Hyperhomocysteine in stroke patients

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Abstract

Homocysteine, an amino acid, has atherogenic and prothrombotic properties by inducing vascular injury via several mechanisms. High homocysteine levels were found in ischemic stroke patients and was associated with early death in the acute period, but not in the outcome of stroke patients. Hyperhomocysteinemia is associated with large vessels stroke subtype and may be a risk factor of stroke. Vitamin therapy especially vitamin B12 and folate may reduce the risk of recurrent stroke. *(J Thai Stroke Soc 2015; 14: 44-49.)*

Homocysteine is an amino acid, formed by the conversion of methionine to cysteine. It is metabolized by 2 divergent pathways: transsulfuration and remethylation. The transsulfuration of homocysteine to cysteine is catalyzed by cystathionine-β-synthase. This process requires pyridoxal phosphate (vitamin B_6) as a cofactor. Remethylation of homocysteine produces methionine. This reaction is catalyzed by methionine synthase or betaine-homocysteine methyltransferase. Vitamin B_{12} is the cofactor for methionine synthase. Elevation of plasma homocysteine occurred in 5-7 percent of general population[1] and may be an independent risk factor for atherosclerotic vascular disease and/or thromboembolism. High plasma homocysteine concentration can be found in those who have genetic defects in the enzyme involved in homocysteine metabolism[2], nutritional deficiencies in vitamin cofactors[3] or other factors including some chronic medical conditions[4] or drugs[5-7](Table 1). The most common form of genetic hyperhomocysteinemia results from production of a thermolabile variant of methylene tetrahydrofolate reductase (MTHFR) with reduce enzymatic activity (C677T mutation) [8]. Homozygous MTHFR genotype is relatively common (5-14% in general population) and causes mild elevation of plasma homocysteine and correlates with low serum folate levels[9]. Plasma folate and vitamin B_{12} levels are the strong determinants of the homocysteine concentration. Homocysteine levels are inversely related to folate consumption. However, this reaches a stable baseline level even folate intake exceeds 400µg/day. Suboptimal vitamin B12 intake with poor absorption might cause elevation of plasma homocysteine concentration[10].

Homocysteine has atherogenic and prothrombotic properties. Homocysteine may induce vascular injury via several mechanisms[11]:

- Homocysteine promotes leukocyte recruitment by upregulating monocyte chemoattractant protein-1 and interleukin -8 expression and secretion.
- The thiolactone metabolite of homocysteine can combine with LDL cholesterol to produce aggregates that are taken up by vascular macrophages in arterial intimal. These foam cells may release the lipid into atherosclerotic plaques.
- Homocysteine increases smooth muscle cell proliferation and enhances collagen production.
- Prothombotic effects include attenuation of endothelial cell tissue plasminogen activator binding sites, activation of factor V and VIIa, inhibition of protein and heparin sulfate, increased fibrinopeptide A and prothrombin fragment 1 and 2, blood viscosity, and decreased endothelial antithrombotic activity due to changes in thrombomodulin function.
- Oxidative stress, by free radicals formed during the oxidation of reduced homocysteine, may direct injure endothelial cells.
- Marked platelet accumulation may be due to direct proaggregatory effect of homocysteine or impairment in endothelium mediated platelet inhibition.
- Prolong exposure of endothelial cells to homocysteine reduces the activity of dimethylarginine dimethylaminohydrolase. This enzyme degrades asymmetric demethylarginine, an endogenous inhibitor of nitric oxide synthase which impairs the production of nitric oxide and contributes to impaired endothelium dependent vasodilation.

Diagnosis of hyperhomocysteinemia

Sensitive assays allow quantification of the tHcy concentration. Approximately 75-85% of homocysteine is protein bound and 15-25% is in acid-soluble free forms[12]. Normal homocysteine concentration ranges between 5-15 µmol/L. Hyperhomocysteinemia is commonly defined according to arbitrary cut-off points (95th percentile) in the distribution of total homocysteine (tHcy) values obtained from the so-called 'normal' population. In some studies, hyperhomocysteinemia has been classified as follows[13]:

- Moderate (15-30 µmol/L)
- Intermediate (30-100 µmol/L)
- Severe (>100 µmol/L)

In Thailand, there was a study demonstrating that the abnormal cut-off point is more than 14 µmol/L[14].

The relationship between homocysteine and stroke

Several studies demonstrated that mean plasma homocysteine concentration is significantly higher in ischemic stroke patients when compared to normal control.[14-16] In acute phase of ischemic stroke, the elevation of plasma homocysteine has positive correlation with the expression of oxidative stress markers and negative correlation with indicators of protective anti-stress activity[17]. A significant increase of antioxidant activity occurred at the first 24 hours after onset and the decreased levels occurred at 1 month later and changes were associated with the severity of clinical conditions. The extent of homocysteine, oxidative stress marker reduction and the contemporary increase in anti-stress biochemical activities were associated with a reduction of NIHSS scores. These findings suggest a role for homocysteine as a potentially modifiable biochemical substance being able to modulate some mechanisms involved in the pathogenesis of ischemic damage. This concluded that hyperhomocysteinemia may be a risk factor for ischemic stroke. Bokhari, et al studied serial changes in plasma homocysteine in acute clinical stroke, and found that average homocysteine levels initially decrease and then gradually rise in stroke patients, especially patients with hemorrhagic stroke after 48 hours of onset[18]. Serum levels of homocysteine were determined as an independent predictor for mortality in the first week but do not affect the functional outcome of alive patients[19]. Tantirittisak T, et al. showed that hyperhomocysteine is associated with a subtype of stroke which is more pronounced in large vessel disease than small vessel disease[14].

A meta-analysis by the Homocysteine Studies Collaboration examined 30 prospective and retrospective observational studies of 16,786 healthy individuals. They founded that, a 25% higher than normal of plasma homocysteine concentration (~3μM/L or 0.41 mg/L) was associated with an 11% higher incidence of ischemic heart disease (OR 0.89, 95%CI 0.83-0.96) and a 19% higher incidence of stroke (OR 0.81, 95%CI 0.69-0.95)[20]. Large observational studies correlating diet with long term risk of vascular events among more than 50,000 healthy individuals indicated that a decrease dietary intake of folate is associated with an increased risk of ischemic stroke and cardiovascular events, independent of major lifestyle and other dietary factors[21]. People with MTHFR TT genotype have a significantly greater mean tHcy concentration and risk of stroke than people with the MTHFR CC genotype[22].

Many trials have indicated that administration of folic acid, vitamin B_6 and vitamin B_{12} decreased serum homocysteine concentration. However, some of these studies failed to demonstrate a direct correlation between vitamin intake and lowered risk for cardio- and cerebrovascular events. The Vitamin Intervention for Stroke Prevention trial (VISP) showed no significant reduction in stroke recurrence between the group that received a low dose vitamin formulation (200μg B_6, 6μg B_{12}, 20μg folic acid) and that received a high dose formulation(25mg B_6, 0.4 mg B_{12}, 2.5mg folic acid)[23]. There was a modest difference in the reduction of tHcy between 2 groups. The explanation for this failure was the very low baseline plasma vitamin B_{12} levels. After excluding the patients that would have causes of low vitamin B_{12} levels, the result showed that stroke incidence in the high dose formula group was almost 21% lower than in the other group, suggesting a beneficial effect of high dose vitamin B_{12} (p=0.049)[24]. Heart Outcomes Prevention Evaluation 2 trial (HOPE-2)[25] and Norwegian Vitamin (NORVIT)[26] trial demonstrated a beneficial effect of folic acid, vitamin B_6 and vitamin B_{12} on plasma homocysteine concentration. The HOPE-s trial indicated that overall stroke incidence (0.88/100 person-years) was lower in the vitamin group when compared to placebo group (1.15/100 person-years) (HR 0.75, 95%CI 0.59-0.97). Vitamin therapy also reduced risk of nonfatal stroke (HR 0.72, 95%CI 0.54-0.95) but did not impact on neurological deficit at 24 hours (p=0.45) or functional outcome at discharge or at 7 days (OR 0.95, 95%CI 0.57-1.56). Results of HOPE-2 trial indicated that vitamin therapy could be beneficial for some particular categories: persons younger than 69 years (untreated dyslipidemia, no medication for coagulopathies), patients with hyperhomocysteinemia, and people from countries where there is no regulation regarding food enrichment with folic acid. A recent meta-analysis study demonstrated that homocysteine lowering therapy could be beneficial in patients with vascular disease in early stages and could be more successful in men than in women[27].

Conclusion

High plasma homocysteine can be found in some stroke patients. Due to its atherothrombotic effect, homocysteine would be an independent risk factor or a marker of ischemic process. Treatment with vitamin B6, B12 and folate could be safe and cost effective in prevention of stroke and cardiovascular diseases.

Table1: *Causes of hyperhomocysteinemia*[11]

Genetic factors	MTHFR TT genotype Heterozygosity for cystathionine β-synthase defects
Physiological factors	Increasing age Male sex Menopause Reduced glomerular filtration rate Increasing muscle mass
Lifestyle factors	Reduced vitamin intake Smoking Coffee Alcohol consumption Physical inactivity
Disease states	Vitamin deficiency Renal failure Hypothyroidism Diabetes mellitus Psoriasis Malignancies
Drugs	Lipid lowering : Cholestyramine, nicotinic acid, fibric acid derivatives Anticonvulsants : Phenytoin, carbamazepine Sex hormone : Androgen Antirheumatic drugs : Methotrexate Others : Ciclosporin, diuretics, levodopa, methionine-loading (oral , intravenous, peritoneal), theophylline, trimethoprim

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บทคัดย่อ

โฮโมซีสเตอีน เป็นกรดอะมิโนชนิดที่มีผลต่อการเกิดภาวะหลอดเลือดตีบตัน โดยทำให้เกิดการอักเสบของผนังหลอดเลือดผ่านขบวนการต่างๆ ระดับโฮโมซีสเตอีนที่สูงในผู้ป่วยโรคหลอดเลือดสมองตีบและอุดตันในระยะเฉียบพลัน พบว่ามีความสัมพันธ์กับการเพิ่มอัตราการเสียชีวิต และมักพบในผู้ป่วยที่มีการตีบตันของหลอดเลือดสมองขนาดใหญ่ แต่ไม่สัมพันธ์กับความพิการของผู้ป่วย มีการศึกษาโดยการให้วิตะมินปริมาณสูงกับผู้ป่วยโรคหลอดเลือดสมองตีบและอุดตันที่มีภาวะโฮโมซีสเตอีนสูงเทียบกับกลุ่มที่ได้รับวิตะมินปริมาณต่ำ พบว่าในกลุ่มที่ได้รับวิตะมินปริมาณสูงมีอัตราการเกิดเป็นซ้ำของภาวะโรคหลอดเลือดสมองตีบและอุดตันน้อยกว่า การให้วิตะมินเสริมอาจมีประโยชน์ในการป้องกันการเกิดเป็นซ้ำของโรคหลอดเลือดสมอง