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Cognitive decline: a vitamin B perspective

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ABSTRACT
Cognitive decline is one of the major causes of disability in older people. A high level of homocysteine, a byproduct of vitamin B, has been linked to brain atrophy, a precursor to cognitive decline leading to dementia and Alzheimer's disease. In addition, a low level of vitamin B is often noted in patients with dementia and Alzheimer's disease and its supplementation has been shown to improve memory and slow the progress of brain atrophy. This information may aid in the use of vitamin B as a preventative measure of severe cognitive decline, and thus reduce the onset of conditions such as, dementia and Alzheimer's disease.

Keywords: Inflammation, Immune system, Immune cells, Ageing, Gerontology

1. Introduction

All ageing humans will develop some degree of decline in cognitive capacity which predisposes some individuals to neurological and psychiatric disorders leading to poor quality of life [1]. Cognitive decline during ageing is multi-factorial, however, this paper focuses on the role of vitamin B during this process. Ageing deteriorates neuronal membranes (loss of myelin sheath) resulting in impaired neurotransmitter synthesis, signaling and overall diminished neuronal function [1]. Over time, symptoms include forgetfulness, inability to focus and decreased problem solving skills. Symptoms may progress to anxiety, depression, dementia and Alzheimer's disease (AD) [2]. Currently there are no drugs or other treatments specifically approved to treat cognitive impairment or prevent its progression.

2. Methodology

Herein, we present a vitamin B perspective in cognitive decline, using PubMed searches with the following key terms: dementia AND (vitamin B1 OR thiamine), dementia AND (vitamin B2 OR riboflavin), dementia AND (vitamin B6 OR pyridoxine), dementia AND (vitamin B9 OR folate OR folic acid), dementia AND (vitamin B12 OR cobalamin), cognitive decline AND (vitamin B1 OR thiamine), cognitive decline

AND vitamin B2 OR riboflavin), cognitive decline AND (vitamin B6 OR pyridoxine), cognitive decline AND (vitamin B9 OR folate OR folic acid), cognitive decline AND (vitamin B12 OR cobalamin), homocysteine AND vitamin B, homocysteine AND dementia, Alzheimer's AND vitamin B. In particular, publications from 2006-2016 are mostly cited.

3. Dementia and Alzheimer's disease

Dementia is a term used for a particular set of cognitive decline symptoms, which often occur with ageing, and includes impaired thinking and memory. There are many different kinds of dementia, the most common is Alzheimers diseases which contributes to 60-70% of cases worldwide (Fig 1). Other forms include vascular dementia, dementia with lewy bodies and dementia caused by diseases, such as, Huntington's, Parkinson's, Creutzfeldt-Jakob's. The process of ageing in humans leads to changes in brain morphology and function, which in turn can lead to an increased risk of disorders of a psychiatric and neurological nature. In fact, over 540 genes have been identified as age-related changes, and changes are progressive throughout adult life which can accurately predict the age of an individual [3]. Interestingly, most age-related genes to be up regulated are of inflammatory and glial origin, whereas, those to be down regulated are mostly cell communication and signaling origin. It is still unclear however, as to how the relationship between ageing and the clinical and molecular features of cognitive diseases such as, dementia and AD are linked. It has been postulated that an increase in life expectancy in western cultures has coincided with an increase in the prevalence of cognitive impairments (dementia, AD etc), and perhaps this is less about disease process and more about the natural process of ageing [4].

AD has been described as the most common disease of ageing. Patients with AD suffer a progressive cognitive decline, and, an inability to form memories. The gradual diminishing of intellectual function eventually leads to complete dependence for all basic life functions and eventual death at a premature age [5]. There are numerous incongruent leads into the pathogenesis of AD. The first histopathological features recognized were the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles. Aneuploidy, synaptic degeneration and hippocampal neuronal loss later became distinguishing features of AD. In fact, post-mortem studies of AD patients, find the existence of these histopathological features in up to 90 % of cases [4]. Mitochondrial dysfunction is also implicated in AD, including, amyloidosis (Aβ), oxidative stress, tau phosphorylation and cell cycling [6]. Further, vascular disease increases Alzheimer's risk. A common finding amongst older adults who meet the neuropathological criteria for AD is the occurrence of cerebral amyloid known as angiopathy. This condition is characterised by Aβ deposits in cerebral blood vessel walls, which leads to intracerebral hemorrhages and impact cerebrovascular function. This occurs as a result of weakening of vessel walls, which can lead to rupture [7].

4. Risk factors contributing to cognitive decline

A number of contributing factors have been associated with cognitive decline in humans. Such factors include: suboptimal nutrition, physical inactivity and sedentary lifestyle, obesity, smoking, hormonal imbalances, low-grade chronic inflammation, oxidative stress and free radical damage to the myelin sheath, cerebrovascular health, high density lipoprotein levels, high cholesterol levels, high homocysteine levels, hypertension, impaired blood glucose and depression [8]. There are certain dietary considerations for improved cognitive function, which include: moderate coffee and red wine intake, fish oil, polyphenols and anthocyanin-containing foods (tea, blueberries, resveratrol), coenzyme Q10, acetyl-L-carnitine, ginkgo bilboa and multi-vitamins – in particular B vitamins.

4.1 The relationship between serum homocysteine in dementia and AD

Epidemiological evidence and longitudinal data flag elevated serum homocysteine as a probable risk factor for cognitive impairment and AD [9]. Homocysteine is a product of the methylation cycle and has been linked to brain atrophy, oxidative stress, DNA damage, increased apoptosis, excitotoxicity and neurodegeneration [9-11]. Methylation is the mechanism by which the body deals with stress, toxins and infections. The methylation pathway deals with the balancing of neurotransmitters and detoxification processes in the body, and controls inflammation. Methylation reactions are involved in almost every chemical reaction undertaken within the body (Fig 2). The result of ineffective methylation reactions within the body is widespread and can result in many health conditions and diseases, including neurological disorders such as anxiety, depression, bipolar disorder, AD, fibromyalgia, neural tube defects, schizophrenia and sleep disorders [12].

The enzyme methionine synthetase catalyzes the methylation of homocysteine to methionine (Fig 2) [13]. The failure of this reaction to take place effectively leads to an increase in blood levels of homocysteine, which can cause metabolic impairment. Several neurodegenerative disorders including Parkinson's, AD, depression and dementia are characterized by increased homocysteine levels [13]. The toxic effect to vascular endothelial and neuronal cells caused by homocysteine elevation is well documented [14, 15]. In order for homocysteine levels to remain low in the central nervous system, an adequate amount of folate is required in the diet, as folate is essential in the methylation of homocysteine to methionine and in the synthesis of S-adenosyl-methionine, which is required for methylation of DNA, proteins and lipids. Several studies have shown that serum homocysteine are significantly higher, and serum folate and vitamin B12 levels lower, in patients with dementia and AD patients [16]. In fact, high homocysteine levels increases risk of brain atrophy which is exacerbated by alcohol [9].

The status of B vitamins is frequently inadequate in the elderly and several studies have shown decreases in cognitive function, which may lead to AD [11]. This leads to the question - would inadequate vitamin B levels contribute to brain malfunctions or are brain malfunctions a result of the ageing process leading to disease? In 107 individuals aged between 60-87 years of age who did not present with symptoms of cognitive impairment, those with lower vitamin B12 and holotranscobalamin (active form of B12) and higher plasma total homocysteine, had a greater decrease in brain volume over a 5 year follow-up period [17]. However, in the Rotterdam study, in 702 individuals aged 55 years and over, there was no difference in patients with higher homocysteine and cognitive decline [18]. This study was carried out over a shorter period, with the mean duration of follow up being 2.7 years. It is possible that the time period for follow up was too short to note any significant change in cognitive decline. The age cut off for the patients in this study was 55 years which is considerably lower than in the previous study in which the age of patients was between 60-87 years of age.

5. B vitamins: link to cognitive decline

Vitamins are dietary components other than carbohydrates, fats, minerals and proteins that are necessary for life. Vitamin B complex plays an important role in the functioning of the methylation cycle, involved in monoamine oxidase production, synthesis of DNA, RNA, protein and phospholipids, and in cell repair. The role of the methylation cycle in detoxification of the body ensures proper immune function and inflammatory balance, maintains DNA, provides energy and balances mood behaviors [19]. Homocysteine, which is solely a product of the methylation cycle acts as a sensitive marker of vitamin B deficiencies [13]. Indeed, low levels of vitamin B1, B2, B6, B9 and B12 result in elevated homocysteine levels and predicts cognitive decline [20].

5.1 Vitamin B1; Thiamine

Thiamine, a water soluble vitamin B, aids in the production of energy from carbohydrates in cells and is essential in the proper functioning of the nervous system. One of the earliest examples of a nutrition deficiency was the link between thiamine deficiency and neurological problems, including that of cognitive deficits. In fact, deficiency in thiamine is highly prevalent in older adults in particular hospitalised and institutionalised patients, and is associated with higher levels of depression and AD [21]. Further, in non-demented volunteers over 60 years of age, low thiamine levels were associated with lower mini-mental state examination (MMSE) scores compared to those with high thiamine concentrations. Hence, low thiamine levels impact on cognitive function. In addition, rats fed on a thiamine deficient diet showed slower response time to an electrical impulse compared to control rats [22]. Repetitive thiamine deficiency in rats causes impaired cognition and brain damage [23]. Despite positive evidence suggesting a link between thiamine deficieney and risks of cognitive decline, there is still much work required, to determine whether thiamine supplementation would be beneficital as a preventative measure for cognitive decline. In particular, given the recent cross-sectional and case control studies reporting that high dietary thiamine intake has a beneficial effect on cognitive function is inconclusive [24].

5.2 Vitamin B2; Riboflavin

Riboflavin or vitamin B2, is a precursor for Flavin adenine dinucleotide (FAD). Riboflavin plays a vital role in the intermediary metabolism of carbohydrates, amino acids and lipids. Due to its ability to play a role in both one and two electron transfer processes, deficiency of riboflavin manifests first within tissues of rapid cellular turnover such as skin and epithelium. This leads to inflammation of membranes of the mouth, skin, eyes and gastrointestinal tract. In a meta-analysis systemic review study on the micronutrient intake of older adults, it was shown that deficiencies in riboflavin and thiamin were linked with poor cognitive outcomes [25]. Interestingly, a link between riboflavin and vitamin D metabolism and insufficient riboflavin availability and imbalance of FAD results in a distinct alteration in structure within the skeletal and central nervous systems [26]. FAD is a coenzyme of methylenetetrahydrofolate reductase (MTHFR). MTHFR is a catalyst for the formation of 5-methylenetetrahydrofolate which in turn assists homocysteine re-methylation by acting as a methyl donor. Riboflavin and folate act synergistically aiding in lower plasma homocysteine levels [27]. In fact, it was noted in a cohort of 126 healthy individuals who were supplemented with folate, that both folate and riboflavin interacted to decrease plasma homocysteine levels likely by increasing the catalytic activity of MTHFR [27]. In addition, riboflavin deficiency causes higher homocysteine levels in patients who carry the variant MTHFR 677T allele (a mutant form of the MTHFR gene which affects the conversion of dietary folate into the active form) regardless of folate status. There was no effect on homocysteine when vitamin B12 (cobalamine) levels were normal or elevated, thus, suggesting the importance of balance in overall vitamin B status [28]. Furthermore, low levels of dietary intake of riboflavin results in worse cognitive outcomes as assessed by the Halstead-reitan categories test (non-verbal test of abstract thinking ability) in 260 individuals over the age of 60 [29].

5.3 Vitamin B6; Pyridoxine

Vitamin B6 (comprising 3 chemically distinct compounds: pyridoxine, pyridoxal and pyridoxamine) is imperative in the regulation of mental function and plays a role in homocysteine re-methylation. It impacts on neurotransmitters which control depression, pain perception and anxiety. Its deficiency results in high homocysteine levels and has been linked to seizures, migraines, cognitive impairment, AD and other forms of dementia. In fact, in 140 individuals who were evaluated by the major depression inventory

scale, there was a clear correlation between cognitive function, depression and pyridoxine levels [30]. Supplementation of vitamin B6 reduces homocysteine blood levels and improves mood, psychotic symptoms in schizophrenia, cognitive function [31] and enhances long term memory [32]. Likewise, high vitamin B doses, of B6, B9 and B12 in elderly subjects with increased dementia risk (mild cognitive impairment based on the Petersen scale), reduced up to 7-fold the amount of cerebral atrophy in grey matter of the brain (key regions associated with AD and dementia), particularly in subjects with high homocysteine levels, thereby slowing cognitive decline [33]. However, even though supplementation of vitamin B6, B9 and B12 lowers homocysteine levels which could delay or prevent decline in cognition, such supplementation has no effect on atherosclerotic lesions in subjects with hyperhomocysteinemia [34]. Interestingly, in animal studies, pyridoxine supplementation does not improve learning and cognitive outcomes, but low levels of serum pyridoxine are linked to worse motor skills [32].

5.4 Vitamin B9; Folate

Vitamin B9 (folate) is required for the synthesis, repair and methylation of DNA and contributes to a number of biological reactions. Folate is naturally found in foods, however, folic acid is an oxidised synthetic form of folate (chemically synthesised in 1943) and often used for fortification of foods (introduced in 1998 as mandatory). Despite folic acid being imperative in reducing neural tube defects and reducing homocysteine serum levels, there is a concern that it may have negative effects in the incidence of colon cancer [35]. Likewise, fortified flour, which has increased levels of folic acid to normal natural folate levels, causes an imbalance and affects negatively affects methylation reactions [36]. However, there is a positive association between low levels of folate and cognitive decline. In a study of 166 patients diagnosed with either dementia, AD, it was found that levels of folate were consistently and significantly higher in the control group than in patients already suffering from a cognitive disease, indicating that folate supplementation in the elderly may be of prime importance in preventing common forms of dementia [37]. In addition, folic acid supplementation, together with pyridoxine and vitamin B12 supplementation in individuals over 70 years old with mild cognitive impairment, showed slower rates of brain atrophy [38] and enhanced verbal delayed recall, global cognition and clinical dementia rating scale [39], in those that also had high serum omega-3 fatty acids levels. This highlights the importance of the inclusion of both omega-3 fatty acids and B vitamins in the diet for prevention of cognitive decline; although a clinical trial with vitamin B and omega-3 fatty acids is required to determine whether the combination is able to slow the conversion from mild cognitive impairment to AD. Recently, it was reported that a nutraceutical formulation, consisting of folate and vitamin B12 amongst others, significantly improved cognitive performance and behavioral and psychological symptoms of dementia in 24 patients with AD [40]. Similarly, in the HAPIEE (health, alcohol and psychosocial factors in Eastern Europe) study comprising 4,166 participants, folate and vitamin B12 were positively associated with performance (verbal fluency, immediate recall) [41]. In addition, in 7,030 postmenopausal women without memory cognitive impairment or probable dementia, monitored for over 5 years, those with folate intake below the recommended daily allowance were associated with increased risk of mild cognitive impairment and probable dementia [42]. Conversely, a 2 year folic acid and vitamin B12 supplementation study in 2,919 individuals over 65 years of age with high homocysteine levels, showed no beneficial effects on performance on 4 cognitive domains, although a small improvement in global cognition was noted [43].

5.5 Vitamin B12; Cobalamin

Vitamin B12 (cobalamin) plays a major role in the normal functioning of the brain and the nervous system. It is involved in cellular metabolism of carbohydrates, proteins and lipids, and acts as a co-factor in myelin formation and the normal physiology of the nervous system. Vitamin B12 deficiency results in

severe symptoms of depression, suicidal behaviors, mania, psychosis and cognitive decline. Low levels of cobalamin increase the risk of cognitive decline, dementia and AD and is linked to a 5-fold increase in the rate of brain atrophy. In fact high vitamin B12 levels protect against brain atrophy associated with AD and cognitive decline [17]. Vitamin B12 methylation reactions affect homocysteine levels, and vitamin B12 deficiency is one of the most common causes of hyperhomocysteinemia which has been associated with increased risk of dementia, in particular AD. The most common cause of B12 deficiency in the elderly is an inability to absorb B12 in the gastrointestinal tract. It has been shown that there is a significant association between brain size and vitamin B12 status in individuals between 61 - 87 years of age [17]. However, a literature search of all published data between 2002-2012 showed 7 systemic reviews and 11 observational studies on the link between vitamin B12, homocysteine status and cognitive decline, indicated that there is an association between high homocysteine concentrations and the onset of dementia (low quality evidence). Based on low-moderate quality evidence vitamin B12 (and folate) supplementation seems slows the rate of brain atrophy, a precursor of dementia and AD [44].

6. Conclusion and future prospects

Cognitive decline leading to dementia and AD affects a growing number of people every year including the families whom are left to care for them. The cause of this disease is thought to be multifaceted involving lifestyle factors such as diet, smoking, alcohol consumption, as well as other medical conditions like diabetes, cerebrovascular disease, hypertension and traumatic brain injury (Fig 3). There is much documented evidence however, that increased homocysteine levels and deficiency of certain B vitamins contribute significantly to the pathophysiology and onset of the disease and its progression. Further research into this disease in terms of the methylation, serum homocysteine levels and supplementation with B vitamins, may uncover hope for new treatment modalities or provide greater insight into preventative measures and predictions of groups at risk for the onset of the disease. However, the association between vitamin B (B1, B2, B6, B9, B12) and the immune system on cognitive changes, requires further research (Fig 3). Further studies are therefore required to determine the link between vitamin B, immune system and cognitive decline.

7. Acknowledgements

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8. References

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Figure Legends

Figure 1. The % occurance of dementia subtypes according to an updated research report commissioned by Alzheimer's Society on Dementia UK [45].

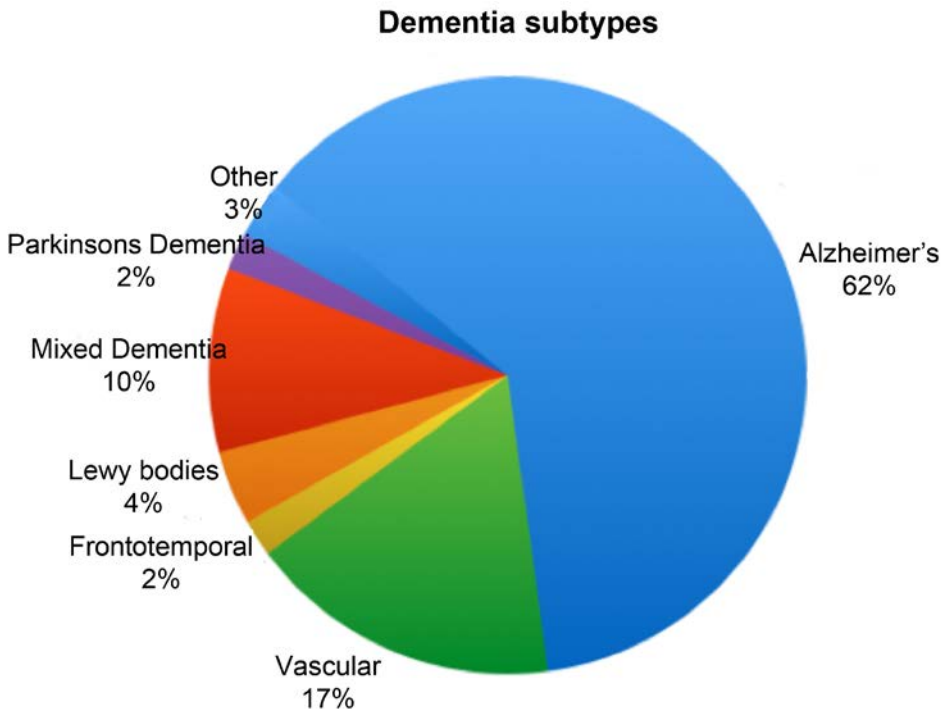

Figure 2. The methionine and folate cycles showing their interaction and vitamin B6, B9 and B12 involvement. Abbreviations: CBS, cystathionine h-synthase; MTHFR, methylenetetrahydrofolate reductase.

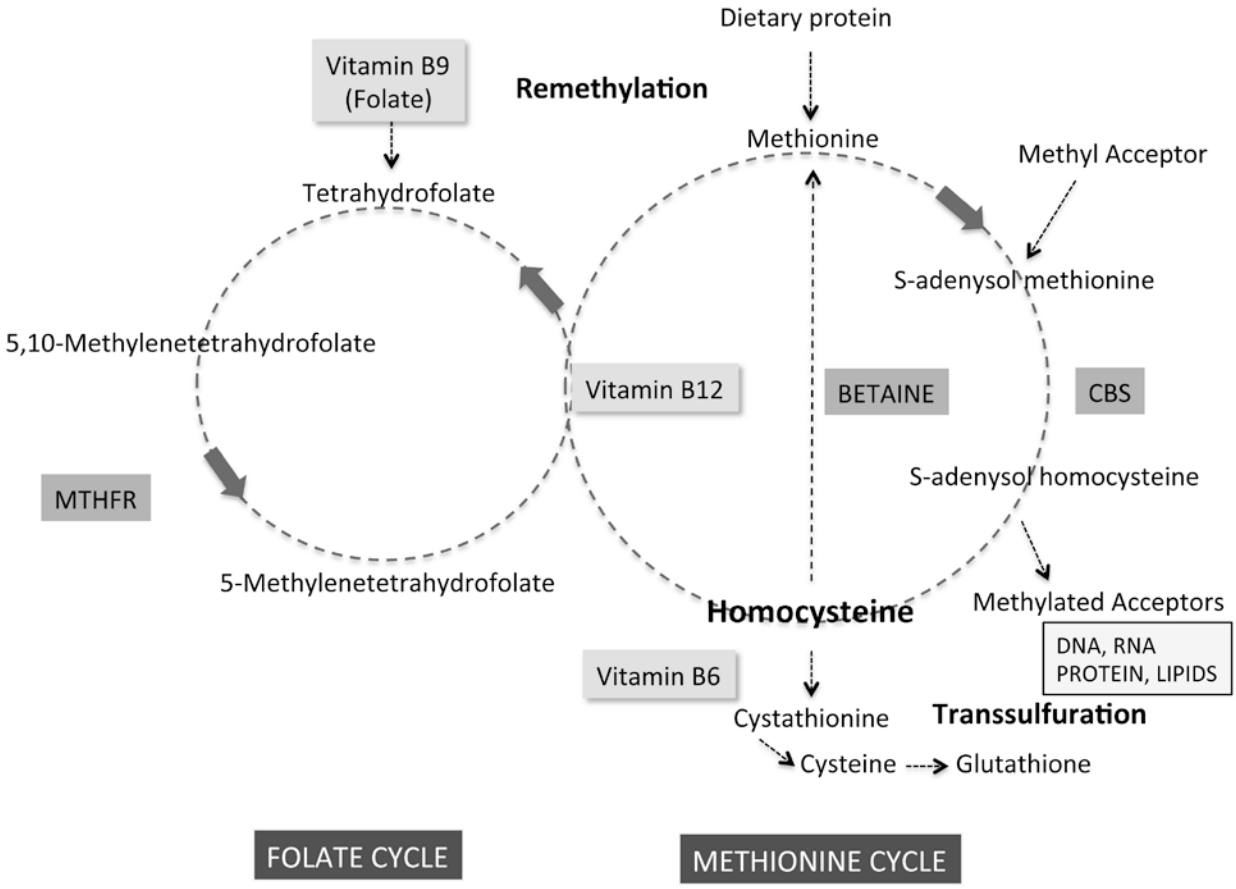

Figure 3. The complexity of cognitive decline. Is there a link between vitamin B deficiency, cognitive decline and the immune system?