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ROLE OF NUTRITION IN ALZHEIMER'S DISEASE: A REVIEW

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ABSTRACT

There has been an increase in prevalence of chronic diseases in elderly population. Alzheimer's disease (AD) is the most common disease of the ageing population and it is estimated to affect 66 million people by 2030 worldwide. It has an estimated economic burden of $305 billion already. It is manifested in the form of dementia and progressive neurodegenerative disease. It is characterised by a progressive deterioration of memory, planning, problem solving, sense of orientation and cognitive function which can result in premature death. As of now there is no effective prevention method nor cure for dementia, therefore more attention is paid to the prevention of this group of diseases through the appropriate diet. An Alzheimer brain synapses are characterised by reduced levels of synaptic proteins and membrane phosphatides. Brain membrane phosphatides dietary precursors are poly unsaturated fatty acids (PUFA), uridyl monophosphate (UMP) and choline. Nutritional intervention given before the onset of the first symptoms of memory loss gives the best results when the number of synapses, cognition, and neuropathological changes in the nervous system compensates with the nutritional status. This delays the symptoms and increases the chances of staying healthy for a longer period of time. It has been proven that dietary habits, which lead to the development of cardiovascular and metabolic diseases, significantly increase the risk of dementia. A diet which promotes the progression of dementia should be avoided viz high carbohydrate diet. On the other hand, a Mediterranean diet rich in antioxidants, fibre, xanthophyll, carotenoids and omega-3 polyunsaturated fatty acids may have a protective effect on the neurodegenerative process. The positive effect of many nutrients on the course of AD is through minimising oxidative damage and inflammation and it has been demonstrated. These include antioxidants like glutathione, coenzymes like coenzyme Q10, vitamins B6, B12, folic acid, unsaturated fatty acids, lecithin, polyphenols, caffeine and some probiotic bacteria. The Mediterranean and DASH diets have been documented to protect against AD. It also opens scope of developing different diets to help prevention of this disease decreasing its burden.

KEYWORDS: Dementia, brain cells, dietary precursor, nutritional intervention.

INTRODUCTION

Since Alzheimer's disease (AD) was first diagnosed by Dr. Alois Alzheimer in 1906, it has gained considerable attention as the most prevalent and most common type of progressive neurodegenerative disease, affecting about 30 million people worldwide before 2010, and the count number is estimated to double every 20 years to reach 66 million in 2030 and 115 million in 2050.[1] The prevalence rate of AD - related dementia also rise substantially with age particularly between 65 to 80 years. It has an estimated economic burden of dollars 1 *tr*illion by year 2050 across the globe but still lacks a cure.[2] There are two main forms of AD: familial AD (FAD) and sporadic AD (SAD), FAD and SAD are largely similar clinically, both characterized by progressive cognitive decline that results in the impairment of forming memories, planning, problem solving, visuospatial skills and orientation. These deficits pose a major barrier to basic functions of daily life especially in the old age and can result in premature death as well.[2] Histopathologically, both subtypes are associated with accumulation of extracellular senile plaques consisting of amyloid- β peptides (αβ) and neurofibrillary tangles formed by hyper - phosphorylated tau protein, resulting in axonal transport defects as well as loss of neurons and synapses in the cerebral cortex and certain subcortical regions.[3]

Occurrence

Dozens of drug and therapeutic strategies attempting to slow or halt neuronal loss and cognitive deficiency of AD are being investigated around the world however, only five pharmacological agents has been approved for clinical AD treatment by the Food and Drug Administration(FDA), including cholinesterase inhibitors tacrine, donepezil, galantamine, rivastigmine and N-

methyl-D-aspartate (NMDA) receptor antagonist memantine. Unfortunately, all these currently available pharmacological therapeutics only relieve symptoms without affecting the major pathological characteristics of AD. Moreover, the effectiveness of these agents varies from person to person as evidenced by a moderate efficiency in no more than 20% of patients and tolerance, noncompliance and side-effects in more than 60% of treated patients.[4,5,6] During the last a few decades, research in epidemiology of dementia and AD has made tremendous progress.[7] These debilitating and financially devastating diseases are expected to increase into the middle of the century, and it is anticipated that greater than 131 million individuals will be affected by 2050 as the population ages, with the incidence for all dementias doubling every 6.3 years from 3.9 per 1000 for ages 60–90 to 104.8 per 1000 above age 90. Prevalence is estimated at 10% for individuals over 65 years and 40% for those over 80 years.[7]

SYMPTOMS

The most common first manifestation of Alzheimer disease is.[8] loss of short-term memory (eg, asking repetitive questions, frequently misplacing objects or forgetting appointments). Other cognitive deficits tend to involve multiple functions, including the impaired reasoning, difficulty handling complex tasks, and poor judgment (eg, being unable to manage bank account, making poor financial decisions), language dysfunction (eg, difficulty thinking of common words, errors speaking and/or writing) &visuospatial dysfunction (eg, inability to recognize faces or common objects). Behaviour disorders eg, wandering, agitation, yelling, persecutory ideation are common.

The National Institute on Aging–Alzheimer's Association diagnostic guidelines also include biomarkers for the pathophysiologic process of Alzheimer disease which are low level of beta-amyloid in cerebrospinal fluid (CSF) and Beta-amyloid deposits in the brain. Other biomarkers indicate downstream neuronal degeneration or injury are elevated levels of tau protein in CSF or tau deposits in the brain detected by PET imaging using radioactive tracer that binds specifically to tau, decreased cerebral metabolism in the temporoparietal cortex and local atrophy in the medial, basal, and lateral temporal lobes and the medial parietal cortex. Laboratory tests eg, thyroid-stimulating hormone, vitamin B12 levels.

ROLE OF NUTRITION

Currently, there are no effective therapies to treat dementia syndromes. Currently, patients with AD receive only symptomatic treatment, which has been proven to slow down the disease progression.[9] Nevertheless, preventative measures help reduce the risk of disease. Proper diet, in addition to being physically and mentally active, can also be effective.[9,10] Dietary habits that lead to the development of cardiovascular and metabolic diseases have been reported to significantly increase the risk of dementia.[11] A Mediterranean diet rich in antioxidants, fiber and omega-3 polyunsaturated fatty acids may also have a protective effect on degenerative process in AD.

Preventive intervention gives the best results if introduced before the first symptoms of dementia appear, i.e., around the age of 50. This is when the nutritional status, number of synapses, cognition, and neuropathological changes in the nervous system compensate each other, which increases the chances of staying healthy for a longer period of time.[12] This review aims to describe the role and effectiveness of a diet in the course and treatment of AD.

ANTIOXIDANTS

Brain tissue is very susceptible to damage, including the one caused by free radicals. Oxidative stress is a condition in which the amount of endogenous or exogenous reactive oxygen species (ROS) exceeds the antioxidant capacity of the cell or organism. There are also non-enzymatic antioxidants such as vitamin E, vitamin C, provitamin and vitamin D3, vitamin A, UA, carotenoids, glutathione, cysteine, creatinine, tocopherols, coenzyme Q10, bilirubin, polyphenols and anthocyanins. In addition, some essential elements, such as selenium, zinc and copper, serve as cofactors for protein cofactors or enzymes with antioxidant activity. It has been shown that oxidative stress may mediate the pathogenesis and progression of dementia, so dietary antioxidants are protective against the risk of cognitive decline.[13]

Researchers indicate that elderly people are deficient in tocopherols so it is recommended to ensure its adequate dietary intake. The main sources of vitamin E are products of plant origin, i.e., vegetable oils, nuts, seeds, green leafy vegetables and some fatty fish (sardines, salmon, herring, trout) or chicken egg yolk.[14] The patients are encouraged to follow antioxidant-rich diet. Vegetables and fruits are rich in antioxidants and their regular consumption may positively affect health and slow down AD development.[15]

Moreover, elderly people have significant vitamin deficiencies due to impaired digestion, nutrients absorption or metabolic disorders. They need less energy so they consume less food, which, in result, leads to insufficient supply of nutrients. The best dietary sources of glutathione include fresh fruits and vegetables such as spinach, broccoli, asparagus, cabbage, garlic, onions, avocado, watermelon and strawberries, as well as walnuts, milk thistle, turmeric and freshly cooked meat. Food processing significantly decreases the amount of glutathione found in food, so canned products are not a good source of this antioxidant. We should also pay attention to the appropriate supply of glutathione precursors, e.g., cysteine and methionine, which can be found in beef, poultry, eggs, as well as in goat's, sheep's and cow's milk. The neuro-protective activity of glutathione involves removing reactive oxygen

species.[16,17] CoQ10 can be found in blackcurrant, cauliflower, peas, and yoghurt. CoQ10 supplement should be consider if dietary intake is insufficient. Many studies have shown that B vitamins (i.e., B2, B6, B12, folic acid and pantothenic acid) enhance the biosynthesis of coenzyme Q10.

VITAMINS B6, B12 AND FOLIC ACID

Vitamin B12 deficiency is associated with cognitive impairment.[18] Moreover, vitamins B6, B12 and folic acid play a key role in metabolism of homocysteine, a by-product with different mechanisms of toxicity. It has been shown that a 5 μmol/L increase in serum homocysteine concentration may lead to ischemic stroke and atherosclerosis of large blood vessels. In addition to its atherogenic effect and inducing atherosclerosis, homocysteine is also considered a neurotoxin. Moreover, its elevated serum concentration is observed in patients with AD. It has been shown that elevated homocysteine levels can destroy dopaminergic neurons in vitro, induce motor impairment in rats, inhibit hippocampal neurogenesis in adult animals, disrupt the blood-brain barrier, and generate ROS. Moreover, elevated homocysteine levels can induce and enhance inflammation, increase the concentration of amyloid-β precursor protein, promote tau protein phosphorylation, and exacerbate amyloid-β pathology. Therefore, elevated homocysteine promotes cognitive dysfunction.[19]

FATTY ACIDS

Improper dietary intake of saturated fatty acids (SFAs) and unsaturated fatty acids may be a risk factor for many diseases, including neurological disorders.[20] High intake of SFAs and trans isomers is a serious risk factor for civilization diseases, including cardiovascular disorders. Excessive intake of SFA can exacerbate cognitive impairment. On the other hand, individuals consuming large amounts of foods rich in monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs), especially from the omega-3 family, had a significantly lower risk of dementia.[21,17]

Fatty acids are the main structural components of cell membranes. The properties of fatty acids depend upon their chain length and the number of double bonds. Humans can't synthesis PUFA and thus it must be obtained from diet. Linoleic acid is found in vegetable oils such as soybean, sunflower, corn, safflower and evening primrose oils. Foods high in alpha-linolenic acid include walnuts, as well as linseed, rapeseed, and soybean oils.

URIC ACID

In many epidemiological studies, hyperuricemia has been recognized as an independent risk factor for cardiovascular diseases. However, uric acid (UA) may also be beneficial due to its antioxidant properties, which may be particularly important in the context of neurodegenerative diseases.[14,18] Besides its strong antioxidant properties, UA also acts as an iron chelator.[19] The use of UA should be analyzed with regard to the etiology of cognitive impairments. It has been shown that in the case of AD and subcortical dementia syndrome of Parkinson's disease, elevated serum UA levels inhibited the disease progression.[14,20] Similar results were obtained in patients with mild cognitive impairment, but it should be emphasized that UA was a protective factor only if its levels were high long before AD onset. The protective effect against degenerative diseases was moderate but significant.[21]

CAFFEINE

Caffeine occurs naturally in coffee beans, cocoa and guarana, yerba-mate, tea leaves and *Cola acuminata*, as well as in 60 other plant species. Caffeine or its metabolites (guaranine, theine, methyltheobromine or methyltheophylline) are added to energy drinks. Caffeine is quickly absorbed by the gastrointestinal tract and it rapidly penetrates cell membranes and the blood-brain barrier (BBB). Its bioavailability is nearly 100%. Caffeine is pharmacologically active within a few minutes after consumption and reaches peak plasma concentration after 40 minutes.[25]

Metabolites secreted by gut bacteria may affect cognitive performance of people with neurological diseases. It has been shown that changes in the composition of gut microbiota may influence depressive disorders as both an etiological and therapeutic factor. Beneficial properties of probiotic bacteria result from anti-inflammatory effect on the digestive system. Probiotics maintain intestinal barrier integrity, thereby preventing its permeability and leakage of pro-inflammatory substances from the intestinal lumen into the bloodstream (e.g., metabolites of pathogenic bacteria, food allergens). Released pro-inflammatory cytokines, interleukins and chemokines intensify the inflammation, which is associated with neurological diseases, including cognitive and depressive disorders.[26,27]

Evidence suggests that diabetes is a risk factor for AD, because altered insulin signaling impairs metabolism of lipids and branched-chain amino acids (BCAAs) in peripheral organs such as the liver and adipose tissue.[28] Therefore, patients with diabetes and AD have higher plasma BCAA concentration.[29,30] Branched chain amino acids include valine, leucine, and isoleucine.

Animal studies have shown that although leucine increases tau phosphorylation, it does not affect amyloid-β accumulation in nervous tissue.[31] Mice fed with BCAA-enriched diet displayed cognitive impairment and higher mortality, although their motor functions were not impaired. In contrast, mice on the low-BCAA diet showed higher cortical threonine and tryptophan levels (and hence serotonin) and performed better on the novel object recognition task.[32] Researchers suggest that excessive intake of BCAA inhibits transport of other amino acids to the brain, which can directly influence synthesis of different neurotransmitters.[33]

DIETS IN ALZHEIMER'S DISEASE

Mediterranean diet can be recommended for patients with AD. This dietary pattern characterized by the abundant consumption of whole grains, fruits, vegetables, pulses, fish, olive oil; moderate intake of dairy products and alcohol (mainly dry red wine); and low consumption of foods rich in saturated fatty acids, such as meat. This diet is rich in antioxidants, B vitamins and unsaturated fatty acids.[34,29] It has been shown that Mediterranean diet not only reduces inflammation and oxidative stress, but is also associated with reduced loss of brain volume and slower progression of AD.[35,31] In addition, it reduces the risk of cardiovascular disease, cancer, type 2 diabetes, and metabolic syndrome. These diseases have a significant impact on the development of dementia, therefore their prevention is also an element of AD prevention.[36,37]

The Dietary Approaches to Stop Hypertension (DASH) diet shares similarities with the Mediterranean diet, as it also involves high intakes of fruits, vegetables, low-fat dairy products and whole grains, vitamins and antioxidants. In addition, DASH diet is rich in minerals such as potassium, magnesium and calcium, and emphasizes the limited intake of refined grain products, sodium and SFAs.[38] However, DASH diet is not efficient in alleviating the symptoms of AD, it only lowers the risk occurrence.

A combination of the Mediterranean and DASH diets is called the MIND diet (MIND stands for Mediterranean-DASH Intervention for Neurodegenerative Delay). This diet is designed to improve cognitive performance and lower the risk of developing neurodegenerative diseases such as AD. In addition to DASH and Mediterranean diets, MIND diet emphasizes the consumption of food products that have a positive effect on brain function such as green leafy vegetables (spinach, kale, lettuce) and berries (strawberries, blueberries, blueberries and raspberries). These products should be eaten 6 times a week. Other food products recommended on the MIND diet include vegetables, nuts, pulses, whole grains, fish, poultry, olive oil, and red wine. On the other hand, the MIND diet encourages limiting the consumption of red meat, butter, margarine, cheese, sweets and fried foods. The above modifications to the diet turned out to be strongly correlated with the lower risk of cognitive disorders. The MIND diet is much more effective in preventing dementia than the Mediterranean diet and the DASH diet alone.[39,40]

CONCLUSION AND FUTURE PROSPECTS

Awareness is the key to lowering the occurrence of AD with the help of right nutrition. Elderly people should know the principles of rational nutrition and remain independent for as long as possible, because this will help slow down the progression of the disease. For this reason, third parties should provide help only if necessary. The clinical value of antioxidants for the prevention of AD is ambiguous. Vitamins C and A do not inhibit the progression of cognitive disorders. Research on the protective effect of vitamin E is contradictory. However, research has revealed that curcumin not only prevents aggregation of new amyloid-β deposits, but also reduces the size of remaining ones. Vitamins B6, B12 and folic acid maintain a healthy nervous system and may be helpful in the treatment of AD. Supplementation should be considered with a physician if such amounts of vitamins cannot be supplied with the diet. Excessive intake of saturated fatty acids can aggravate cognitive disorders. On the other hand, consuming unsaturated fatty acids prevents cognitive decline. Hyperuricemia may prevent the development of dementia and alleviate the disease course of AD. Caffeine may protect against cognitive disorders and dementia due to its neuroprotective and neuromodulatory properties. Probiotics, particularly *Lactobacillus* spp., can improve synaptic plasticity, stimulate hippocampal neurogenesis, regulate hypothalamic- pituitary-adrenal (HPA) axis and reduce the level of oxidative stress. High levels of BCAA may contribute to cognitive decline and higher mortality. However, a diet low in these amino acids may indirectly raise brain serotonin levels.

The Mediterranean diet not only reduces inflammation and oxidative stress, but is also associated with reduced loss of brain volume and slower AD progression. DASH diet has positive results if followed for a longer period of time, even before the first symptoms of dementia begin to appear, and therefore it can only be used as the prevention of cognitive decline. However, the MIND diet turned out to be much more effective in preventing dementia than the Mediterranean and DASH diets alone.

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