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Research Article

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Cerebrovascular and Brain Abnormalities in Autosomal-Dominant Polycystic Kidney Disease: Role of 3d Time-of-Flight Magnetic Resonance Angiography

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Abstract

Introduction: The association of intracranial aneurysms and autosomal-dominant polycystic kidney disease (ADPKD) is well recognized. The aim of this study was to assess the prevalence of asymptomatic intracranial aneurysms and to verify the presence of other cerebral abnormalities in patients with ADPKD by Magnetic Resonance Angiography screening.

Materials and methods: From January 2009 to September 2013, 56 patients with ADPKD (25 M, 31 F; mean age 40 years, range 24- 63 years) underwent brain Magnetic Resonance Imaging including 3D time-of-flight MR angiography and T2-weighted Turbo-Spin-Echo axial sequences. Magnetic Resonance studies were examined by two experienced neuroradiologists (20 years). If an intracranial aneurysm was detected, cerebral Computed Tomography Angiography was recommended and further action were discussed with the interventional neuroradiologist.

Results: Nine saccular intracranial aneurysms were detected in 56 patients, located in the anterior circulation (5 internal carotid arteries, 1 anterior communicating artery and 3 middle cerebral arteries). Four patients underwent endovascular treatment with flow-diverter devices. We additionally found internal carotid artery abnormal diameter and course (6), basilar artery hypoplasia (1), basilar artery dolichoectasia (1), asymmetric anterior cerebral (4) and vertebral (14) arteries, vascular anatomic variants (3), venous drainage anomaly (1), arachnoid cysts (6), large bilateral choroid plexus cysts (1) and mega cisterna magna (2).

Conclusions: The prevalence of asymptomatic intracranial aneurysms (16.1%), higher compared to the general population (1%) and similar to literature reports in autosomal dominant polycystic kidney disease (6-16%), confirmed the importance of the Magnetic Resonance Angiography screening in these patients.

Keywords

Polycystic kidney disease, Angiography; intracranial aneurysms; ADPKD

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Introduction

Autosomal-dominant polycystic kidney disease (ADPKD) is the most frequent renal hereditary disorder. Although kidney involvement with progression to end stage renal disease is the most common clinical feature, ADPKD is a systemic disorder associated with various extra renal manifestations such hepatic and pancreatic cysts and cerebrovascular and brain abnormalities [1], that contribute to the associated morbidity and mortality [2]. Despite the recent basic and clinical researches ADPKD remains a therapeutic challenge [3-6].

Cerebrovascular complication with rupture of intracranial aneurysm (IAs) is the most devastating of the extra renal manifestations that accounts for 4% to 7% of deaths in patients with ADPKD and for severe neurological deficit or disability in survivals. Compared with the general population, patients with ADPKD have an increased frequency of IAs with estimates of prevalence ranging from 4% to 41% [7]. The subarachnoid hemorrhage (SAH) due to the rupture of ICANs in ADPKD occurs more often and at younger age compared to the general population [8].

In clinical practice, the indications for screening of IAs in ADPKD are limited to subgroups of patients with either a family history of IA or previous aneurysm rupture, those undergoing major elective surgery, or those in a high-risk occupation [8]. Unfortunately, except for a positive family history of SAH, no risk factors for IAs in patients with ADPKD have been defined [9], which means that we are not able to identify all patients with a risk for SAH from IA rupture. However, as some authors support systematic screening for IAs in patients with ADPKD [10], our study was designed to determine the prevalence of IAs or other possible vascular and cerebral abnormalities by Magnetic Resonance Angiography (MRA), in order to evaluate the role of MRA screening in these patients.

Material and Methods

All patients with a new diagnosis of ADPKD attending the Department of Nephrology of the Federico II University of Naples between January 2009 and September 2013 were considered for recruitment. The diagnosis of ADPKD was performed according to the unified ultrasonographic criteria [11] in addition to a family history of polycystic kidney disease. We excluded all patients with signs or symptoms of neurological disorders. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee. All patients provided written informed consent. Enrolled patients underwent to brain magnetic resonance imaging (MRI) evaluation at the Department of Diagnostic Imaging of Federico II University of Naples. These evaluations were performed per center practice with a 1.5 T MRI system (Gyroscan Intera, Philips Medical System, Best, The Netherlands). MRI was performed by using a 3-dimensional time-of-flight sequence (3D TOF, TE 65 ms; TR 6.9 ms; flip angle 20°; slice thickness 1.40 mm; FOV 175×200 mm) without contrast medium injection; maximum intensity projection (MIP) and multi-planar reformation (MPR) reconstructions were used for subsequent MRI analysis. Additionally, a standard Turbo-Spin-Echo (TSE) T2-weighted (w) axial sequence was acquired for the study of the brain (TE 100 ms; TR 4451.4 ms; slice thickness/gap 5.00/1.00 mm; FOV 230×184 mm). Two experienced

neuroradiologists examined the images in order to detect the eventual presence of IAs, vascular abnormalities or anatomical variants. Morphologic characteristics of the aneurysms and parent arteries, such as diameter, course and volume, were measured. Patients with ICANs found at MRI and normal to mild renal function (glomerular filtration rate, GFR>60 ml/min/1.73 m^2) were subsequently recommended for Computed Tomography Angiography (CTA) and digital subtraction angiography (DSA), as a reference standard for comparison. Further actions were discussed with the interventional neuroradiologist.

The primary analysis of this study is the estimation of the frequency of IAs detected in patients with ADPKD. The frequency was estimated and a 95% CI constructed for the estimate. Other data were expressed as mean ± SD and processed with the statistical software SPSS 15.0 (SPSS Inc). Quantitative and qualitative data were analyzed with variance analysis and the χ^2 test, respectively. Logistic regression was used to analyze the factors. $P<0.05$ was considered statistically significant.

Results

We studied 31 females (F) and 25 males (M) with a mean age of 40 years (range 24-63 years); 14 patients had a first-degree familial relationship, including 2 siblings. 23 patients had a positive family history, defined as first or second degree relatives with IAs or SAH.

The prevalence of IAs in 56 patients was 16.1%. MRI screening detected 9 unruptured IAs in 8 patients (4M, 4F), as 1 female patient showed two aneurysms. 4 patients had a positive family history of IAs or SAH; one of them had experienced aortic dissection (type A) 9 months before performing MRI. All ICANs were saccular, small-size aneurysms, with a mean diameter of 5 mm (range 3 mm to 8 mm), and 4 of them demonstrated wide neck. All IAs were found in the anterior circulation: 5 along the internal carotid artery (ICA), 1 at the anterior communicating artery (AcA) and 3 at the middle cerebral artery (MCA). Patients with IAs detected by MRI subsequently underwent CTA and DSA, which confirmed all 9 aneurysms. No additional aneurysms were found by DSA. These patients were referred to our center for treatment. 3 of them were lost during the follow-up. The female patient with two IAs had a 6 mm aneurysm at the bifurcation of right MCA, which was treated with microsurgical clipping. The patient with a 5 mm AcA IA refused both surgical and endovascular treatment, choosing a conservative strategy. She unfortunately suffered SAH 25 months after MRI and underwent clipping at another institution. The other ones (2F, 2M), including the patient with 2 IAs, underwent endovascular treatment by flow-diverter devices (FDD) (PIPELINE ev3 Chestnut Medical Inc.). They were 4 small IAs: 2 of the ICA (mean diameter 3.33 mm, range 3-4 mm; neck mean diameter 2.5 mm, range 2.5-3 mm) (Figure 1), and 1 of the M1 segment of the MCA (diameter 8 mm; neck 5 mm). After treatment, these patients were monitored for clinical evolution, patency of the covered vessel and aneurysmal occlusion: at 1 week by neurological exam, 1 month by CTA, 3 months by DSA, and 6 months by CTA in 1 case and by MRI in 2 cases. The follow-up images demonstrated total IA occlusion in all four patients: the occlusion period was 3 months (Figures 1 and 2). Other vascular abnormalities or variants detected in our 56 patients included 2 cases of ICA hypoplasia, 1 ICA dolichoectasia, 1 basilar artery (BA) dolichoectasia, 3 cases of ICA kinking (extra cranial segment), 1 BA hypoplasia, 14 vertebral artery (VA) asymmetries (two for unilateral hypoplasia), 4 anterior cerebral arteries (ACA) asymmetries (unilateral hypoplasia of A1 horizontal segment), 1 ACA trifurcation, 2 posterior cerebral artery (PCA) "fetal" origin, 1 venous drainage anomaly. Additional findings included arachnoid cysts in 4 patients, large bilateral choroid plexus cysts in 1 patient and a mega cisterna magna in 2 patients.

Discussion

The well-known association between ADPKD, IAs and other intracranial vascular abnormalities has been attributed both to the contributory role of acquired factors as cigarette smoking and arterial hypertension as in the general population, both to PKD1 and PKD2 mutations which play a role in the structural integrity of blood vessels [12].

Polycystins could be instrumental in the functional interaction between arterial smooth muscle cells and adjacent elastic tissue or endothelial cells, so a mutation in their genes could disrupt this interaction and weakens the vessel wall [13].

ADPKD individuals have a higher prevalence of IAs than the general population. Three large studies have found a prevalence range of IAs of 4% to 11.7%, in contrast to the 1% prevalence in the general population [14-17].

In our series, we found a prevalence of 16.1% for IAs in patients with ADPKD, which is higher than the above mentioned reports, but it is similar to the prevalence of asymptomatic IAs in patients with ADPKD and a familial history of IA or SAH found in a study by Pirson et al. [8], and to the prevalence found by Niemczyk et al in a sample of Polish patients [18]. Moreover, the distribution of IAs between female and male patients was equal in our series, according to previous reports [2,9]. The characteristics of IAs differ between our series and some of the previous reports. MCA is the most frequent site of IAs in ADPKD patients and almost 5% to 10% IAs are located in the posterior circulation, whereas ICA is the most frequent site of IAs in the general population. In our study, IAs were most frequently located in the ICA (5/9), accounting for more than half of the detected IAs; no IA was detected in the posterior circulation. To our knowledge this is the first Italian MRA screening study on ADPKD population reported in literature in the last 20 years. We studied 56 patients coming from Southern Italy and we could attribute our results to ethnical differences. No previous report regarding this population can confirm or oppose our results, which are similar to those ones reported by Xu et al. [19]. 1 of 3 ADPKD patients shows multiple IAs [8], while in our series we found only 1 patient with 2 IAs (a 6 mm MCA bifurcation IA and a 3 mm ICA IA). Furthermore, large IAs (>15 mm) seem to occur more often in in ADPKD patients (27%) than in general population (10%) [20]. We detected small IAs with a mean diameter of 5 mm. As reported by Hughes [21], the majority of unruptured IAs detected by MRA screening in patients with ADPKD is small, with over 90% smaller than 10 mm and over 70% smaller than 6 mm in diameter, as in our study population. According to the ISUIA study, they should belong to the lowest-risk natural history group [22]. Whether the very low risk of rupture of small IAs in the general population found in the ISUIA can be extrapolated to patients with ADPKD remains to be proved. Nevertheless, the incidence of ruptured IAs in patients with ADPKD is estimated to be fivefold that of the general population, as well as the prevalence of asymptomatic IAs in these patients. The mean age of rupture of IAs in ADPKD patients is approximately 40 years, which is similar to that observed in other familial forms of IAs, but occurs 10 years earlier than in the general population [23].

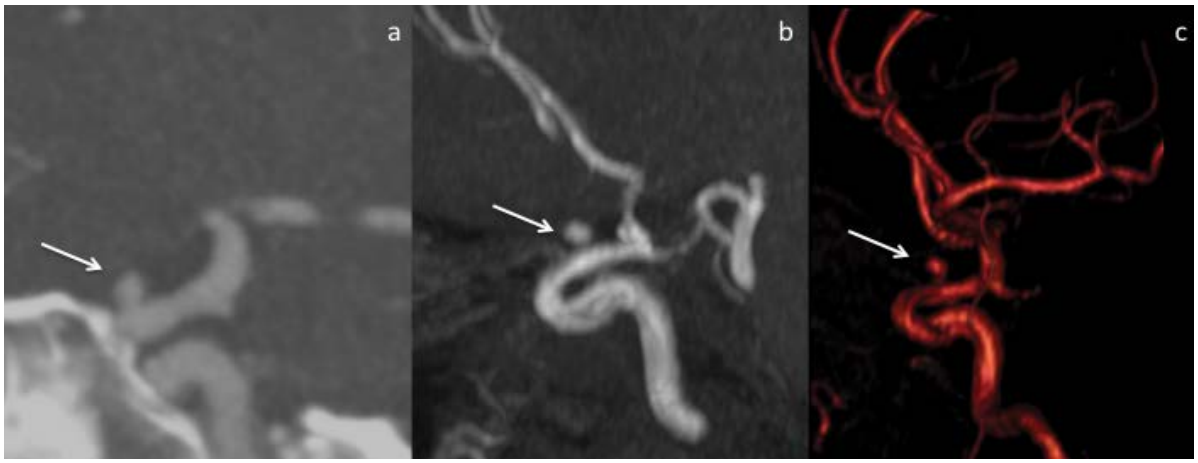

Figure 1: 48-year-old woman with autosomal-dominant polycystic kidney disease and intracranial aneurysm. CT-angiography (MPR, a) and MR-angiography (3D TOF, MIP and VR, b-c) show the presence of a small saccular aneurysm of the left ICA ophthalmic segment (white arrow).

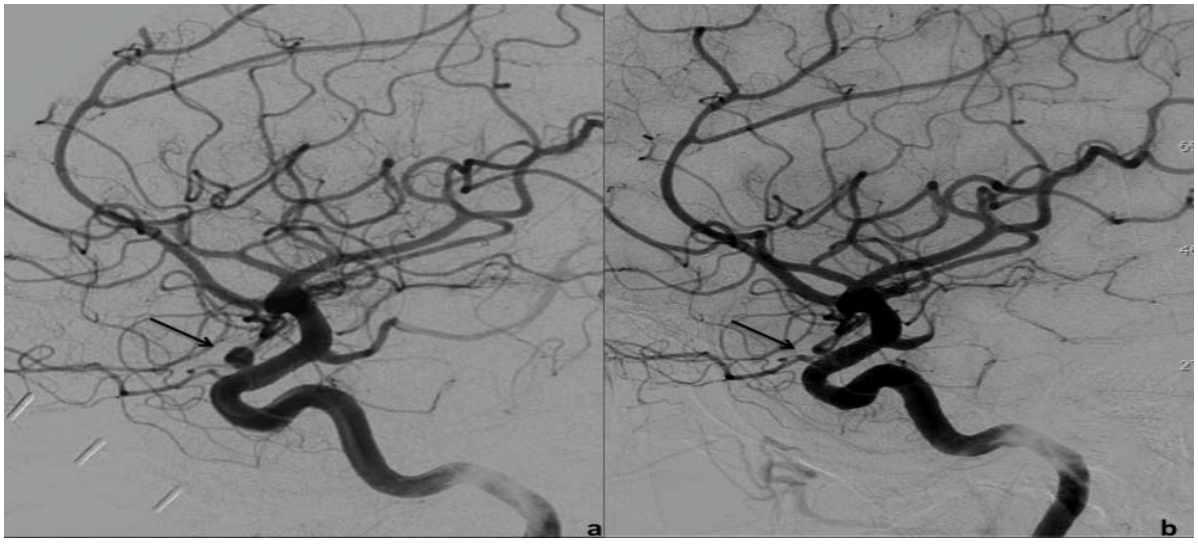

Figure 2: 48-year-old woman with autosomal-dominant polycystic kidney disease and intracranial aneurysm (same case). Digital subtraction angiography (a) confirms the presence of the aneurysm of the left ICA ophthalmic segment; follow-up DSA (b) 3 months after treatment by flow-diverter device (PIPELINE EV3 Chestnut Medical Inc.) demonstrates total occlusion of the sack (black arrow).

The most frequent site of ruptured IAs in patients with ADPKD is the anterior communicating artery (AcA), which is similar to patients without ADPKD [23]. We had only 1 patient who developed SAH for a ruptured IA: she had a 5 mm AcA aneurysm with irregular walls. We can hypothesize that the rupture can be linked to the poor efficacy of the conservative treatment, especially to the inadequate control of hypertension. A positive family history, defined as first or second degree relative with SAH or IAs, was reported in 40% of patients with ADPKD. In patients without ADPKD the proportion of patients with an affected first or second degree relative approximates 14% [22]. In our study, we found prevalence of 41.1% for positive family history and of 50% in ADPKD patients with IAs. The importance of a MRA screening program for IAs in ADPKD population has been widely assessed [24-26]. The lower risk rates of morbidity and mortality achieved with aneurysm surgery prior to hemorrhage, combined with advances in imaging techniques and endovascular management, have made screening for asymptomatic aneurysms more attractive, particularly in high-risk groups such ADPKD patients [27]. The risk of screening asymptomatic IAs followed by treatment should be weighed against the risks of SAH, linked to a family history of IAs and the higher aneurysm rate in these patients: ADPKD patients with a family history of IAs have a higher prevalence of IAs and may be at increased risk for rupture. Furthermore, IAs in patients with familial SAH and ADPKD tend to rupture at a smaller size than those in people without these conditions [23,26]. The strategy of choice should aim at improved life expectancy or the best quality-adjusted survival. On account of this, we decided to study ADPKD patients although asymptomatic and recommended treatment despite the small sizes of the aneurysms. One decision analysis suggested that MRA screening for asymptomatic IAs in ADPKD young individuals, as our study group, would increase life expectancy and reduce socioeconomic burden of ADPKD [26]. The decision of screening

should also take into consideration patients' knowledge and feeling about the risks of IAs rupture and prophylactic treatment. Although IAs found in our screening program are small and in the anterior circulation, we assumed that any benefit from microsurgical or endovascular approaches would be balanced against their significant cost and the anxiety it would generate in those in whom IA was found but no treatment proposed. We opted for treatment by flow-diverter devices (FDD) in three patients, because on our experience we achieved good results using these devices for small IAs with relatively wide neck [27,28,29] although the majority of trials proved their efficacy particularly for wide-neck or large/giant aneurysms. Many authors sustain the high cost of FDD against the cheapest use of coils; however, we opted for FDD as we know from the literature review that a big part of recanalization of IAs treated by coiling involves mostly small and wide-neck IAs, as those found in our study series. Nevertheless, decisions regarding the management of unruptured IAs are complex and multiple factors need to be considered, including size, morphology, and site, prior and familial history of SAH, patient age and general health. However, because >50% of ruptured IAs in ADPKD patients are >10 mm in diameter, the treatment of IAs > 5 mm is increasingly considered, especially in young individuals who have an IA treatable by coiling or stenting [26-28]. We believe that these patients should be assessed on an individual basis taking all the relevant risk factors into account before deciding treating or not for IAs. Moreover, we detected 2 patients with vascular dolichoectasia (1 of ICA and 1 of BA) in our study population: the patient with BA experienced also aortic dissection (type A) 9 months before performing MRI. Examiners should direct their attention to this vessel abnormality in ADPKD patients, because dolichoectatic vessels are of clinical importance as a source of potential complications [30,31]. Limitations of the present study include the relatively low number of subjects, which could explain the main differences between our results and the previous literature, as well as the limited clinical data.

In conclusion, the prevalence of asymptomatic IAs in our study (16.1%), higher compared to the general population (1%) and similar to literature reports in ADPKD (6-16%), confirms the importance of the MRA study of the intracranial circle in these patients, even if asymptomatic. Decisions about the management of eventually discovered IAs should be based on multiple factors, assessing any patient on an individual basis taking all the relevant risk factors into account.

Ethical Statement

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee. All patients provided written informed consent.

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