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Review article

Nutrition and cognitive impairment in the elderly

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As the number of older people is growing rapidly worldwide and the fact that elderly people are also apparently living longer, dementia, the most common cause of cognitive impairment is getting to be a greater public health problem. Nutrition plays a role in the ageing process, but there is still a lack of knowledge about nutrition-related risk factors in cognitive impairment. Research in this area has been intensive during the last decade, and results indicate that subclinical deficiency in essential nutrients (antioxidants such as vitamins C, E and β-carotene, vitamin B_{12}, vitamin B_6, folate) and nutrition-related disorders, as hypercholesterolaemia, hypertriacylglycerolaemia, hypertension, and diabetes could be some of the nutrition-related risk factors, which can be present for a long time before cognitive impairment becomes evident. Large-scale clinical trials in high-risk populations are needed to determine whether lowering blood homocysteine levels reduces the risk of cognitive impairment and may delay the clinical onset of dementia and perhaps of Alzheimer's disease. A curative treatment of cognitive impairment, especially Alzheimer's disease, is currently impossible. Actual drug therapy, if started early enough, may slow down the progression of the disease. Longitudinal studies are required in order to establish the possible link of nutrient intake – nutritional status with cognitive impairment, and if it is possible, in fact, to inhibit or delay the onset of dementia.

Dementia: Vitamins: Homocysteine: Elderly: Alzheimer's disease

Preservation of cognitive ability well into old age is essential to promote an adequate health status (Elias, 1998). As stated by the American Dietetic Association (1996), food and nutrition add an important dimension to improve health. Therefore, the most practical outcome of research in the relationship between diet and nutrition to ageing would be a better understanding of how nutrition-related behaviours can help to maintain an optimal quality of life (Rosenberg & Miller, 1992).

It is the purpose of the present review to summarise the significant findings about the alterations of nutritional status on cognitive impairment, specifically dementia in old age. As a curative treatment is currently impossible, we wanted to know if there are dietary and nutritional factors that may inhibit or delay the onset of dementia and slow-down its progression. Therefore, we have reviewed the most relevant articles published in the last 5 years as identified by a Medline search.

Cognitive impairment

Dementia, which is the most common cause of cognitive impairment (Callahan *et al.* 1995) and defined as significant memory impairment and loss of intellectual functions, interferes with the patient's work, usual social activities or relationship with others (Gottfries *et al.* 1998), and thus, it is a common and devastating public health problem (Miller, 1999).

Abbreviations: AD, Alzheimer's disease; tHyc, total serum homocysteine; VD, vascular dementia.

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In 1992, the incidence of moderate to severe dementia in Europe was approximately 1000/100 000 person-years among people older than 65 years. The prevalence rate in this age group is about 10 % (Launer, 1992). WHO has estimated that 25–29 million people in the world suffer from dementia (World Health Organization, 1999). Nowadays, Alzheimer's disease (AD) is the 12th death cause in USA for all ages, and the 8th death cause for those aged 65 years and older (NCHS, 1999). In Europe, 80 000 people die of AD and other dementias every year, the diseases being the 13th most important cause of death for all ages (World Health Organization, 2000). The experts estimate that in this century, it will be more prevalent than AIDS, cancer and cardiovascular diseases (World Health Organization, 1999).

It is well-known that age is a risk factor for dementia (Carr *et al.* 1997), therefore, dementia prevalence increases with advancing age (Callahan *et al.* 1995). In a 20 year follow-up study carried out in elderly men and women, cognitive performance was a strong predictor of mortality, in particular of death from ischaemic stroke (Gale *et al.* 1996).

There are numerous changes that occur in the brain with dementia: cerebral volume loss due to neuronal death, the build-up of pathologic debris such as neurofibrillary tangles and neuritic plaques and the build-up of intracellular degradation products; this neuronal loss occurs along with an overall decrease in neurotransmitter metabolism for acetylcholine, dopamine, and serotonin (Agronin, 1998). There are also normal age-associated decreases in sensory acuity, in secondary memory function, and in overall cognitive processing speed (Agronin, 1998). Cerebral blood flow decreases with advancing age (Ramirez-Lassepas, 1998).

Depression among elderly people with reversible cognitive loss often manifests with concomitant vascular disease and can also precede the development of non-vascular dementia (Bell *et al.* 1992).

Two pathologically distinct subtypes of dementia, vascular dementia (VD) and AD, constitute the vast majority of cases (World Health Organization, 1999).

Alzheimer's disease

AD is the most common cause of dementia in the aged. In the USA, the prevalence rates reported are as high as 25·6 % among patients older than 75 years and 47 % of those over 85 years (Callahan *et al.* 1995); the total annual cost approached $70 billion in 1997 (Carr *et al.* 1997). About 4 million Americans have been diagnosed with AD, which results in health care costs greater than $100 billion dollars/year (Diaz Brinton & Yamazaki, 1998).

The age-adjusted prevalence of AD increases exponentially after age 65 years and the estimation is that 50 % of women will be affected after 85 years (Birge, 1998). Oestrogen may play a critical role in the preservation of brain function with advancing age, and thus, it has been stated that oestrogen deficiency may accelerate brain ageing. In fact, data indicate that there could be a relationship between oestrogen and AD. Obese women are relatively protected from AD compared with thin women, as oestrogen is stored in fat tissue, this is the major endogenous source of oestrogen in menopausal women (Birge, 1998). Birge (1997) has confirmed an improvement in mental function after administering oestrogens in a randomised, controlled clinical trial. The proposed benefits may be partly attributable to its potent intrinsic antioxidant activity (Lethem & Orrell, 1997). *In vitro* studies demonstrated that oestrogens block the neurotoxic effect of β-amyloid (see later) in the neuronal cells. Like the vitamin E molecule, the oestrogen molecule possesses a hydroxyl group and a lipophylic carbohydrate chain coupled to a mesomeric ring system. It is supposed that the phenolic hydroxyl group gives a H atom to the hydroxyl radical or the lipid peroxide radical and in this way eliminates the free radical (for review, see Birkhäuser *et al.* 2000).

AD is a neurodegenerative disorder characterised by loss of memory and progressive decline of cognitive abilities (Gray, 1989; Knopman, 1998). Usual brain ageing affects different regions of the brain than those initially affected by AD (Birge, 1998). The characteristic AD lesions are extracellular senile plaques formed by amyloid β protein, and intraneuronal neurofibrillary tangles (Selkoe, 1997; Behl & Holsboer, 1998). AD is associated with several early-onset personality changes, including apathy, egocentricity, and increases in irritability, aggression, and impulsiveness (Agronin, 1998).

Vascular dementia

VD is the second most frequent cause of dementia in the elderly after AD (Fassbender *et al.* 1999). Stroke is a major cause of VD (Chui *et al.* 1992; Miller, 1999). By lowering the risk of stroke in individuals of any age but especially in those older than 65 years the incidence of VD will be decreased (Ramirez-Lassepas, 1998). Most of the common risk factors for stroke are nutrition-related, as hypertension, heart disease, peripheral vascular disease, diabetes, obesity, hyperlipidaemia and hyperuricaemia can be modified by diet (Wolfram, 1995; Tang *et al.* 1998). Thus, diet-related prevention of VD may be possible (Fig. 1).

Nutrition-related risk factors

Hypertension

Hypertension has been proposed as a risk factor for VD and AD (Elias, 1998). For example, participants in the Goteborg study who developed dementia between ages 70 and 79 years had higher systolic blood pressure at age 70 years and higher diastolic blood pressure at ages 70 and 75 years than those who were not demented (Skoog *et al.* 1996). The investigators hypothesised that increased blood pressure can raise the risk for dementia by causing small-vessel disease and white matter lesions in the brain (Elias, 1998) (Fig. 1). In a study from the UK, diastolic blood pressure was a significant independent correlate of cognitive function (Gale *et al.* 1996).

Hypercholesterolaemia

It has been suggested that cholesterol fractions could be involved in both AD and VD (Bonarek *et al.* 2000; Wehr

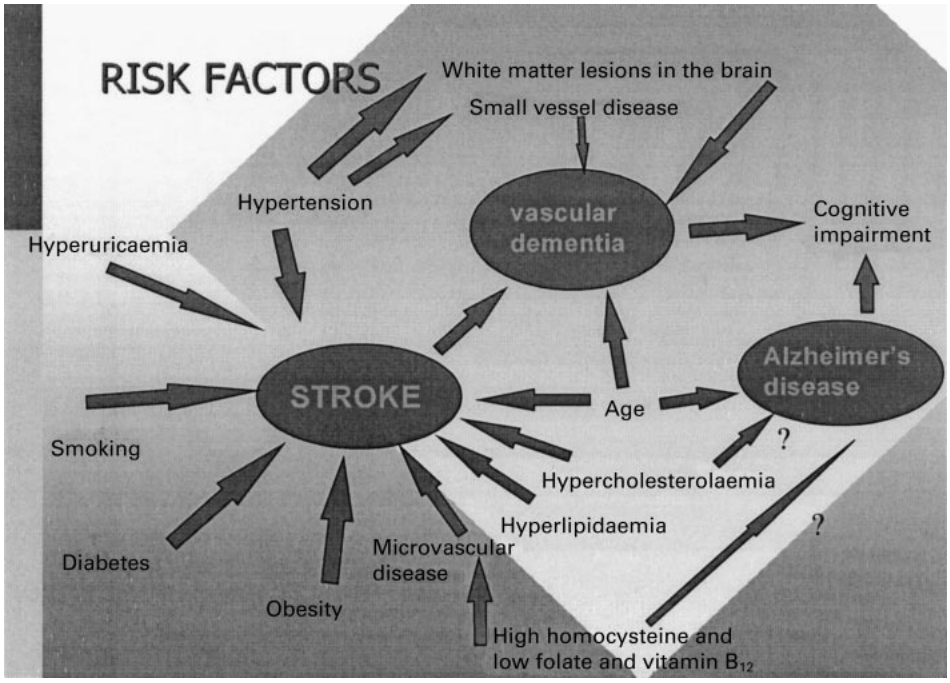

Fig. 1. Nutrition-related risk factors for dementia. ?, aspects needing further research.

et al. 2000) (Fig. 1). Elevated levels of LDL-cholesterol have been recently associated with the risk of dementia with stroke in elderly patients (Moroney *et al.* 1999). Hypercholesterolaemia has also been found to be independently correlated with memory dysfunction in a stroke-free cohort (Desmond *et al.* 1993). Hypercholesterolaemic diets may lead to β-amyloid plaque deposition (Lethem & Orrell, 1997), as apolipoprotein, which transports cholesterol in the blood and binds to β-amyloid, is reduced in AD patients due to the presence of the apolipoprotein E4 gene (Prince *et al.* 2000). Recently, Lutjohann *et al.* (2000) have speculated that 24*S*-hydroxycholesterol, which is higher in AD and VD patients than in healthy control subjects, could be used as an early biochemical marker of dementia. 24*S*-hydroxycholestrol is an enzymically oxidized product of cholesterol mainly synthesized in the brain. Only the *S*-form occurs physiologically.

Amino acids

Plasma levels of several amino acids have been studied in few studies related to dementia. Significantly lower levels of tryptophan and methionine have been observed in plasma samples from AD patients compared with control subjects (Fekkes *et al.* 1998). The plasma tyrosine:large neutral amino acids ratio and the plasma taurine:plasma methionine +serine ratio are significantly higher in the AD patients. The first ratio (tyrosine:large neutral amino acids) reflects the amount of tryptophan and tyrosine available for serotonin and noradrenaline–dopamine synthesis in the central nervous system (Fernström & Wurtman, 1972); the second ratio taurine; methionine+serine is a reflection of the status of the amino acids involved in transmethylation processes (Fekkes *et al.* 1998).

Homocysteine, folate, vitamin B_6 and vitamin B_{12}

The amino acid homocysteine, which is a risk factor for vascular disease, seems to play a role in the pathophysiology of dementia in older people (Bell *et al.* 1992; Nilsson *et al.* 1996; Clarke *et al.* 1998). It may be defined as the metabolic link in the pathogenesis of atherosclerotic vascular diseases and old-age dementia (Parnetti *et al.* 1997). Both folate and vitamin B_{12} are required in the methylation of homocysteine to methionine and in the remethylation and synthesis of *S*-adenosylmethionine (Bottiglieri, 1996; Parnetti *et al.* 1997), a major methyl donor in the central nervous system. Vitamin B_6 in its active form pyridoxal phosphate, is a coenzyme of cystathionine synthase and cystathionine lyase. Both enzymes are required for metabolism of homocysteine to cystein (Pietrzik & Brönstrup, 1997), but this may be an inefficient means of disposing of homocysteine in the human brain due to low enzyme activity (Snowdon *et al.* 2000). The relationship between homocysteine and folic acid, vitamins B_6 and B_{12} approaches the concept defined by Rosenberg & Miller (1992) of subclinical vitamin deficiency and neurocognitive function in elderly people.

Homocysteine is produced entirely from the methylation cycle, as it is totally absent from any dietary source (Pietrzik & Brönstrup, 1997; Fekkes *et al.* 1998).

The relationship of homocysteine catabolism to deficiencies of vitamins suggests that hypovitaminosis could contribute to hyperhomocysteinaemia in subcortical vascular encephalopathy, a distinct type of VD (Fassbender *et al.* 1999) and dementia from the Alzheimer type (Clarke *et al.* 1998; Miller, 1999; Snowdon *et al.* 2000). The neurological and behavioural effects of clinical vitamin deficiencies have been described after the discovery of vitamins (Botez *et al.* 1977; Elsborg *et al.* 1979), but a

description of such effects is not the object of this present article.

It has been suggested that the hyperhomocysteinaemia in the psychogeriatric population may be due to an increased frequency of impaired genetic capacity to metabolise homocysteine in these patients (Nilsson *et al.* 1996; Regland *et al.* 1999). Once the levels are increased, Fassbender *et al.* (1999) and Araki *et al.* (1999) have suggested that homocysteine injures the small penetrating cerebral arteries and arterioles rather than larger brain-supplying arteries. Fassbender *et al.* (1999) cited many studies that had described the association between elevated homocysteine concentrations and carotid artery disease. In their own study, they investigated homocysteine concentrations in microangiopathic diseases and found that hyperhomocysteinaemia was an independent risk factor for subcortical vascular encephalopathy (odds ratio 5·7, $P < 0{\cdot}0001$, 95 % Cl 2·5–12·9), even stronger than any other vascular risk factors that are currently believed to cause subcortical vascular encephalopathy.

The prevalence of high total serum homocysteine (tHcy) is age related, and hyperhomocysteinaemia is common in elderly people (Gottfries *et al.* 1998). Nevertheless, in the study carried out by Bell *et al.* (1992), comparing depressed young adult with depressed elderly patients, homocysteine was highest in the older patients who had concomitant vascular diseases. Of the demented people studied by Carmel *et al.* (1995), 44 % had higher serum methylmalonic acid (an indicator of vitamin B_{12} deficiency) and/or homocysteine levels. Patients with AD studied by Joosten *et al.* (1997) had significantly higher mean tHcy levels than control subjects. The demented and non-demented patients with other psychiatric disorders have significantly higher tHcy concentrations than control subjects; in addition, demented patients show the lowest blood folate and serum creatinine levels in comparison with the other non-demented groups studied (Nilsson *et al.* 1996). In the study of Clarke *et al.* (1998), mean serum tHcy levels were significantly higher in patients with clinically diagnosed dementia of Alzheimer type and histologically confirmed AD than control subjects. Mean serum folate and vitamin B_{12} levels were significantly lower in AD patients than in controls. Recently, Snowdon *et al.* (2000) found a significant correlation between several neuropathologic indicators of AD at autopsy and low folate levels that had been measured while these patients were alive. Patients with subcortical vascular encephalopathy exhibit significantly higher concentrations of homocysteine and lower plasma concentrations of vitamins B_6 and B_{12}, compared with control subjects (Fassbender *et al.* 1999). Diabetic patients with cerebrovascular disease have been reported to show significantly higher levels of tHcy than control subjects (Araki *et al.* 1999); in addition, tHcy levels correlate negatively with cognitive test scores. According to Araki *et al.* (1999), this outcome could suggest that elevated tHcy levels may lead to cognitive impairment in elderly diabetic patients. It is also interesting to mention the study of McCaddon *et al.* (1998), where AD patients had significantly higher tHcy and lower B_{12} levels than control subjects. Low levels of B_{12} correlated negatively with cognitive scores assessed using CAMDEX and its CAMCOG scale (Roth *et al.* 1986).

Research to date concerning tHcy concentrations and brain function suggest that hyperhomocysteinaemia due to disturbed monocarbon metabolism may contribute to cognitive impairment and AD (Clarke *et al.* 1998; McCaddon *et al.* 1998; Miller, 1999) (Fig. 1), and therefore can be considered a sensitive marker of cognitive impairment (Gottfries *et al.* 1998). On the other hand, elevated plasma homocysteine concentrations are a sensitive marker for cobalamin and folate deficiency (Bottiglieri; 1996; Nilsson *et al.* 1996; Parnetti *et al.* 1997; McCaddon *et al.* 1988; Fassbender *et al.* 1999). There is evidence that the relationship between dietary folic acid intakes and mean tHcy concentrations is not linear and that serum tHcy concentrations do not decrease further at total folic acid intakes >300 μg/d (Lewis *et al.* 1999).

Deficiencies of the B vitamins (folate, vitamin B_6 and vitamin B_{12}) may play a role in the pathogenesis of cognitive impairment in the elderly (Gottfries *et al.* 1998). A higher prevalence of folic acid deficiency (Goodwin *et al.* 1983; Clarke *et al.* 1998) and vitamin B_{12} deficiency (Carmel *et al.* 1995; Swain, 1995; Clarke *et al.* 1998; Fassbender *et al.* 1999) has been reported in psychogeriatric patients suffering from depression and dementia than in control subjects. Some findings support the hypothesis that aberrations in the B_{12} dependent transmethylation reactions might be involved in the pathogenesis of dementia, and suggest that the evaluation of erythroctyte ATP:1-methionine *S*-adenosyltransferase activity may be a useful marker for the detection of such an aberration. Gomes-Trolin *et al.* (1995) have observed significantly lower kinetic parameters for 1-methionine *S*-adenosyltransferase in patients with dementia than in age-matched control subjects. The vitamin B_{12} deficiency syndrome is characterised by five stages, the fifth of which results in irreversible neuropsychiatric manifestations (Swain, 1995).

Antioxidants

The relationship between antioxidant status and vascular events has been studied in prospective studies and randomised clinical trials. Oxidative damage may be central to the neurodegenerative process in both VD and AD (Lethem & Orrell, 1997; Sinclair *et al.* 1998; Foy *et al.* 1999; Markesbery & Carney, 1999). Patients with VD and AD may have a degree of disturbance in antioxidant balance which may predispose them to increased oxidative stress, particularly lipid peroxidation (Knopman, 1998; Pitchumoni & Doraiswamy, 1998; Sinclair *et al.* 1998). There are numerous antioxidants in the diet and they have different effects but tend to act synergistically as free-radical scavengers (Lethem & Orrell, 1997). It has been hypothesized that β-carotene (Jama *et al.* 1996) as well as other antioxidants such as vitamin C (Gale *et al.* 1996) and vitamin E (Sano *et al.* 1997) may reduce the progression of atherosclerosis and dementia. In general, brain tissue is highly susceptible to free-radical damage because of its low level of endogenous antioxidants. Vitamin E may have a potential therapeutic role in AD by protecting the integrity of the muscarinic receptor (Lethem & Orrell, 1997; Sano *et al.* 1997). This theory is based on the findings of the studies made *in vitro* by Frey *et al.* (1996) and Venters *et al.*

(1997), who have reported that an endogenous inhibitor of antagonist binding to the muscarinic acetylcholine receptor is elevated 3-fold in the AD brain. This inhibitor contains free haem, a well-established source of oxidative stress capable of generating free radicals and neurotoxicity. According to these authors, the antioxidants vitamins E and C protect the muscarinic acetycholine receptor from irreversible inhibition by the endogenous inhibitor or haem (for review, see Venters *et al.* 1997).

Supporting results for the oxygen free radical hypothesis are those obtained by Riviere *et al.* (1998) in France. In their study, AD patients had lower plasma vitamin C levels than control subjects. In addition, plasma vitamin C concentrations in the patients decreased in proportion to the degree of cognitive impairment, despite similar vitamin C intakes in all cases. Vitamin E levels in the AD patients remained stable, not decreasing in proportion to the degree of cognitive impairment.

Trace elements, such as Fe, Al, Hg and Cu seem to have a role in the generation of reactive oxygen species and the cascade of lipid peroxidation in the AD brain *in vivo* (Pitchumoni & Doraiswamy, 1998). However, there is increasing evidence that free radical damage not only affects brain lipids, but also carbohydrates, proteins, and DNA (Markesbery & Carney, 1999), and contribute to the neurone death in neurodegenerative disorders.

Non-nutritional factors

Obviously, there are some non-nutritional factors that influence cognitive function. The number of years of education, age (Callahan *et al.* 1995; Gale *et al.* 1996; Fraser *et al.* 1996; Haller *et al.* 1996), intelligence quotient (Haller *et al.* 1996), and lifestyle habits (Gale *et al.* 1996) correlated with test scores and cognitive function. Subjects with a higher educational level seem to have healthier eating habits than those with a lower educational level (Lappalainen *et al.* 1998). In addition, there are genetic components, which are independent risk factors for both VD and AD (Carr *et al.* 1997; Clarke *et al.* 1998). The role of a thermolabile gene variant of the enzyme 5,10-methylenetetrahydrofolic acid reductase, which develops a substantially lower enzyme activity than the wild-type form and is associated with moderately elevated total homocysteine levels (Pietrzik & Brönstrup, 1997), is currently being studied in the development of dementia (Tysoe *et al.* 1997; Parnetti *et al.* 1997; Chapman *et al.* 1998; Regland *et al.* 1999), but was not associated with AD or VD in study of Clarke *et al.* (1998), who found associations of AD and VD with high homocysteine and low vitamin B_{12} and folate concentrations. There may be nutrient–gene interactions that influence AD and VD.

Treatment

Early detection of AD is still a problem for primary care physicians, but of undoubted importance Carr *et al.* 1997; lhl *et al.* 2000) because any antidementia treatment is not likely to reverse existing neuronal damage but rather to slow down the disease progression (Small & Leiter, 1998; Markesberry & Carney, 1999) or even to alter the course of the cognitive impairment (Callahan *et al.* 1995). Maintaining the AD patient longer in a more functional stage is clearly a desirable benefit (Doraiswamy & Steffens, 1998). Due to the data obtained in their study, Fassbender *et al.* (1999) speculated that progression of VD in patients with identified hyperhomocysteinaemia could be prevented by supplementation with vitamins implicated in the methionine cycle, i.e. vitamins B_6, B_{12} and folate.

Oestrogen, anti-inflammatory drugs, and vitamins C and E are currently under study based on their ability to promote cell metabolism and survival, counteract inflammatory responses, and protect neurones from oxidative damage (Carr *et al.* 1997; Behl & Holsboer, 1998; Birge, 1998; Diaz Brinton & Yamazaki, 1998; Knopman, 1998; Morris *et al.* 1998). Other practical pharmacological approaches include cholinesterase inhibitors (which are the only class of agents that have consistently demonstrated efficacy in multicentre, well-controlled AD trials (for review, see Doraiswamy & Steffens, 1998; Knopman, 1998), selegiline (Rosler *et al.* 1998; Schneider, 1998), vasoactive agents (Schneider, 1998), folic acid and vitamin B_{12} (Bottiglieri, 1996), ubiquinone (Pitchumoni & Doraiswamy, 1998), and ginkgo biloba (Maurer *et al.* 1997; Doraiswamy & Steffens, 1998; Behl, 1999). Reviewing available data on these therapies and using models from medical illnesses such as cancer and hypertension, some authors (Doraiswamy & Steffens, 1998; Simonson, 1998) have recently stressed the urgent need for evaluating combination therapies to address the problem in early AD.

Prophylaxis

A healthy diet might be associated with a better cognitive function in elderly people (Chandra *et al.* 1991; Huijbregts *et al.* 1998; Solfrizzi *et al.* 1999). Several studies have compared non-demented adults and elderly subjects, dietary intake and plasma concentration of nutrients with cognitive status, the latter assessed by means of specific cognitive tests: Mini mental state examination (Folstein *et al.* 1975), Mattis dementia rating scale (Mattis, 1976), Hodkinson abbreviated mental test (Gomez de Caso *et al.* 1994). Several authors have come to the conclusion that micronutrients may protect against cognitive impairment in elderly people (Goodwin *et al.* 1983; Gale *et al.* 1996; Haller *et al.* 1996; Schmidt *et al.* 1998). Riggs *et al.* (1996) have observed in healthy male subjects that both lower plasma concentrations of vitamin B_{12} and folic acid and higher concentrations of homocysteine are associated with poorer spatial copying skills. Higher plasma vitamin B_6 levels are related to better performance on two measures of memory. In the SENECA study, Haller *et al.* (1996) observed highly significant but weak positive correlations between the total Mini mental state examination scores and plasma lycopene, α-carotene, β-cryptoxanthin, total carotene, β-carotene, α-tocopherol, cobalamin, and folic acid levels. In the Austrian Stroke Prevention study, individuals with poor cognitive function by means of the Mattis dementia rating scale have been reported to show significantly lower plasma concentrations of β-carotene and α-tocopherol than those scoring adequately on the test (Schmidt *et al.* 1998). Other authors have suggested that a

balanced diet, rather than the quantity of individual nutrients or foods, may result in a good cognitive function (Huijbregts *et al.* 1998).

A high energy intake in middle age has been associated with lower cognitive function in old age (Fraser *et al.* 1996), as apparently occurs in some animals. This suggests that a lower consumption of energy in middle age may decelerate the decline in cognitive function seen with ageing. This aspect needs further research.

The typical 'Mediterranean' diet, which includes a high consumption of olive oil and fish (Varela, 1992) and therefore elevated intakes of monounsaturated fatty acids and ω−3 polyunsaturated fatty acids, seems to be protective against age-related cognitive decline (Kalmijn *et al.* 1997; Solfrizzi *et al.* 1999). This outcome can be due in part to the antioxidant compounds in olive oil (tocopherols and polyphenols), and in part to the role of fatty acids in maintaining the structural integrity of neuronal membranes (Solfrizzi *et al.* 1999) Advancing age has been shown to be associated with an increase in monounsaturated fatty acid content together with a decrease in polyunsaturated fatty acid content within neuronal membranes (Lopez *et al.* 1995).

Many authors suggest vitamin supplementation to enhance nutritional status of elderly people (Chandra *et al.* 1991; Carmel *et al.* 1995; Chandra, 1997; Galan *et al.* 1997; Kelly, 1998; Paleologos *et al.* 1998), especially folic acid, because the costs and risks associated with supplementation of low doses are relatively small in contrast to the benefits. For example, Carmel *et al.* (1995) have proposed supplementation with cobalamin, for although long-standing dementia does not improve, treating such patients with this vitamin could have other concrete benefits. In the study carried out by Brönstrup *et al.* (1999) on elderly people with elevated tHcy, the supplemented group (1·65 mg pyridoxine, 3 (μg cyanocobalamin and 400 μg folic acid/d for 4 weeks) had a significant reduction in tHcy compared with controls. The extent of the reduction has been related to tHcy concentration prior to treatment and to plasma folic acid concentration at baseline. This means that the higher the plasma tHcy and the lower the plasma folic acid concentration before supplementation, the more effective was the supplement on plasma levels.

Another challenge is the fortification of specific foodstuffs with vitamins, classified as functional foods. Koehler *et al.* (1997), analysing the dietary intake of an elderly population, have found that folic acid fortification of bread and grains increased the mean folic acid intake by 16·5 %. Based on these results, the US Food and Drug Administration have mandated the fortification of some foodstuffs (flour, bread) with folic acid since 1 January 1998.

The data obtained in a prospective study of 633 people that were older than 65 years have demonstrated that the use of supplements containing high doses of vitamins E and C may lower the risk of AD (Morris *et al.* 1998). However, in the same study, there was no relationship between AD and the general use of multivitamins.

It is not yet clear whether increasing consumption of antioxidants in the diet will help to prevent or delay cognitive impairment. However, standard dietary recommendations for healthier lifestyles (e.g. eating more fruit and vegetables) may have the added potential benefits of increasing antioxidant intake and helping to protect cognitive function (Lethem & Orrell, 1997; Paleologos *et al.* 1998).

On the other hand, we should bear in mind that incipient dementia may also change dietary habits (Jama *et al.* 1996), that is, malnutrition can be a consequence rather than a cause of cognitive impairment (Gale *et al.* 1996; Lethem & Orrell, 1997; Cattin *et al.* 1997; Schmidt *et al.* 1998). As Marcus & Berry (1998) cited in their recent review article, patients with AD may experience reduced appetite because of reduced levels of plasma and brain neuropeptide Y and brain neuroadrenaline, which are both feeding stimulants. Likewise patients with AD may show disturbed feeding behaviours, are easily distracted from eating and may verbally refuse to eat (Durnbaugh *et al.* 1996). Patients with dementia can suffer from agnosia (difficulties in interpreting sense data related to vision, taste, smell, or touch) and apraxia (incapacity in opening the mouth due to motor disturbance), which can impair eating (Marcus & Berry, 1998). In addition, there is a significant decrease in olfactory function in AD (Doty, 1991). All these factors can cause patients to refuse food because they cannot recognise a certain object as food (Norberg & Athlin, 1989).

Conclusions

Cognitive impairment has in most cases a multifactorial origin. From this review, it can be concluded that AD and VD partly share the same risk factors, which is consistent with the current opinion about a link existing between these two types of dementia. Nutrition-related risk factors may include inadequacy of essential nutrients (vitamins B_{12}, B_6, and folate and antioxidants C, E and β-carotene) and nutrition-related disorders, as hypercholesterolaemia, hypertriacylglycerolaemia, hypertension, and diabetes (Fig. 1). Some of the risk factors can be present over a long time before cognitive impairment becomes evident. Severe or even moderate malnutrition may cause an enhanced risk of dementia and AD in susceptible people. However, even optimal intake of nutrients does not protect people from dementia.

There are no curative treatments of cognitive impairment, especially AD. The only possibility is that treatment may delay or slow down disease progression. More therapeutic research is needed. Large-scale clinical trials in high-risk populations are needed to determine whether lowering blood homocysteine levels reduces the risk of cognitive impairment, the clinical onset of dementia and AD. Longitudinal studies are also required to establish possible links between nutrient intake (i.e.nutritional status) and cognitive impairment, and whether it is possible to inhibit or delay the onset of dementia by dietary modifications.

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