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Silent Risk, Real-World Insight From an Italian Center: Rethinking Intracranial Aneurysm Screening in ADPKD



To the Editor: We read with great interest the comprehensive review by Borghol et al¹ on the screening and management of intracranial aneurysms (IAs) in autosomal dominant polycystic kidney disease (ADPKD), a topic of high clinical relevance and ongoing debate. Their work presents a balanced and thorough synthesis of current evidence, acknowledges the limitations of existing screening strategies, and outlines critical areas where future guidelines may evolve.

Our experience as a national ADPKD reference center in Italy with more than 500 cases managed through a multidisciplinary framework² strongly aligns with many of the key messages highlighted in the review. In particular, we agree

that the true burden of IAs in ADPKD is likely to be underestimated when relying solely on family history and that broader, more inclusive screening strategies are urgently needed.

As noted in the review, the reported prevalence of unruptured IAs in ADPKD ranges from 8% to 12%, rising to more than 20% in patients with a positive family history and approximately 6% in those without. These figures are consistent with our cohort of 350 systematically screened patients, in whom we identified 29 IAs (8.3%). Four of these aneurysms met criteria for high rupture risk and were treated promptly. Notably, none of these 4 patients had a known family history of aneurysms or were aware of such a predisposition, a finding that mirrors data cited in the review from Flahault et al,³ in which most aneurysmal ruptures occurred in patients without a documented familial risk. This reinforces the authors' concern that family history alone is an unreliable screening trigger and may fail to capture a substantial number of high-risk individuals. Whereas the absolute rupture rate in ADPKD is relatively low, it is significantly higher than in the general population.¹ In this context, we strongly support the authors' implication that a broader and more proactive screening policy is essential to prevent catastrophic and often silent vascular events in these patients.

Genotype-based risk stratification is another area of significant clinical interest. Although the review correctly noted that no definitive causal association has been established between specific *PKD1* variant types and IA risk,¹ several studies have reported a higher

prevalence of aneurysms in patients with *PKD1* pathogenic variants, particularly in those with a positive family history.⁴⁻⁶ However, these findings remain inconclusive, limited by cohort heterogeneity and ascertainment bias. Nonetheless, it is well established that *PKD1* truncating mutations are associated with a more severe systemic phenotype, including earlier hypertension onset, faster increase in total kidney volume, and more rapid progression to end-stage kidney disease.⁷⁻⁹ Given this recognized link to disease severity, it is biologically plausible—and increasingly suspected—that truncating *PKD1* mutations may also confer increased susceptibility to vascular complications such as IAs.

Our real-world data reinforce this hypothesis: 22 of 29 patients with IAs in our cohort carried truncating *PKD1* mutations, including 3 with confirmed de novo variants. Whereas these observations do not prove causality, they support the case for genotype-informed screening strategies, particularly in patients with limited or absent family history. Other reports have described specific *PKD1* variants (eg, c.G10086T)⁵ and mutations located in the 5' region of the gene as potentially associated with increased IA risk.⁶ In addition, increased total kidney volume—more commonly seen in *PKD1* truncating carriers—has been independently associated with aneurysm formation.¹⁰

When universal screening is not feasible, we advocate strongly for targeted screening of all carriers of *PKD1* truncating mutations, including those with de novo mutations or unknown familial background. This approach aligns with the review's suggestion that genotype-phenotype

correlations, although not yet fully defined, may meaningfully guide screening decisions.

Furthermore, we endorse the recommendation for magnetic resonance angiography (MRA) to be the preferred screening modality because of its safety, accuracy, and noninvasive nature. In our practice, MRA has been well accepted by patients and has not led to undue anxiety, especially when screening is offered within a structured and informed clinical context. Patients often express relief in obtaining concrete information about their cerebrovascular risk, which in turn enhances adherence and trust.

Whereas cost considerations are valid, we believe that a once-in-a-lifetime or 5-year interval MRA study in a population with a rare but potentially devastating complication represents a reasonable and ethically sound investment. The cost-benefit ratio compares favorably with the high morbidity and mortality associated with aneurysmal subarachnoid hemorrhage.

We commend Borghol et al for their thorough and thoughtful review. Our clinical experience and real-world data strongly support their conclusion that a broader and more inclusive approach to IA screening in ADPKD is clinically

justified and may be ethically necessary to prevent avoidable cerebrovascular events. We hope that future recommendations will incorporate these insights to better protect this vulnerable population.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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