Acta Neurol. Belg., 2009, **109**, 181-188

Ischemic stroke and hyperhomocysteinemia: truth or myth?

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Abstract

Hyperhomocysteinemia is generally acknowledged as a treatable risk factor for atherotrombotic diseases, but a causal relationship between both is not yet definitively established. Hyperhomocysteinemia 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.

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. Because of the low cost and safety of the therapy, the American Heart and Stroke Association advises to treat patients with a stroke and hyperhomocysteinemia daily with 0,4 mg folic acid, 2,4 µg vitamin B12 and 1,7 mg vitamin B6. A significant benefit in secondary prevention is not yet proven. The results of larger follow-up trials have to be published.

Key words: Hyperhomocysteinemia; methionine-homocysteine metabolism; ischemic stroke; secondary prevention; vitamin therapy.

Introduction

Acute stroke is the third most frequent cause of death in the USA and Europe; the yearly incidence is about 200 on 100 000 persons in Belgium (Laloux, 2003). In adults and mainly the older population cerebrovascular accidents (CVA) are strongly related to cardiovascular risk factors such as hypertension, hypercholesterolemia, diabetes, nicotine-abuse and obesity. During the last years hyperhomocysteinemia has also been put forward as a cardiovascular risk factor.

A recent case of a young man with a cerebrovascular accident and hyperhomocysteinemia in association with a methylenetetrahydrofolate reductase C677T (MTHFR C677T) gene mutation led us to perform a literature research about the relationship between homocysteine and cerebrovascular disease. The meaning and significance of tracing and treating hyperhomocysteinemia in the secondary prevention of an ischemic stroke are reviewed.

Case history

A 26-year-old man is hospitalized via the emergency unit with a left hemiplegia and reduced consciousness. He presents at the emergency room more than three hours after the onset of symptoms. He has been smoking one pack of cigarettes a day for the last 10 years. No alcohol abuse is reported. There is a case history of amphetamine and cocaine abuse. The patient has not used these drugs for six years. There is no history of epilepsy, vasculitis, headache, infections or coagulation disorders. There is no family history of cerebrovascular disease.

The initial blood examination shows no particularities apart from the increased creatine kinase (1055 U/L, reference value: 10-195 U/L). Toxicological screening is negative.

The initial computer tomography (CT) of the skull is normal. There is no evidence for intracranial haemorrhage. Because of the time delay - exceeding more than three hours - between onset of symptoms and arrival at the emergency room, the patient is no candidate for intravenous thrombolysis. A magnetic resonance imaging (MRI) of the brain shows an infarction of the middle cerebral artery territory with oedema and a light shift of the median brain structures to the left side. At the moment of the MRI the patient suddenly develops a generalized epileptic seizure. This is considered a contra-indication for intra-arterial thrombolysis. Aspirin (300 mg) is given intravenously and low molecular weight heparin is started in a preventive dose subcutaneously once a day.

The arterial duplex of the neck vessels shows no significant stenosis. A CT angiography of the neck vessels shows no dissection, no significant stenosis or no ulcerative plaques at the height of the carotid arteries or the circle of Willis. A transoesophagal echocardiography cannot establish an emboligenic source. A continuous ECG recording shows no significant arrhythmias.

To elucidate the origin of an ischemic stroke at a young age, further examination is done for thrombophilia and certain metabolic diseases with increased cardiovascular risk. Factor VIII is 186% (reference value (ref.): 60-160%, thrombogenic risk starting from 195%). Basal homocysteine level is increased (79,5 µmol/l , ref.: < 16 µmol/l), which is confirmed after a few days (79,4 µmol/l). Folic acid is normal (5,2 ng/ml with ref.: 2-9,1 ng/ml) and vitamin B12 is low (108 pg/ml with ref.: 197-866 pg/ml). Additional genetic analysis reveals that the patient is homozygote for the methylenetetrahydrofolate reductase (MTHFR) C677T gene mutation. A treatment with folic acid, vitamin B6, and vitamin B12 is started. Upon control six weeks after starting the vitamin therapy, homocysteine levels were normalized. The patient recovers partially from his left hemiplegia and can leave the rehabilitation centre after about two months with a spastic left hemiparesis.

Homocysteine

Homocysteine is a sulphurous amino acid that is formed as an intermediary product during the conversion of the essential amino acid methionine to cysteine (Fig. 1). 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 (Welch *et al.*, 1998; Kaul *et al.*, 2006). Hyperhomocysteinemia originates from a deviation in the

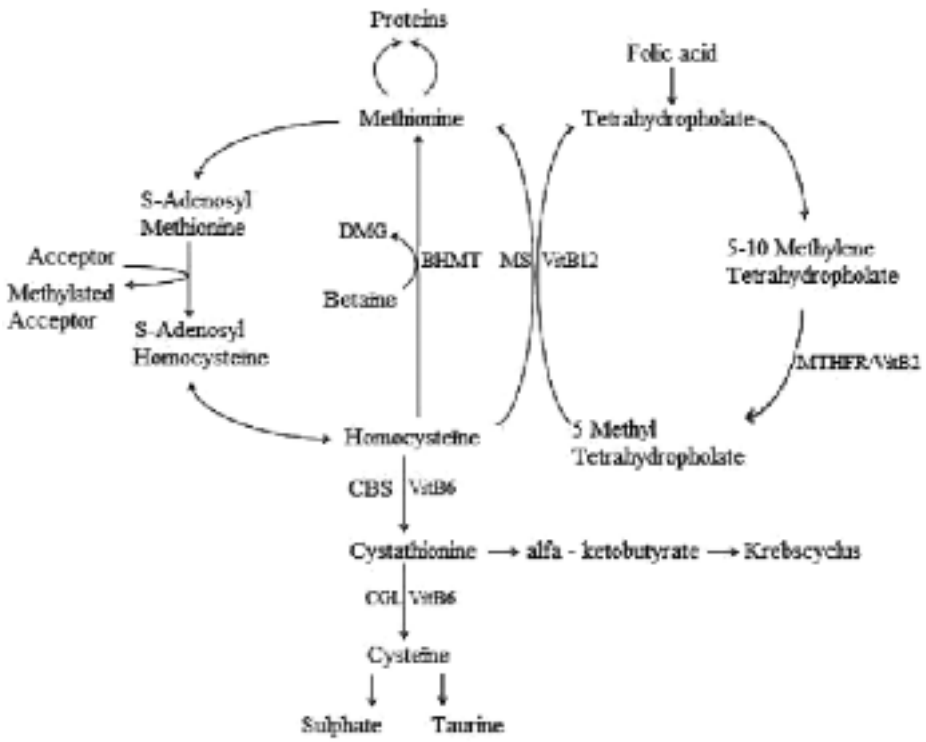

FIG. 1. — The methionine-homocysteine metabolism

Homocysteine can be converted metabolically via two routes, namely via transulfuration or remethylation. Through the transulfuration route homocysteine is converted to cysteine by CBS with co-enzyme vitamin B_6. Furthermore homocysteine can be remethylated to methionine in two ways; either by BHMT or by MS. MS is working with co-enzyme vitamin B12, for which folic acid plays an important role as 5-MTHF that is formed through MTHFR from 5,10 MTHF(Welch *et al.*, 1998; Kaul *et al.*, 2006).

CBS: cystathionine-β-synthase, BHMT: betaine-homocysteine methyltransferase, MS: methionine synthase, 5-MTHF: 5-methylenetetrahydrofolate, MTHFR: methylenetetrahydrofolate reductase, DMG: dimethylglycine, CGL: cystathionine-gamma-liase.

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 anaemia, systemic lupus erythematosus (SLE), end stage diabetes, cancers and medication (Kaul *et al.*, 2006; Vanbrabant *et al.*, 2001; Wierzbicki, 2007; Hankey, 2006) (Table 1). Moreover homocysteine levels themselves are an indication for the cause of hyperhomocysteinemia (Vanbrabant *et al.*, 2001). Mild hyperhomocysteinemia (30-100 µmol/l) is caused in 60% of the cases by the homozygote thermo-unstable variant of the MTHFR-mutation. This originates through a point mutation of amino acid 677 (677 C→T) of MTHFR, which causes an alanine-valine substitution. This thermo-unstable variant is characterised in vitro by its thermo-unstability at 46°C. In vivo it is associated with 50% reduction of the enzymatic activity of MTHFR, which results in an increase of the homocystein levels with 25%. This effect is mainly seen in individuals with low folic acid levels. About 10 to 12% of the population is estimated to be carrier of this homozygote mutation (Welch *et al.*, 1998; Kaul *et al.*, 2006; Wald *et al.*, 2002). The MTHFR 677TT genotype has a heightened risk of about 20% for atherothrombotic diseases (Kaul *et al.*, 2006; Casas *et al.*, 2005). On the contrary, severe hyperhomocysteinemia (> 100 µmol/l) is mostly caused by homozygote cystathionine-β-synthase (CBS) deficiency or by homozygote thermo-stable (thermo-unstable at 55°C) MTHFR deficiency. Homozygote CBS deficiency, better known as the classic congenital homocystinuria, is an autosomal recessive disease with a mutation at the height of the CBS gene situated on chromosome 21. The prevalence fluctuates between 1/100000 and 1/344000. Clinically this disease is characterized by skeleton abnormalities, lens luxation, mental retardation, tromboembolism and premature atherosclerosis (Welch *et al.*, 1998).

Homocysteine and cerebrovascular disease

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 (Kaul *et al.*, 2006; Wald *et al.*, 2002; Pezzini *et al.*, 2006; The Homocysteine Studies Collaboration, 2002) (Table 2). Hyperhomocysteinemia is an independent risk factor for atherosclerosis of the coronary, cerebral and peripheral blood vessels (Welch *et al.*,1998; Kaul *et al.*, 2006; Spence *et al.*, 2005). 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 (Welch *et al.*, 1998; Pezzini *et al.*, 2006). The precise pathophysiological mechanism through which hyperhomocysteinemia enhances atherosclerosis and -thrombosis is not yet fully known. It is known however that homocysteine causes endothelial cell injury and thereby initiates the process of premature atherosclerosis (Hankey, 2006; Pezzini *et al.*, 2006).

Table 1

Causes of hyperhomocysteinemia (Welch *et al.*, 1998; Kaul *et al.*, 2006; Wierzbicki, 2007)

Genetic defects	Vitamin deficiencies	Other factors
1. Cystathionine-β-synthasedeficiency (homozygote/heterozygote) 2. 5,10 methylenetetrahydrofolate reductase deficiency (thermo-stable/thermo-unstable) 3. Methioninesynthasedeficiency 4. Genetic defects in the vitamin B12 metabolism	1. Lack of folic acid 2. Lack of vitamin B12 3. Lack of vitamin B6	1. Lifestyle factors (smoking, coffee, alcohol abuse) 2. Chronic renal insufficiency 3. Hypothyroidism 4. Pernicious anaemia 5. SLE 6. End stage diabetes mellitus 7. Cancers (breast, ovarium, pancreas) 8. Drugs (folate antagonists, methotrexate, anti-epileptica, theophylline, lipid modifiers) 9. age 10. male sex 11. menopause 12. hepatic dysfunction

Table 2

Summary of key studies investigating the association between homocysteine (HCY) and cardiovascular disease

Observational Studies	Subjects	Major end points	Mean follow-up (years)	Mean total homocysteine level at baseline (µmol/L)		Odds Ratio (95% CI)
				Cases	Controls	
Retrospective Study						
European Concerted Action Project (1997)	750 male and female cases + 800 controls	Atherosclerotic vascular disease (cardiac, cerebral and peripheral)	No follow-up	11.25	9.73	Vascular disease: 2.2 (1.6 - 2.9)[1]
Prospective Studies						
British Regional Heart Study (Perry *et al.*, 1995)	107 male cases + 118 controls	Fatal and non-fatal stroke	12.8	13.7[2]	11.9[2]	Stroke: 2.8 (1.3 - 5.9)[3] *
Rotterdam Study (Bots *et al.*, 1999)	224 male and female cases + 533 controls	Stroke and MI	2.7	Stroke: 13.4 MI: 17.3	15.2	Stroke: 2.53 (1.19 - 5.35)§* MI: 2.43 (1.11 - 5.35)§*
North Karelia Project (Alfthan, 1994)	265 male and female cases + 269 controls	Fatal and non-fatal MI, stroke	9	Men: 10.0 Women: 9.6	Men: 9.8 Women 9.2	Stroke or MI: Men: 1.05 (0.56 - 1.95)† Women 1.22 (0.66 - 2.78)†
Meta-analysis	Studies	*Participants*	Key findings	Conclusion		
Homocysteine Studies Collaboration (2002)	30 prospective or retrospective observational studies	*5073 IHD events and 1113 stroke events*	An increase in plasma HCY levels by 25% (i.e. about 3 µmol/L) was associated with *11% and* 19% excess risk for IHD and stroke respectively‡	Elevated homocysteine is a modest independent predictor of IHD and stroke risk in healthy populations		
Wald *et al.* (2002)	72 MTHFR polymorphism studies and 20 prospective studies	*16 849 cases with controls (polymorphism studies) and 3820 participants (prospective studies)*	Lowering HCY levels by 3 µmol/L would reduce the risk of stroke by 24% *(IHD by 16%, DVT by 25%)*	Strong evidence that the association between homocysteine and CVD is causal		
Casas *et al.* (2005)	111 MTHFR polymorphism studies	*13928 participants*	An increase in plasma HCY levels by 1.93 µmol/L was associated with 1.26-fold increase in CVA risk	Strong evidence that the association between homocysteine and CVD is causal		

[1] for the top fifth vs the bottom four fifths of the total HCY distribution
[2] geometric mean
[3] for the fourth vs the first quarter of total HCY levels
* statistically significant
§ highest compared with lowest fifth of total HCY levels
† for >= 95th percentile vs < 95th percentile of total HCY levels
‡ after adjustment for other cardiovascular risk factors and regression dilution bias

IHD: ischemic heart disease, HCY: homocysteine, CVD: cardiovascular disease, MI: myocard infarct, DVT: deep venous thrombosis.

Hyperhomocysteinemia is generally acknowledged as a risk factor for atherotrombotic diseases, but a causal relation between both has not yet been conclusively established (Kaul *et al.*, 2006; Wald *et al.*, 2002; Wald *et al.*, 2006). 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 (Wald *et al.*, 2002; Casas *et al.*, 2005). 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 (Casas *et al.*, 2005). 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 (Wald *et al.*, 2002; the Homocysteine 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 (Wald *et al.*, 2002; Casas *et al.*, 2005; Wald *et al.*, 2006).

Yet there is no conclusive evidence for a causal relationship between homocysteine en atherotrombotic 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 (Pezzini *et al.*, 2006). Important confounding factors with observational studies are low folic acid concentrations and other environmental factors that influence the homocysteine levels (Table 1). 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 (Kaul *et al.*, 2006; Pezzini *et al.*, 2006; the Homocysteine Studies Collaboration, 2002).

Diagnostics and screening

Homocysteine is best measured when the patient is sober (Kaul *et al.*, 2006). Homocysteine can also be determined after methionine loading. This is a more sensitive way for the detection of mild hyperhomocysteinemia (Welch *et al.*, 1998; Kaul *et al.*, 2006). 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 on stroke (Boers *et al.*, 1985). Despite these findings, it is still advised to determine homocysteine levels for patients with an ischemic stroke because the therapy is safe and cheap (Sacco *et al.*, 2006). 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 (Kaul *et al.*, 2006).

Treatment of hyperhomocysteinemia

A daily folic acid intake of 0,5 to 5 mg makes the plasmahomocysteine 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 (Bazzano, 2006).

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 (The Heart Outcomes Prevention Evaluation 2 Investigators, 2006; Bonaa *et al.*, 2006; Ebbing *et al.*, 2008; Albert *et al.*, 2008) (Table 3).

Table 3

Summary of randomized controlled trials investigating the effect of vitamin supplementation on cardiovascular risk

Study	Participants	Medical history	FU (y)	Dose (mg/day)			[HCY]↓ (µmol/l)	Outcomes						Conclusion
				FA	VitB12	VitB6		Number of patients (%)		RR (95% CI)		P-value		
								Stroke	CE	Stroke	CE	Stroke	CE	
HOPE-2	5522 -HD (2758) -Placebo (2764)	Vascular diseases and diabetes mellitus	5	2.5 Placebo	1	50	2.4↓ 0.8↑	4 5.3	32.6 32.2	0.75 (0.59 – 0.97)	1.03 (0.94 – 1.13)	0.03	0.57	No significant effect on CE Significant effect on stroke
NORVIT	3749 - group A - group B - group C - group D	MI	3,3	0.8 0.8 / Placebo	0.4 0.4 /	40 / 40	3,6↓ 3.1↓ No change No change	2.24 2.99 2.36 2.86	21.45 17.96 18.74 18.24	*1 1.02 (0.68 – 1.51) *2 0.81 (0.54 – 1.20) *3 0.83 (0.47 - 1.47)	1.08 (0.93 – 1.25) 1.14 (0.98 – 1.32 1.22 (1.00 – 1.50)	0.94 0.29 0.52	0.31 0.09 0.05	No significant effect
VISP	3680 -HD (1827) -LD (1853)	Recent stroke	2	2.5 0.02	0.4 0.006	25 0.2	2.4↓ 0.3↓	9.2 8.8	18.0 18.6	1.0 (0.8 - 1.3)	1.0 (0.8 - 1.1)	0.80	0.61	No significant effect
WENBIT	3096 undergoing coronary angiography - group 1 - group 2 - group 3 - group 4	Coronary artery disease or aortic valve stenosis	3,2	 0.8 0.8 / Placebo	 0.4 0.4 /	 40 / 40	 2.8↓ 2.8↓ No change No change	 1.4 2.2 2.6 2.4	 12.2 16.3 13.7 12.5	 † 0.72 (0.44 – 1.17) ‡ 0.87 (0.54 – 1.40)	 1.09 (0.90 – 1.32) 0.90 (0.74 – 1.09)	 0.19 0.56	 0.36 0.28	No significant effect
WAFACS	5442 women - HD - Placebo	Cardiovascular disease or >= 3 coronary risk factors	7,3	2.5 Placebo	1	50	2.3↓ No change	2.5 2.3	14.9 14.3	1.10 (0.78 – 1.56)	1.03 (0.90 – 1.19)	0.57	0.65	No significant effect
VITATOPS	8000 -HD -Placebo	Stroke//TIA	4	2 Placebo	0.5	25	Not yet known	Not yet known						
SEARCH	12064 - HD - Placebo	MI	7	2 Placebo	1		Not yet known	Not yet known						

*1 Folic Acid and B12 vs. No Folic Acid and B12 (comparison of group A + B with C + D)
*2 B6 vs. No B6 (comparison of group A + C with B + D)
*3 Folic Acid, B12 and B6 vs. Placebo (comparison of group A with group D)
† Folic Acid vs. Non-Folic Acid (comparison of group 1 + 2 with 3 + 4)
‡ B6 vs. No B6 (comparison of group 1 + 3 with 2 + 4)

HD: high dose, LD: low dose, FA: folic acid, HCY: homocysteine, FU: follow-up, y: years
CE: combined end points:
- HOPE 2 : total ischemic events (composite of death from cardiovascular causes, MI, stroke, hospitalization for unstable angina or revascularisation)
- NORVIT : composite of recurrent myocardial infarction, stroke and sudden death attributed to CHD
- VISP : ischemic stroke, CHD or death
- WENBIT : all cause death, nonfatal acute myocardial infarction, acute hospitalization for unstable angina pectoris and nonfatal thomboembolic stroke
- WAFACS : a composite of MI, stroke, coronary revascularization, or CVD mortality.

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-2 (Hankey, 2006; 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 (Wald *et al.*, 2002; The Homocysteine Studies Collaboration, 2002; Spence, 2007). So, it seems likely that even if vitamin therapy does not significantly reduce cardiovascular events, it will reduce the risk of stroke (Spence, 2007). 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 athero-embolic 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 (Spence, 2007). 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 (The Homocysteine Studies Collaboration, 2002; Spence, 2007).

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) (Toole, 2004; 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 (Toole *et al.*, 2004). 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 (Spence *et al.*, 2005). These significant results of the VISP efficacy analysis and the significant reduction of stroke in HOPE-2 support a beneficial effect of vitamin therapy (Spence, 2007). 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 homocysteine 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 (Sacco *et al.*, 2006). The normalisation of the plasma homocysteine concentrations happens within 2 to 6 weeks after the start of the therapy (Toole *et al.*, 2004). 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 Organisation Executive Committee, 2008). Further studies are much awaited.

Conclusion

There are strong clues in favour of a causal relation between hyperhomocysteinemia and atherothrombotic diseases. Homocysteine levels can be lowered effectively by a combination therapy with folic acid, vitamin B12 and vitamin B6, but to this day it could not be proven if such a therapy also reduces the cerebrovascular risk. Larger and longer follow up studies are necessary to establish this. At this moment it is therefore not advised to screen every stroke patient for hyperhomocysteinemia in view of secondary prevention. It is reasonable to screen those stroke patients 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. 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. However, the beneficial effect of vitamin substitution therapy in the secondary prevention after ischemic stroke remains to be proven.

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