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Cerebral aneurysms in patients with autosomal dominant polycystic kidney disease—to screen, to clip, to coil?

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Introduction

Subarachnoid haemorrhage (SAH) from ruptured intracranial saccular aneurysms of the circle of Willis is a devastating event with a mortality rate of over 25% and an additional high risk of permanent disability [1–5]. The high incidence of intracranial aneurysms in patients with autosomal dominant polycystic kidney disease (ADPKD) has long been recognized. The availability of non-invasive screening methods for asymptomatic aneurysms and the major advances in microsurgical and endovascular techniques raise the question of whether systematic screening and treatment of those patients is warranted. Because many variables have to be taken into account in order to evaluate the natural risk as opposed to the risk of prophylactic treatment, a clear consensus has not been reached and decision processes vary among institutions. Based on recent data we discuss the risks and benefits of screening and prophylactic treatment of asymptomatic intracranial aneurysms in patients with ADPKD.

Incidence of asymptomatic intracranial aneurysms in patients with ADPKD

Ideally, to determine the overall frequency, the incidence of new aneurysms and their potential growth rate, ADPKD patients should be identified genotypically during childhood and systematically screened for the presence of aneurysms throughout life. Such a study is not available. Furthermore, there are also no genetic or phenotypic markers predicting the presence of aneurysms in the individual ADPKD patient. Both types of ADPKD, i.e. PKD1 and PKD2, have been associated with aneurysms.

In a post-mortem study on 89 ADPKD patients, Schievink and co-workers [6] reported a 22.5% prevalence of intracranial aneurysms. Huston *et al.* [7] reported a prevalence of 10% in 85 ADPKD patients screened by MR angiography. Ruggieri *et al.* [8] found a similar prevalence of 11.7% in 93 patients and a higher frequency in 27 patients with a definite or suspected family history for aneurysms. In those two clinical studies, only one patient with an aneurysms was younger than 30 years, i.e. 24 years. He had a 3-mm aneurysm of the petrous segment of the internal carotid artery, which is associated with a very low risk of bleeding. All of the detected aneurysms were smaller than 7 mm in diameter. These findings were confirmed by Ronkainen *et al.* [9].

Based on the available literature, the following conclusions can be drawn: (i) the prevalence of aneurysms in adult ADPKD patients is approximately 10%; (ii) the great majority of such aneurysms is small, less than 10 mm, often less than 5 mm in diameter; (iii) familial clustering does occur; (iv) aneurysms are rarely present in patients younger than 30 years of age, and if so they are very small and are not detected by MR angiography; (v) as compared to patients with sporadic aneurysms, no significant differences concerning number and location of aneurysms have been identified in ADPKD patients.

The natural history of asymptomatic intracranial saccular aneurysms

The approximately 10 in 100 000 per year incidence of aneurysmal SAH in the general population [10] has been constant in recent decades all over the world, except in Finland, where a two- to three fold higher incidence of SAH has been documented [11]. The prevalence of aneurysms in post-mortem, angiographic and MR series ranges between 1 and 7% [12–14]. A recent realistic estimate gives a frequency of 2% [14] in individuals without risk factors for aneurysms.

Clearly, the risk of rupture increases with increasing size of the aneurysm [15]. However, even aneurysms smaller than 5 mm can rupture [16], as documented also in an ADPKD patient [17]. The mean maximal diameter of aneurysms at the time of rupture varies between 6 and 10 mm. In a recent, large retrospective study on 1449 patients with a mean follow-up of 7.5

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years [18], size, location in the posterior circulation and a previous history of SAH from another aneurysm have been identified as predictors of rupture. The reported rate of rupture was surprisingly low: 0.05–0.5% per year for aneurysms smaller than 10 mm and approximately 1% per year for larger ones. The rupture rate for aneurysms larger than 25 mm was 6% per year during the first year. These results partially contradict several previous studies, which were included in a recent meta-analysis of the literature by Rinckel *et al.* [14]. They reported an overall risk of rupture of 1.9% per year (0.7% for aneurysms of 10 mm in diameter and less; 4% for larger ones) and a risk of 0.8% per year for asymptomatic aneurysms in patients without a previous history of SAH.

In summary, the risk of aneurysm rupture depends mainly on its size, on a history of previous bleeding from another aneurysm, and on its location (the posterior circulation is at higher risk). Because most aneurysms detected in ADPKD patients are less than 10 mm in diameter the yearly risk of bleeding is low. However, the cumulated risk, remains significant. It obviously depends on the expected survival, which may be about 60 years in ADPKD patients [19]. Based on the annual risk of rupture and the expected survival, the approximate individual risk can be calculated (see Table 1). SAH from aneurysms is responsible for death in a relatively small proportion of patients with ADPKD [19]. However, the mean age at rupture in patients with ADPKD is between 35 and 40 years [19–21], that is 10–20 years earlier than in patients with sporadic SAH. This suggests that ADPKD *per se* is a risk factor for aneurysm rupture. The risk of developing new aneurysms in patients with a documented aneurysm may be as low as 2%. Although growth of aneurysms during long-term follow-up has been documented [22], it is probably a rare event.

The accuracy of Angio-MR examinations for screening

The gold standard for the diagnosis and preoperative planning is the conventional four-vessel arteriography. Although the risk of death and permanent neurological injury of this procedure is approximately 0.5%, it might be higher in patients with ADPKD (see below). Angio-MR carries no risk and the contrast medium Gd-DTPA is not nephrotoxic. Its value in the detection of aneurysms is now well established [23,24]. Angiographically confirmed aneurysms of 6 mm or more in diameter have been detected with 100% sensitivity by two or more blinded readers with time-of-flight-MRA [25]. The sensitivity decreased to 87.5, 68.2, 60 and 55.6% for aneurysms with a diameter of 5,4,3 and 2 mm respectively. There were no false positive results in these studies.

Table 1. Cumulative risk of aneurysm rupture depending on the yearly risk of rupture and expected survival at diagnosis according to the multiplicative law of probability

Expected survival (years)	yearly risk (%)				
	0.5%/year	1%/year	2%/year	3%/year	4%/year
10	5	9.5	18	26	34
20	9.5	18	33	46	56
30	14	26	46	60	71
40	18	33	55	70	80

Modified from Ref 30: risk of haemorrhage (in %) $= 1-(1-\text{yearly risk})^{\text{years of expected survival}} \times 100$.

The risk of angiography

Because cerebral panangiography is still an obligatory examination before treatment, its risk has also to be considered. There are few data on the specific risk of cerebral angiography in the subgroup of patients with ADPKD. The careful analysis of Chapman *et al.* [26], reported a 25% rate of transient complications, *i.e.* in eight of 32 patients: vasospasm with headache and nausea in two, severe headache in two, scotoma in two, scotoma and numbness of the hand in one, and asymptomatic dissection of one vertebral artery in one patient. All patients recovered completely after 48 h. None of the patients had significant elevation of the creatinine level after administration of contrast medium.

The risk of microsurgical clipping

Craniotomy and microsurgical clipping is still the treatment of choice for aneurysms. A properly clipped aneurysm can be considered as cured. The great majority of authors do not report the efficiency of clipping, presumably because experienced neurosurgeons can rely on their intraoperative findings and perform control angiograms only in especially difficult cases. Microsurgical clipping of unruptured aneurysms is technically much easier and carries a lower risk of death or permanent morbidity than intervention after SAH. The results of surgery in unruptured or incidental aneurysms are well summarized in two recent meta-analyses of the literature [27,28]. The most important determinants for morbidity or mortality were the size and the location of the aneurysm. For non-giant (<25 mm) anterior circulation aneurysms mortality was 0.9% and morbidity 1.9% in contrast to 3 and 12.9% respectively for aneurysms in the posterior circulation. Giant aneurysms carried a much higher risk, i.e. 7.4% mortality and 26.9% morbidity for aneurysms in the anterior and even 9.6% mortality and 37.9% morbidity for aneurysms in the posterior circulation. In our opinion, however, the value of meta-analyses is limited. The risk of clipping an asymptomatic aneurysm has to be judged individually by an experienced neurosurgeon.

The role and risk of endovascular coiling

As discussed above, there are patients in whom the operative risk is unreasonably high in relation to the natural risk. In such cases, especially for some large aneurysms and for aneurysms of the posterior circulation, the endovascular treatment is a good alternative. Using recent interventional neuroradiological techniques, a microcatheter can be navigated into the aneurysm. Its lumen is then occluded by deposition of electrolytically or mechanically detachable coils. However, the feasibility of this procedure depends on the local vascular anatomy, on the shape of the aneurysm, and on the experience of the endovascular neuroradiologist or neurosurgeon. Ideally, the aneurysm should have a small neck, i.e. the ratio maximal aneurysm diameter: neck diameter should be 2 or more.

A definite cure has probably been achieved when the lumen of the aneurysm has been completely occluded. However, the long term follow-up is still unavailable. In a recent series of 115 patients with incidental aneurysms, a 63% rate of complete occlusion has been reported [29]. This underlines the importance of the proper selection patients with incidental aneurysms for coil therapy, because incomplete occlusion is not ideal. The overall morbidity and mortality was 5% in this study and was mostly due to embolism. However, a positive trend over time was observed suggesting a learning curve; the last 65 patients treated using intraoperative heparinization showed no complications [29].

Endovascular coiling is the preferred method for patients over 65 years of age.

Conclusion

Because of (i) the relatively high prevalence of aneurysms in patients with ADPKD (approximately 10%), (ii) the significant annual risk of rupture (0.5–2%), and (iii) the potential catastrophic sequelae of SAH (>50% mortality and permanent disability), we feel that systematic screening with Angio-MR is advisable. Screening is specially indicated in relatives of patients with a known aneurysm. Because there is little chance to detect aneurysms before the age of 30 years and because then the risk of aneurysmal rupture is extremely small, screening is not recommended before the third decade of life. It remains unclear how often screening should be repeated, but a 5–10-year interval has been proposed and seems reasonable. If an aneurysm is detected by MR angiography, treatment options should be discussed with an experienced team of neurosurgeons and interventional neuroradiologists. Treatment is recommended when the individual risk of rupture is higher than the risk of treatment. The latter depends mainly on the age and general condition of the patient as well as on the size and location of the aneurysm. Microsurgical clipping is still the treatment of choice, when feasible, because it is curative. Endovascular coiling is a good alternative in older patients.

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