

## Can Omega-3 Fatty Acids Improve the Cognitive Function in People with Dementia Due to Alzheimer's Disease?

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**Abbreviations:** AD: Alzheimer's Disease; NFT: Neurofibrillary Tangles; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; IL: Interleukin; CSF: Cerebrospinal Fluid

### Editorial

Late onset dementia due to Alzheimer's disease (AD) is one of the most prevalent causes for morbidity in elder people above 65 years of age in both developing and developed countries. It remains as an unbeatable challenge to clinicians. The cognitive and functional decline in patients with AD is attributed to several etiological factors including genetic factors. Familial predisposition with environmental factors can be considered as the major etiological factor that contributes the incidence of late onset AD. Though the exact pathophysiology that causes the incidence of AD has not yet been established, consistent research during the last few decades has demonstrated the role of extracellular  $\beta$ -amyloid plaque and intracellular neurofibrillary tangles (NFT) in the brain cells [1]. Various etiological factors favor the formation of  $\beta$ -amyloid<sub>42</sub> ( $A\beta_{42}$ ) peptide and hyper phosphorylated tau protein that later aggregate to form  $\beta$ -amyloid plaque and NFT, respectively. The oxidative stress, inflammation, hypoxia, impairment of mitochondrial functions and Apo E4 protein of *APOE* gene

are the factors increase the formation and decrease the clearance of  $A\beta_{42}$  peptide [2-5].

The progression of the disease causes wide spread amyloid plaque formation which begins in the hippocampal region and gradually results in brain atrophy. The disease in its chronic state causes loss of social function, autonomy and independence of the patient. The quality of life of both patient's and care givers will be severely impaired. Hence, diagnosis and the disease-modifying treatments should be initiated at the earliest in order to prevent its progression. Diagnosis of dementia due to AD or non-AD, such as dementia due to front temporal lobar degeneration, Parkinson disease, Lewy bodies or vascular dementia, is challenging to clinicians due to overlapping signs and symptoms. To certain extend, diagnosis could be possible by observing the signs and symptoms with brain image using fluorescent probes and the level of  $A\beta_{42}$  in the plasma or CSF. Among these, signs and symptoms alone have limited application in the diagnosis of majority of AD cases from that of non-AD.

Most of the drugs used in dementia are costly and are not free from adverse effects. Food and Drug Administration, US approved acetylcholine esterase inhibitors for treating dementia [6]. Among the various acetylcholines esterase inhibitors described so far (tacrine, galactamine,

rivastigmine and donepezil), donepezil at 10 mg/day is found to be beneficial among others and showed no adverse effect [7]. However, its effect on improving the cognitive function in various stages of the disease is debatable. Nevertheless the effects from drug therapy during the advanced stage of the disease, an early therapy in subjects with familial risk for the AD is worthwhile. Therefore, an early diagnosis is demanded.

Epidemiological and research data recommend the beneficial role of omega-3 fatty acids mainly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) supplementation in improving the cognitive function [8]. Low level of EPA and DHA in erythrocyte was associated with cognitive decline in patients [9]. EPA plus DHA at 1.7- 1.8 g/day for 6 months could improve the cognitive function in patients with mild cognitive impairment [9-11]. Based on 21 cohort studies, Zhang et al. concluded that DHA at 8 g/d found to lower the risk of dementia due to AD or effective in mild cognitive impairment. At least 1-serving of fish/week can lower the risks of dementia due to AD [12]. Early studies showed that DHA supplementation was effective either alone or in conjunction with antioxidants [13]. Combination with natural antioxidant like curcumin can dilate the cerebral endothelium as well as can boost the cognitive effects of curcumin [14]. However, this area needs to be explored further in different populations across the world.

The anti-inflammatory activity of EPA and DHA is the major contributory effect responsible for the exhibited effect. This can be ascribed to inhibition of nuclear factor kappa-B in macrophage and thus down regulate the expression of inflammation associated genes like tumor necrosis factor-alpha, interleukin (IL)-6, IL-8, and monocyte chemoattractant protein-1 [15,16]. The anti-inflammatory lipid mediators such as resolvins, maresins and protectins produced from DHA can also contribute to the beneficial effect [17]. Furthermore, activation of nuclear factor- erythroid-2 related factor 2 increases the superoxide dismutase activity in monocytes/macrophages [18]. Omega-3 fatty acid supplementation can enhance the pro-brain-derived neurotrophic factor which in turn reduces the synaptic plasticity to improve the learning and memory. DHA can decrease the A $\beta$ <sub>42</sub> formation by decreasing the  $\gamma$ -secretase activity in the hippocampus and parietal cortex aged transgenic mouse. Concluding the anti-inflammatory and antioxidant activity of omega-3 fatty acids, they can be recommended as a prophylactic agent against dementia. However, population based long term clinical trials are scant to establish the beneficial effect.

Systematic review based on large clinical trials conducted so far revealed no beneficial effect in people with

dementia due to AD or non-AD causes [19]. Hence, it can be concluded that the beneficial effect reported so far might be based on small numbers of trials for short period. Therefore, there is scope for further research in subjects with dementia at the earliest. So, further studies are warranted to monitor the effects of omega-3 fatty acids supplementation alone and in combination with other antioxidant for a long period.

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