Clinica Chimica Acta 433 (2014) 5–11

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

Homocysteine and migraine. A narrative review

Giuseppe Lippi [a,*], Camilla Mattiuzzi [b], Tiziana Meschi [c], Gianfranco Cervellin [d], Loris Borghi [c]

[a] Laboratory of Clinical Chemistry and Hematology, Academic Hospital of Parma, Parma, Italy
[b] Service of Clinical Governance, General Hospital of Trento, Trento, Italy
[c] Department of Clinical and Experimental Medicine, Academic Hospital of Parma, Parma, Italy
[d] Emergency Department, Academic Hospital of Parma, Parma, Italy

ARTICLE INFO

Article history:
Received 22 January 2014
Received in revised form 26 February 2014
Accepted 26 February 2014
Available online 5 March 2014

Keywords:
Homocysteine
Migraine
Headache
Cardiovascular disease

ABSTRACT

Recent evidence suggests that migraine is associated with an increased risk of cardiovascular disorders, so that it is increasingly hypothesized that this primary form of headache may be linked to thrombotic diseases by some biological pathways and risk factors. Homocysteine, a sulfur-containing molecule, is now recognized as an independent risk factor for a variety of thrombotic disorders, especially ischemic heart disease and stroke. This article is hence aimed to provide an overview of epidemiological evidence about the association between homocysteine and migraine published in cross-sectional, prospective or interventional studies. Overall, the evidence gathered from cross-sectional studies that measured plasma homocysteine levels suggests that the epidemiological link between the plasma concentration of this biomarker and migraine is very weak, at best. Contradictory evidence emerged from interventional studies, in which treatment of hyperhomocysteinemia with folic acid or vitamin B supplementation was effective to lower plasma homocysteine and decrease frequency and/or severity of migraine. The association remains largely speculative, however, since it could not be clearly demonstrated that these two biological effects were directly linked. The only study that has assessed homocysteine in cerebrospinal fluid reported that the concentration of this biomarker in migraine patients was significantly increased compared to controls. Although this evidence must be obviously confirmed in larger trials, some putative mechanisms may support a causal link between increased generation of homocysteine in the brain environment and migraine.

Contents

1. Introduction

Homocysteine is a simple sulfur-containing molecule (HSCH2CH2CH[NH2]CO2H), which slightly differs from the amino acid cysteine for the presence of a single adjunctive methylene group. This compound is actively synthesized in humans from its precursor (methionine) throughout a complex metabolic pathway that involves several essential enzymes and co-factors, namely methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MS), cystathionine beta synthase (CBS), folic acid (also known as vitamin B9), vitamin pyridoxine (also known as vitamin B6) and cobalamin (also known as vitamin B12) (Fig. 1) [1]. The

Abbreviations: CBS, cystathionine beta synthase; CPS1, carbamoyl-phosphate synthase 1; CUBN, cubilin; DPEP1, dipeptidase 1; FUT 2, fucosyltransferase 2; GABA, gamma-amino butyric acid; GTPB10, GTP-binding protein 10; HIS, International Headache Society; HNF1A, hepatocyte nuclear factor-1α; MMACHC, methylmalonic aciduria (cobalamin deficiency) CblC type with homocystinuria; MS, methionine synthase; MTHFR, methylenetetrahydrofolate reductase; MTR, 5-methyltetrahydrofolate-homocysteine methyltransferase; MUT, methylmalonyl CoA mutase; NMDA, N-methyl-D-aspartate; NOX4, NADPH oxidase 4; SLC17A3, solute carrier family 17 (sodium phosphate), member 3.

* Corresponding author at: U.O. Diagnostica Ematochimica, Azienda Ospedaliero-Universitaria di Parma, Via Gramsci, 14, 43126 Parma, Italy. Tel.: +39 0521 703050, +39 0521 703791.
E-mail addresses: glippi@ao.pr.it, ulippi@tin.it (G. Lippi).

http://dx.doi.org/10.1016/j.cca.2014.02.028
0009-8981/

derangement of this metabolic cycle caused by inherited or acquired deficiency of one or more enzymes and co-factors is frequently accompanied by various degrees of hyperhomocysteinemia. As regards the genetic basis of hyperhomocysteinemia, a recent meta-analysis of genome-wide association studies totaling 44,147 subjects has concluded that 13 loci were associated with plasma homocysteine levels. More specifically, significant interactions were detected for polymorphisms in the following genes: *MTHFR*, 5-methyltetrahydrofolate-homocysteine methyltransferase (*MTR*), *CBS*, carbamoyl-phosphate synthase 1 (*CPS1*), methylmalonyl CoA mutase (*MUT*), NADPH oxidase 4 (*NOX4*), dipeptidase 1 (*DPEP1*), methylmalonic aciduria (cobalamin deficiency) CblC type with homocystinuria (*MMACHC*), solute carrier family 17 (sodium phosphate), member 3 (*SLC17A3*), GTP-binding protein 10 (*GTPB10*), cubilin (*CUBN*), hepatocyte nuclear factor-1α (*HNF1A*) and fucosyltransferase 2 (*FUT2*) [2].

The substantial involvement of homocysteine in human disease has been appreciated for long, when McCully first hypothesized a link between some cases of vascular disease and homocystinuria, in 1969 [3]. In the following decades, this original hypothesis has been confirmed by a large number of studies, so that hyperhomocysteinemia is now regarded as a risk factor for a kaleidoscope of thrombotic disorders [4]. Humphrey et al performed a systematic search of the literature to identify primary prevention trials that assessed the risk of coronary heart disease associated with hyperhomocysteinemia. The relative risk (RR) associated with 5-μmol/L increase in plasma homocysteine level estimated from pooled data of the 21 studies included in the meta-analysis was found to be 1.18 (95% CI, 1.10–1.26) [5]. As regards stroke, the Homocysteine Studies Collaboration meta-analyzed data from prospective or retrospective studies including a total of 1113 stroke events, and estimated that a 25% reduction of plasma homocysteine levels (i.e., approximately 3 μmol/L) was associated with a significantly reduced risk (Odds Ratio [OR], 0.81; 95% CI, 0.69–0.95) [6]. Homocysteine may also have a role in the pathogenesis of peripheral occlusive artery disease. Khandanpour et al carried out an electronic search to identify observational studies that reported homocysteine levels in patients with peripheral occlusive artery disease compared to unaffected controls [7]. The following meta-analysis of 14 relevant trials including 2291 cases and 6525 controls showed that an increase of 4.3 μmol/L of plasma homocysteine was associated with a RR of 4.31 (95% CI, 1.71–6.91) for peripheral occlusive artery disease. Den Heijer et al performed a meta-analysis of all relevant studies exploring the association between homocysteine and venous thrombosis [8]. Overall, 27 studies were identified (24 retrospective, 3289 cases; 3 prospective, 476 cases), which allowed to estimated that a 5-μmol/L increase in plasma homocysteine level was associated with a RR of 1.27 (95% CI, 1.01–1.59) for venous thrombosis in prospective trials, and a RR of 1.60 (95% CI, 1.10–13.4) in retrospective studies. In another recent meta-analysis of four studies including 972 subjects (212 cases and 760 controls), Lauw et al concluded that hyperhomocysteinemia is significantly associated with cerebral venous thrombosis, displaying an OR of 2.99 (95% CI, 1.32–6.75; $p = 0.009$) [9].

Besides the convincing evidence that has emerged from meta-analyses of epidemiological studies, data obtained from interventional trials aimed at investigating whether homocysteine lowering treatments were effective to decrease the thrombotic risk does not unequivocally support the role of this biomarker in the pathogenesis of cardiovascular disorders, with one notable exception, that is stroke. Lee et al carried out a meta-analysis of published studies that investigated the efficacy of folic acid supplementation in prevention of stroke and found that this treatment was associated with a mild benefit in reducing the risk (RR 0.93; 95% CI, 0.85–1.03), with a more evident benefit in nonsecondary prevention trials (RR, 0.89; 95% CI, 0.79–0.99) and in studies combining folic acid and vitamin B (RR 0.83; 95% CI, 0.71–0.97) [10]. In another and more recent meta-analysis published by Ji et al and including 14 randomized controlled trials with 54,913 participants, it was concluded that lowering homocysteine with B vitamin supplementation was effective to significantly reduce the overall risk of stroke events (RR 0.93; 95% CI, 0.86–1.00; $p = 0.04$) [11].

According to the International Headache Society (IHS), migraine should be considered a primary form of headache, which is typically characterized by pain located above the orbitomeatal line, and which can be preceded by focal neurological symptoms (i.e., aura) [12]. Due

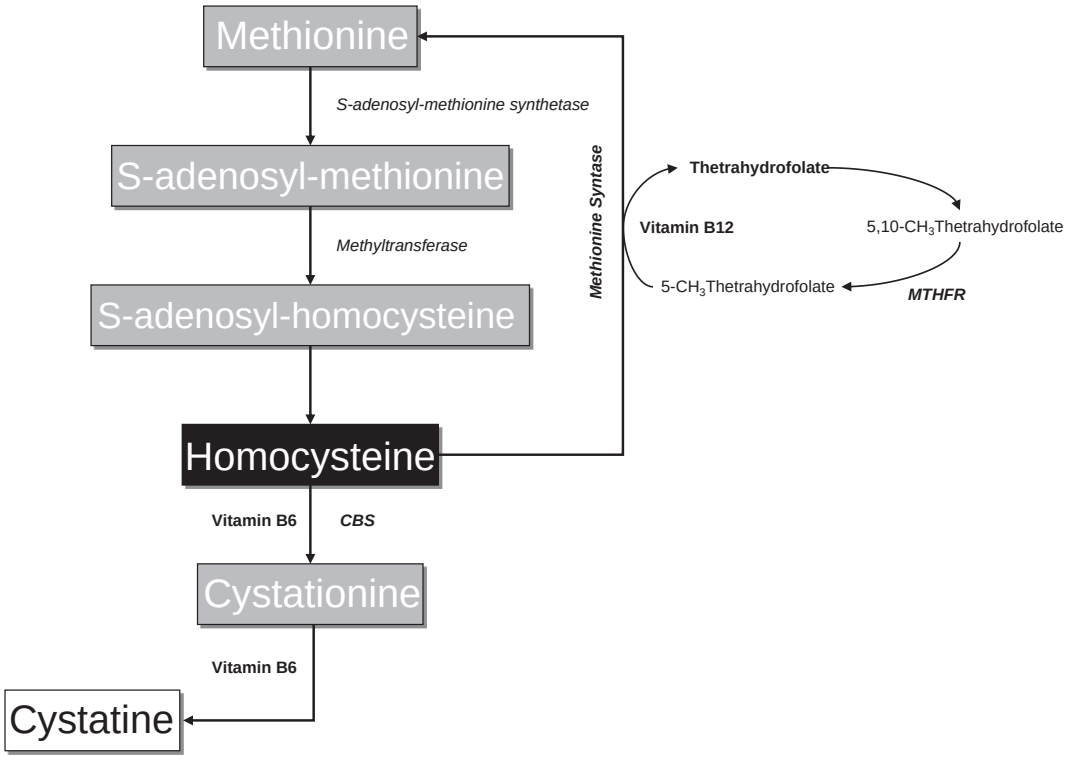

Fig. 1. Metabolism of homocysteine. CBS; cystathionine beta synthase; MTHFR, methylenetetrahydrofolate reductase.