Supplementation of Pyridoxine, Folate and Cobalamin in Older People: An Analysis on their Effect on Hyperhomocysteinemia and Dementia

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Abstract: Prevalence of dementia above age of 65 years is very high. Due to the unavailability of an effective screening tool in most of the primary care practices, majority of the elder patients with early dementia are undiagnosed. Despite the advances in the field of dementia research, no pharmacologic agents were found to be beneficial in Alzheimer's disease. Sulphur containing derived amino acid homocysteine (Hcy) has been demonstrated well in human ailments. Vitamins such as B6, folate and B12 deficiency were manifested as one of the etiological factors for hyperhomocysteinemia (HHcy) in elder people. Though the folic acid plus vitamin B12 therapy was effective in reducing the HHcy, their effect on dementia or Alzheimer's disease is debatable. This review article discusses the recent observation on the effect of vitamin therapy on HHcy in dementia.

Keywords: Alzheimer's disease, homocysteine, hyperhomocysteinemia, vitamin B12, vitamin B6, folate.

1. INTRODUCTION

In elder subjects, the prevalence as well as burden of the dementia syndrome is high especially above 65 years of age. Due to the unavailability of an effective screening tool in most of the primary care practices, majority of the elder patients with early dementia are undiagnosed. Pharmacologic and nonpharmacologic agents in the treatment of mild to moderate Alzheimer's disease, one of the major causes for dementia shows mixed responses. Ongoing research during the last decade has emphasized the role of derived sulphur containing amino acid homocysteine (Hcy) in human ailments. Hcy is formed from the metabolism of essential amino acid methionine. Only trace amount of Hcy is maintained in the plasma either by its effective conversion to cysteine via transsulfuration pathway or conversion back to S-adenosyl methionine. This conversion is depending on the availability of vitamins such as pyridoxine (B6), folate and cobalamin (B12). The reference normal level of total Hcy in fasting serum or plasma sample is ranging from 5-15 micromoles/L. An increase to the upper limit of reference level has been observed in people over 65 years of age. Total Hcy level above the 15 micromoles/L is considered as hyperhomocysteinemia (HHcy). The level between 15-25 micromoles/L is considered as mild HHcy. Hereditary HHcy in children is associated with the inborn errors of Hcy metabolism. In elder people, the deficiency of B6, folate and B12 vitamins can be the major etiological factor for HHcy. Apart from the dietary factors, lifestyle factors such as chronic cigarette smoking and alcoholism were also associated with HHcy in adults.

2. ROLE OF HYPERHOMOCYSTEINEMIA IN DEMENTIA

HHcy has role in the pathophysiology of several human ailments. A recent review describes the role of HHcy in ocular diseases [1]. The association of HHcy in most of the pathogenesis has been ascribed to the direct cytotoxic effect or indirectly related to inflammation and oxidative stress. Moreover, post-translational modification by homocystinylation of various proteins may alter their structure and functions. Among the proteins, lysine oxidase, an enzyme involved in the maturation of collagen and elastin in connective tissue is mainly affected by such homocystinylation. Furthermore, modification of arginine results in the formation of asymmetric dimethyl arginine (ADMA) which is an inhibitor of endothelial nitric oxide synthase and, thereby, curtail the nitric oxide release in endothelium. This has been explained for the vasoconstriction and endothelial injury. A positive correlation of ADMA level and HHcy has been reported [2]. An increase in ADMA has been associated with approximately 4 fold increase in the risk for atherosclerosis [3].
Recent studies demonstrated the role of HHcy in neurodegenerative diseases. This can be explained with the oxidative stress as well as the direct cytotoxicity of Hcy on nerves (Fig. 1). HHcy has been suggested as a cause for the development Alzheimer's disease and other forms of dementia. Xu et al. demonstrated the cerebral aneurysm formation in rat results from the methionine rich diet-induced HHcy [4]. Hcy level has been correlated with white matter lesions and silent brain infarcts. The odd for such findings were elevated in subjects with Hcy level above 8 micromoles/L. Hippocampal and cortical atrophy were also positively correlated with the Hcy level. Hogervorst et al. demonstrated that with each 5 μmol/L increase of plasma total Hcy, the risk for leukoaraiosis was significantly increased [5]. Porter et al. suggested the possible link of HHcy with the risk of dementia and Alzheimer's disease [6].

![Deficiency of pyridoxine (B6), folate and cobalamine (B12) results in the declined conversion of homocysteine (Hcy) to cysteine (Cys) and S-adenosyl methionine (SAM). This will result in hyperhomocysteinemia (HHcy) which will induce the inflammation, and oxidative stress. The oxidative stress and neurotoxic effect can be correlated to the Hcy mediated over activation of N-methyl-D-aspartate receptor. HHcy induces the asymmetric dimethyl arginine formation (ADMA) which decreases the nitric oxide (NO) level and, thereby, produce endothelial injury. All these effects finally result in cognitive dysfunction in addition to the B6 and B12 deficiency associated neurological crisis.](image-url)

### 3. Vitamin Deficiencies and Dementia

Vitamin deficiencies could influence the memory function and thereby, might contribute to the age-associated cognitive impairments including dementia. This can be ascribed to the metabolic derangements. Low dietary intake was the most common cause for folate deficiency, while malabsorption and increased requirements during ageing were explained for the low B12 and B6 status, respectively. These vitamin deficiencies can elevate the Hcy level in older people and, therefore, an irreversible cognitive dysfunction in vitamin deficiency has been explained with the HHcy.

The protective roles of folate, B12 and B6 in deficiency diseases in older people are increasingly recognized. Clinical trials showed that 2 mg of folic acid plus 1 mg of vitamin B12 once daily for 12 weeks could significantly lowered the serum Hcy level. Combination of vitamin B12 and folic acid in patients with mild to moderate cognitive impairment due to Alzheimer's disease or mixed dementia did not show any benefit when compared to the placebo [7]. Hence, their effect on dementia or Alzheimer's disease is debatable.

Despite the etiological factors, epidemiological studies were also demonstrated the poor B6 status in older people. Though the supplementation of B6 (20 mg pyridoxine hydrochloride) once per day for 12 weeks could improve its blood level and reduced the Hcy level, clinical trials found statistically insignificant benefits on mood or cognition [8]. Furthermore, a combination of the three vitamins i.e. B6 (5 mg), B12 (0.5 mg) and folic acid (1 mg) supplementation for 26 weeks in 89 patients with mild to moderate AD patients in Taiwan showed a decreased Hcy level without any significant beneficial effects on the cognition or on the performance of daily living activities [9].
4. CONCLUSION AND FUTURE PERSPECTIVES

The results of the studies concluded that supplementation of vitamin B6, folate and B12 in elder subjects can correct their deficiency manifestations as well as attenuate the HHcy without any significant benefit on the cognitive dysfunction. Most of the clinical trials so far conducted were in diagnosed AD patients with mild or moderate disease where the Hcy level was already high. Therefore, a more prospective case controlled study on Hcy level and supplementation of these vitamins in elder subject prior to the cognitive impairment is warranted. Furthermore, the possible benefits from the supplementation of B6 in healthy elder people with cognitively impairment or dementia are also need to be evaluated.

REFERENCES