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The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: A preliminary randomized double-blind placebo-controlled study

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ABSTRACT

A 24-week, randomized, double-blind placebo-controlled study was carried out to test the feasibility of using omega-3 polyunsaturated fatty acids (PUFAs) monotherapy in people with cognitive impairment and to explore its effects on cognitive function and general clinical condition in these participants. Twenty three participants with mild or moderate Alzheimer's disease and twenty three with mild cognitive impairment were randomized to receive omega-3 PUFAs 1.8 g/day or placebo (olive oil). The data of 35 (76%) participants with at least one post-treatment visit was analyzed. There were no severe adverse effects in either group and it suggests that omega-3 PUFAs were well tolerable in this population. The treatment group showed better improvement on the Clinician's Interview-Based Impression of Change Scale (CIBIC-plus) than those in the placebo group over the 24 week follow-up ($p=0.008$). There was no significant difference in the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) change during follow-up in these two groups. However, the omega-3 fatty acids group showed significant improvement in ADAS-cog compared to the placebo group in participants with mild cognitive impairment ($p=0.03$), which was not observed in those with Alzheimer's disease. Higher proportions of eicosapentaenoic acid on RBC membranes were also associated with better cognitive outcome ($p=0.003$). Further studies should be considered with a larger-sample size, diet registration, higher dosages, comparisons between different combinations of PUFAs, and greater homogeneity of participants, especially those with mild Alzheimer's disease and mild cognitive impairment.

1. Introduction

Alzheimer's disease (AD) is the most common age-related neurodegenerative disease and has become an urgent public health issue in most areas of the world. Mild cognitive impairment (MCI) has been suggested to represent a prodromal stage of AD with up to 80% of patients receiving an AD diagnosis within 6 years (Cherrier et al., 2005). Recent evidence suggests that omega-3 polyunsaturated fatty acids (PUFAs) may play an important role in cognitive function in patients with AD (Mazza et al., 2007).

PUFAs are derived solely from dietary sources and mainly include *n*−6 (omega-6) fatty acids such as arachidonic acid (AA, C20:4*n*−3), synthesized in the body using linoleic acid (LA, 18:2*n*−6) as a precursor, and *n*−3 (omega-3) fatty acids such as eicosapentaenoic acid (EPA, C20:5*n*−3) and docosahexaenoic acid (DHA, C22:6*n*−3), synthesized from alpha linolenic acid (ALA, 18:3*n*−3) (Yehuda et al., 2002). However, recent evidences showed that only 2 to 10% of ALA was converted to DHA or EPA, which suggested that EPA and DHA are likely to be dietary (Ross et al., 2007). Marine fish are the principal sources of DHA and EPA (Shahidi and Miraliakbari, 2004).

Abbreviations: AA, arachidonic acid; AD, Alzheimer's disease; ADAS-cog, the cognitive portion of the Alzheimer's Disease Assessment Scale; ALA, linolenic acid; CIBIC-plus, Clinician's Interview-Based Impression of Change Scale; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDRS, Hamilton Depression Scale; LA, linoleic acid; MCI, Mild cognitive impairment; MMSE, Mini Mental Status Examination; PUFAs, polyunsaturated fatty acids.

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Higher total intake of *n*−3 PUFAs, particularly DHA, has been found to be associated with reduced risk of AD (Morris et al., 2003). Lower levels of EPA, DHA, and total *n*−3 fatty acids in the plasma phosphatidylethanolamine fraction have been found in patients with AD and MCI (Conquer et al., 2000). In prospective studies, higher plasma DHA level associated with reduction in the risk of dementia and predicted less decline of sensorimotor speed and complex speed (Schaefer et al., 2006; Dullemeijer et al., 2007). Limited evidences seem to suggest a possible association between *n*−3 PUFAs and reduced risk of dementia (Issa et al., 2006).

In animal studies, DHA has been found to increase hippocampal acetylcholine levels and its derivative, neuroprotectin D1, may decrease apoptosis (Aid et al., 2005; Lukiw et al., 2005). EPA or DHA administration has been found to improve learning ability in experimental designs (Hashimoto et al., 2005a,b; Song and Horrobin 2004).

In open-label studies, improvement of Mini Mental Status Examination (MMSE) scores or life quality were found after supplementation of EPA or combination of *n*−3 and *n*−6 fatty acids in patients with AD (Otsuka 2000; Yehuda et al., 1996), however, another study found no clinical benefit of ethyl-EPA on cognition (Boston et al., 2004). A pilot study suggested combination of AA and DHA may improve the cognitive dysfunction in organic brain damages or MCI rather than AD (Kotani et al., 2006). Recently, one larger-sample size randomized double-blind placebo-controlled study found 1.6 g DHA and 0.7 EPA added to cholinesterase inhibitors did not delay cognitive decline in mild to moderate AD, but showed positive effects in patients with MMSE>27 (Freund-Levi et al., 2006). This supplementation did not result in marked effects on neuropsychiatric symptoms except for possible positive effects on depressive symptoms and agitation symptoms in subgroups (Freund-Levi et al., 2008).

Given these inconsistent findings, we carried out a preliminary double-blind placebo-controlled study to investigate the feasibility of using omega-3 PUFAs (EPA combined with DHA) monotherapy in patients with AD or MCI and to explore its effects on cognitive function and general clinical condition in these participants. Associations between changes in cognitive function and erythrocyte membrane composition of total *n*−3 PUFAs, EPA or DHA were also assessed.

2. Experimental procedures

2.1. Study subjects

This study had been approved by the institutional review board of Taipei City Hospital and registered at the Clinicaltrials.gov website (NCT00628017). Written informed consent was obtained from all participants and from their legal representatives before enrollment. Potential participants were recruited through newspaper advertisements on the basis of complaints of memory difficulties with respect to themselves or a cared-for other. All of them received a diagnostic interview, MMSE, and Logical Memory delayed-recall from the Wechsler Memory Scale III.

Participants were eligible if they fulfilled the diagnosis of AD according to the American Psychiatric Association, DSM-IV criteria (American Psychiatric Association, 1994), with mild or moderate severity, or amnesic MCI. Mild to moderate AD was defined by an MMSE score between 10 and 26, and a Clinical Dementia Rating (CDR) score of 1 or 2. Amnesic MCI was operationalised as: (Petersen et al., 1999) (1). Subjective memory impairment by the patient and/or an informant, (2) objective memory impairment falling at least 1.5 standard deviations or more below age- and education-specific norms (Logical Memory delayed-recall score from the Wechsler Memory Scale III) (Wecherler, 1997), (3) relatively normal performance in other cognitive domains, (4) no impairment in activities of daily living, and (5) failure to meet DSM-IV criteria for dementia. This definition is developed by the researchers at Mayo Clinic and is the most popular and widely used clinical criteria until now (Jelic et al., 2006). The inclusion age range for participants was between 55 and 90 years old.

2.2. Enrolled procedure

Potential participants received an assessment by a psychiatrist or neurologist. Thorough medical, psychiatric and neurological assessments were performed. CT brain imaging was carried out to exclude vascular dementia. For participants without imaging data, the Hachinski's Ischemic Scale was used (Hachinski et al., 1975). Blood tests including folic acid, vitamin B12, thyroid function, and routine biochemistry were also carried out to exclude primary causes of dementia or cognitive impairment.

Exclusion criteria were as follows: inadequate motor or sensory capacity to comply with testing; any ischemic lesion on brain CT reported by the radiologist; a modified Hachinski Ischemic Scale score>4; a 17-item Hamilton Depression Scale (HDRS) (Hamilton, 1960) score>13; abnormal levels of folic acid, vitamin B12, or thyroid function; severe cormobidity, including another neurodegerative diseases, another chronic debilitating neurological illness (e.g. cerebral palsy), brain trauma, tumors, severe pulmonary, renal, liver disease, cardiac disease, or autoimmune disease, or conditions expected to cause death within 1 year. Participants with a diagnosis of alcoholism, schizophrenia, and bipolar disorder were excluded. Participants receiving cholinesterase agents during the screen or taking NSAID on a long-term basis were also excluded. Concomitant medications such as anticholinergics, anticonvulsants, and antipsychotics were not administered during the course of study. Agents with potential neuroprotective effects, such as Vitamin E, fish oil supplementation, and *Ginkgo biloba*, were discontinued during the trial period if they were used before the study.

2.3. Randomization and intervention

A 24-week, randomized, double-blind study was carried out to compare the effects of omega-3 PUFAs against placebo. Eligible participants were randomly allocated to one of two groups. The randomization process was carried out by another member of staff independent of the study and blind to the assessment. Group 1 received omega-3 PUFAs as 3 capsules twice daily (total daily omega-3 fatty acid dosage of 1080 mg of EPA and 720 mg of DHA). Group 2 received three identical placebo capsules twice daily which contained olive oil esters. Identical gelatin capsules were used. Both treatment and placebo capsules were vacuum deodorized and supplemented with tertiary-butyl hydroquinone, 0.2 mg/g, and tocopherols, 2 mg/g, as antioxidants. The source of the omega-3 fatty acids was menhaden fish body oil concentrate.

2.4. Clinical assessments

Participants were assessed and the capsules replenished every 6 weeks after starting the trial. The primary outcome measures were the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) (Rosen et al., 1984), and the Clinician's Interview-Based Impression of Change scale which included caregiver-supplied information (CIBIC-plus) (Schneider et al., 1997). These two measurements were assessed at baseline and at weeks 6, 12, 18, and 24.

The ADAS-cog is a sensitive and reliable psychometric scale (Rosen et al., 1984). It consists of 11 items, and scores range from 0 (no impairment) to 70 (very severe impairment). To reduce the potential for practice effects at subsequent visits, different word lists were used. The CIBIC-plus uses information obtained during an independent clinical interview to assess disease severity and progression of illness. The change from baseline at subsequent visits is scored by the same interviewer using a 7-point Likert-type scale, in which 1 represents markedly improved; 4, no change; and 7, markedly worse. Secondary