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COMMENTARY

Limitations of Current Treatment of Alzheimer's Disease and Proposed Plan to Improve it

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Summary

Alzheimer's Disease (AD), a progressive irreversible neurological disease is characterized by memory loss, reduced ability of thinking and reasoning, difficulty in performing daily tasks, and neuropsychiatric disorders. Alzheimer's disease has been grouped into two forms sporadic AD and familial AD. This disease undergoes three phases during progression (a) Minimal Cognitive Impairment (MCI), (b) early stage of AD, and (c) full-blown AD.

During last decades several internal stressors which participate in the development and progression of Alzheimer's disease (AD) have been identified. They include increased oxidative stress [1], and oxidative stress-induced chronic neuroinflammation [2,3], mitochondrial dysfunction [4,5], autophagic dysfunction [6], impaired omega 3 function[7,8], increased production of beta-amyloids [9-12], and hyperphosphorylation of tau protein [13,14], Other internal stressors include intestinal dysbiosis, loss of collagen, and progressive loss of acetylcholine.

Current approaches to treatment of AD

Elevating acetylcholine levels: One of the current approaches to treat AD is to elevate the levels of acetylcholine by inhibiting acetylcholinesterase by drugs such as Donepezil (Aricept), Galantamine, and Rivastigmine (Exelon) [15] or Xanomeline, a stimulator of muscarinic receptor [16,17] in the cholinergic neurons. The effectiveness of these drugs depends upon the viability of cholinergic neurons which continue to die because of oxidative and inflammatory damage. Therefore, their effectiveness in improving memory lasts only for a few months. None of these drugs addressees the causes of the disease. Preventing oxidative stress and chronic inflammation would prolong the effectiveness of these drugs.

Use of antibodies of beta-amyloid peptides: The FDA approved anti-amyloid antibody includes lecanemab, aducanumab, and donanemab. In patient with early phase AD, treatment with donanemab for 76 weeks improved cognitive function and ability to perform daily function of living compared to placebo group. In early phase AD, treatment with lecanemab for 18 months, reduced the levels of beta-amyloids, but it decreased only

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modestly the rate of cognitive decline. Toxicity of this treatment includes cerebral edema or effusion (mostly asymptomatic) [18-20]. These antibodies do not address the causes of the disease. In addition, these anti-amyloid antibodies do not influence the rate of production of new beta-amyloids; therefore, under the best condition, their effectiveness in improving AD symptoms may be short-lived. Other approaches for the treatment of AD can include reducing the production of beta-amyloids by inhibiting gamma secretase, and action of beta-amyloids which kill cholinergic neurons by generating free radicals [21,22].

Drugs used to treat behavior abnormalities in patients with AD: The patients with advanced AD also exhibit several behavior abnormalities which include anxiety, depression, apathy, aggression, agitation, sleep disturbances, and psychosis (hallucinations, and delusion) [23,24]. Currently used drugs for treatment of anxiety and depression include fluoxetine (Prozac), paroxetine (Paxil), fluvoxamine (Luvux), citalopram (Celexa), escitapram (Cipralex), and sertraline (Zoloft). These drugs have adverse side-effects after a long-term consumption. Therefore, non-toxic agents that can improve these behavioral symptoms should be identified.

Proposed plan to improve current treatment of AD

Reducing oxidative stress and chronic inflammation by proposed micronutrient mixture: This mixture contains vitamin A (retinyl palmitate), vitamin E (both d- alpha-tocopherol acetate and d-alpha-tocopheryl succinate), natural mixed carotenoids, vitamin C (calcium ascorbate), vitamin D3, all B-vitamins, coenzyme Q10, alpha-lipoic acid, N-acetylcysteine (NAC), resveratrol, curcumin, quercetin, green tea extract, and minerals selenium and zinc. This micronutrient mixture has no iron, copper, manganese or heavy metals.

None of the current drugs for the treatment of AD have addressed one of the major internal stressors oxidative stress and chronic inflammation which contribute to the development and proregression of this disease. Proposed micronutrient mixture would simultaneously reduce oxidative stress and chronic inflammation, and improve mitochondrial function, and autophagic function [25].

Prolonging the effectiveness of inhibitors of acetylcholinesterase: Proposed micronutrient would protect cholinergic neurons from oxidative damage that would allow inhibitors of acetylcholinesterase to maintain the elevated levels of acetylcholine for a long period of time.

Reducing production and toxicity of beta-amyloids and hyperphosphorylation of tau protein by proposed micronutrients: Antioxidants can reduce production of beta-amyloids by inhibiting the activity of gamma-secretase which cleaves APP to generate beta-amyloids and toxicity of beta-amyloids by destroying free radicals. Antioxidants also reduce hyperphosphorylation of tau protein [26-28]. Therefore, it is likely that the proposed micronutrient mixture may also reduce the production and action of beta-amyloids and hyperphosphorylation of tau protein. Therefore, it is likely that proposed micronutrient mixture may provide alternative to antibodies of beta-amyloids.

Reversing intestinal dysbiosis with probiotics with prebiotics may improve treatment of AD

Intestinal dysbiosis occurs in AD [29-31]. Supplementation with Probiotics with prebiotics may reverse intestinal dysbiosis by changing composition of bacteria in favor of beneficial bacteria which produces beneficial short-chain fatty acids such as butyric acid, acetic acid, and propionic acid during fermentation of prebiotics. Probiotics with prebiotics reduces the markers of pro-inflammatory cytokines, and improves immune function, as well as cognitive function in animal models of AD. It also would improve Mild Cognitive Impairment (MCI) and cognitive function in patients with AD [29,30].

Improving structural integrity and cognitive function in AD by restoring loss of collagen with collagen peptides: Collagen represents approximately 30% of total body's protein [32]. One of the most important functions of collagen in the brain to maintain its structural integrity and the levels of collagen type VI which acts as a neuroprotective agent [33,34]. Loss of collagen gradually occurs in the brain because of increased collagenase activity leading to impairment of structural integrity and loss of memory. Importance of collagen in maintaining structure was demonstrated by a clinical study in which daily supplementation with 5 g of collagen hydrolysates for a period of 4 weeks improved structural integrity of the brain and cognitive function in AD [33]. Collagen hydrolysates also protected the brain from inflammatory damage [35]. To maintain

increased levels of collagen in the brain for a long time, collagen peptides formulation must contain inhibitors of collagenase which degrades collagen.

Restoring levels of omega 3 and its function by using omega 3: Epidemiologic studies suggest that low blood levels of omega 3 increases the risk of AD [8]. Most studies show that supplementation with omega-3 fatty acids may be useful in improving memory function in an early phase of Alzheimer's disease. Other studies suggest that omega-3fatty acids supplementation may be useful in improving cognitive function in Alzheimer's disease [36]. Attenuation of decline in cognitive function was observed in older healthy individuals and those suffer from Alzheimer's disease who take omega-3 fatty acids regularly [37]. A recent review has shown that long-term consumption of omega-3-fatty acids showed a 64% reduction in the risk of Alzheimer's dementia or cognitive decline as well as reduced the levels of beta-amyloids, while short-term supplementation with omega-3 fatty acids has produced inconsistent results [38].

In the brain of AD patients, reduced utilization of glucose causes decreased production of energy [39]. that can lead to increased beta-amyloids deposits and hyperphosphorylation of tau protein. It has been reported that diabetes type II increases the risk of AD by 50% [40,41].

Normally, insulin receptor-mediated activation of AKT, also called protein kinase B, causes translocation of glucose transporter-4 (GLUT-4) from the cytoplasm to the cell surface membrane which then allows the entry of glucose inside the neurons for generating energy. The development of insulin resistance in the brain increases the risk of developing AD [42]. because of reduced uptake of glucose causing decreased production of energy. In AD patients with insulin resistance, omega-3 directly activates insulin receptor-linked AKT to improve glucose uptake [43].

Reducing abnormal behaviors associated with advanced AD by supplementation with CBD (Cannabidiol): The patients with advanced AD exhibit several behavior abnormalities which include anxiety, depression, apathy, aggression, agitation, sleep disturbances, and psychosis (hallucinations, and delusion) [23,24]. Treatment with CBD reduced agitation and anxiety [44]. CBD acts as a partial agonist of dopamine receptor D2 and produced anti-psychotic effect like that produced by prescription a drug aripiprazole [45]. In a mouse model of depression, administration of CBD causes rapid and sustained anti-depression effect by enhancing cortical serotonin receptor [46,47]. CBD stimulates serotonin receptor and inhibited serotonin re-uptake [48,49]. CBD protects neuronal death by preventing the release of glutamate by activating anandamide, one of the ligands of endocannabinoid system, which stimulates Endocannabinoid Receptor (CB1R) that acts as an antagonist of glutamate receptor (NMDAR) [50,51]. CBD also plays an important role in reducing the progression of AD. For example, CBD reduces gliosis, neuroinflammation, and phosphorylation of tau protein. It reverses and prevents cognitive deficits in rodent AD model, and protects against beta-amyloid-induced death of cholinergic neurons [52]. Excessive release of glutamate causes hyperactivity which can lead to neuronal death. CBD inhibits glutamate release, neuronal apoptosis, and production of Neurofibrillary Tangles (NFT) [50].

Conclusion

Internal stressors which participate in the development and progression of Alzheimer's disease (AD) include increased oxidative stress and oxidative stress-induced chronic neuroinflammation, mitochondrial dysfunction, autophagic dysfunction, impaired omega 3 function, increased production of beta-amyloids, and hyperphosphorylation of tau protein. Other internal stressors include intestinal dysbiosis, loss of collagen, and progressive loss of acetylcholine. Addressing one or two internal stressors at a time may not provide sufficient benefits in patients with AD. To improve the treatment of AD, all internal stressors must be addressed at the same time. Proposed plan to supplement with a micronutrient mixture, probiotics with prebiotics, collagen peptides, omega 3, and CBD (Cannabidiol) would reduce all internal stressors at the same time; and thereby, markedly improve the current treatment of Alzheimer's disease.

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