Case Report

Hyperhomocysteinemia for Alzheimer’s Disease: Risk Factor, Biomarker or Both?

Federico Cacciapuoti*
Department of Internal Medicine and Geriatry, Second University of Naples, Italy

Abstract

Background: Alzheimer’s disease (AD) is the most common display of neurodegeneration. It is a multifactorial disease both at early- and late-onset. A number of studies have found that H-Hcy can be significantly correlated with increased risk of AD in the late onset form only.

Methods and Results: Several evidences shown that H-Hcy may promote AD by more than one mechanism including impair lipoprotein E genotype, involved in lipid transport and neuronal repair and synaptogenesis. But, endothelial dysfunction; neurotoxicity; apoptosis; Ca++ dysregulation; neuronal DNA damage and homocysteic acid (N-methyl-D-aspartate agonist) production are also responsible of AD. Some of these have a causal connection with AD. Others act a simple marker of different conditions, such as DNA hypometilation consequent to H-Hcy. Both these mechanisms can induce AD, acting such as risk factor or marker at the same time.

Conclusions: Conclusively, H-Hcy can act such as risk factor, marker, or both for AD pathogenesis by unknown mechanisms.

ABBREVIATIONS

AD: Alzheimer’s Disease; H-Hcy: Hyper-homocysteinemia; Hcy: Homocysteine; APOE: Apolipoprotein E; HDL: High Density Lipoproteins; m ROS: Reactive Oxygen Species; SAH: S-Adenosyl-Homocysteine

INTRODUCTION

Alzheimer’s disease (AD) is the world’s most common neurodegenerative disorder that continuously rises with increased lifespan. Globally, more than 26 million people have been diagnosed with AD and are projected to exceed 100 million by year 2050. Two clinical forms of AD are described: an early onset AD (rare) occurring between the ages 30-60 years that is gene-dependent. A late-onset AD (more frequent) evident over 65 to 80 years of age. A number of factors have been proposed that might account the beginning of late-onset AD. Among these: vascular derangements, advanced age, gender, renal dysfunction, behavioral problems, baseline cognitive status, lifestyle, etc. there are. Increased concentrations of homocysteine (H-Hcy) levels have also been frequently linked with AD pathogenesis but, the relationship between AD and Hcy appears to be complicated by the aging [1-3].

Hcy is a sulfur-containing produced from dietary methionine. When methionine levels are low, Hcy is remethylated into methionine: a process that requires vitamin B12 and folic acid as cofactors. When methionine levels are high, Hcy condensates to serine to form cystathionine, and subsequently, cysteine (through the trans-sulfuration pathway). Normally, about 50% of Hcy is remethylated, the remained Hcy is trans-sulfurated through a biochemical process requiring vitamin B6 as cofactor. This pathway yields cysteine, used to make glutathione, a powerful antioxidant that protects cellular components against oxidative damage (Figure 1).

In this report, we discuss if H-Hcy has been associated with an increased risk of developing AD or is a simple marker reflecting an underlying process responsible for both H-Hcy and the AD development. A disease risk factors can be defined as measurable biological characteristics of an individual that precede a well-defined outcome and are directly in the biological causal pathology. In contrast, biomarkers are biological indicators for processes involved in developing a disease.

Concerning this topic there is some contradictory evidence, and it remains controversial whether H-Hcy is an AD risk factor or merely biomarker. Some cohort studies suggested a direct relationship between elevated Hcy concentrations and risk for AD [1,4,5]. But, other authors did not find a cause-effect relationship between H-Hcy and AD [6]. A direct connection between H-Hcy and AD pathogenesis has been reported in the Rotterdam Scan Study [7], in the Banbury B12 Study [8] and in the Northern Manhattan Study [9] but, the Washington Heights-
In wood Columbia Ageing Project (WHICAP) reported no direct relation [6]. An increased Hcy concentration can act as risk factor for AD through several mechanisms: Apolipoprotein E (APOE) genotype is one of the major lipid acceptors, able to remove cholesterol from cells and generate HDL particles involved in neuronal repair and synaptogenesis after injury [10]. In normal conditions, APOE4 isoform exhibits higher levels of Aβ peptide, senile plaques and neurofibrillary tangles. So, APOE4 isoform seems to be a major risk factor for AD. On the contrary, APOE3 isoform has a protective effect. Hcy impairs APOE3 function, reducing APOE3-mediated HDL generation, whereas it does not affect APOE4 function. Therefore, an increased Hcy concentration seems to favour AD pathogenesis. An experimental study performed in knock-out mice confirmed that Hcy interferes with APOE3, impairing its ability to generate HDL [11]. Recently Elias and al. confirmed that cognitive decline and impaired cerebral performance directly depend on increased Hcy serum levels [12]. A positive relationship among H-Hcy, APOE and cognitive decline in older adults was also hypothesized by Bruce et al., [13]. Another study found that H-Hcy impairs the integrity of blood-brain barrier (BBB), leading to cell damage and cognitive decline until AD [14]. It is known that Hcy is excitotoxic to cortical neurons in cell culture, suggesting a causal role for the amino acid in the cholinergic deficit, typical of AD [15]. In addition, some derivative products of Hcy such as homocysteic acid, analog to glutamate and N-methyl-D-aspartate (NMDA), can act as agonist on the NMDA receptor. That induces an excitatory neurons' damage, including cognitive impairment and AD [16,17]. In confirmation of the excitotoxic theory, a protective effect of methylcobalamin, a vitamin B12 analog, against glutamate cytotoxicity was also described [18]. To further testify the neuro-degenerative effects typical of AD induced by H-Hcy, Kim et al., and Rajagopolan et al., demonstrated that elevated Hcy levels can cause hippocampal or cortical atrophy and white matter changes [19,20]. Some studies also provide evidence that H-Hcy directly could affect beta-amyloid and tau metabolism [21]. Finally, injection of Hcy into rat brain increases Aβ levels and tau phosphorylation [22,23]. Other mechanisms have been proposed to explain the connection between H-Hcy and AD, such as impaired DNA repair mechanism leading to apoptosis and other types of damages [24,25]. Schilling and Eder found that Hcy and other thiols are able to produce a variety of ROS strongly implicated in the pathogenesis of Alzheimer disease, through the Aβ stimulation by unknown mechanism [26]. Further, Tchantchou et al., demonstrated that Hcy acts by reducing the activity of some antioxidants, as glutathione, probably by increasing glutathione-S-transferase activity [27]. Hcy can also augment the toxicity of Aβ by exacerbating their pro-oxidant activity [28]. But, H-Hcy can also act as marker for the disease. Particularly, the prevalence of S-Adenosyl-Homocysteine (SAH) in the Methionine cycle, causes the hypomethylation of some substrates because it acts as inhibitor of methyltransferases [29]. In detail, DNA hypomethylation arrests the cells' cycle at G1/S transition via Cyclin gene, inhibiting endothelial cells growth. This process, in turn, can be responsible for endothelial dysfunction and proliferation of vascular smooth muscle cells, subsequently evolving to early atherosclerosis [29]. So, macro- and micro-angiopathy, endothelial dysfunction, impaired nitric oxide activity and increased oxidative stress can be cause of vascular dementia and AD [30].

According to these observations, a question there is: does H-Hcy itself damage blood vessels and neurons, or it is a marker for deficiency or depletion of other interconnected compounds (SAH), or both? [31,32]. The answer to this question rises from therapeutic interventions performed with vitamins of B group. Hyperhomocysteinemic patients treated with these nutraceuticals differently reply. On the basis of their behaviour we report that, when H-Hcy acts such as a direct cause (risk factor) of AD, folates and B vitamins supplementation decreases both Hcy levels and the risk of AD [33,34]. On the contrary, if DNA hypomethylation prevails so that it is only an indicator (marker) of increased AD risk, despite folic acid and B6-12 vitamins supplementation reduces the elevated Hcy plasma levels; it does not significantly influence AD [35-37]. H-Hcy may also act as a risk factor and a marker for AD at the same time. In these cases, folates and vitamin B12 supplementation also lowers Hcy levels and prevents or delays cognitive impairment and AD [38].

CONCLUSIVE REMARKS

Some conditions dependent of H-Hcy, as DNA hypomethylation, seem to be a powerful marker than a causal factor of cognitive decline and AD. In that case, folate and vitamin B6-12 supplementation appears to be useless because it not reduce the incidence of these diseases, although lowers H-Hcy levels. But, increased Hcy levels can act as a direct cause (risk factor) of cognitive impairment and AD. When that happens, vitamin B6-12 and folic acid supplementation acts both reducing H-Hcy concentration and AD risk. Finally H-Hcy inducing AD, can behave oneself both as risk factor and marker simultaneously. In this occurrence, folate and vitamin B6-12 supplementation also reduce both Hcy serum concentration and AD risk. The different reply to B vitamins treatment we allow to hypothesize that H-Hcy
may act as risk factor, marker, or both by unknown mechanisms. These conclusions are only partially in agreement with Zhuo et al., affirming that H-Hcy can be risk factor, marker or neither for AD [39]. Nevertheless, other studies with a larger sample size need to confirm or refute the conclusions reported.

CONFLICTS OF INTEREST

The author declares no potential conflict of interest with respect to the review and/or publication of this article.

REFERENCES


