

## EDITORIAL

## ALZHEIMER'S DISEASE: FROM GENES TO NUTRITION

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Alzheimer's disease (AD) is widely identified as the most common cause of sporadic dementia. Its aetiology is still debated, as despite several hypotheses, different factors seem to play a role in its establishment and development. Recent studies have proposed a possible preventing role of nutrition. The weight loss typical of earlier phase of disease and the finding of malnutrition as a common trait between patients leads to hypothesize that a supplementation of specific nutrients seems to be useful and effective in terms of improvement of cognitive functions. Malnourished patients show also altered parameters when investigating inflammation markers: for example, hyperhomocysteinemia is a typical finding in elderly affected by dementia, and it can be prevented and corrected by using a proper nutrients supplementation. Pro-inflammatory state can be reduced with supplementation of polyunsaturated fatty acids, vitamins of the group B and phosphatidylserine, that can act reducing IL-1 $\beta$  (pro-inflammatory cytokine) and improving IL-10 (anti-inflammatory cytokine) synthesis. While investigating the role of nutrition, it seems to be deeply linked with genetic; a genetic onset AD-related could be latent and can be influenced by nutritional attitude. AD can be considered a sort of latent clinical condition that would disclose or not, depending also on micro-environment and nutritional parameters. The genetic expression can be influenced by assumptions or not of specific nutrients, with the promotion of different pro- or anti-inflammatory settings. The specific role of each micronutrient (in particular vitamins) and trace elements still needs to be punctuated, as they are involved in a pool of different reactions. Also genes acts not independently but in an interconnected pattern, in which the role of a single gene needs to be cleared, depending on others. This complex system of predisposing conditions and a possible role of nutrition as modulator of the inflammatory state is the object of this review.

This review of the recent literature emphasizes how this field of study inherent nutrition is extremely promising in terms of prevention and of treatment of Alzheimer's disease. Moreover, the literature

reinforces the need for early intervention in AD and suggests that multi nutritional intervention, targeting multiple aspects of the neurodegenerative process during the earliest possible phase in the development

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of the disease, is likely to have the greatest therapeutic potential.

AD is the most common cause of sporadic dementia, as it affects 60% of cognitive impaired patients; it commonly affects middle and late life, and it is considered an age-related disease. In 2010, 35.6 million people affected were estimated, and there are 7.7 million of new cases/year. In the next 20 years there is an increasing incidence of about 50%, and cases will double in 2050 (1). The typical symptoms are difficulties in remembering names and recent events in an early stage, together with apathy and depression. Lately other behavioral findings are expressed, like impaired judgment, disorientation, confusion, behavior changes, and difficulties in speaking, swallowing, and wandering. In the latest phase of disease, the patient is unable to communicate and to provide to its basic needs, requires constant care and in most cases dies because of systemic diseases.

AD therapy is nowadays based on acetylcholinesterase inhibitors (AChEI) drugs, as acetylcholine (ACh) loss, the neurotransmitter produced by neurons referred to as cholinergic neurons that in the central nervous system is believed to be involved in learning, memory, and mood, has been identified as one of the most important cause of neuronal impairment. The main therapeutic target is to increase ACh in the synaptic cleft: even if this is not the unique lack in neurotransmission, the “anti-dementia” drugs approved and used since now work on this target (2).

In recent years, there has been increasing evidence supporting the role of nutrition in AD (3). A number of dietary factors such as antioxidants, vitamins, polyphenols, and fish have been reported to decrease the risk of AD, while saturated fatty acids, high-calorie intake, and excess alcohol consumption were identified as risk factors. The aim of this study was to quantitatively review evidence between genes and nutrition on incident Alzheimer's disease.

## GENETICS

While the single etiological events that lead to AD have not been clearly resolved, it is now generally accepted that genetic factors clearly play a major role in AD by an age-dependent dichotomous model (4).

On the one hand, early-onset (<65) familial AD (EOFAD) is caused by defects in any of three different genes: the amyloid  $\beta$  protein precursor (APP) on chromosome 21 (5), the presenilin 1 (PSEN1) on chromosome 14 (6), and the presenilin 2 (PSEN2) on chromosome 1.

These mutations are rare and highly penetrant in early-onset familial AD, they are transmitted in an autosomal dominant fashion and have contributed greatly to our current knowledge of the pathogenesis of AD, as they result in specific phenotypic profiles to patients with dementia: the amyloidogenic pathology associated with APP, PSEN1, and PSEN2 (7).

Among susceptibility genes the apolipoprotein E (APOE) gene (19q13.2) (AD2) is the most prevalent risk factor for AD especially in those subjects harboring the APOE-4 allele whereas carriers of APO E-2 allele might be protected against dementia. APOE-related pathogenic mechanism are also associated with brain aging and with neuropathological hallmarks of AD. Unlike the mutations in the known EOFAD genes, APOE- $\epsilon$ 4 is neither necessary nor sufficient to cause AD but operates as a genetic risk modifier. Carriers of the APE-4 genotype show different conditions in biochemical and clinical markers as higher blood pressure and LDL-cholesterol levels, reduced blood histamine levels in brain, brain haemodynamics atrophy markedly increased, faster cognitive deterioration, and the age at onset is 5–10 years earlier in approximately 80% of AD cases harboring the APOE-4/4 genotype by decreasing the age of onset in a dose-dependent manner (8).

These discoveries show new directions in AD research and underscored the role of oxidative stress, chronic inflammation, immune system, lipid and cholesterol metabolism, synapse and molecular trafficking, as relevant genomic pathways and subject of further investigations.

## PATHWAYS

Genetic factors that induce EOFAD or associated to Load underscore a reduced set of genomic and metabolic pathways related to the pathology (9).

The Amyloid hypothesis, amyloid pathway that is directly and strongly supported by the mendelian

dominant factors as APP PSEN1 and PSEN2 8 as well as elevated expression of amyloid pathway genes BACE1 SP1 and CLU (10).

Other pathways that have been highlighted by GWAS analysis: Immune system and inflammation that is underscored by genetic factors as CR1, CD33, MS4A4A and MS4A46. Lipid metabolism and cholesterol that is strongly supported by the APO E gene and by many others newly discovered genetic factors as CLU, ABCA7, and ACE, SORL1. Endocytosis and trafficking -synaptic cell membrane that is underscored by genetic factors as BIN1, PICALM and CD2AP. These pathways are not strongly linked to the amyloid hypothesis that has driven so much recent thinking and open up avenues for intensive research with regard to the potential for therapeutic intervention (11).

### TWINS AND EPIGENETICS

The total heritability of the more common non Mendelian form of AD has been established in the work of Gatz using the largest population -based twin study. Results show that it is still very high, with estimates ranging from 60 to almost 80% in the best fitting model, leaving the remainder to environmental factors. This work shows in particular a strong prob and wise concordance for twins couples in dementia and AD. This concordance is higher in monozygotic men (44% tot dementia 45% AD) in monozygotic women (58% tot dementia, 61% AD), weaker in dizygotic men (25% tot dementia, 19% AD) and women (45% tot dementia, 41% AD). The pathological manifestations in AD patients may have preceeding initiating events occurred in early stages of brain development. In particular a direct role for metal esposition has been proposed for animal models and human studies. The environmental exposure of rats to the metal lead from birth to postnatal day 20 showed a delayed overexpression of APP an elevation of its amyloidogenic A $\beta$  product in old age (12). The exposure to metal lead of infantile cynomologous monkeys (*Macaca fascicularis*) shows a clear correlation to Alzheimer's disease like pathology, with amyloid plaques and elevated expression of amyloid pathway genes (APP, BACE1, SP1), in aged individuals (13). The possibility that developmental exposure to lead could result in the

formation of AD pathology in humans is further supported by findings in a patient that survived from severe lead toxicity at 2 years of age, but died of severe mental deterioration with senile plaques and NFT (neurofibrillary tangles) at the age of 42.

### MITOCONDRION

Given the fundamental contribution of the mitochondrial genome (mtDNA) for the respiratory chain, the association between mtDNA inherited variants and multifactorial diseases and AD has been investigated by a number of studies that, however, didn't reach a general consensus on the correlation between mtDNA haplogroups and AD (14). Mitochondrial respiratory chain (MRC) impairment has been in fact detected in brain, muscle, fibroblasts and platelets of Alzheimer's patients, indicating a possible involvement of mitochondrial DNA (mtDNA) in the aetiology of the disease (15). mtDNA mutations through heteroplasmic transmission might modify age of onset of the disease, conferring phenotypic heterogeneity and contributing to the neurodegenerative process, probably due to an impairment of MRC and/or translation mechanisms. Moreover an interaction between APOE polymorphism and mtDNA inherited variability in the genetic susceptibility to sporadic AD has been proposed (16).

### NUTRITIONAL RISK FACTORS

The critical observations considered in a recent review are that dietary saturated fats and cholesterol cause BBB dysfunction, resulting in the blood-to-brain delivery of apo B lipoprotein-A $\beta$ . In some individuals, dietary-induced disturbances in BBB integrity may be the initiating event for AD. If cerebrovascular disturbances are central to AD aetiology and progression, then considering strategies to positively influence integrity is a therapeutic priority. Presently, drug strategies used to treat AD are focussed on maintaining cell-cell communication rather than cerebrovascular function. Cholesterol is increasingly recognized to play a major role in the pathogenesis of AD. This is based on four lines of investigation(1): the lipoprotein ApoE4 coordinates the mobilization and redistribution of cholesterol

in the brain and affects the age of onset(2), intracellular cholesterol stimulates  $\gamma$ -secretase and amyloid-precursor-protein (APP)/ $\beta$ - amyloid processing(3), cholesterol-lowering drugs (statins) reduce the prevalence of AD (4) and elevated plasma cholesterol in midlife is associated with an increased risk for AD. Interestingly, rabbits fed with a 2% cholesterol diet display an accumulation of intracellular immunolabeled  $\beta$ - amyloid after 4 to 8 weeks (17) and hypercholesterolemia accelerates the amyloid pathology in a transgenic mouse model (18). Cholesterol does not pass the BBB and is synthesized locally in the brain and degraded to 24-hydroxy-cholesterol, which is transported outside the brain into the bloodstream. Cholesterol regulates  $\gamma$ -secretase with enhanced processing of  $\beta$ -amyloid(1–42). It is hypothesized that a breakdown of the BBB causes influx of cholesterol, with subsequent activation of  $\gamma$ -secretase and enhanced  $\beta$ -amyloid(1–42) production. These findings are consistent with the concept that AD is a dietary-fat induced phenotype of vascular dementia and accumulation of beta-amyloid-lipoprotein complexes may be an amplifier of dietary induced inflammation.

Synapse loss is a principal cause of cognitive decline, thus enhancing synapse formation is a compelling and novel interventional target. Synapse formation and elimination occurs throughout life and individual brain synapses are presently thought to be permanently remodeled in the adult brain. Because the cognitive disturbances of AD best correlate with loss of hippocampal and cortical synapses (19), it has been hypothesized that a possible therapeutic strategy might involve steps to restore such synapses. Preclinical studies indicate that such an effect can be induced by co- administration of rate-limiting precursors for membrane phosphatide synthesis, such as the nucleotide uridine, omega-3 polyunsaturated fatty acids, and choline (20). These nutrients synergistically increase brain levels of the phosphatide molecules that comprise the bulk of synaptic membranes, and brain levels of specific synaptic proteins, suggesting that they also increase synapse formation. Moreover, administration of combinations of these nutrients produces major increases in hippocampal dendritic spines, the anatomical precursor of and surrogate marker of new synapses and enhances cognitive function. These

combined observations raise the question as to whether these nutrients have a role in the management of AD, especially of its main symptom—memory dysfunction.

In terms of a human model to support biological plausibility, it has been proposed that patients with AD may have specific nutrient needs that could be a consequence of the disease process itself, or reflect a low intake or reduced bioavailability of specific nutrients needed for synapse synthesis and function (21).

Given this background, recently clinical trials using supplements that contain the nutrients that have been discussed, have been studied in patients with Alzheimer's disease. The results of these preliminary studies are encouraging in terms of improved memory performance.

Proinflammatory cytokines, e.g., interleukin-1 $\beta$  (IL1 $\beta$ ) modulate central nervous system functions and may contribute to the etiology of MCI and AD. Animal studies suggest that intervention with specific nutrients (PUFAs, B-vitamins, and phosphatidylserine) has the potential to reduce plasma levels of inflammatory IL1 $\beta$  and thereby attenuate associated behavioral changes by counteracting its neuroendocrine and immune effects (22). On the other hand, dietary supplementation with eicosapentaenoic acid can stimulate the formation of the anti-inflammatory cytokine IL10 (22). Several studies strongly suggest a link between diets and AD leading to the notion that Dietary Restriction (DR) may delay or prevent AD (23).

Biochemical and molecular analyses of the brains of old rats and mice that had been maintained on calorie restricted diets reveal a retardation of brain changes that occur during aging of animals fed ad libitum including increases in levels of GFAP and oxidative damage to proteins and DNA (24).

However, there is still a debate about whether DR works to increase life span, and by extension, other benefits in humans although the bad effects of dietary excess remain unchallenged. Nevertheless, data from population based studies suggest that a lower calorie intake leads to a lowered risk of AD and PD (25). DR is known to induce neuroprotective molecules that have a role in resistance of neurons to oxidative, metabolic, excitotoxic and apoptotic insults (26). DR is known to induce expression of several different

neurotrophic factors like brain derived neurotrophic factor (BDNF) in brain cells. However, before rushing to advocate DR as a treatment paradigm it is important to recognize that the treatment may be too late and even be counterproductive.

### NUTRITIONAL STATUS AND BODY COMPOSITION

Given the paucity of modifiable risk factors of AD, the potential preventive role of nutrition has aroused increasing interest.

Weight loss is one of the characteristics of the disease, being already present during the initial phase (27). Common to chronic disorders, there is ample evidence that lifestyle influences AD risk and progression. Good nutrition, but also physical activity and environmental enrichment confer synergistic reduction in AD risk (28).

The causes of the weight loss are complex and not still completely known; the decreasing of the body mass is set to the changes of the behavioral sphere, the anorexia, the increasing of the energy expense linked to wandering and the interaction with drugs (29). As regards the changes of the behavioral sphere, both the neurons of olfactory epithelium, that the sphere of taste, are one of the targets of the degenerative process of the disease. For this reason, the decreasing of the olfactory sensitiveness and gustatory check in subjects with Alzheimer disease (AD) can determinate a smaller interest for the foods. The weight loss is associated with a protein malnutrition and generally to a decrease of muscle mass, defined as sarcopenia.

Even the malnutrition associated with overweight can be a critical issue, because these subjects have an high risk to develop dementia and cognitive disease. Beydoun underlines that an excess of body weight, represents a potentially harmful condition. In fact, exists an association between body mass index and dementia.

The connection between obesity and dementia derives from the inflammatory effects of visceral adiposity and co-morbidity factors derived from it. The study of Saragat (30) showed that there is a strong link among cognitive score, nutritional status and body composition.

Interestingly, is the data about the relationship

between the elderly with dementia and sarcopenic-obesity.

### VITAMINS: FOCUS ON B12, B9, C, K, D

As regards nutrients, numerous studies demonstrated that most vitamins have been directly evaluated in the setting of cerebral functioning (31). Individuals with low serum concentrations of vitamin B12 and folate may have an increasing risk to develop Alzheimer's disease, even in the absence of a deficiency intake of these substances. Through the analyzes carried out by Malouf (32), was observed an association with Alzheimer's disease, whereas both of the two vitamins, and not the only vitamin B12 or folic acid alone.

The comparison among the subjects with low levels with those with normal levels of both vitamins, the first ones seem to have the double risk to develop the Alzheimer disease (32). The risk of dementia associated with the low levels of vitamin B12 and folic acid, it has been greater also in subjects with good cognitive basic functions.

Malouf et al. (32) have given different hypotheses forward to justify the connection between hyperhomocysteinemy, folic acid deficiency, vitamin B12 and neuropsychiatric disease. Hyperhomocysteinemy is the greater risk factor to develop cerebrovascular and cognitive diseases. Even vitamin K has been involved in nervous tissue biochemistry. Research carried out by Ferland (33) on antioxidant properties of the vitamin K, indicate that the vitamin concentration is lower in the bearers of the gene APOE4. Recent studies have demonstrated the abilities of vitamin k to inhibit the cellular death linked to nervous cells oxidation. There is a convincing evidence that vitamin K has important actions in the nervous system as a unique cofactor to the  $\gamma$ -glutamyl carboxylase enzyme; vitamin K contributes to the biological activation of proteins Gas6 and protein S, ligands for the receptor tyrosine kinases of the TAM family (Tyro3, Axl, and Mer) (33). It has been suggested that vitamin K may have an effect on neuronal damage and that supplementation can lead benefit for the treatment of this disease.

In addition to vitamins B12, B9 and K, vitamin C and E, which have a protective effect on the immune

and inflammatory processes of the subjects with AD.

For example, the apoE4 genotype may be associated with lower vitamin E retention in peripheral tissues. This is possibly related to an altered lipoprotein metabolism including increased alpha-TOH retention in LDL, a decreased expression of lipoprotein receptors and impaired cellular vitamin E delivery system, and a greater intracellular degradation of tocopherols in the apoE4 genotype (34). Both tissue vitamin E retention and biomarkers of chronic inflammation may be affected by the apoE genotype. Epidemiological and experimental evidence suggest a better vitamin D status in apoE  $\epsilon$ 4 than  $\epsilon$ 3 subjects indicating a certain advantage of  $\epsilon$ 4 over  $\epsilon$ 3 (35).

#### MINERALS: FOCUS ON ZINC, COPPER, SELENIUM, IRON

Dysfunctional homeostasis of transition metals is believed to play a role in the pathogenesis of AD by forming reactive species through metal amyloid complexes.

Modulating metals has been proposed as a therapeutic strategy for AD; bivalent cation chelators such as clioquinol and its later derivatives are being developed as a novel AD drug. The copper metal has been also the subject of studies with results that involve both the synaptic transmission and as a factor in the oxidative abnormalities: The serum level of copper Alzheimer discriminates vascular dementia; the level of serum copper in discordant monozygotic twins was higher in the twin suffering from Alzheimer's disease.

Zinc supplementation was found to reduce both A $\beta$  and tau pathologies in the hippocampus and to delay hippocampus-dependent memory deficits in AD mouse model. Iron mediates the oxidative stress in AD, and an imbalance in iron homeostasis is thought as a precursor to AD. Diets excessive in Fe together with a high intake of saturated fat acids have been recommended to be avoided in the elderly (36).

#### POLYUNSATURATED FATTY ACIDS N-3

As regards n-3 fatty acids, several epidemiologic studies have shown that regular fish consumers have a decreased risk of dementia or AD and better

cognitive performances (37). The protective effect of fish consumption has been attributed to its high content of long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs), particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The beneficial effect of long-chain n-3 PUFAs against dementia may be explained by their major structural and functional roles in neurone membranes, their vascular and antiinflammatory properties, as well as their potential ability to modulate neuroinflammation and the expression of neuronal-plasticity-related genes (38). As the dry weight of the brain is composed of 60% fat, it is not surprising that dietary fatty acids strongly influence the structure and composition of brain cell membranes (31). Membrane and neurotransmitter precursors (e.g., docosahexaenoic acid (DHA), uridine, choline, tyrosine, and tryptophane) are required to maintain electrical signalling and the constant restructuring of interconnected neurons. The biosynthesis of EPA and DHA from their precursor  $\alpha$ -linolenic acid (ALA) is limited and seems to decrease with aging (39). Thus, the major source of EPA and DHA is diet, mainly via fatty fish consumption (40). High dietary intake of long-chain n-3 PUFAs has been shown to be associated with a lower risk of dementia or cognitive decline (37, 41). However, some studies have not shown such a protective association (42, 23). Such inconsistent results may be explained by the weak association between dietary intake and the bioavailability of fatty acids.

#### POLYPHENOLS

The oxidative stress, the undue oxidation of biomolecules leading to cellular damage, promotes many studies of antioxidants in the prevention of AD. Polyphenols are natural antioxidants that provide protective effects to AD through a variety of biological actions, such as interaction with transition metals, inactivation of free radicals, inhibition of inflammatory response, modulation in the activity of different enzymes, and effects on intracellular signaling pathways and gene expression. Several animal studies have demonstrated that polyphenols inhibited a formation and attenuated cognitive deterioration. Data from a randomized, double-blind controlled clinical trial of polyphenols

supplementation in 100 subjects showed that polyphenols contained in antioxidant beverages might benefit AD patients by decreasing homocysteine concentrations in AD patients (43).

People take about 14.4 mg flavonoids per day which comes from fruits, vegetables, wine and tea. Several studies have suggested that inclusion of antioxidant-rich foods in the diet is helpful to improve cognitive performance in humans (43). High consumption of foods richest in flavonoids such as vegetables and fruits is positively correlated with cognitive performance in elderly people. Importantly, better cognition in elderly non-demented people is related to dietary intake of flavonoid-rich foods including chocolate, wine and tea, and there is dose-dependent association between intake of these foods and cognitive performance (44).

Natural polyphenolic compounds exhibit their antioxidant effect by quenching free radical species and/or promoting endogenous antioxidant capacity

#### FUTURE DIRECTIONS

In future, we will focus our attention on antioxidants that have been shown to protect against A $\beta$ -induced oxidative stress, ferulic acid, various polyphenols, including quercetin and resveratrol,  $\alpha$ -lipoic acid, N-acetyl-L-cysteine (NAC), curcumin, epigallocatechin gallate (EGCG), and  $\gamma$ -glutamylcysteine ethyl ester (GCEE). Brain-accessible antioxidants with both radical scavenging properties and ability to induce protective genes are hypothesized to be helpful in treatment for AD (44).

Recently, coenzyme Q10 (CoQ10) was found to affect the PI3K pathway. Choi H. et al. (2010) found that CoQ10 could restore amyloid  $\beta$  (A $\beta$ )25-35 oligomer-inhibited proliferation of NSCs by focusing on the PI3K pathway (45).

CoQ10 treatment decreased brain levels of protein carbonyls, a marker of oxidative stress. CoQ10 treatment resulted in decreased plaque area and number in hippocampus and in overlying cortex immunostained with an A $\beta$ 42-specific antibody (46).

Also recent data from clinical trials indicate that melatonin supplementation slows down the progression of cognitive impairment in AD patients. Melatonin efficiently protects neuronal cells from A $\beta$ -mediated toxicity via antioxidant and anti-amyloid

properties. It not only inhibits A $\beta$  generation, but also arrests the formation of amyloid fibrils by a structure-dependent interaction with A $\beta$  (47).

#### CONCLUSIONS

Alzheimer disease (AD) is the most common cause of dementia in elderly patients. Identification of risk factors for AD would contribute to the understanding of AD pathogenesis and thus, help in the development of preventive methods, also in consideration of the fact that an effective drug therapy is lacking today.

Early-onset familial AD is associated with mutations of the genes encoding amyloid precursor protein (APP), presenilin 1 (PS-1), or PS-2, resulting in the overproduction of amyloid beta-protein. Epidemiological and case-control studies have led to the identification of several risk factors for sporadic AD. The most concrete genetic risk factor for AD is the epsilon4 allele of apolipoprotein E gene (APOE). In addition, several genes such as CTNNA3, GAB2, PVRL2, TOMM40, and APOC1 are known to be the risk factors that contribute to AD pathogenesis. On the other hand, Environmental agents (e.g., heavy metals), intrinsic factors (e.g., cytokines), and dietary factors (e.g., cholesterol) perturb gene regulation in a long-term fashion, beginning at early developmental stages; however, these perturbations do not have pathological results until significantly later in life.

Dietary factors may interact with disease-causing or predisposing genes in molecular cascades that either promote or prevent the degeneration of neurons.

A genetic onset AD-related could be latent and can be influenced by nutritional attitude; from this point of view, AD can be considered a sort of latent clinical condition that would disclose or not, depending also on micro-environment and nutritional parameters. A possible link between inflammation, nutrition and genetic assessment may be the fact that the assumption or not of nutrients can influence genetic expression, leading to production of inflammatory mediators. Their presence seems to have a role both in AD onset and development, and the modification of inflammatory status may play a role in slowing disease progression.

There are three major conceptual aspects related to nutrient-gene interactions with potential influence on aging and dementia: direct interactions in which nutrients act as transcription factors that can bind to DNA that induces the expression of the gene; interactions epigenetic in which the nutrients alter the structure of DNA or histone that alters gene expression, and genetic variations through which different SNPs modifies or alters the expression of the gene.

There is a bidirectional influence of nutrients on genomic factors and of genomic factors on the metabolism of nutritional factors to keep a homeostatic equilibrium in health conditions. In addition, many dietary factors may exert a deleterious or toxic effect on neurons (dietary mutagens, genotoxins, Maillard reaction compounds and melanoidin structures, plant neurotoxins, heavy metals, and ultratrace elements such as aluminium and arsenic) while malnutrition or overnutrition can contribute directly or indirectly to induce the cognitive deterioration with underlying conditions that affect the function of the brain.

Consideration of mechanistic evidence to date suggests that several nutritional components can effectively counteract the negative processes in AD, e.g., by promoting membrane formation and synaptogenesis, enhancing memory/behavior, improving endothelial function, and cerebrovascular health.

Moreover, nutrition may prove to be a valuable asset in “quenching the fires” of inflammation that characterize AD. Finally, since oxidative stress is an early change in aging that is superimposed upon a stress vulnerable aging brain, early nutritional intervention may prevent or delay the onset of this disease.

The perspectives for further investigations are several: first of all, it is fundamental to define which are the nutritional situations at greater risk, in order to identify and treat them before clinical manifestations. A role for malnutrition in developing cognitive disorder is clear but it still needs to be punctuated; the researches results indicates that treatment is possible and useful if started properly. The importance to define the role of each micronutrient and trace elements (as in some cases, like for copper, there are still disputes) will lead to a more correct use of supplementation, calibrated on patient's actual needs. It would be useful to study

their effects in vitro, in particular how the genetic expression can be modified and influenced by their presence or lack.

The potential influence of nutrition on cognitive impairment and on the development and prevention of AD in particular, is therefore a topic of increasing interest in the scientific community. This review summarizes the key research findings in this growing field of investigation, also in relation to genomic factors and inflammatory pathway.

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