Hyperhomocysteinemia with Recurrent Ischemic Stroke in Young: Truth or Myth?
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1. Abstract
Stroke in young is now a major health concern in developing countries along with Coronary Artery Disease (CAD). Among the undetermined etiological factors thrombophilic disorders constitute 60% cases of stroke. Hyperhomocysteinemia is generally acknowledged as a treatable risk factor for atherothrombotic diseases, but a causal relationship between both is not yet definitively established. It has been associated with various vascular diseases including premature peripheral vascular, cerebrovascular, and coronary artery disease. It originates from a deviation in the methionine-homocysteine metabolism including disturbances of enzymes, vitamin deficiencies and different other factors. Observational studies, genetic polymorphism studies and several meta-analyses implicate already a causal relation between homocysteine and cerebrovascular diseases. Hyperhomocysteinemia leads to oxidative damage to the vascular endothelium and proliferation of the vascular smooth muscles which create a prothrombotic condition, and contributes to the development of premature atherosclerosis. It is useful to determine homocysteine levels for stroke who present no clue for vascular disease and thrombosis, who have an ischemic stroke at a young age and who have a family history of premature atherosclerosis. Here in we present a 45-year-old male presented with recurrent ischemic stroke, on evaluation hyperhomocysteinemia is noticed. In this case hyperhomocysteinemia seems to be the only risk factor responsible for stroke.

2. Introduction
Stroke is one of the foremost causes of morbidity and mortality throughout the world, posing a major socio-economic challenge in the occupational and neuro-rehabilitational programmes for ‘stroke-survivors.’ Stroke in young adults occurs in individuals less than 45 years of age and accounts for 10% of all strokes [1]. Numerous risk factors for stroke have been identified and modification of these factors is the crux of primary and secondary prevention [2]. Despite recent advances, only two-third of all strokes can be attributed to known causal risk factors [3]. Large Clinical Trials of LDL cholesterol-lowering therapy reported adverse events in up to 19% of patients, despite this powerful intervention. This observation has intensified the search for ‘new non lipid’ risk factors for Atherosclerotic Vascular Disease (ASVD) [4]. Recently, there has been much interest in homocysteine, a sulfur containing amino acid as an important risk factor for vascular diseases including stroke, independent of the long-recognized factors like dyslipidemia, hypertension, diabetes mellitus, and smoking, [5] although its association was described many decades ago [6]. During the last decade, numerous studies observed a strong positive correlation between hyperhomocysteinemia and ischemic stroke [7–12] while others couldn’t establish the same [13,14].

3. Case report
A 45-year-old gentleman with history of old ischemic stroke with residual right hemiparesis (for 15 years), not known to have diabetes mellitus, hypertension, ischemic heart disease or obstructive airway disease presented with left sided weakness and restlessness for 1 day. He has been smoking one pack of cigarettes a day for the last 20 years. No alcohol or other substances abuses were reported. There was no history of loss of consciousness, convulsion, vomiting, headache, fever, swallowing or speech difficulties. There was no family history of cerebrovascular disease. His elder brother had history of premature cardiovascular disease. On general examination – no significant abnormality was noticed. He was hemodynamically stable. Detailed neurological examination – higher intellectual functions, cranial nerves sensory system – normal. Motor system – power of left upper and lower limb was found to be 4/5 with plantar extensor on right side. There was confabulation and gait apraxia. Rest of the examinations were normal. Lab Inves...
tigations Haemoglobin -16.5gm/dl, total leucocyte count –11000 cells/mm3, platelets -3.4 lakhs, ESR-10 mm/hr. urine examination-normal. Serum creatinine -0.5mg/dl, RA-negative, CRP-negative, Anti ds-DNA-negative, ANA-negative, p-ANCA-negative, c-ANCA-negative, Ultra sound abdomen imaging–normal, ECG-normal, Chest–X ray PA view–normal. RBS-5.2mmo/L. Fasting lipid profile–normal. trans thoracic echocardiography -Normal, to elucidate the origin of an ischemic stroke at a young age, further examination was done for thrombophilia and certain metabolic diseases with increased cardiovascular risk. APLA Ab’s(IgM and IgG)- normal; Antithrombin activity-116%(normal 75%-125%); Serum Homocysteine-29.7umol/l(normal <15 7 umol/l), Protein-S activity-106% (50%-140%); Protein-C activity -81%(normal 60-130%). Folic acid is normal (5,2 ng/ml with ref.: 2-9.1 ng/ml) and vitamin B12 is normal (291.4 pg/ml with ref.: 197- 771 pg/ml). The initial Computer Tomography (CT) of the skull was normal except old left parietal infarct (Figure 1). There was no evidence for intracranial hemorrhage. A Magnetic Resonance Imaging (MRI) of the brain showed acute right sided parietal infarct (Figure 2).

4. Discussion

Homocysteine is a sulphurous amino acid that is formed as an intermediary product during the conversion of the essential amino acid methionine to cysteine (Figure 3). Normal homocysteine levels vary between 5-15 μmol/l. Hyperhomocysteinemia is classified in three classes depending on the plasma levels: between 16-30 μmol/l, 31-100 μmol/l and > 100 μmol/l; which corresponds respectively with a light, mild and serious form of hyperhomocysteinemia [15,16].
Hyperhomocysteinemia originates from a deviation in the methionine-homocysteine metabolism. There are various causes that can lead to hyperhomocysteinemia: hereditary abnormalities that lead to disturbances of enzymes related to the homocysteine metabolism, vitamin deficiencies and different other factors such as lifestyle factors, chronic renal insufficiency, hypothyroidism, pernicious anemia, Systemic Lupus Erythematosus (SLE), end stage diabetes, cancers and medication [15, 17,18,19]. Moreover homocysteine levels themselves are an indication for the cause of hyperhomocysteinemia [17]. Mild hyperhomocysteinemia (30-100 μmol/l) is caused in 60% of the cases by the homozygote thermo unstable variant of the MTHFR-mutation.

Table 1: Causes of hyperhomocysteinemia

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<td>8. Drugs (folate antagonists, methotrexate, antiepileptics, theophylline, lipid modifiers)</td>
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Incidence of hyperhomocysteinemia varies between 1 in 50,000 and 1 in 200,000. By far the most common cause of mild to moderate elevations in homocysteine is a dietary deficiency of folate and/or vitamin B [12]. In 1969 it was suggested for the first time that there was a connection between increased homocysteine levels and atherosclerotic diseases. This hypothesis was backed by different successive observational studies [15,20,21]. Hyperhomocysteinemia is an independent risk factor for atherosclerosis of the coronary, cerebral and peripheral blood vessels [15,16,22]. Yet, homocysteine would not be as important as the more classic risk factors such as smoking, hypercholesterolemia, diabetes mellitus and hypertension. However, there is a synergistic effect between homocysteine and the classic risk factor smoking, as was the case in our patient, and arterial hypertension [16,20]. The precise pathophysiological mechanism through which hyperhomocysteinemia enhances atherosclerosis and thrombosis is not yet fully known. Plasma homocysteine is considered to promote arterial endothelial dysfunction, enhances thromboxane-A2 formation and platelet aggregation, smooth muscle proliferation, increased activation of factor V and X, and increased fibrinogen levels, reduced antithrombin activity and increased binding of lipoprotein (A) to fibrin 23,24 Thus it induces a prothrombotic state that causes premature atherosclerotic vascular disease [25].

Hyperhomocysteinemia is generally acknowledged as a risk factor for atherothrombotic diseases, but a causal relation between both has not yet been conclusively established [15,21]. The best way to work out causality and restrict bias and disturbing factors to a minimum is through randomization, for example through Mendelian randomization. The MTHFR C677T polymorphism is already selected at random with the formation of gametes, so that its relation to stroke is not biased or disturbed. After all, individuals with or without the MTHFR mutation have as much chance of other cardiovascular risk factors [21,26]. Individuals who are homozygote for the MTHFR C677T gene mutation have higher plasma homocysteine concentrations in comparison to those with the CC genotype and have a higher risk of a stroke. This implicates a causal relation between homocysteine and vascular diseases [26]. Meta-analyses of both observational as well as genetic polymorphism studies also point to strong evidence for a causal relation between homocysteine and cardiovascular diseases [21].
ine Studies Collaboration, 2002). As a matter of fact, the risk number calculated from meta-analysis of genetic polymorphism studies is comparable to the risk number calculated from meta-analyses of non-genetic observational studies. Because both type of studies have different sources of mistakes, their consistency in risk number again suggests a causal role for homocysteine [21,26]. Yet there is no conclusive evidence for a causal relationship between homocysteine and atherothrombotic diseases. Theoretically genetic confounding is possible with Mendelian randomization, at which polymorphic variants of the MTHFR genotype influence the lifestyle and socio-economical factors. This way, individuals with the TT genotype can be destined to an unhealthy lifestyle, low socio-economical status or risk factors for the development of a stroke [20]. Important confounding factors with observational studies are low folic acid concentrations and other environmental factors that influence the homocysteine levels. Furthermore, the levels are higher after a stroke or with pre-existing atherosclerosis. This is shown by the stronger association that is reported between homocysteine and stroke in retrospective studies than in prospective studies, as the levels are measured respectively after and before a stroke [15,20] (the Homocysteine Studies Collaboration, 2002).

Homocysteine is best measured when the patient is sober [15]. Homocysteine can also be determined after methionine loading. This is a more sensitive way for the detection of mild hyperhomocysteinemia [15,16]. Because a causal relation between hyperhomocysteinemia and stroke is unclear, the question remains what’s the place of diagnostics within the clinical practice. Moreover, there is insufficient evidence that reducing hyperhomocysteinemia also contributes to a lowering of the risk of stroke [27]. Despite these findings, it is still advised to determine homocysteine levels for patients with an ischemic stroke because the therapy is safe and cheap [28]. Furthermore, it is useful to determine homocysteine levels for patients with an ischemic stroke with no clue for vascular disease and thrombosis, with an ischemic stroke at a young age and with family history of premature atherosclerosis [15].

A daily folic acid intake of 0,5 to 5 mg makes the Plasma homocysteine level drop with about 25%. Daily vitamin B12 intake of at least 0,4 mg makes the level drop further with 7%. Vitamin B6 is mainly important in the decrease of the homocysteine levels after methionine loading (The Heart Outcomes Prevention Evaluation 2 Investigators, 2006). The effect of these treatments on the cerebrovascular risk is disputed. The meta-analysis of the Homocysteine Studies Collaboration suggests that a lowering of the homocysteine levels with 25% would make the risk of cardiovascular diseases drop with 11% and of stroke with 19% (The Homocysteine Studies Collaboration, 2002). This is inconsistent with the findings of various recent randomized controlled trials. In 2006 there was a meta-analysis of randomized controlled studies, that showed no advantage of vitamin therapy on vascular diseases or mortality 29.

The Heart Outcomes Prevention Evaluation (HOPE-2), the Norwegian Vitamin Trial (NORVIT), the Western Norway B Vitamin Intervention Trial (WENBIT) and the Women’s Antioxidant and Folic Acid Cardiovascular Study (WAFACS) were not able to prove the beneficial effect of vitamin therapy on mortality by cardiovascular or cerebrovascular events in a population with cardiovascular diseases in medical history [30-32] (The Heart Outcomes Prevention Evaluation 2 Investigators, 2006). Although the HOPE-2 study could not support a significant effect of vitamin therapy on the above described combined end points, yet there was a significant 24% reduction of stroke with vitamin therapy in the HOPE-219(The Heart Outcomes Prevention Evaluation 2 Investigators, 2006). Furthermore, the rate of stroke reduction in HOPE-2 was consistent with previous meta-analyses that predicted a 19-24% decrease of stroke with the reduction of total homocysteine seen in HOPE-2 [21,22] (The Homocysteine Studies Collaboration, 2002). So, it seems likely that even if vitamin therapy does not significantly reduce cardiovascular events, it will reduce the risk of stroke [22]. The different pathogenesis of stroke and myocardial infarction can explain this. Virtually all myocardial infarctions are due to rupture of a coronary plaque with in situ thrombosis, whereas most strokes are atheroembolic or embolic and some strokes are due to venous thrombosis. Therefore, stroke is much more likely to reflect the increased thrombosis that results from elevated serum homocysteine [22]. The Homocysteine Studies Collaboration also predicted almost twice the effect of a lowering plasma homocysteine level on the risk reduction of stroke than on the risk reduction of myocardial infarction [22] (The Homocysteine Studies Collaboration, 2002). There are two randomized controlled trials that study the effect of vitamin therapy on vascular disease for a study population with a transient ischemic attack or stroke in the medical history: the Vitamins in Stroke Prevention Study (VISP) and the Vitamins to Prevent Stroke Study (VITATOPS) [33] (the Vitamins to Prevent Stroke Trial, 2002). After two years of follow up the VISP study could not prove the effect of vitamin therapy on cardiovascular or cerebrovascular risk and mortality. Possible causes for the limited effectiveness of the VISP study are: folic acid intake through cereal products, parenteral vitamin B12 therapy, vitamin B12 malabsorption and renal insufficiency [33]. For this reason, a subgroup analysis of the VISP study was made, from which it appeared that the population that takes a high dose of vitamins has a 21% lower risk of cardiovascular disease, stroke or mortality in comparison with the population that takes a low dose of vitamins 22. These significant results of the VISP efficacy analysis and the significant reduction of stroke in HOPE-2 support a beneficial effect of vitamin therapy [22]. Several ongoing bigger and longer follow up trials, VITATOPS and the Study Of The Effectiveness Of Additional Reductions In Cholesterol And Homocysteine (SEARCH) are now trying to clarify whether there are patients with stroke who may benefit from ho-
mocysteine lowering (The Vitamins to Prevent Stroke Trial, 2002; SEARCH study Collaborative Group Oxford, 2007).

At this moment, the American Heart and Stroke Association still advises to treat patients with a stroke and hyperhomocysteinemia (> 10 μmol/l) daily with 0.4 mg folic acid, 2.4 μg vitamin B12 and 1.7 mg vitamin B6 because of the low cost and safety of the therapy 28. The normalization of the plasma homocysteine concentrations happens within 2 to 6 weeks after the start of the therapy [33]. The European guidelines do not advise vitamin substitution for patients with stroke and hyperhomocysteinemia because of the lack of evidence for the reduction of stroke recurrence and the possible risk of increasing vascular events (European Stroke Organization Executive Committee, 2008). Further studies are much awaited.

5. Conclusion
Increased homocysteine level is an important risk factor for the development of ischemic stroke in all populations especially in younger age group. Hypertension and smoking per se are important contributory factors for hyperhomocysteinemia. Absolute values of high-homocysteine levels cannot be established. Because of the low cost and security of the therapy a daily combined vitamin therapy is advised to patients with an ischemic stroke and hyperhomocysteinemia. It will be worthwhile to consider homocysteine lowering (The Vitamins to Prevent Stroke Trial, 2002; SEARCH study Collaborative Group Oxford, 2007).

References


