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Epidemiology and genetics of intracranial aneurysms

F. Caranci[a,1], F. Briganti[a,2], L. Cirillo[b,3], M. Leonardi[b,4], M. Muto[c,*]

[a] Unit of Neuroradiology, Department of Diagnostic Radiology and Radiotherapy, Federico II University, Naples, Italy
[b] Neuroradiology service, Bellaria Hospital, Bologna, Italy
[c] Neuroradiology Service Cardarelli Hospital Naples, Italy

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ABSTRACT

Intracranial aneurysms are acquired lesions (5–10% of the population), a fraction of which rupture leading to subarachnoid hemorrhage with devastating consequences.

Until now, the exact etiology of intracranial aneurysms formation remains unclear.

The low incidence of subarachnoid hemorrhage in comparison with the prevalence of unruptured IAs suggests that the vast majority of intracranial aneurysms do not rupture and that identifying those at highest risk is important in defining the optimal management. The most important factors predicting rupture are aneurysm size and site.

In addition to ambiental factors (smoking, excessive alcohol consumption and hypertension), epidemiological studies have demonstrated a familiar influence contributing to the pathogenesis of intracranial aneurysms, with increased frequency in first- and second-degree relatives of people with subarachnoid hemorrhage. In comparison to sporadic aneurysms, familial aneurysms tend to be larger, more often located at the middle cerebral artery, and more likely to be multiple.

Other than familiar occurrence, there are several heritable conditions associated with intracranial aneurysm formation, including autosomal dominant polycystic kidney disease, neurofibromatosis type I, Marfan syndrome, multiple endocrine neoplasia type I, pseudoxanthoma elasticum, hereditary hemorrhagic telangiectasia, and Ehlers-Danlos syndrome type II and IV.

The familial occurrence and the association with heritable conditions indicate that genetic factors may play a role in the development of intracranial aneurysms.

Genome-wide linkage studies in families and sib pairs with intracranial aneurysms have identified several loci on chromosomes showing suggestive evidence of linkage, particularly on chromosomes 1p34.3–p36.13, 7q11, 19q13.3, and Xp22.

For the loci on 1p34.3–p36.13 and 7q11, a moderate positive association with positional candidate genes has been demonstrated (perlecan gene, elastin gene, collagen type 1 A2 gene).

Moreover, 3 of the polymorphisms analyzed in 2 genes (endothelial nitric oxide synthase T786C, interleukin-6 G572C, and interleukin-6 G174C) were found to be significantly associated with ruptured/unruptured aneurysms: the endothelial nitric oxide synthase gene single-nucleotide polymorphisms increased the risk, while IL-6 G174C seemed protective.

More recently, two genomic loci (endothelin receptor A and cyclin-dependent kinase inhibitor 2BAS) have been found to be significantly associated with intracranial aneurysms in the Japanese population; endothelin-1 is a potent vasoconstrictor produced by the endothelial cells.

Until now, there are no diagnostic tests for specific genetic risk factors to identify patients who are at a high risk of developing intracranial aneurysms.

Knowledge of the genetic determinants may be useful in order to allow clues on stopping aneurysm formation and obtain diagnostic tools for identifying individuals at increased risk. Further multicenter studies have to be carried out.

* Corresponding author at: Neuroradiology service Cardarelli Hospital Naples Italy 7,Cardarelli street Naples, Italy. Tel.: +39 0817473838; fax: +39 0817473125.
E-mail addresses: ferdinandocaranci@libero.it (F. Caranci), frabriga@unina.it (F. Briganti), mutomar@tiscali.it (M. Muto).
[1] Ferdinando Caranci, Unit of Neuroradiology, Department of Diagnostic Radiology and Radiotherapy, Federico II University, Naples via S. Pansini 5, 80131 Naples (Italy). Tel.: +39 817464646; fax: +39 817462597.
[2] Francesco Briganti, via S. Pansini 5, 80131 Naples, Italy. Tel.: +39 817464251; fax: +39 817462597.
[3] Neuroradiology service Bellaria Hospital, Bologna, Italy.
[4] Neuroradiology service, Bellaria Hospital, Bologna, Italy.

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1. Introduction

Intracranial (saccular or berry) aneurysms (IAs) are acquired lesions, accounting for about 80% of all nontraumatic subarachnoid hemorrhages (SAH) [1].

IAs affects 5–10% of the general population [2], a fraction of which will rupture and lead to devastating consequences.

Unruptured IAs are rarely noted in children (0,5–4,6% of all aneurysms) and appear to develop with increasing age [3,4]: the prevalence of harboring an IA within the population aged over 30 years is between 3.6 and 6.5% [5–9].

Women may be more likely to have an aneurysm than men (3:1 ratio of women compared with men in unruptured – 8, 9). IA may occur alone (70–75%) or as multiple aneurysms (25–30%) [10].

The incidence of unruptured IAs seems to be increasing with the continuous evolution of Magnetic Resonance angiography (MRA) and Computed Tomography angiography (CTA) imaging techniques [11,12].

SAH due to IA rupture occurs around 1.24 times more often in women than in men [13] and 2.1 times more often in blacks than whites [14].

The annual incidence of SAH has wide variations between geographical regions. A World Health Organization (WHO) study found a 10-fold variation in the age-adjusted annual incidence in Europe and Asia, from 2.0 per 100,000 population in China to 22.5 cases per 100,000 in Finland [15]. The risk of rupture depends on the size and location of the aneurysms and has been reported to be 2.7% per year in a Japanese population [11] and 1.9% in a white population [16].

Most patients have no symptoms or complaints until the aneurysm ruptures. In some cases, there are some warning signs that an aneurysm is present, such as pain above and behind the eye, cranial nerve paralysis, or headache and neck pain secondary to a leakage of blood from the aneurysm, so-called "sentinel bleed" [17].

2. Risk factors for intracranial aneurysms

The exact etiology of IA formation remains unclear; they are usually acquired lesions because of congenital defects in the wall of a blood vessel, atherosclerotic changes, trauma, or infectious emboli [17].

The progress in understanding the pathogenesis of IAs has been hampered by its multifactorial nature.

High-resolution modern imaging technique, often performed for the evaluation of vague and nonspecific symptoms and concerns, have increased the detection of asymptomatic sporadic IA. When an intracranial aneurysm is detected, its treatment (or simply observation) is often a significant management dilemma.

The optimal management strategy for IAs must take into account numerous factors, including aneurysm factors (such as site, size, morphology, presence of thrombus, location), as demonstrated on brain imaging, and patient factors (including age, medical history, history of prior SAH, positive family history of IAs or SAH).

The low incidence of SAH in comparison with the prevalence of unruptured IAs suggests that the vast majority of IAs do not rupture and that identifying those at highest risk is important in defining the optimal management [18].

Early retrospective studies suggested that IA size was the main predictor of rupture with SAH, with annual rupture rates of 3.3% per year for those 10–15 mm, 5.6% per year for 16–25 mm, and 8.9% per year for >25 mm [19].

In another retrospective study, concerning 142 untreated patients with an unruptured IA were followed for a mean of 19.7 years, the annual rupture risk for IA < 10 mm in diameter was 1.1% per year, and 2.8% per year for IA > 10 mm [20].

The largest natural history study of unruptured IAs is the International Study of Unruptured Intracranial Aneurysms (ISUIA) [9,21]. Over a mean of 7.5 years, the unruptured IA rupture rate in 727 patients without a prior history of SAH was about 0.05% per year for IAs less than 10 mm in maximum diameter and 1% per year for those ≥10 mm. IA location also predicted an increased risk of rupture with posterior communicating/internal carotid, vertebrobasilar/posterior cerebral, and basilar tip location aneurysms being at the highest risk.

These values differed from 722 patients with a prior history of SAH, who showed a 0.5% rupture rate per year for <10 mm IAs, 0.7% for >10 mm IAs. Again, aneurysm location was a predictor of SAH, with aneurysms in the basilar tip location being those at highest risk.

ISUIA provided the largest prospective natural history study of unruptured IAs. In 1692 patients with arteriographically confirmed unruptured IAs identified prospectively and followed for a mean of 4.1 years, 1077 did not have a prior history of SAH, and 615 had a prior history of SAH from some other aneurysm; IA size and site were the most important factors predicting IA rupture.

For patients without prior SAH, the lowest-risk aneurysms were those in the anterior circulation (excluding cavernous internal carotid or ICA aneurysms), <7 mm in diameter. The annual rupture rates for anterior circulation aneurysms (excluding cavernous ICA aneurysms) were 0.5% (7–12 mm), 2.9% (13–24 mm), and 8% (>24 mm). For vertebrobasilar circulation or posterior communicating artery aneurysms, the annual rupture rates by aneurysm size were 0.5% (<7 mm), 2.9% (7–12 mm), 3.7% (13–24 mm), and 10% (>24 mm).

In patients with unruptured IAs <7 mm in diameter and a history of SAH, the annual rupture risk was somewhat higher (0.3% for anterior circulation aneurysms, 0.7% for posterior circulation or posterior communicating aneurysms).

Other than aneurysm size, the conditions leading to IA formation and rupture have not been fully delineated [22].

A meta-analysis of all longitudinal and case-control studies for risk factors for SAH from 1966 to 2005 concluded that environmental risk factors include smoking, excessive alcohol consumption and hypertension, while a less robust risk factor was non-white ethnicity [23].

Inflammatory and immunological reactions may also be related to IAs formation and rupture [24], although not so established as in abdominal aneurysms; moreover, a decrease in both circulating estrogen levels and cerebrovascular estrogen receptor density may contribute to an increased risk of IAs pathogenesis and rupture in women during and after menopause [25].

The influence of the risk factors may lead to a thickening of the intimal layer and subsequently increases hemodynamic strain in the more elastic portions of the vessel wall [26], so contributing to IA formation and development.

Despite the evidence for environmental factors contributing to the pathogenesis, they fail to completely explain IAs formation, growth, and rupture, particularly in young adults.

In addition to ambiental factors, epidemiological studies have demonstrated that familial predisposition is a well recognized non-modifiable risk factor for the formation and rupture of IAs.

While the modifiable risk factors are the most prevalent ones, familial occurrence is the strongest risk factor [27]; however, the mode of Mendelian inheritance is uncertain in most families [12].

There is an increased frequency of IAs and SAH in first- and second-degree relatives of people with SAH: a family history of SAH or IA is noted in 10% of first-degree relatives and 15% of second-degree relatives [28].