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

Hosam Al-Jehani1,2, Mahmoud Yamani3, Yasser Orz3, Bassem Shiekh4

1Department of Neurosurgery, King Fahd University Hospital, University of Dammam, Al-Khobar, Saudi Arabia, 2Department of Neurosurgery, King Fahad Medical City, Riyadh, 3Department of Surgery, Taibah University, Al-Madina Al-Monawarah, Saudi Arabia, 4Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University Health Centre, Montreal, Canada

Correspondence: Dr. Hosam Al-Jehani, Department of Neurosurgery, King Fahd Hospital of the University, P.O. Box 40121, Al-Khobar 31952, Saudi Arabia. E-mail: hjehani@uod.edu.sa

ABSTRACT

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

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
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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[17,18]} Familial cerebral aneurysms tend to rupture in younger patients, particularly females, than sporadic aneurysms.\textsuperscript{[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.”\textsuperscript{[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.\textsuperscript{[17,18,22]} A poor outcome of rupture is more frequent in familial cerebral aneurysms patients than in patients who experience a sporadic aneurysm.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[23]} 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.\textsuperscript{[20,27]} 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.\textsuperscript{[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.\textsuperscript{[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%.\textsuperscript{[29]}

Different populations and ethnic groups present differing risk factors for SAH due to the difference in genetic profile of these populations.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[32,34]} These genetic mutations could prove useful in identifying aneurysms that are at risk of rupturing and guide their therapy.\textsuperscript{[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.\textsuperscript{[37]} Several reports however, support screening for familial aneurysms, but this is challenged in the recent literature.\textsuperscript{[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.\textsuperscript{[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 50 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.\textsuperscript{[41,42]}

MR angiography is evolving as a screening tool to detect intracranial aneurysms.\textsuperscript{[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.\textsuperscript{[45]} Technical refinements in computed tomography (CT) angiography renders it a useful and more accessible modality of investigation to detect intracranial aneurysms.\textsuperscript{[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 aneurysmal SAH, particularly those patients who are more than 50 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.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

**REFERENCES**

1. Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: A systematic review. Stroke 1997;28:660-4.
2. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: A meta-analysis. Lancet Neurol 2009;8:635-42.
3. ter Berg HW, Dippel DW, Limburg M, Schievink WI, van Gijn J. Familial intracranial aneurysms. A review. Stroke 1992;23:1024-30.
4. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. Neurology 1998;50:1413-8.
5. Alg VS, Sofat R, Houlden H, Werring DJ. Genetic risk factors for intracranial aneurysms: A meta-analysis in more than 116,000 individuals. Neurology 2013;80:2154-65.
6. Wardlaw JM, White PM. The detection and management of unruptured intracranial aneurysms. Brain 2000;123(2Pt 2):205-21.
7. Ammar A, al-Rajeh S, Ibrahim AW, Chowdhary UM, Awada A. Pattern of subarachnoid haemorrhage in Saudi Arabia. Acta Neurochir (Wien) 1992;114:16-9.
8. Qari FA. Profile of stroke in a teaching university hospital in the western region. Saudi Med J 2000;21:1030-3.
9. al Rajeh S, Awada A, Niazi G, Larbi E. Stroke in a Saudi Arabian National Guard community. Analysis of 500 consecutive cases from a population-based hospital. Stroke 1993;24:1653-9.
10. Bokhari YA, Batari AH, Alnahdi YA, Almekhlafi MA, Baeesa SS. Aneurysmal subarachnoid hemorrhage affects the younger age groups in a Saudi academic center. Ann Saudi Med 2015;35:36-40.
11. Kissela BM, Sauerbeck L, Woo D, Khoury J, Carrozzella J, Pancioli A, et al. Subarachnoid hemorrhage: A preventable disease with a heritable component. Stroke 2002;33:1321-6.
12. Bromberg JE, Rinkel GJ, Algra A, van Duyn CM, Greebe P, Ramos LM, et al. Familial subarachnoid hemorrhage: Distinctive features and patterns of inheritance. Ann Neurol 1995;38:929-34.
13. Lozano AM, Leblanc R. Familial intracranial aneurysms. J Neurosurg 1987;66:522-8.
14. Norgård Ø, Angquist KA, Fodstad H, Forsell A, Lindberg M. Intracranial aneurysms and heredity. Neurosurgery 1987;20:236-9.
15. ter Berg HW, Bijlsma JB, Veiga Pires JA, Ludwig JW, van der Heiden C, Tulleken CA, et al. Familial association of intracranial aneurysms and multiple congenital anomalies. Arch Neurol 1986;43:30-3.
16. Wills S, Ronkainen A, van der Voet M, Kuivaniemi H, Helin K, Leinonen E, et al. Familial intracranial aneurysms: An analysis of 346 multiplex Finnish families. Stroke 2003;34:1370-4.
17. Leblanc R. Familial cerebral aneurysms. Can J Neurol Sci 1997;24:191-9.
18. Ruijgrok YM, Rinkel GJ, Algra A, Raaymakers TW, Van Gijn J. Characteristics of intracranial aneurysms in patients with familial subarachnoid hemorrhage. Neurology 2004;62:891-4.
19. Broderick JP, Brown RD Jr, Sauerbeck L, Hornung R, Huston J 3rd, Woo D, et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. Stroke 2009;40:1952-7.
20. Stehbens WE. The pathology of intracranial arterial aneurysms and their complication. In: Fox JL, editor. Intracranial Aneurysms. New York: Springer-Verlag; 1983.
21. Pope FM, Nicholls AC, Narcisi P, Bartlett J, Neil-Dwyer G, Doshi B. Some patients with cerebral aneurysms are deficient in type III collagen. Lancet 1981;1:975-3.
22. Leblanc R. Familial cerebral aneurysms. A bias for women. Stroke 1996;27:1050-4.
23. Ruijgrok YM, Rinkel GJ, Wijmenga C. Familial intracranial aneurysms. Stroke 2004;35:59-60.
24. Rinkel GJ. Intracranial aneurysm screening: Indications and advice for practice. Lancet Neurol 2005;4:122-8.
25. Ruijgrok YM, Rinkel GJ. Genetics of intracranial aneurysms. Stroke 2008;39:1049-55.
26. Chapman AB, Johnson AM, Gabow PA. Intracranial aneurysms in patients with autosomal dominant polycystic kidney disease: How to diagnose and who to screen. Am J Kidney Dis 1993;22:526-31.
27. Chapman AB, Rubinstein D, Hughes R, Stears IC, Earnest MP, Johnson AM, et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. N Engl J Med 1992;327:916-20.
28. Brunneau M, Rynkowski M, Smida-Rynkowska K, Brodchi J, De Witte O, Lubicz B. Long-term follow-up survey reveals a high yield, up to 30% of patients presenting newly detected aneurysms more than 10 years after ruptured intracranial aneurysms clipping. Neurosurg Rev 2011;34:485-96.
29. Wermter MJ, Rinkel GJ, van Gijn J. Repeated screening for intracranial aneurysms in familial subarachnoid hemorrhage. Stroke 2005;34:2788-91.
30. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: An updated systematic review of epidemiological studies. Stroke 2005;36:2773-80.
31. Onda H, Kasuya H, Yoneyama T, Takakura K, Hori T, Takeda J, et al. Genomewide-linkage and haplotype-association studies map intracranial aneurysm to chromosome 7q11. Am J Hum Genet 2001;69:804-19.
32. Olson JM, Vongpunsawad S, Kuivaniemi H, Ronkainen A, Johnson AM. Some patients with cerebral aneurysms are deficient in type III collagen. Lancet 1981;1:975-3.
33. Foroud T, Sauerbeck L, Knox CM, Greebe P, Ramos LM, et al. Familial intracranial aneurysms: A review. Stroke 1992;23:1024-30.
34. Khurana VG, Meissner I, Sohni YR, Bamiel WR, McClelland RL, Cunningham JM, et al. The presence of tandem endothelial nitric oxide synthase gene polymorphisms identifying brain aneurysms more prone to rupture. J Neurosurg 2005;102:326-31.
35. Yasuno K, Bakircioğlu M, Low SK, Bilgävar K, Gaál E, Ruijgrok YM, et al. Common variant near the endothelin receptor type A (EDNRA) gene is associated with intracranial aneurysm risk. Proc Natl Acad Sci U S A 2011;108:19707-12.
36. Nahed BV, Bydon M, Ozturk AK, Bilguvar K, Bayrakli F, Gunel M. Genetics of intracranial aneurysms. Neurosurgery 2007;60:213-25.
37. Kirkpatrick PJ, McConnell RS. Screening for familial intracranial aneurysms. BMJ 1999;319:1512-3.
38. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, et al. Recommendations for the management of patients with unruptured intracranial aneurysms: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2000;31:2742-50.
39. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, et al. Recommendations for the management of patients with unruptured intracranial aneurysms: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Circulation 2000;102:2500-8.
40. Bor AS, Rinkel GJ, van Norden J, Wermers MJ. Long-term, serial screening for intracranial aneurysms in individuals with a family history of aneurysmal subarachnoid haemorrhage: A cohort study. Lancet Neurol 2014;13:585-92.
41. Brown RD Jr, Huston J, Hornung R, Foroud T, Kallmes DF, Kleindorfer D, et al. Screening for brain aneurysm in the Familial Intracranial Aneurysm study: Frequency and predictors of lesion detection. J Neurosurg 2008;108:1132-8.
42. Takao H, Nojo T, Ontomo K. Screening for familial intracranial aneurysms: Decision and cost-effectiveness analysis. Acad Radiol 2008;15:462-71.
43. Sohn CH, Sevick RJ, Frayne R. Contrast-enhanced MR angiography of the intracranial circulation. Magn Reson Imaging Clin N Am 2003;11:599-614.
44. Bomsans H, Marchal G, Van Hecke P, Vanhoenacker P. MRA review. Clin Imaging 1992;16:152-67.
45. Gibbs GF, Huston J 3rd, Bernstein MA, Riederer SJ, Brown RD Jr. 3.0-Tesla MR angiography of intracranial aneurysms: Comparison of time-of-flight and contrast-enhanced techniques. J Magn Reson Imaging 2005;21:97-102.
46. Green D, Parker D. CTA and MRA: Visualization without catheterization. Semin Ultrasound CT MR 2003;24:185-91.
47. Göltz P, Struffert T, Knossalla F, Saake M, Ott S, Ganslandt O, et al. Angiographic CT with intravenous contrast injection compared with conventional rotational angiography in the diagnostic work-up of cerebral aneurysms. AJNR Am J Neuroradiol 2012;33:982-7.