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Autosomal dominant polycystic kidney disease (ADPKD) is a common (prevalence 1 in 400 to 1000)⁸ single gene hereditary disorder characterized by progressive development of bilateral renal cysts eventually leading to chronic kidney disease and array of extrarenal abnormalities. ADPKD is caused by mutations in either of the two genes encoding plasma membrane-spanning polycystin 1 and polycystin 2 (PKD1 and PKD2, respectively).⁵ Mutation in either of the polycystins (PKD1-85%, PKD2-15%) can disrupt the function of the other which is to regulate tubular and vascular developments in the kidneys and other organs.

Unruptured Intracranial Aneurysm in ADPKD: An Overview with Illustrative Report of Three Cases

Autosomal dominant polycystic kidney disease (ADPKD) is a common single gene hereditary disorder characterized by progressive development of bilateral renal cysts eventually leading to chronic kidney disease and an array of extrarenal abnormalities including intracranial aneurysm (ICAN). While the association of ICAN with ADPKD is undisputed, its management is not standardized. Conflicting data about the benefits of screening to the efficacy of different treatment modalities have not helped establish any opinion. We report three such cases managed surgically at Hiroshima University Hospital and discuss and review the literature regarding ADPKD and ICAN. Decision for surgical management of these cases were multifactorial and not exclusively because of ADPKD. There is a lack of sufficient randomized data on these topics and until such results are available, neurosurgeons are likely to resort to bit-part data and weigh the risk-benefit factor in individual patients and proceed accordingly.

Key Words: ADPKD, endovascular treatment, subarachnoid hemorrhage, unruptured aneurysm

^{5, 19} Resultant vascular manifestations include intracranial aneurysms and dolichoectasias, thoracic aortic and cervicocephalic artery dissections, and coronary artery aneurysms.¹⁹

Consequently, prevalence of intracranial aneurysm (ICAN) in ADPKD patients is higher than in general population. As Xu et al. have noted, a large variation in prevalence (4%-41%)²¹ has been reported. An estimated prevalence of unruptured intracranial aneurysm (UIA) detected by presymptomatic screening was put at 9.3% by Irazabal et al.⁸ Xu et al. reported an overall prevalence of 12.4% for ICAN in patients with ADPKD.²¹ ADPKD



Figure 1: Case no 1, A) conventional angiography showing Lt. ACA aneurysm, B) interhemispheric approach, C) after application of aneurysm clip



Figure 2: Case 2, A) CTA showing bilobed A.com aneurysm, B) CTA showing bilobed A.com aneurysm, C) MRI demonstrating A.com aneurysm as flow void

patient with family history of ICAN or hemorrhagic stroke are more likely to harbor ICAN themselves (21.6%).²¹ Torres et al. put this figure at 16%.¹⁹

We discuss three different ADPKD cases with unruptured intracranial aneurysms (UIA) that were managed at Hiroshima University Hospital. All three cases were referred to the Department of Neurosurgery by the treating nephrologist.

Illustrative Case I

A 37-year-old woman was diagnosed with PKD 6 years previously when ultrasonography during her pregnancy revealed cysts in her kidneys and liver. Subsequent follow ups revealed a 7mm azygous anterior cerebral artery (ACA) aneurysm (Figure 1). At the time of hospitalization, there was no evidence of renal or hepatic function abnormality. Microcytic anemia was present (Hemoglobin- 10.2 gm/dL). Neurologically, the patient was unremarkable. Patient was on anti-hypertensives. Family history was suggestive of PKD in her father with two instances of unspecified surgical intervention for intracranial hemorrhage.

Patient was managed surgically. A single clip was used to obliterate the aneurysm via interhemispheric approach following bicoronal skin incision and craniotomy. Follow-up angiography 8 days post-operative revealed complete occlusion of the aneurysm.

Her post-operative hospital stay was uneventful. No complications were encountered during immediate or subsequent follow-ups relating to our procedure.

Illustrative Case II

A 61-year-old male patient of PCKD with a history of coronary artery stenting and on oral antiplatelet agent had a 7mm anterior communicating artery (A.Com) aneurysm. Patient as such was asymptomatic of his aneurysm. He was diagnosed as PKD patient when tests to investigate his prostate revealed cysts in kidneys warranting further tests. Renal functions were not compromised. The aneurysm was single and arising from the anterior communicating artery. Patient was managed surgically: the aneurysm was clipped with a 7mm straight Sugita clip following right pterional approach. Peri-operative period was uneventful. Cerebral angiography on 9th post-operative day revealed complete aneurysm neck occlusion (Figure 2).

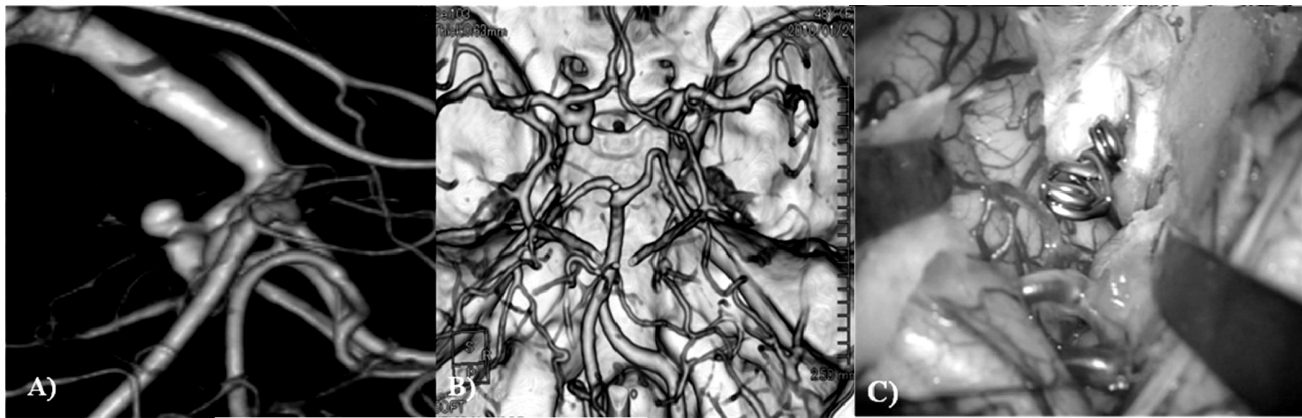


Figure 3: Case 3, A) CTA showing aneurysm at ICA, B) CTA showing ICA aneurysm, C) CTA showing ICA aneurysm post clipping

Illustrative Case III

A 48-year-old hypertensive female patient was diagnosed with PCKD when she was investigated for hematuria 4 years earlier. MRI revealed an aneurysm, 5 mm in size at left internal carotid– anterior choroidal artery (IC-Ach) and middle cerebral artery (MCA) bifurcation. Urologists suspected increase in aneurysm size during subsequent follow up and referred to neurosurgery.

Surgical technique: Frontotemporal craniotomy, pterional approach. Aneurysm neck was clipped using 5 mm slightly curved titanium clip and 7 mm straight titanium clip. Peri-operative period was uneventful (Figure 3).

Discussion

Prevalence of intracranial aneurysm has been estimated between 0.2 and 9% of the population, depending on study types. Rinkel et al. in 1998 published a systematic review of 23 previously reported studies. The prevalence of intracranial aneurysm was 3.7% in retrospective angiography studies, 6% in prospective angiography studies; 0.4% in retrospective autopsy studies and 3.6% in prospective autopsy studies.¹⁷ Their study concluded a prevalence of ICAN at approximately 2%. However, with the advent of better and powerful technological marvels, more intracranial vascular pathologies are being diagnosed than previously reported. Igase et al. reported 8.4 % prevalence of unruptured intracranial aneurysm (UIA) with 3T MRI.⁶

Commonest amongst monogenic disorder, ADPKD affects 1 in 400-1000 individuals. Apart from the renal cysts, extrarenal manifestations such as hypertension, hepatic cysts, and intracranial aneurysms (ICAN) are common. Chapman et al. has documented frequency of ICAN in ADPKD patients with/without any neurological symptoms ranging from 11-60% of the patients evaluated.³ Prevalence of ICAN in patients with ADPKD was

reported as (relative risk [RR], 4.4 [2.7 to 7.2]) by Rinkel et al.¹⁷ Consequently, with a RR of around 5 fold and a prevalence rate of similar proportions, prevalence of ICAN in ADPKD does not seem to be any higher than in general population.

However, most of these reports are from an era when MRI was sparingly used for the purpose and radiological advances have come a long way since. Recent literatures in the topic have yielded a more concurring data. ICAN prevalence of 21.6%, 8.3% and 11.0% in patients with positive, possible and negative family history of hemorrhagic stroke or ICAN respectively has been documented by Xu et al.²¹ Torres et al. put the numbers at 16% and 6% for positive and negative family history for ICAN in ADPKD patients.¹⁹

Gibbs et al. followed-up 17 ADPKD patients with ICAN for 92 months and concluded that the risk of growth and development of new aneurysms in patients with small (<7 mm in diameter) UIAs detected by pre-symptomatic screening is low and thus the risk of rupture may not be higher than that reported among non-ADPKD aneurysms.⁴ They also highlighted the fact that 67% of the patients in the study had a family history of intracranial aneurysm and as such concluded that their data does not support a substantial increase in risk for rupture in this particular population. However, the study does not differentiate whether the family history of aneurysm implies mere presence of aneurysm or actual SAH due to aneurysmal rupture or mixed data as stratified by Xu et al.

The most significant unresolved issue is how the risk posed by an untreated UIA varies with time.¹² Natural course of UIA varies according to the size, location, and shape of the aneurysm.^{7,18} UIA that are ≥ 7 mm, are located in the anterior communicating or internal carotid–posterior communicating arteries, and have a daughter sac are associated with an increased risk of rupture.¹⁸ So do unruptured aneurysms constantly pose a threat of rupture (constant risk) or they pose the greatest threat when they form (early high risk).¹²

Some authors have suggested periodic screening of high risk subjects^{11,15,18} while others advocate very selective screening for UIAs in ADPKD patients, while emphasizing that widespread screening is not of much value.^{4,8,12,20} Neumann et al. argue that screening for ICAN is widely insufficiently performed, should not be restricted to families with a history of cerebral events and should be started before end-stage renal failure.¹⁴

Optimal management of both ruptured and UIA is controversial and constantly evolving. As such, it is important to consider the factors that support the treatment of an ICAN with either surgical clipping or placement of detachable coils. In few of these cases, either of the method can be appropriate and the decision is largely influenced by difficult to quantify variables such as patient preference or operator availability or expertise.² Decision making is further complicated by the fact that these interventions do not entirely eliminate the risk of SAH. Incomplete occlusion occurs in 5% of clipped and 15% to 30% of coiled aneurysms and the risk of regrowth of a successfully clipped aneurysm is 0.26% to 0.52% per year. Furthermore, patients with aneurysms have a 0.89% to 1.8% risk of de novo aneurysm formation.⁸ Individuals with ADPKD and ICAN appear to be at moderate risk for new ICANs and increase in size of existing ICANs; mortality and risk of recurrent rupture, however, appear to be low^[1].

A 1994 meta-analysis of 28 articles by King et al. revealed a 4.1% morbidity rate and a 1.0% mortality rate while acknowledging the insufficiency of data to suggest the risk factor for the surgical outcomes for asymptomatic UIA.⁹ Mortality of 2.6% and a morbidity of 10.9% was reported following a meta-analysis of 61 studies by Raaymakers et al.¹⁶ A recent review article, ahead of print, puts the risk of unfavorable outcome for surgical clipping at 6.7%, and a risk of death at 1.7%.¹⁰ Meta-analysis of literature from 2003-2008 with 5044 patients by Naggara et al. for ICAN patients who underwent endovascular treatment (EVT) yields mortality of 2.0% and unfavorable outcome, including death, at 1 month at 4.8%.¹³ The authors, however, refrain from claiming that EVT is superior to surgery for treatment of ICAN in light of the fact that there is a lack of randomized controlled trial (RCT) studies in this area as a lot of factors might have influenced the results like referring difficult aneurysm cases for surgery. There is no reliable data available which assesses the risk of different surgical modalities in treating ICAN in ADPKD patients.

Pre-emptive intervention of UIA in ADPKD patients could be beneficial in patients with intact renal function than after the deterioration sets in as the natural history of ADPKD is characterized by decades of normal renal function, despite progressive enlargement and cystic transformation of the kidneys.²⁰ In addition to the cumulative risk of rupture of aneurysm with each year, surgical option could be further complicated by the co-

morbid states encountered in chronic renal failure cases. However, in selecting the treatment modality, aneurysm-related issues such as surgical accessibility or shape of aneurysms may be more important than the patients' dialysis status and prophylactic hemodialysis may be contemplated for nonhemodialysis patients.²² Another major deterrent is a lack of sufficient data to implicate several possible risk factors including gender, family history of ICAN, presence of hypertension, end stage renal disease (ESRD) at follow-up, or a history of smoking with formation of new ICAN or changes in existing ones in ADPKD cases.¹ There is also dearth of studies where cases of UIA found by screening is tallied against those cases with ruptured ICAN in ADPKD patients and how the demographics of these two categorically different population correlate.

Rationale for intervention in each of the illustrative cases:

Case I

- a. Positive family history of subarachnoid hemorrhage (SAH)
- b. Complex aneurysm shape
- c. Easy aneurysm accessibility by craniotomy
- d. Higher chances of complete aneurysm obliteration by clipping

Case II

- a. History of coronary artery disease (CAD) with stenting and regular use of antithrombotic agent.
- b. Family history: His hypertensive father died after he lost consciousness following a bout of headache aged 59 years suggesting SAH
- c. Aneurysm was larger than its parent artery
- d. Higher chances of complete aneurysm obliteration by clipping

Case III

- a. Increase in aneurysm size over time. (Aneurysm wall was thinned out and fragile intraoperatively)
- b. Higher chances of complete aneurysm obliteration by clipping
- c. Patient's father had renal failure with stroke (unspecified)

As evident from the discussion, there is no definitive management strategy of ICAN in ADPKD patients. The points enumerated in each of the illustrated cases above demonstrates the individualized holistic approach employed by us.

These illustrative cases demonstrate that treatment strategy of aneurysm cases in ADPKD patients need not differ qualitatively from other groups. It may be a while before a uniform guideline for management is proposed for this condition.

For clinicians in developing world who do not have the luxury of frequent investigative follow up of their patients, this article might serve as a guide to approach such cases.

Conclusions

The association of ICAN with ADPKD is undisputed. However, there is no uniform guideline or consensus regarding the optimum management strategy of UIA in ADPKD patients. Results of different studies regarding the risk-benefit factor on the modalities of intervention either EVT or surgery and expectant follow-up are wide and differing. Lack of sufficient randomized data on these topics and the resultant use of sub-standard data by researchers, which are mostly self-acknowledged by the authors, has not helped form any opinion. Until such results are available, neurosurgeons are likely to resort to bit-part data and weigh the risk-benefit factor in individual patients and proceed accordingly.

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