD patients with aneurysmal subarachnoid hemorrhage, and with reported the frequencies of 19% (28), 32% (14), and 34% (29) among sporadic cases of ICA in the general population. On the other hand, in two smaller studies on presymptomatic screening in ADPKD, three of four ADPKD patients with incidental ICA detected by conventional angiography (3) and two of ten ADPKD patients with incidental ICA detected by MRA (2) had multiple aneurysms. Although no additional aneurysms were found in four of our patients who had conventional angiography or autopsy, we cannot exclude the possibility that a few small aneurysms may not have been detected by MRA. Three or four of the five patients with multiple ICA in the studies by Ruggieri et al. (2) and Chapman et al. (3) had a family history of ICA. The patient in our study with multiple aneurysms also had a strong family history of ICA and aneurysmal subarachnoid hemorrhage. Therefore, multiple aneurysms in ADPKD patients may be more likely to be found in association with symptomatic ICA and a strong family history of aneurysms.

In summary, the results of this study indicate that MRA is an appropriate technique to follow-up small incidental ICA in patients with ADPKD and that the risk for rapid growth of these aneurysms is low. In addition, although these results should be viewed as preliminary, they suggest that the frequency of multiple aneurysms and the rate of development of de novo aneurysms in patients with ADPKD and ICA are not markedly different from those observed in sporadic aneurysms in the general population. These risks may be higher in certain families with a strong family history of ICA and subarachnoid hemorrhage, with or without associated ADPKD. On the basis of these observations, MRA follow-up of small asymptomatic
incidental ICA, initially at 1-yr intervals, and of patients with a previous history of aneurysmal rupture, possibly at 3-yr intervals, appear to be appropriate management decisions. It is no less important to remind patients with ADPKD that correctable factors such as a history of smoking and, possibly, hypercholesterolemia have been found to be independent risk factors for aneurysmal rupture (30) and that the presence of hypertension increases the morbidity and mortality associated with aneurysmal rupture (7,11).

REFERENCES