REVIEW PAPER

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The role of diet and antioxidants in the prevention of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia among elderly. It is a progressive, neurodegenerative disorder of the brain which leads to the deterioration of cognitive, behavioral and impaired daily functioning and causes the gradual loss of independence. A significant portion of risk for dementia in old age is associated with lifestyle. Three important protective factors are diet, which should be rich in antioxidants, exercise and good cardiovascular health. It is believed that Mediterranean diet has a protective effect from dementia. This diet, rich in fruit and vegetables, legumes, olive oil, whole wheat bread, fish and seafood, with reduced consumption of red meat is also protective from cardiovascular diseases and promotes a healthy long life. There were some studies on the etiology of AD which noted an important role of vitamin B6, B12 and folic acid. All of them are involved in the metabolism of homocysteine, which is regarded as an independent risk factor for the development of AD, atherosclerosis and thrombosis. We also know that supplementation of vitamins C and E in the diet can be protective from AD. On the other hand we know that obesity and undernutrition can increase the risk of development of AD. As we can observe the aging of population we should remember that nutrition constitutes an interesting approach for the prevention of age-related brain disorders.

Keywords: Alzheimer's disease, reactive oxygen species, nutrition.

Introduction

Alzheimer's disease (AD) is progressive, neurodegenerative disorder of the brain which leads to the deterioration of cognitive, behavioral and impaired daily functioning and causes the gradual loss of independence. Multi-infarct dementia (vascular dementia), Parkinson's disease, Lewy body disease, Creutzfeldt-Jakob disease, Pick's disease, Huntington's disease are less common forms of dementia among elderly [1]. AD currently affects about 2% of the population in developed countries and its incidence is forecasted to increase significantly with the aging of the population [2]. US Census Bureau data predict that the number of people over 65 years amounting to about 35 million in 2000, will increase to 70 million in 2050, while the population of people over 85 years old will increase from 4.2 million in 2000 to 21 million in 2050 [3]. AD is the leading form of dementia in North America and Europe and it constitutes the significant part of care cost in these countries. It is considered as a global public health priority [4, 5]. Etiology of AD is multi-factorial and it compounds of genetic and environmental factors including diet, physical activity, smoking and alcohol abuse. Barnes and Yaffe suggested that diabetes mellitus, midlife hypertension, midlife obesity, smoking, depression, and cognitive and physical inactivity are the main modifiable risk factors and represent around 50% of all cases of AD [6]. Diabetes, hypertension, and obesity are the civilization diseases where proper diet and physical activity are important elements of prevention and

treatment. Dietary intake and nutritional state appear to be environmental lifestyle- related factors that might contribute to pathogenesis and slowing down AD [7–9]. Genetic factors are important especially in the generally accepted division of Alzheimer's disease into two types: sporadic AD and family AD [10]. Sporadic AD also known as late-onset AD constitutes more than 90% of all cases and occurs in patients aged 65 years old and older. The risk increases having the APOE ε4 allele of apolipoprotein E (APOE) genotype [11]. Family AD is more sporadic form of early onset AD as its symptoms occur in younger age. Genetic variants of the amyloid precursor protein (APP) gene, presenilin 1 (PSEN 1) gene and presenilin 2 (PSEN 2) gene have been suggested to be associated with family AD [12].

Alzheimer Disease and oxidative damage

Amyloid ß (Aß) and tau are two main proteins playing an important role in pathogenesis of AD [13]. Formation of neuritic plaques composed of insoluble form of Aß in the brain and the accumulation of hyperphosphorylated form of tau in neurofibrillary tangles are the most important steps in the pathogenesis of AD [14–16]. Aß accumulation in the hippocampal region of the brain is thought to induce toxic effects, oxidative stress and immune response that lead to cognitive impairment [17]. The hyperphosphorylation of tau protein worsens the axonal transport and causes neuronal dysfunction in the central nervous system. Abnormal neurofibrillary tangles induce inflammatory response and activate cells (microglia, astrocytes, macrophages and lymphocytes) which causes exaggerated production of cytokines and chemokines [18]. Both, Aß and tau protein, induce inflammation in the vulnerable regions of the brain. This is considered to be an important factor in the onset of AD. The inflammatory process leads to neuronal dystrophy, overproduction of reactive oxygen species (ROS) and increased formation of Aß in the cerebral cortex and subcortical regions [19, 20]. ROS are produced in the oxidative process which is the part of physiological reaction of the brain as a part of cellular signalling, metabolism and keeping the homeostasis [21, 22]. The lack of balance between the formation of free radicals and their removal is the cause of oxidative stress. Oxidative stress results in increased oxidation of lipids, proteins and nucleic acids which leads to cellular dysfunction. Chronic oxidative stress along with oxidative damage of the cerebral microvasculature and brain cells have become a potential pathogenesis of many neurodegenerative diseases such as age-related mild cognitive impairment, Parkinson's disease and Alzheimer's disease [23, 24]. Authors of the prospective study made in 2014 emphasize the increased oxidative stress in AD [25]. Exposing human body cells to chronic oxidative stress may exacerbate production of ROS and cause the death of cells including neurons. Amyloid ß can provoke oxidative stress by itself which is thought to be a crucial factor in the pathogenesis of AD [26, 27]. The collection of Aß in the brain causes the dysfunction of mitochondria and metabolic disturbances as well as increased formation of the ROS [28]. Amyloid beta, as a derivative of transferrin, has strong affinity to transition metal ions such as iron, copper and zinc. It is able to reduce Fe3+ and Cu2+ producing ROS [29]. The human body has a mechanism to inactivate and detoxify ROS. The main antioxidants in the nervous system are superoxide dismutase, glutathione peroxidase and catalase. Some data show decreased levels of antioxidants in the plasma of patients with AD. The most important one is glutathione peroxidase which is a selenium-containing enzyme. Its activity in the blood is well correlated to the level of plasma selenium (Se) [30]. Pillai et al. have shown that Se deficiency is associated with cognitive decline, and that selenoproteins may inhibit the neurodegeneration in AD [31]. On the other hand Loef et al. concluded that there is no evidence for the role of Se in the treatment of AD [32]. However it still allows speculation on a potential preventive relevance. In a prospective study Krishnan and Rani noted that the blood Se may not be involved in regulating oxidative stress in AD. A longitudinal study which correlates plasma and cerebrospinal fluid Se and selenoprotein levels should be done [25]. The similar conclusions were reached by authors of systematic review and meta-analysis analyzing plasma nutrients among patients with AD [33]. The meta-analysis has shown significantly lower plasma levels of folate and vitamins A, B12, C and E in a group of AD patients compared to control population. There is a strong belief that vitamin A, vitamin C and vitamin E which are antioxidants may be beneficial in slowing the progression and preventing AD [34–36].

Alzheimer Disease and diet

Dietary intake and nutritional state are important environmental factors that affect the human body regardless of gender, age or comorbidity [37]. Proper nutrition is an important element of lifestyle, which plays

a significant role in the human biological aging process. The quality of the food is also an important part of prevention and treatment of non-communicable, chronic metabolic diseases, the incidence of which increases with age [38]. Among these diseases is AD. They are included into neurodegenerative disorders.

An increasing number of publications emphasize the role of diet and dietary components in the development and treatment of dementia [39–41]. It is well known that nutritional deficiencies and a poorly balanced diet can lead to disturbances in the functioning of the body. Thus, some of the food components can serve a protective function, reducing the risk of developing diseases. Conducted epidemiological studies emphasize the role of the Mediterranean diet in reducing the risk of developing dementia and AD [42–44]. This diet, rich in fruit and vegetables, legumes, olive oil, whole wheat bread, fish and seafood, taking account of reduced consumption of red meat, is the source of all components of food. The importance of the individual components of the Mediterranean diet as a prevention of cognitive impairment is confirmed by numerous independent studies. Berr et al. conducted four-year follow-up and showed that a diet rich in olive oil reduces the risk of cognitive deficits among the elderly [45]. A prospective study in France over seven years and of 1416 people aged at least 68 years, assessed the effect of consumption of fish and meat on the risk of developing dementia [46]. Increased consumption of fish and seafood (at least 1 time per week) was associated with a significantly lower incidence of dementia. The benefits from consumption of fish was confirmed by the study made on a much larger population – 6158 people aged at least 65 years [47]. Hung et al. demonstrated that fatty fish consumption was associated with a lower risk of dementia and AD in people without the APOE ε4 [48]. During long-term follow-up, conducted among Swedish twins, it has been shown that fruit and vegetable intake was associated with a lower risk of developing dementia and AD in women [49]. It has been demonstrated in a study of 193 healthy volunteers (aged 45 to 102 years) that regardless of gender, age, BMI and lipid parameters, people with a higher daily intake of fruit and vegetables performed better cognitive tests [50]. It has been stated that healthy subjects of any age with a high daily intake of fruit and vegetables have higher antioxidant levels, lower levels of biomarkers of oxidative stress, and better cognitive performance than healthy subjects of any age consuming low amounts of fruit and vegetables. Diet composition similar to the Mediterranean diet seems to be the most appropriate and may exert a long-term beneficial effect on the functioning of the brain [51, 52]. This diet is worth recommendation as it lessens cognitive decline, reduces the progression of mild cognitive impairment to AD and the overall risk of developing AD, and decreases mortality among patients with AD. Thus, high consumption of fish, olive oil, vegetables and fruit with a low glycemic index, seeds, beans, moderate consumption of wine and diary products such as cheese or yogurt, and low consumption of red meat and products without additional sugar is recommended. This diet is also recommended to reduce the risk of cardiovascular diseases, obesity, diabetes and hypertension. Therefore it seems to be a good way not only to prevent dementia but also to stay in a better health [53].

The high content of antioxidants in fruit and vegetables is one of the advantages of the Mediterranean diet. Omega-3 acids (α-linolenic acids) and omega-6 acids (linoleic acids) which belong to polyunsaturated fatty acids (PUFA) are equally important. It is also known that PUFA are precursors of leukotrienes, prostaglandins and cell membranes. Vegetable oils (sunflower, soybean, corn, rapeseed) and the acid of the omega-3 family – fish oil, linseed oil and walnuts are the source of linoleic acids in the human diet.

The importance of fish and seafood consumption in the prevention of AD was punctuated by Barberger-Gateau et al. [46] and by the authors of Rotterdam Study [54]. Kalmijn et al. found that a high intake of total fat, saturated fat and cholesterol was associated with an increased risk of dementia. On the other hand they have assessed that the diet rich in fish reduced the risk of AD.

Increased content of omega-3 in a serum and in a diet was reducing the risk of dementia which was noted in few studies [55–57]. Some authors say that there is no significant correlation between PUFA intake and the risk of dementia, including AD [58–60]. Therefore the importance of fats, especially PUFA, in the etiopathogenesis of AD requires further investigation.

Alzheimer Disease and vitamins

Healthy eating and proper diet will ensure proper nutrition regardless of age and provide the body with all the essential nutrients, including micro- and macronutrients. Please note that in the elderly, we often deal with comorbidities, and above all the involuntary changes in the process of digestion and absorption. The unbalanced diet and increased demand for

protein and vitamins in the elderly is caused by the decreased absorption from the digestive tract which causes significantly reduced health [61]. It is commonly known that the brain is susceptible to oxidative stress and damage as a result of its high metabolic rate and relatively lower regenerative capacity. The brain uses approximately 20% of total body oxygen consumption. A number of publications emphasize the role of both, the antioxidant vitamins (E, C, carotenoids including vitamin A) and vitamins involved in the metabolism of homocysteine (vitamin B6, B12 and folic acid). An excessive amount of ROS, in addition to the development of the inflammatory processes, also contributes to faster aging. The neural tissue manifests large oxygen consumption, increased mitochondria density and a high content of polyunsaturated fatty acids in the cell membranes. This causes elevated sensitiveness to harmful action of the free radicals and peroxides [62]. The significant role in the prevention of this damage plays vitamin E (tocopherol). In the 90s a group of scientists from Australia, showed a relationship between the concentration of vitamin E in the serum and cognitive function among people over 60 years of age. Their studies have been conducted to increase the prevention of stroke [63]. Perkins et al. reported a relationship between low serum level of vitamin E and cognitive impairment [64]. In study, which was carried out among 4809 participants showed that there had been no correlation between the level of vitamin C, carotenoids including vitamin A and cognitive function. Also, there was a study conducted in a group of 442 people which showed the reversed result – ascorbic acid, carotenoids, and their plasma concentration only were associated with a better performance of memory [65]. The protective role of the products containing vitamin E in diet was observed in seven-year prospective study made among 815 healthy people over 65 years of age. They found it as a preventing factor against the development of AD [66]. Ortega et al. emphasized the importance of an adequate supply of vitamin E in the diet. They made an analysis of the diet of elderly people for 5 days [67]. The smaller intake of vitamin E in the diet and its lower concentration in the serum was associated with worse outcomes of the cognitive tests. It is punctuated that not only the alpha-tocopherol, but different forms of vitamin E as well, play an important role in the prevention of AD [68]. Vitamin E which comes from dietary supplements has not been shown to reduce Alzheimer's disease risk. Many common supplements provide alpha-tocopherol only. Most of them do not replicate the range of forms of vitamin E that we find in regular food. It has been shown that high intake of alpha-tocopherol reduces serum concentrations of gamma- and delta-tocopherols [69]. It could be the explanation why the higher intake of vitamin E with food was associated with reduced Alzheimer's disease incidence in the study made by Morris et al. [66]. Similarly, in the Rotterdam Study, high vitamin E intake from natural sources was associated with reduced dementia incidence [70]. There was also a prospective study of 4,740 people over 65 years old, that has shown that supplementation of vitamin E and C was associated with a reduction in the incidence of AD [71]. Equally, another study made among 5395 participants, aged over 55, showed that a high intake of vitamin E and C was associated with a lower risk of AD. This association was noticed regardless of the level of education and the presence of APOE ε4 [72]. However, the reports describing the role of other antioxidative vitamins are divergent. In a large prospective cohort study made by Devore at al., intake of vitamin C, carotenoids and flavonoids had no effect on the risk of dementia including AD [70].

Studies on the role of diet in pathogenesis and course of AD underlined an influence of vitamins B6, B12 and folic acid. These vitamins are involved in the metabolism of homocysteine, which is in the human body as an intermediate product formed from exogenous, derived from protein intake methionine on the way to endogenous cysteine. Homocysteine is regarded as an independent risk factor for atherosclerosis and thrombosis. High blood levels of homocysteine (hyperhomocysteinemia) are also a risk factor for the development of cognitive disorders and dementia including AD [73, 74]. Elevated level of homocysteine and decreased level of vitamin B12 in the plasma of patients with AD was demonstrated by Malaguarnera et al. [75]. In a nearly 10 years study conducted among older people without dementia we had observed that folate intake was associated with a lower risk of developing AD [76]. This dependency was not observed for vitamin B12, vitamin C and carotenoids. There was a publication punctuating that serum levels of vitamin B12 and folic acid may be important in preventing AD [77]. In another study of 370 people without senile dementia over the age of 70 it has been observed that low levels of vitamin B12 and folic acid in their blood correlated with an increased risk of developing AD. The level of folic acid below 10 pmol/L and vitamin B12 below 150 pmol/L doubled the risk of dementia. Walker et al. demonstrated that long-term supplementation with folic acid at a daily dose of 400 mg and vitamin B12 at dose of 100 mg, improved cognitive function. It was

made on the basis of two years of observation [78]. On the other hand we have also found reports of large prospective studies with no association between the consumption of vitamin B6, vitamin B12 and folic acid and the risk of AD [79, 80]. We also know that elevated levels of homocysteine are neurotoxic and linked with cardiovascular dysfunction, cognitive decline, increased risk of dementia and brain atrophy [81].

The role of vitamins in the prevention and course of AD is not clear. There is still a need to make further research where several other dependencies should be considered like comorbidities or the way of supplementation of vitamins.

Conclusion

AD is the most common form of dementia and affects about 2% of the population in developed countries. It will still increase with the aging of the population. Therefore, effective prevention and alleviation of symptoms associated with AD is so important. The proceedings should aim to delay the time of development and reduce the prevalence of cognitive impairment which would allow elderly to live longer and independently. Currently available medications may reduce the symptoms of AD and slow down the progression of the disease however these do not lead to a complete cure. It explains why the knowledge of risk factors of AD should become important part of proceedings. We know that diabetes mellitus, midlife hypertension and obesity, smoking, depression and cognitive and physical inactivity are the main modifiable risk factors which represent about 50% of AD cases. Lifestyle, including proper nutrition and proper weight are important factors in prevention of diseases mentioned before. We also know that diet is a part of non-pharmacological prevention of cardiovascular diseases. The Mediterranean diet improves the health and reduces the risk of many diseases including AD. The supplementation of antioxidative vitamins, such a vitamin C and E, seems to reduce the risk of AD. What we should remember is that malnutrition accompanies AD quite often. There has been some studies saying that accelerated loss of weight may precede the diagnosis of AD [82, 83]. The importance of the single components of the diet, like berries, has not been documented well and requires further analysis [84].

Nevertheless the components of diet play an important role in reducing oxidative stress, modulating the immune response, reducing inflammation process and in providing elements for the body construction. Following that we may understand why the diet is so important for proper brain function and that it may be protective from AD. However, there are only few randomized clinical trials that have been designed to test the role of diet in cognitive decline and in dementia including AD. We still need more studies to prepare the multi-nutrient strategy for people with dementia and to unravel the specific influence of each dietary component on cognitive functions. We should be aware of synergistic interactions between different nutrients and we should keep in mind that there is a positive impact of antioxidants on our brain. We should also remember that connecting medications with non- pharmacological treatment like appropriate diet, physical and mental activity may improve the overall functioning of patients with dementia.

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