

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Serum Homocysteine and Intracranial Aneurysms

*Mei-Ling Sharon Tai, Tsun Haw Toh, Hafez Hussain  
and Kuo Ghee Ong*

## Abstract

Subarachnoid haemorrhage (SAH) occurs as a result of rupture of intracranial aneurysms. SAH causes significant morbidity and mortality. In addition, SAH leads to significant financial burden. In this chapter, we will look into the association between raised serum homocysteine and intracranial aneurysms. In a study on the Han Chinese patients with intracranial aneurysm who were admitted to the hospital, the mean serum total homocysteine level in the patient group with intracranial aneurysm was significantly higher than those in the control group. In the same study, the patients with raised serum homocysteine had 2.196 higher risk of developing intracranial aneurysms. Ren et al. proposed that homocysteine should be seen as an indicator of the risk of intracranial aneurysm and not a direct cause of intracranial aneurysm. In another study, homocysteine increases the development of intracranial aneurysms in rats. Endothelial damage is an early change in the walls of intracranial aneurysms. Polymorphisms of the genes coding for the various components of the vessel walls may be associated with the formation of intracranial aneurysms. In a previous animal study, the size of intracranial aneurysms is significantly smaller in the mice with inducible nitric oxide synthase (iNOS) compared with the mice without iNOS.

**Keywords:** homocysteine, aneurysm, intracranial, serum, subarachnoid haemorrhage

## 1. Introduction

### 1.1 Subarachnoid haemorrhage

Subarachnoid haemorrhage (SAH) is caused by rupture of intracranial aneurysms [1, 2]. Approximately 5–15% of the stroke patients have ruptured intracranial aneurysms [3, 4].

Aneurysmal SAH leads to a prolonged hospital stay [1]. Therefore, aneurysmal subarachnoid haemorrhage results in a significant financial burden in the USA [1]. In addition, aneurysmal SAH causes approximately 45% mortality in 30 days [3, 5]. As many as 30% of the patients who survived the SAH had moderate to severe neurological deficit and disability [3, 5].

## 1.2 Intracranial aneurysms

Saccular intracranial aneurysms are abnormal focal outpouchings of cerebral arteries [3]. The prevalence of intracranial aneurysms in the adult population in the USA is 1–5% [3, 6]. Most of the intracranial aneurysms are small [3]. Approximately 50–80% of all the intracranial aneurysms do not rupture [3, 7].

Intracranial aneurysms are usually sporadically acquired lesions [3]. A rare familial form is present, and this is associated with conditions such as cerebral arteriovenous malformations (AVMs), autosomal dominant polycystic kidney disease (ADPKD), fibromuscular dysplasia, Marfan syndrome and Ehlers-Danlos syndrome [3, 5]. Multiple genetic susceptibilities may be acting synergistically in the development of SAH [5, 8]. The increase in the familial risk of developing SAH is nearly four times higher among first-degree relatives [5, 9, 10].

Unruptured aneurysms can potentially result in cranial nerve palsies such as third cranial nerve palsy and rarely brainstem compression [3, 7, 11]. These patients have a higher risk of rupture of intracranial aneurysm [3, 7]. They have an annual risk of aneurysmal rupture of about 6% [3, 12].

## 1.3 Homocysteine

Homocysteine is an endogenous, nonstructural protein which contains sulphur [13]. Homocysteine is involved in the metabolism pathway of methionine and cysteine [13, 14]. Homocysteine can be irreversibly degraded to cysteine via the trans-sulphuration pathway or remethylated back to methionine [15]. The biochemistry of methionine is regulated by the enzymes controlling homocysteine concentration [15]. An elevated level of serum homocysteine is the intermediate product of methionine metabolism [16].

In addition, the metabolism of homocysteine is dependent on nutritional factors comprising of vitamin B<sub>12</sub> and folic acid [16, 17]. A reduction in the levels of vitamin B<sub>12</sub> and folic acid causes an increase in serum homocysteine levels [16]. Homocysteine also plays an important role in the metabolism of folic acid and catabolism of choline which are both vital for the regulation of methionine [15]. Homocysteine is very important for the cellular homeostasis [15].

Normal level of total concentration of homocysteine in plasma of healthy people is between 5.0 and 15.0 mmol/l. [13] Raised serum homocysteine is an independent risk factor for cardiovascular diseases [13, 15, 18]. Elevated serum homocysteine is associated with a rise in morbidity and mortality [18, 19].

An increase in serum homocysteine results in oxidative stress and systemic inflammation which in turn leads to an accelerated telomere shortening [13, 19]. Furthermore, elevated serum homocysteine damages endothelial cells [13]. As a result, the blood vessels are less flexible and the process of haemostasis is disturbed [13]. **An increase in serum homocysteine can be treated by folic acid, vitamin B12 and vitamin B6 supplements** [13, 15].

## 2. Homocysteine and intracranial aneurysm

Ren et al. conducted a study on the Han Chinese patients with intracranial aneurysm who were admitted to the hospital [17]. In this study, the mean serum total homocysteine level in the patient group with intracranial aneurysm was significantly higher than those in the control group [17]. In addition, homocysteine had an adjusted odds ratio of 2.196 ( $P = 0.012$ ) for the development of intracranial aneurysm [17].

Furthermore, raised serum homocysteine was reported to be an independent risk factor for development of intracranial aneurysms [17]. Ren et al. proposed that homocysteine should be seen as an indicator of the risk of intracranial aneurysm and not a direct cause of intracranial aneurysm [17].

In the same study, an association between serum total homocysteine and folate and vitamin B<sub>12</sub> in the patients with intracranial aneurysm was present [17]. The serum total homocysteine level was negatively correlated with folate and vitamin B<sub>12</sub> levels in the study by Ren et al. [17]. Folic acid and vitamin B<sub>12</sub> are therefore found to be protective against formation of intracranial aneurysms [17]. This is due to the roles of vitamin B<sub>12</sub> and folic acid in the regulation of the metabolism of homocysteine [17]. In a previous study, insufficient plasma level of one or more B vitamins may potentially result in high levels of serum homocysteine [16].

In the study conducted by Xu et al., homocysteine increases the development of intracranial aneurysms in rats, possibly by the different effects on the expression of molecules which are essential for vascular wall modeling [20]. The formation of intracranial aneurysms is associated with chronic inflammation [20].

Endothelial damage is one of the early changes in the walls of intracranial aneurysms resulting from inflammation [20]. An increase in serum homocysteine has been reported to damage the vascular endothelium [20]. This in turn leads to the development of atherosclerosis [20].

### 3. Polymorphism

Interestingly, polymorphism of the genes coding for the various components of the vessel walls has been proposed to be associated with the development of intracranial aneurysms [5, 8].

Polymorphisms involving homocysteine metabolism can also promote formation of abdominal aortic aneurysms, dissection of the cervical arteries and atherosclerosis [5, 21, 22].

Moreover, the expression of matrix metalloproteinase-2 (MMP-2), endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF) and MMP-2 in the walls of intracranial aneurysm was increased by methionine treatment in Xu et al.'s study [20].

Furthermore, autosomal recessive deficiency in cystathionine-synthase is involved in homocysteine metabolism [5, 23]. This deficiency in cystathionine-synthase presents together with the development of intracranial aneurysms [5, 23].

In the study by Semmler et al., polymorphisms of homocysteine metabolism are possible risk factors for the formation of intracranial aneurysms [5]. The G-allele of RFC1c.80G→A and the insertion allele of DHFRc.594 + 59del19bp polymorphisms may result in intracranial aneurysm formation [5]. The G-allele of the missense polymorphism Tc2c.777C→G may protect from the development of intracranial aneurysm [5]. This G-allele of the Tc2c.777C→G polymorphism has been reported to affect the vitamin B<sub>12</sub> binding affinity and the ability to transport vitamin B<sub>12</sub> into tissues [5, 24–26]. This causes a decrease in remethylation of homocysteine to methionine by vitamin B<sub>12</sub>-dependent MTR [5, 24–26].

### 4. Role of nitric oxide in homocysteine metabolism

Impairment of homocysteine metabolism may lead to an accumulation of asymmetric dimethylarginine [27, 28]. Asymmetric dimethylarginine is a major

endogenous inhibitor of nitric oxide (NO) and is a good predictor of early cardiovascular diseases and mortality [27–30]. In addition, the availability of NO is a major requirement for the development of intracranial aneurysms [5, 31].

In an animal study conducted in rodents, the development of intracranial aneurysm was prevented by inhibition of nitric oxide synthase (NOS) [5, 31]. Inducible nitric oxide synthase (iNOS) is expressed in human and rat cerebral aneurysms [2]. In another animal study, the size of intracranial aneurysms is significantly smaller in the mice with iNOS compared to the mice without iNOS [2, 5].

Aminoguanidine is a relatively selective inhibitor of iNOS [2]. Aminoguanidine reduces the number of the aneurysms in rats [2]. In the study by Sadamasa et al., iNOS possibly has management potential in the prevention of the progression of cerebral aneurysms, though it is not necessary for the initiation of cerebral aneurysm [2].

However, in another study, there was no association between homocysteine and intracranial aneurysms. Notably, this study was conducted comparing a case group (patients with intracranial aneurysms) with a control group consisting of patients with arteriovenous malformation (AVM) as well as no aneurysms [14].

## **5. Management**

Raised serum homocysteine can be properly managed with dietary changes [17]. An increase in serum homocysteine can be treated by folic acid, vitamin B<sub>12</sub> and vitamin B<sub>6</sub> supplements [13, 15]. Folic acid and vitamin B<sub>12</sub> supplements can prevent the development and progression of intracranial aneurysm [17].

## **6. Conclusion**

In conclusion, we believe that there is association between raised serum homocysteine and development or progression of intracranial aneurysms. In the future, more case-control research studies can be conducted to compare the patients with intracranial aneurysms and patients without intracranial aneurysms and AVM.

## **Acknowledgements**

We would like thank Dr. Abdul Rashid Mat Mahidin, Dr. Esther Yeow Kar Mun, Dr. Lattish Rao Threemurthy and Dr. Parathythasan a/l Rajaandra for their help.

## **Funding source**

This chapter is supported by the University of Malaya UMCares grant RU013-2017C.

IntechOpen

### **Author details**

Mei-Ling Sharon Tai<sup>1\*</sup>, Tsun Haw Toh<sup>1</sup>, Hafez Hussain<sup>2</sup> and Kuo Ghee Ong<sup>2</sup>

1 Division of Neurology, Department of Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia

2 SOCSO Tun Razak Rehabilitation Centre, Melaka, Malaysia

\*Address all correspondence to: [sharont1990@gmail.com](mailto:sharont1990@gmail.com)

### **IntechOpen**

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Modi S, Shah K, Schultz L, Tahir R, Affan M, Varelas P. Cost of hospitalization for aneurysmal subarachnoid hemorrhage in the United States. *Clinical Neurology and Neurosurgery*. 2019;**182**:167-170
- [2] Sadamasu N, Nozaki K, Hashimoto N. Disruption of gene for inducible nitric oxide synthase reduces progression of cerebral aneurysms. *Stroke*. 2003;**34**:2980-2984
- [3] Brisman JL, Song JK, Newell DW. Cerebral aneurysms. *The New England Journal of Medicine*. 2006;**355**:928-939
- [4] Bederson JB, Awad IA, Wiebers DO, 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**:2742-2750
- [5] Semmler A, Linnebank M, Krex D, Götz A, Moskau S, Ziegler A, et al. Polymorphisms of homocysteine metabolism are associated with intracranial aneurysms. *Cerebrovascular Diseases*. 2008;**26**(4):425-429
- [6] Wiebers DO, Whisnant JP, Huston J III, et al. Unruptured intracranial aneurysms: Natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;**362**:103-110
- [7] Connolly ES, Solomon RA. Management of unruptured aneurysms. In: Le Roux PD, Winn HR, Newell DW, editors. *Management of Cerebral Aneurysms*. Philadelphia: Saunders; 2004. pp. 271-285
- [8] Ruigrok YM, Rinkel GJ, Wijmenga C. Genetics of intracranial aneurysms. *Lancet Neurology*. 2005;**4**:179-189
- [9] Teasdale GM, Wardlaw JM, White PM, Murray G, Teasdale EM, Easton V. The familial risk of subarachnoid haemorrhage. *Brain*. 2005;**128**:1677-1685
- [10] Schievink WI, Schaid DJ, Michels VV, Piepgras DG. Familial aneurysmal subarachnoid hemorrhage: A community-based study. *Journal of Neurosurgery*. 1995;**83**:426-429
- [11] Schievink WI. Intracranial aneurysms. *The New England Journal of Medicine*. 1997;**336**:28-40
- [12] Wiebers DO, Whisnant JP, Sundt TM Jr, O'Fallon WM. The significance of unruptured intracranial saccular aneurysms. *Journal of Neurosurgery*. 1987;**66**:23-29
- [13] Baszczuk A, Kopczyński Z. Hyperhomocysteinemia in patients with cardiovascular disease. *Postępy Higieny i Medycyny Doświadczalnej (Online)*. 2014;**68**:579-589
- [14] Rosi J, Morais BA, Pecorino LS, Oliveira AR, Solla DJF, Teixeira MJ, et al. Hyperhomocysteinemia as a risk factor for intracranial aneurysms: A case-control study. *World Neurosurgery*. 2018;**119**:e272-e275
- [15] Tinelli C, Di Pino A, Ficulle E, Marcelli S, Feligioni M. Hyperhomocysteinemia as a risk factor and potential nutraceutical target for certain pathologies. *Frontiers in Nutrition*. 2019;**6**:49
- [16] Selhub J, Jacques PF, Wilson PW, et al. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA*. 1993;**270**:2693-2698
- [17] Ren JR, Ren SH, Ning B, Wu J, Cao Y, Ding XM, et al. Hyperhomocysteinemia as a risk factor for saccular intracranial

aneurysm: A cohort study in a Chinese Han population. *Journal of Stroke and Cerebrovascular Diseases*. 2017;**26**(12):2720-2726

[18] Azad MAK, Huang P, Liu G, Ren W, Teklebrh T, Yan W, et al. Hyperhomocysteinemia and cardiovascular disease in animal model. *Amino Acids*. 2018;**50**(1):3-9

[19] Pusceddu I, Herrmann W, Kleber ME, Scharnagl H, Hoffmann MM, Winklhofer-Roob BM, et al. Subclinical inflammation, telomere shortening, homocysteine, vitamin B<sub>6</sub>, and mortality: The Ludwigshafen Risk and Cardiovascular Health Study. *European Journal of Nutrition*. 2019;**25**. [Epub ahead of print]

[20] Xu Y, Tian Y, Wei HJ. Methionine diet-induced hyperhomocysteinemia accelerates cerebral aneurysm formation in rats. *Neuroscience Letters*. 2011;**494**:139-144

[21] Casas JP, Bautista LE, Smeeth L, Sharma P, Hingorani AD. Homocysteine and stroke: Evidence on a causal link from Mendelian randomisation. *Lancet*. 2005;**365**:224-232

[22] Arauz A, Hoyos L, Cantu C, Jara A, Martinez L, Garcia I, et al. Mild hyperhomocysteinemia and low folate concentrations as risk factors for cervical arterial dissection. *Cerebrovascular Diseases*. 2007;**24**:210-214

[23] Yap S, Boers GH, Wilcken B, Wilcken DE, Brenton DP, Lee PJ, et al. Vascular outcome in patients with homocystinuria due to cystathionine beta-synthase deficiency treated chronically: A multicenter observational study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2001;**21**:2080-2085

[24] Afman LA, Lievers KJ, van der Put NM, Trijbels FJ, Blom HJ. Single nucleotide polymorphisms in the

transcobalamin gene: Relationship with transcobalamin concentrations and risk for neural tube defects. *European Journal of Human Genetics*. 2002;**10**:433-438

[25] Afman LA, van der Put NM, Thomas CM, Trijbels JM, Blom HJ. Reduced vitamin B<sub>12</sub> binding by transcobalamin II increases the risk of neural tube defects. *QJM*. 2001;**94**:159-166

[26] Miller JW, Ramos MI, Garrod MG, Flynn MA, Green R, Transcobalamin II. 775G 1 C polymorphism and indices of vitamin B<sub>12</sub> status in healthy older adults. *Blood*. 2002;**100**:718-720

[27] Ito A, Tsao PS, Adimoolam S, Kimoto M, Ogawa T, Cooke JP. Novel mechanism for endothelial dysfunction: Dysregulation of dimethylarginine dimethylaminohydrolase. *Circulation*. 1999;**99**:3092-3095

[28] Stuhlinger MC, Tsao PS, Her JH, Kimoto M, Balint RF, Cooke JP. Homocysteine impairs the nitric oxide synthase pathway: Role of asymmetric dimethylarginine. *Circulation*. 2001;**104**:2569-2575

[29] Schnabel R, Blankenberg S, Lubos E, Lackner KJ, Rupprecht HJ, Espinola-Klein C, et al. Asymmetric dimethylarginine and the risk of cardiovascular events and death in patients with coronary artery disease: Results from the AtheroGene study. *Circulation Research*. 2005;**97**:e53-e59

[30] Cooke JP. Asymmetrical dimethylarginine: The uber marker? *Circulation*. 2004;**109**:1813-1818

[31] Fukuda S, Hashimoto N, Naritomi H, Nagata I, Nozaki K, Kondo S, et al. Prevention of rat cerebral aneurysm formation by inhibition of nitric oxide synthase. *Circulation*. 2000;**101**:2532-2525