Review Article

Familial Intracranial Aneurysms in Saudi Arabia: What Do We Need To Do?

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A B S T R A C T

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating event with significant morbidity and mortality. The incidence of SAH might be influenced by environmental factors but genetic predisposition is evolving as an important effector in the risk of development of intracranial aneurysms and rupture of aneurysms. This requires strategies for effective screening of family members at risk of developing such a phenotype, in order to deliver preventive treatment to these target lesions. We discuss the potential for implementing these strategies in the Saudi Arabian health system and the future implications on our care for such a vulnerable group of subjects.

Key words: Familial intracranial aneurysms, intracranial aneurysms, screening

ملخص البحث:

النزيف الدماغي السحاني أو ما يسمى بأم الدم يمثل نوعاً خطيراً من النزيف الدماغي ينتج عنه نسبه عاليه من التلف الدماغي والضرر الوظيفي مما قد يؤدي إلى الوفاة. السبب الأكثر شيوعا لهذا النوع من النزيف هو انفجار الشرايين الدماغية الواسعة لضعفها وترهل جدرانها. وقد وجد من الدراسات المختلفة أن أهم أسباب هذا التمدد هي العوامل الوراثية، والتي قد تتفاعل مع بعض العوامل البيئية كالتدخين مما قد يزيد من نسبه حدوث النزيف. علماً بأنه من غير المعروف أيا من هذه العوامل الوراثية هي الأكثر شيوعا في المملكة . ولذا يقترح الباحثون مجموعه من التوصيات بخصوص الفحص العائلي للكشف عن وجود هذه التوسعات لتوفير العلاج الاحترازي لها قبل حدوث النزيف.

INTRODUCTION

Subarachnoid hemorrhage (SAH) from the rupture of an intracranial aneurysm is associated with a poor prognosis. A range of population-based studies has revealed that fatalities from aneurysmal SAH ranges between 40% and 50%, with those who suffer a disability and have to depend on others for their day-to-day living ranges between 20% and 60%.[1,2] The incidence of SAH increases with age, with prevalence changing from 1% at age 35 years to 8% at age 65 years.[3] About 50% of the patients who experience a SAH are below the age of 55, which carries a significant burden on the patient, family, and society.[4,5] International statistics for the incidence of SAH only report 6-10% of all hemorrhagic strokes encountered in medical practice.[6] Our group and others reported on the incidence of SAH in Saudi Arabia and found it to be 1-2%, which is much lower than that reported internationally.[7-9] In published and

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nonpublished observations, the intracranial aneurysms encountered by vascular neurosurgeons in Saudi Arabia generally occur in younger patients and are structurally more complex, raising the possibility of an underlying vasculopathy factor; whether this is genetic or environmental is yet to be determined.[10]

Several studies have addressed the independent risk factors for aneurysmal SAH such as smoking, (odds ratio of 3.1), hypertension, (odds ratio of 2.6), and excessive use of alcohol.[11] Family history of aneurysmal SAH remains the strongest risk factor for aneurysm formation and the development of SAH, which is unfortunately nonmodifiable leading to an undue stress factor on the family and the treating physician alike.[11,12]

ARE FAMILIAL ANEURYSMS DIFFERENT FROM SPORADIC ANEURYSMS?

Numerous studies have described familial aneurysms, which is when two or more patients within the same family where first and second degree relatives have an intracranial aneurysms, ruptured, or unruptured.[13-16] In comparison to sporadic aneurysms, familial aneurysms are generally larger at the time of diagnosis, more often located on the middle cerebral artery, and more likely to be multiple than sporadic aneurysms.[17,18] Familial cerebral aneurysms tend to rupture in younger patients, particularly females, than sporadic aneurysms.[18,19] This is supportive of the congenital theory of aneurysm formation because it would take longer for the process supporting the degenerative theory alone to form an aneurysm if not expedited by a genetic "insult."[20,21] Familial aneurysms tend to rupture within the same decade in families and in identical twins, they tend to rupture within 5 years of each other. The size of ruptured familial cerebral aneurysms appears to be smaller, especially in women, than sporadic aneurysms.[17,18,22] A poor outcome of rupture is more frequent in familial cerebral aneurysm patients than in patients who experience a sporadic aneurysm.[17,23]

Of patients with SAH attributable to an aneurysm, between 9% and 14% will have a family history of SAH in a first degree relative compared to 3-6% of age-matched controls.[12]

In family members with only one affected first-degree relative, the risk of harboring an unruptured intracranial aneurysm is approximately 4%. Family members with two or more affected first-degree relatives have an approximate 8% risk of harboring an unruptured intracranial aneurysm.[24]

Genetic studies of familial intracranial aneurysm

Organized genetic studies, such as general population-based studies or targeted at-risk-population screening studies should be conducted to assess the incidence of SAH in Saudi Arabia and the assumed more virulent nature familial SAH. However, there are several limitations to such genetic studies. Varying definitions of familial aneurysms are present in literature, implying a different genetic load in the families studied, and thus may lead to different findings.[25] The reported genetic studies assumed a mode of inheritance for which the analysis was conducted, while in reality, the mode of inheritance is unknown, and most likely heterogeneous. A factor in such heterogeneity is the multitude of syndromes associated with aneurysm formation, with one study reporting that as many of 10-15% of patients suffering from polycystic kidney disease, which is autosomal dominant, may develop an intracranial aneurysm.[26,27] Another contribution to this heterogeneity comes from the disease associated with a risk factor of aneurysm formation such as coarctation of the aorta, fibromuscular dysplasia, and pheochromocytoma. These conditions are reported to be associated with intracranial aneurysm, which is probably due to hypertension, and other abnormalities that occur in the vessel wall.[4]

Within each family, even if a member was deemed a nonaffected sibling (no aneurysm on initial screening), it is difficult to determine whether or not they are nonaffected longitudinally, because aneurysms can develop later in life.[28] Another study in relatives of affected families with a negative screen, reported the chance of developing an aneurysm within 5 years of the screening is 7%.[29]

Different populations and ethnic groups present differing risk factors for SAH due to the difference in genetic profile of these populations.[23,25,30]

Genetics of aneurysms interact with environmental factors

Familial aneurysms exhibit a different behavior in their incidence and clinical presentation, which is probably due to the different mechanisms, by which they form and progress. One can hypothesize that the process is not just genetically determined; other factors may influence the usual pathway conducive to aneurysm behavior, such as environmental factors. The interaction between environmental factors and genetics may result in a predisposition of the arterial wall to weakness, with a higher risk of developing large and multiple aneurysms in patients with familial aneurysms than in patients with sporadic aneurysms.

One study showed positive evidence for linkage on 7q11 in the vicinity of the elastin gene, another study found linkage on 19q12-13, which contains several loci related to cerebrovascular disease.[31] In our opinion, this represents a strong potential locus to study, because of the young age of the patients encountered in cerebrovascular practice in Saudi Arabia, who have more structurally complex aneurysms. Potential evidence of a gene-smoking interaction was found for chromosomes 4, 7, and 12. It was found that polymorphic variant endothelial nitric oxide synthase alleles and their corresponding genotypes were between 2 and 4 times more frequent among patients with SAH than in those with unruptured lesions, with the presence of two or three variant alleles was associated with an 8.6-11.4 increase in the odds of presenting with a ruptured brain aneurysm.[32-34] These genetic mutations could prove useful in identifying aneurysms that are at risk of rupturing and guide their therapy.[35,36] Until we know the genetics of aneurysms in our region, it is not possible to apply such findings to individuals at risk in our population.

Recommendations for screening of familial intracranial aneurysms

Recommendations regarding screening for asymptomatic, unruptured intracranial aneurysms in family members with one or more affected first-degree relatives are controversial. Previous decision analyses showed that there was no benefit of screening for asymptomatic, unruptured intracranial aneurysms in these populations.[37] Several reports however, support screening for familial aneurysms, but this is challenged in the recent literature.[38-40] It is our opinion that screening would be more beneficial in the presence of a known risk factor, such as connective tissue disease.

The familial intracranial aneurysm (FIA) study is a multicenter study, in which the primary objective is to define the susceptibility genes related to the formation of intracranial aneurysms.[33] First-degree relatives of those affected with intracranial aneurysms are offered screening with magnetic resonance (MR) angiography if they were previously unaffected, are >30 years of age, and have a history of smoking and/or hypertension. The study found that 19.1% had at least one intracranial aneurysm, and 17.2% of the affected patients had multiple aneurysms. The FIA study concluded that among the affected patients' first-degree relatives who are 30 years of age or older, those who are women or have a history of smoking or hypertension are at increased risk of suffering an intracranial aneurysm and should be strongly considered for screening. A recent cost-effective analysis study suggested that MR angiography screening for asymptomatic, unruptured intracranial aneurysms in family members with two or more first-degree relatives with aneurysmal SAH is cost-effective, especially for patients 50 years and older.[41,42]

MR angiography is evolving as a screening tool to detect intracranial aneurysms.[43,44] The interobserver agreement in defining an intracranial aneurysm in asymptomatic patients is excellent, and advances in MR angiography have further improved this interobserver agreement, even among small aneurysms.[45] Technical refinements in computed tomography (CT) angiography renders it a useful and more accessible modality of investigation to detect intracranial aneurysms.[46,47]

CONCLUSIONS AND RECOMMENDATIONS

The priority for neurosurgeons dealing with patients with SAH in Saudi Arabia is to identify the magnitude of the problem in the country by conducting countrywide collaborative screening surveys to measure the incidence and prevalence of intracranial aneurysms and SAH. This can be initiated in referral centers as well as referring hospitals in the different regions of the country. From such efforts, we can construct a registry of all aneurysm cases and focus our attention on providing the necessary resources to improve the capture of the index cases of SAH and distribute these resources in areas of need, in case such a pattern emerges with "clustering" of SAH in a specific region. Such a registry could be used as a prospective tool for longitudinal follow-up of new index cases of SAH, which are identified and treated in specialized centers. This registry would also serve to identify patients fitting the definition of familial aneurysms and facilitate the recommendation of screening when appropriate. It is our recommendation to offer screening, using MR or CT angiography to the first-degree relatives of patients with aneurismal SAH, particularly those patients who are more than 30 years of age, smokers, have a history of hypertension or of female gender. This should be followed by conventional angiography, if the results are equivocal or the diagnostic result warrants interventional treatment. The screening examinations should be repeated every 5-10 years to rule out latent development of aneurysms in these first-degree relatives. Such an approach might in some cases raise a psycho-social stress on the family member, which has to be explored with the person as a "partner-in-care." It is advisable that such a strategy is conducted within a few designated centers; each with a well-defined and

designated catchment area, to allow reliable databases to be generated and allow for efficient longitudinal follow-up of this "at-risk" population.

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Conflicts of interest

There are no conflicts of interest.

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