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Serum Homocysteine and Intracranial Aneurysms

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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 B₁₂ and folic acid [16, 17]. A reduction in the levels of vitamin B₁₂ 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 B₁₂ in the patients with intracranial aneurysm was present [17]. The serum total homocysteine level was negatively correlated with folate and vitamin B₁₂ levels in the study by Ren et al. [17]. Folic acid and vitamin B₁₂ are therefore found to be protective against formation of intracranial aneurysms [17]. This is due to the roles of vitamin B₁₂ 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 B₁₂ binding affinity and the ability to transport vitamin B₁₂ into tissues [5, 24–26]. This causes a decrease in remethylation of homocysteine to methionine by vitamin B₁₂-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 B₁₂ and vitamin B₆ supplements [13, 15]. Folic acid and vitamin B₁₂ 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.

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