Clinica Chimica Acta 450 (2015) 316–321

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Invited critical review

Homocysteine in ocular diseases

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ARTICLE INFO

Article history:
Received 30 July 2015
Received in revised form 1 September 2015
Accepted 3 September 2015
Available online 4 September 2015

Keywords:
Cataract
Glaucoma
Diabetic retinopathy
Hyperhomocysteinemia
Visual impairment
Folate
Vitamin B12

ABSTRACT

Homocysteine (Hcy) is a derived sulfur-containing and non-proteinogenic amino acid. The metabolism of Hcy occurs either through the remethylation to methionine or transsulfuration to cysteine. Studies have identified hyperhomocysteinemia (HHcy) as one of the possible risk factors for a multitude of diseases including vascular, neurodegenerative and ocular diseases. Association of HHcy with eye diseases such as retinopathy, pseudoexfoliative glaucoma maculopathy, cataract, optic atrophy and retinal vessel atherosclerosis is established. The molecular mechanism underlying these ocular diseases has been reported as impaired vascular endothelial function, apoptosis of retinal ganglion cells, extracellular matrix alterations, decreased lysyl oxidase activity and oxidative stress. The formed homocysteine-thiolactone in HHcy has stronger cytotoxicity and pro-inflammatory properties which can induce lens opacification and optic nerve damage. The metabolism of Hcy requires enzymes with vitamins such as folic acid, vitamins B12 and B6. Despite the mixed conclusion of various studies regarding the level of these vitamins in elder people, studies recommended the treatment with folate and B12 to reduce Hcy levels in subjects with or without any defect in the enzymes involved in its metabolism. The levels of Hcy, folate, B6 as well as B12 should be measured early in patients with visual impairment that would aid to screen patients for life-threatening disorders related with HHcy. Elder patients may supplement with these vitamins in order to attenuate the ocular damages. This article discusses the association of Hcy in ocular diseases and the possible mechanism in the pathogenesis.

Contents

1. Introduction

Although substantial progress has been made in the development of techniques in the surgical interventions of eye diseases, visual impairment and blindness remain the major challenges to most of the developing countries. Main causes of visual impairment reported by WHO were glaucoma, cataract, diabetic retinopathy, age-related macular degeneration (AMD), corneal opacities, onchocerciasis, childhood blindness and trachoma. Unoperated cataract (33%) remains the major avoidable blindness. More than 90% of the world's visual impairment are reported in developing countries and is unequally distributed across various age groups. More than 82% of people who are blind are 50 years of age and older [1]. Nutrition is one of the important determinants of health and is often under diagnosed over the age of 65 [2]. Despite no uniformly accepted definition for malnutrition in the elderly, some indicators including specific vitamin deficiencies have been well described [3].

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http://dx.doi.org/10.1016/j.cca.2015.09.007
0009-8981/

Homocysteine (Hcy), a derived sulfur-containing and non-proteinogenic amino acid which is formed in trace amount during the metabolism of essential amino acid, methionine. The metabolism of Hcy occurs through the remethylation to methionine or conversion to cysteine which requires coenzymes such as vitamins B6, and B12, and methyl folic acid. Deficiencies in these vitamins are associated hyperhomocysteinemia (HHcy)—an abnormally very high level of Hcy in blood. HHcy has been implicated in the pathogenesis of a variety of diseases including cardiovascular and neurodegenerative disorders [4–6]. Association between Hcy and nervous system disorders was first documented in patients with severe cystathionine beta synthase deficiency [7,8]. Since then, elevated level of Hcy has been reported in several diseases. Approximately, 3-fold higher risk for white matter damage was found at concentrations of Hcy above 11.9 μmol/L than below 8.6 μmol/L [9].

There is multitude of diseases in the elderly associated with HHcy such as heart failure, stroke, dementia, and bone fracture [10]. High plasma Hcy concentrations with low folate and B6 are associated with an increased risk for extracranial carotid-artery stenosis [11,12]. The impaired endothelium dependent vasodilatation due to the chronic elevation of plasma Hcy level can be the mechanism underlying the vascular diseases. Recent evidences indicate that HHcy may be associated with ocular diseases. In this review, we discuss the role of HHcy in ocular diseases.

2. Factors increase homocysteine level in the body

Hcy is derived from the dietary methionine. Normally, it is remethylated to methionine by methionine synthase with the help of methyl folate and B12 (Fig. 1). It can also be converted to cysteine by pathway initiated with the trans-sulfuration reaction with serine to form cystathionine by cystathionine β-synthase and B6. These two pathways deplete intracellular Hcy in a healthy manner. Therefore, accumulation of Hcy in cells depends on the activities of methionine synthase, cystathionine β-synthase. The free Hcy can also be converted into homocysteine-thiolactone (Hcy-T) as an error-editing reaction by methionine tRNA synthetase which occurs in all human cells [13]. The Hcy-T is secreted from cells to plasma where it is hydrolyzed to free Hcy and this futile cycle will be prominent, when the remethylation or transsulfuration pathways are limited or defective.

Compared to Hcy, the Hcy-T has been proven to be more cytotoxic. The highly reactive Hcy-T can easily acylate amino groups of proteins under physiological conditions. Both, free and Hcy-T can involve in post-translational modifications of protein such as N-homocysteinylation or S-homocysteinylation. Mechanism of N-homocysteinylation involves acylation of Lys ε-amino group of protein by the activated carboxyl group of Hcy-T [14–17]. The S-homocysteinylation is directly dependent on the levels of Hcy in the blood, where it nonenzymatically forms adducts with disulfide linkages with the sulfhydryl residues of the protein [15,16,19–21]. Thus, the protein bound Hcy forms exist as either N-homocysteinylated or S-homocysteinylated forms.

The total plasma Hcy level is determined by genetic factors or factors that were acquired during the lifetime. Fasting plasma Hcy concentration for healthy adults of young age is 5–15 μmol/L. Hcy concentrations greater than 15 μmol/L are considered as HHcy and level 15–25 μmol/L considered as mild HHcy [21]. In humans, approximately 70–80% of total plasma Hcy is protein bound. The level of N-homocysteinylated proteins in human plasma ranges from 0.3 to 23% of total Hcy, whereas the Hcy-T is present in very trace amount. Majority of the unbound Hcy is oxidized to homocystic acid or combined with cysteine to form mixed disulfide and a small amount exists as a free reduced homocysteine [15,16,19–21].

The plasma concentration of Hcy may indicate the nutritional status of the B-vitamins [22]. Studies showed that plasma Hcy concentration is inversely related to the intake and plasma levels of folate and B6 as well as B12 levels. Therefore, oral and dental issues, esophageal motility and atrophic gastritis may affect nutritional status of these vitamins and thus the level of Hcy. In elderly population, B_{12} deficiency is expected to be high owing to the strict vegetarian diet, prevalence of *Helicobacter pylori* infection, atrophic gastritis or due to other gastrointestinal changes occurring with age that may impair B12 absorption [23]. Some of the previous reports revealed that for some elderly people with a reduced intake of caloric diet, it may be difficult to meet daily requirements of micronutrient [24,25]. The level of Hcy in the blood is increased in conditions such as deficiency of enzymes involved in the metabolism such as methyltetrahydrofolate reductase or cystathionine-β-synthase. In addition to these, a high level of serum Hcy is observed in systemic arterial hypertension, diabetes mellitus, chronic renal insufficiency, or in malignant neoplasms. Additionally, habitual smoking and coffee intake, some medications, alcohol consumption and physical activity may also affect Hcy levels [26].

3. Association of hyperhomocysteinemia in eye diseases

HHcy has been implicated in visual dysfunction. In the ocular system, many evidences indicated HHcy as a risk factor for variety of diseases, including retinal arteriosclerosis [27], glaucoma [28,29], exudative age-related macular degeneration [30,31] and macular and optic atrophy due to retinal vascular occlusion or non-arteritic ischemic optic neuropathy (Fig. 2) [32,33]. The third National Health and Nutrition Examination Survey reported the association of blood Hcy and the nutritional determinants with the age-related maculopathy

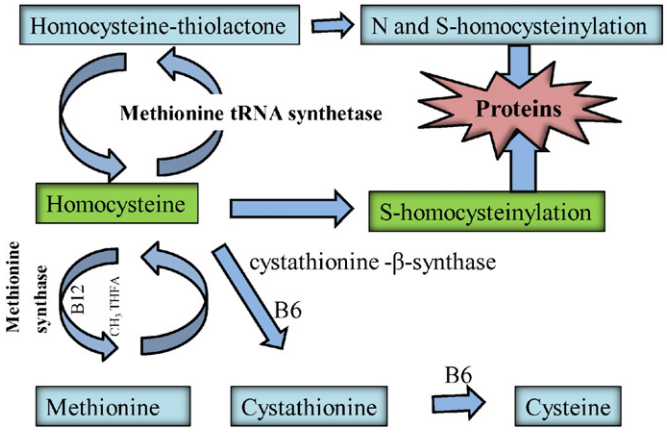

Fig. 1. Metabolism of homocysteine (Hcy). Hcy that is formed during the transmethylation reactions is converted back to methionine in the presence of methyl THFA and B12. A fraction of Hcy can be converted to cysteine. Excess of Hcy or its metabolite homocysteine—thiolactone can involve in homocysteinylation, a post translational modification of proteins.

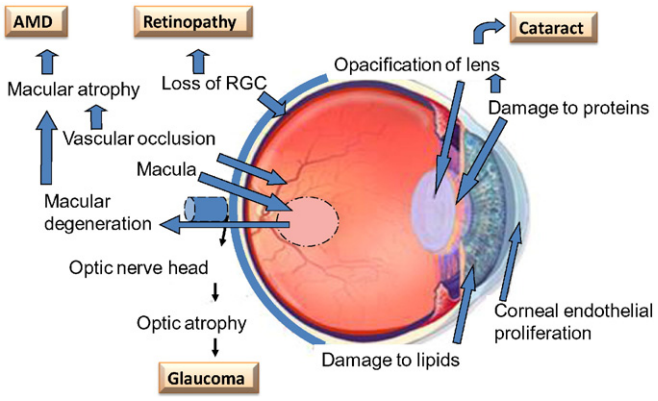

Fig. 2. Structures in the eye damaged during hyperhomocysteinemia and the associated ocular diseases. AMD: age-related maculopathy; LOX: lysyl oxidase RGC: retinal ganglion cells.