HYPERHOMOCYSTEINEMIA

Nikolaos P. Margos[1], John Ellul[2]

[1] School of Medicine, University of Patras, University Campus, Rio, Greece
[2] Department of Neurology, University Hospital of Patras, Patra, Greece

INTRODUCTION

Homocysteine is a non-proteinogenic amino acid and differs from cysteine by an additional methylene bridge. It is synthesized from methionine and can be recycled into methionine or converted into cysteine in the presence of certain B vitamins (Figure 1).

Homocystinuria, a rare autosomal disorder characterized by steep elevation of homocysteine in plasma and urine, is always accompanied by systemic clinical manifestations. On the contrary, hyperhomocysteinemia is characterized by a less markedly elevated level of homocysteine (above 15 μmol/L) in serum measurements [1]. Hyperhomocysteinemia is more common than homocystinuria and affects 5-7% of the general population [2].

High levels of homocysteine are associated with increased cerebrovascular, cardiovascular, and thromboembolic diseases, and appear to be an independent marker of atheromatic disease [3, 4]. There is clear evidence that lowering homocysteine levels is beneficial in both slowing the acceleration of brain atrophy [5] and in decreasing cardiovascular risk in patients with homocystinuria [6]. Nonetheless, the evaluation and treatment of hyperhomocysteinemia still remains controversial, as studies have shown that homocysteine-lowering therapies do not significantly affect the prevention of stroke and/or coronary heart disease [7, 8].

ETIOLOGY

Genetic factors: The most common form of genetic hyperhomocysteinemia results from a mutated methylene tetrahydrofolate reductase (MTHFR) that has reduced enzymatic activity, thus leading to the accumulation of homocysteine in serum, especially in mutated MTHFR C677T homozygotes [4, 9]. A marked ethnic and geographical variation of the mutated enzyme has been observed [10], with 8% to 20% of the affected individuals being homozygous in North America, Europe, and Australia [11]. Additionally, *MTHFR* A1298C polymorphism has been associated with an increased risk for schizophrenia [12].

Vitamin deficiencies: Vitamin B12, folate and vitamin B6 deficiencies can all lead to increased blood levels of homocysteine since they are used as cofactors in the enzymatic pathways of homocysteine metabolism [13, 14]. Decreased B12 absorption and intake may play an important role in elevating serum homocysteine levels in older adults, while low intake of folate as a cause of hyperhomocysteinemia is relatively common in the general population.

Other causes include: chronic kidney disease (due to impaired renal excretion), drugs (i.e. fibrates, nicotinic acid, metformin, methotrexate) though with uncertain clinical significance, smoking and hypothyroidism [3, 15, 16].

CLINICAL PRESENTATION

The clinical presentation of hyperhomocysteinemia depends on the underlying etiology, and in most cases moderately increased homocysteine serum levels produce no apparent symptoms. However, markedly elevated levels are associated with atherogenic and prothrombotic properties. Intimal thickening, elastic lamina disruption, smooth muscle hypertrophy, marked platelet accumulation and the formation of platelet-enriched thrombi can all be signs of vascular injury induced by homocysteine [17].

Most importantly, homocysteine induced vascular injury can cause cardiovascular and cerebrovascular disease, peripheral arterial disease, and heart failure [4, 7, 18, 19]. Studies have shown that a 5μmol/L increase in homocysteine levels is associated with a 20% higher risk for coronary heart disease (CHD) [20]. Ischemic stroke has also been associated with hyperhomocysteinemia [21, 22]. However, lowering homocysteine levels does not seem to decrease cardiovascular events in contrast to the well-known effectiveness of traditional vascular risk factors management [23, 24].

Moreover, the association of hyperhomocysteinemia with venous thromboembolism (VTE) remains to this day controversial. Even though some studies conclude that hyperhomocysteinemia is a risk factor for VTE [25, 26], additional research suggests that this may be due to confounding factors [27, 28]. An association with neurodegenerative diseases such as Alzheimer disease, cognitive decline – dementia and Parkinson's disease, has also been reported [29]. Furthermore, a clear relationship between hyperhomocysteinemia and obstetric complications has not been established. Some studies have reported

Figure 1. Homocysteine metabolic pathway [46]

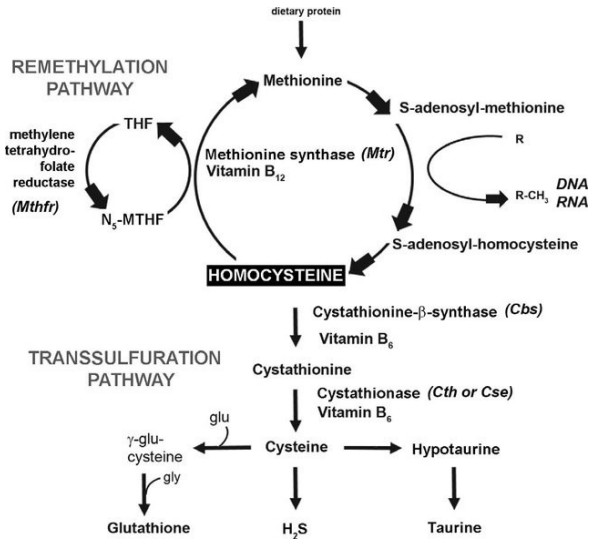
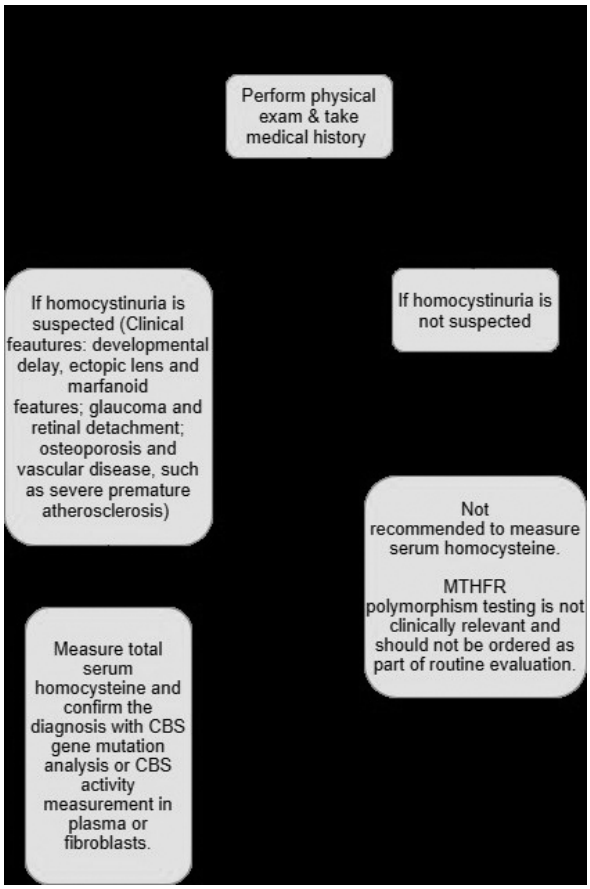


Figure 2. Evaluation of hyperhomocysteinemia



preeclampsia, abruptio placentae, fetal growth restriction and neural tube defects as possible side effects [30, 31]. However, a more recent meta-analysis showed no connection between MTHFR mutations and obstetric complications [32].

Other disease associations such as hip fractures, schizophrenia and osteoporosis [33, 34] have been reported, but are not always clearly linked with hyperhomocysteinemia [35]. Hyperhomocysteinemia and possible disease associations are shown in Table 1.

EVALUATION

Evaluation (Figure 2) should initially include a complete physical examination and thorough medical history. Although there is no recommended screening for hyperhomocysteinemia, physicians should always check homocysteine levels if homocystinuria (cystathionine β-synthase (CBS) deficiency) is suspected. The four most prevalent CBS mutations include p.Ile278Thr, p.Thr191Met, p.Gly307Ser, and p.Trp323Ter [36]. Clinical features of this disease include developmental delay, ectopic lens and marfanoid features. Children and young adults often present with glaucoma and retinal detachment, alongside osteoporosis and vascular disease, such as severe premature atherosclerosis [37]. Homocystinuria due to CBS deficiency is a rare, but potentially lethal disease, thus prompt diagnosis leads to better prognostic outcomes. Diagnosis should be made by measurement of total serum homocysteine (tHcy).

Table 1. Hyperhomocysteinemia & possible disease associations

Hyperhomocysteinemia & possible disease associations
Vascular disease (cardiovascular, cerebrovascular)
Venous Thromboembolism
Alzheimer disease
Cognitive decline - dementia
Parkinson disease
Obstetric complications (i.e. preeclampsia, abruptio placentae, fetal growth restriction)
Hip fractures, osteoporosis
Schizophrenia

Elevated tHcy accompanied by borderline or high plasma methionine concentrations makes the diagnosis very likely. CBS deficiency should be confirmed by mutation analysis of the biallelic pathogenic CBS variant and/or measurement of CBS activity in plasma or fibroblasts [38].

In patients who lack homocystinuria clinical features and present with cardiovascular disease, stroke or venous thromboembolism, it is not recommended to measure tHcy. MTHFR polymorphism testing is not clinically relevant and, should not be ordered as a part of a routine evaluation [39].

Total homocysteine must be measured in patient plasma/serum. The samples must be collected after the patient has fasted overnight and analyzed as soon as possible to avoid falsely decreased or elevated homocysteine levels. Refrigeration of the samples inhibits homocysteine accumulation for at least 4 hours [40].

For the record, normal homocysteine levels range between 5-15 μmol/L.

Kang et al. classified hyperhomocysteinemia in 1992 [1]:

- Moderate: 15-30 μmol/L.
- Intermediate: 30-100 μmol/L.
- Severe: >100 μmol/L.

TREATMENT

A large meta-analysis that included 71,422 participants showed that homocysteine lowering therapy (HLT) such as folate, vitamin B12, or vitamin B6 does not reduce the risk for myocardial infarction [41].

Interventions to reduce plasma homocysteine level in post-stroke patients did not have any effect in mitigating the severity of ischemic stroke outcome [23]. In addition, recurrent VTE is not prevented in patients with hyperhomocysteinemia that are treated with HLT [42]. Similarly, no clear evidence that HLT is useful in neurodegenerative diseases exists.

Nevertheless, advocates of treating hyperhomocysteinemia with B vitamins and folate still exist. For instance, a small study reported that HLT can improve cognitive function in patients with hyperhomocysteinemia and schizophrenia. A possible mechanism linking hyperhomocysteinemia to schizophrenia depends on the interaction of homocysteine with NMDA receptors. It also initiates oxidative stress, causes mitochondrial dysfunction and cell apoptosis. [34] Additionally, a review paper suggests HLT initiation when serum levels exceed 15 μmol/L [43].

Finally, the only medical condition where treating hyperhomocysteinemia would have an effect in patient prognosis and symptom management is homocystinuria. HLT in this patient group does indeed lower cardiovascular risk [44, 45].

CONCLUSION

In conclusion, hyperhomocysteinemia still remains a controversial occurrence, which is often considered a secondary manifestation and possibly entails several cardiovascular and metabolic implications. Still, more research is needed for clear correlations with diseases to be made, and for more clinically relevant therapeutic options to be developed.

REFERENCES

[1] Kang SS, Wong PW, Malinow MR. Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease. *Annu Rev Nutr.* 1992;12:279-298.
[2] McCully KS. Homocysteine and vascular disease. *Nat Med.* 1996;2:386-389.
[3] Bostom AG, Carpenter MA, Kusek JW, et al. Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the Folic Acid for Vascular Outcome Reduction in Transplantation trial. *Circulation.* 2011;123:1763-1770.
[4] Park WC, Chang JH. Clinical Implications of Methylenetetrahydrofolate Reductase Mutations and Plasma Homocysteine Levels in Patients with Thromboembolic Occlusion. *Vasc Specialist Int.* 2014;30:113-119.
[5] Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PLoS One.* 2010;5:e12244.
[6] Malinow MR, Bostom AG, Krauss RM. Homocyst(e)ine, diet, and cardiovascular diseases: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation.* 1999;99:178-182.
[7] Lee M, Hong KS, Chang SC, et al. Efficacy of homocysteine-lowering therapy with folic Acid in stroke prevention: a meta-analysis. *Stroke.* 2010;41:1205-1212.
[8] Li Y, Huang T, Zheng Y, et al. Folic Acid Supplementation and the Risk of Cardiovascular Diseases: A Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc.* 2016;5.
[9] Antoniades C, Shirodaria C, Leeson P, et al. MTHFR 677 C>T Polymorphism reveals functional importance for 5-methyltetrahydrofolate, not homocysteine, in regulation of vascular redox state and endothelial function in human atherosclerosis. *Circulation.* 2009;119:2507-2515.
[10] Wilcken B, Bamforth F, Li Z, et al. Geographical and ethnic variation of the 677C>T allele of 5,10 methylenetetrahydrofolate reductase (MTHFR): findings from over 7000 newborns

from 16 areas world wide. *J Med Genet.* 2003;40:619-625.
[11] Moll S, Varga EA. Homocysteine and MTHFR Mutations. *Circulation.* 2015;132:e6-9.
[12] Rai V, Yadav U, Kumar P, et al. Methylenetetrahydrofolate reductase A1298C genetic variant& risk of schizophrenia: A meta-analysis. *Indian J Med Res.* 2017;145:437-447.
[13] Robinson K, Arheart K, Refsum H, et al. Low circulating folate and vitamin B6 concentrations: risk factors for stroke, peripheral vascular disease, and coronary artery disease. European COMAC Group. *Circulation.* 1998;97:437-443.
[14] Rimm EB, Willett WC, Hu FB, et al. Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA.* 1998;279:359-364.
[15] Cianciolo G, De Pascalis A, Di Lullo L, et al. Folic Acid and Homocysteine in Chronic Kidney Disease and Cardiovascular Disease Progression: Which Comes First? *Cardiorenal Med.* 2017;7:255-266.
[16] Kumar A, Palfrey HA, Pathak R, et al. The metabolism and significance of homocysteine in nutrition and health. *Nutr Metab (Lond).* 2017;14:78.
[17] Fu Y, Wang X, Kong W. Hyperhomocysteinaemia and vascular injury: advances in mechanisms and drug targets. *Br J Pharmacol.* 2018;175:1173-1189.
[18] Cheng SW, Ting AC, Wong J. Fasting total plasma homocysteine and atherosclerotic peripheral vascular disease. *Ann Vasc Surg.* 1997;11:217-223.
[19] Vasan RS, Beiser A, D'Agostino RB, et al. Plasma homocysteine and risk for congestive heart failure in adults without prior myocardial infarction. *JAMA.* 2003;289:1251-1257.
[20] Humphrey LL, Fu R, Rogers K, et al. Homocysteine level and coronary heart disease incidence: a systematic review and meta-analysis. *Mayo Clin Proc.* 2008;83:1203-1212.
[21] Zhang T, Jiang Y, Zhang S, et al. The association between homocysteine and ischemic stroke subtypes in Chinese: A meta-analysis. *Medicine (Baltimore).* 2020;99:e19467.
[22] Homocysteine Studies C. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA.* 2002;288:2015-2022.
[23] Poddar R. Hyperhomocysteinemia is an emerging comorbidity in ischemic stroke. *Exp Neurol.* 2021;336:113541.
[24] Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke.* 2021;52:e364-e467.
[25] Ray JG. Meta-analysis of hyperhomocysteinemia as a risk factor for venous thromboembolic disease. *Arch Intern Med.* 1998;158:2101-2106.
[26] den Heijer M, Rosendaal FR, Blom HJ, et al. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. *Thromb Haemost.* 1998;80:874-877.
[27] Lijfering WM, Coppens M, van de Poel MH, et al. The risk of venous and arterial thrombosis in hyperhomocysteinaemia is low and mainly depends on concomitant thrombophilic defects. *Thrombosis and haemostasis.* 2007;98:457-463.
[28] Ospina-Romero M, Cannegieter SC, den Heijer M, et al. Hyperhomocysteinemia and Risk of First Venous Thrombosis: The Influence of (Unmeasured) Confounding Factors. *Am J Epidemiol.* 2018;187:1392-1400.
[29] Sharma M, Tiwari M, Tiwari RK. Hyperhomocysteinemia: Impact on Neurodegenerative Diseases. *Basic Clin Pharmacol Toxicol.* 2015;117:287-296.
[30] Hague WM. Homocysteine and pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2003;17:459-469.
[31] Kupferminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. *N Engl J Med.* 1999;340:9-13.
[32] Ren A, Wang J. Methylenetetrahydrofolate reductase C677T polymorphism and the risk of unexplained recurrent pregnancy loss: a meta-analysis. *Fertil Steril.* 2006;86:1716-1722.
[33] van Meurs JB, Dhonukshe-Rutten RA, Pluijm SM, et al. Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med.* 2004;350:2033-2041.
[34] Trzesniowska-Drukala B, Kalinowska S, Safranow K, et al. Evaluation of hyperhomocysteinemia prevalence and its influence on the selected cognitive functions in patients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2019;95:109679.
[35] Gerdhem P, Ivaska KK, Isaksson A, et al. Associations between homocysteine, bone turnover, BMD, mortality, and fracture risk in elderly women. *Journal of Bone and Mineral Research.* 2007;22:127-134.
[36] Weber Hoss GR, Sperb-Ludwig F, Schwartz IVD, et al. Classical homocystinuria: A common inborn error of metabolism? An epidemiological study based on genetic databases. *Mol Genet Genomic Med.* 2020;8:e1214.
[37] Sacharow SJ, Picker JD, Levy HL. Homocystinuria caused by cystathionine beta-synthase deficiency. 2017.
[38] Morris AA, Kozich V, Santra S, et al. Guidelines for the diagnosis and management of cystathio-

nine beta-synthase deficiency. *J Inherit Metab Dis.* 2017;40:49-74.
[39] Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. *Genet Med.* 2013;15:153-156.
[40] Ubbink JB, Vermaak WJ, van der Merwe A, et al. The effect of blood sample aging and food consumption on plasma total homocysteine levels. *Clin Chim Acta.* 1992;207:119-128.
[41] Marti-Carvajal AJ, Sola I, Lathyris D, et al. Homocysteine-lowering interventions for preventing cardiovascular events. *Cochrane Database Syst Rev.* 2017;8:CD006612.
[42] Ray JG, Kearon C, Yi Q, et al. Homocysteine-lowering therapy and risk for venous thromboembolism: a randomized trial. *Ann Intern Med.* 2007;146:761-767.
[43] Kang SS, Rosenson RS. Analytic Approaches for the Treatment of Hyperhomocysteinemia and Its Impact on Vascular Disease. *Cardiovasc Drugs Ther.* 2018;32:233-240.
[44] Wilcken DE, Wilcken B. The natural history of vascular disease in homocystinuria and the effects of treatment. *J Inherit Metab Dis.* 1997;20:295-300.
[45] Miller ER, 3rd, Juraschek S, Pastor-Barriuso R, et al. Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels. *Am J Cardiol.* 2010;106:517-527.
[46] Cui X, Navneet S, Wang J, et al. Analysis of MTHFR, CBS, Glutathione, Taurine, and Hydrogen Sulfide Levels in Retinas of Hyperhomocysteinemic Mice. *Invest Ophthalmol Vis Sci.* 2017;58:1954-1963.