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General review

Unruptured intracranial aneurysms: An updated review of current concepts for risk factors, detection and management

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ABSTRACT

The management of patients with unruptured intracranial aneurysms (UIAs) is a complex clinical challenge and constitutes an immense field of research. While a preponderant proportion of these aneurysms never rupture, the consequences of such an event are severe and represent an important healthcare problem. To date, however, the natural history of UIAs is not completely understood and there is no accurate means to discriminate the UIAs that will rupture from those that will not. Yet, a good understanding of the recent evidence and future perspectives is needed when advising a patient with IA to tailor any information to the given patient's level of risk and psychoaffective status. Thus, this review addresses the current concepts of epidemiology, risk factors, detection and management of UIAs.

1. Introduction

An intracranial aneurysm is an acquired focal outpouching (typically either saccular or fusiform) of a cerebral artery wall [1]. Its most feared complication is rupture, causing blood to erupt into the subarachnoid space with potentially fatal and frequently disabling outcomes [2,3]. The consequences of an aneurysmal subarachnoid hemorrhage (aSAH) are devastating, with at least a quarter of such patients not surviving the rupture or its immediate complications, while leaving roughly half the survivors with permanent disabling neurological deficits [4].

With the greater availability of technical improvements and the ever-widening indications for noninvasive vascular neuroimaging [5], unruptured intracranial aneurysms (UIAs) are increasingly being discovered incidentally and an steadily

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growing number of patients are being referred to or seeking counseling from specialized centers regarding opportunities for screening (for example, for fear of occult UIAs after a relative has suffered an aSAH) [6]. However, UIAs represent a challenging situation to manage for several reasons:

- while the vast majority of UIAs never rupture [7–9], the consequences of such an event are severe and represent a major healthcare problem [4,10];
- the natural history of UIAs is still not entirely understood and there is no accurate way to discriminate UIAs likely to rupture from those that will not [11,12];
- the currently available treatments for repairing UIAs are invasive and associated with non-trivial morbidity, a risk particularly relevant in previously asymptomatic patients [13];
- the popular belief that an UIA is an imminent and ever-present peril has important psychosocial effects in patients with identified but untreated UIAs [14,15].

Therefore, screening might, in some cases, not achieve its ultimate goal of improving quality years of life.

As a consequence, when offering screening for UIAs or advising for interventional vs. conservative management in patients with UIAs, physicians face a complex situation where no option is risk-free.

The optimal management and counseling should therefore focus on tailoring each encounter to the patient's specific level of risk and psychoaffective status, based on the available (albeit incomplete) evidence.

The American Heart Association (AHA)/American Stroke Association (ASA) issued guidelines for the management of UIAs in 2015 [16]. The present review does not intend to provide further guidelines, but aims to address the latest evidence on the epidemiology, natural history, risk factors, clinical and imaging presentations, treatment and follow-up of UIAs.

2. Epidemiology and natural history

2.1. *Epidemiology*

The reported prevalence of UIAs varies by assessment modality [magnetic resonance imaging (MRI), computed tomography (CT), conventional angiography, autopsy] and subpopulation sampling, but remains rather consistently between 2% and 6% [17–20].

The largest epidemiological study to date, published in 2011 [18], aggregated the results of 68 studies in a meta-analysis of 94,912 patients with 1450 UIAs. In their report, the investigators estimated the prevalence of UIAs in a fictitious population, with a mean age of 50 years and 50% male, at 3.2% (95% CI: 1.9–5.2%). The study showed that the prevalence of UIAs was influenced by the presence of polycystic disease, a positive family history, older age and female gender, but did not differ across geographical regions [18]. In particular, they found no higher prevalence of UIAs in Japan and Finland (an issue that has triggered intense debates over the past decades) [21,22].

There are only very scanty data available on incident UIAs, as they would require extensive long-term longitudinal studies with repeated imaging assessments in large populations [16]. In one recent study carried out in patients already diagnosed with at least one saccular IA, the cumulative incidence of de novo formation of UIAs was estimated to be as low as 0.23% per patient–year [23]. However, more studies are needed to confirm this estimate in different settings.

2.2. *Natural history*

The natural history of UIAs is currently conceptualized as a sequential process in which:

- the UIA develops;
- the UIA evolves (with morphological and size changes);
- the UIA ruptures, or not [13].

Temporal characteristics of the process are as yet poorly understood.

Although much remains to be elucidated to understand why some UIAs evolve and rupture while others do not, there have nonetheless been some remarkable advances in the field of UIA research, leading to evidence that the genesis of IAs include flow-driven inflammatory and wall-remodeling processes [24,25].

There is also strong evidence that UIAs differ pathologically from those that have ruptured, with the latter presenting with more histological, structural and molecular feed-forward wall-weakening processes [26]. Understanding the mechanisms responsible for the initiation and maintenance of these processes would add tremendous insight to our current understanding of UIA natural history and perhaps even lead to accurate prediction of the risk of rupture.

At the population level, previous studies, including the large International Study of Unruptured Intracranial Aneurysms (ISUIA) [27], have demonstrated that UIAs have a totally different evolution in patients with vs. without a history of aSAH compared with other IAs. In the study, the annualized risk of rupture was $\sim$0.05% in patients with no history of aSAH, whereas it was close to 11-fold higher in those with a previous aSAH (0.55%). More recently, a large prospective cohort study of 2252 patients with a cumulative total of 7388 aneurysm–years found an overall rupture incidence of 0.76% per year (95% CI: 0.58–0.98%), which was significantly increased for aneurysms $\geq$ 10 mm with daughter sacs, and for UIAs located in the vertebrobasilar and internal carotid–posterior communicating arteries [28], which was in line with previously reported findings [29,30].

However, the only ''lifelong'' longitudinal study was conducted in Finland and included 118 patients, with a total follow-up until death or an aSAH of 2187 person–years. In this study of patients aged 51.3 years on average at inclusion, almost 30% of UIAs ruptured over a median 18.5 years of follow-up, and 25% of patients with UIAs $<$ 7 mm in size suffered an aSAH, thus yielding much higher annualized estimates. Yet, the question of the external validity of such studies, which have included only Finnish (and Japanese patients), has been consistently raised [21], leading to their

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