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Short Communication Open Access

Reasons Why Omega-3 Polyunsaturated Fatty Acids Produce Mixed Results in Alzheimer's Disease Prevention Studies

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Abnormal aging that epitomizes Alzheimer's disease (AD) is accompanied by memory and cognitive deficits that interfere with daily activities. As scientists look for causes and means of treating AD, omega-3 (n-3) polyunsaturated fatty acids (PUFA) are gaining significance because of their importance in brain function and their depletion in AD [1]. A direct remedy is dietary supplementation studies that have unfortunately yielded mixed results. The perplexing question is why some studies have beneficial outcomes while others report no effects on AD-associated cognitive or memory problems. Factors that may account for these discrepancies include an incomplete understanding of PUFA metabolic pathways and inadequate study design. Most findings are based on epidemiological observations rather than placebo-controlled intervention studies. From examining these studies, it is evident that any improvement in the outcome must include a better understanding of omega-3 fatty acid metabolism, standardization of initial clinical observations, assurance of pharmaceutical quality of omega-3 supplements, and genetics based selection of study participants combined with quantifiable outcomes.

Consideration of omega-3 metabolism and biochemical pathways- PUFAs that are enriched in neuronal tissues belong to two major groups; omega-6 (n-6) and omega-3 (n-3). The precursors of omega-6 and omega-3 cannot be synthesized by humans and must be obtained from diets, and are thus essential fatty acids. Once obtained from the diet, these precursors undergo a series of elongation and desaturation reactions catalyzed by competing enzymes. Arachidonic acid (AA, C20:4n-6) is the main omega-6 fatty acid while eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) are the major omega-3 fatty acids. While age is the greatest AD risk factor, genetic variants that may differentially metabolize and deliver PUFA into the brain are now known to contribute to AD pathology. For example, ApoE E4 allele carriers process DHA differently, so study participants with unrelated genotypes may not respond to the same intervention [2]. Serum levels of PUFAs are also controlled by the rate limiting enzyme, delta-6 desaturase. Desaturase haplotypes regulate omega fatty levels in different races [3]. Moreover, most Western diets are high in lipids and loaded with omega-6 PUFAs. Since the omega-6/omega-3 ratio is critical for efficacy [4], there is a need for dietary health questionnaire, and counseling to regulate dietary fatty acids in intervention studies. An essential component of these trials should also accurately measure PUFA levels in plasma/serum or red blood cells before and after intervention to ensure uptake and potential delivery into the brain. Biochemical endpoints to be considered should include: a) an increase in plasma omega-3 levels. b) Measures of omega-6/omega-3 ratios. c) DHA/AA and EPA/AA or (DHA+EPA)/AA ratios as indices of improved anti-inflammatory capacity.

Study designs and clinical factors to consider for omega-3 intervention studies - Less than 2% of hundreds of omega-3 studies examining AD outcomes meet minimum inclusion criteria for controlled clinical trials [5]. In most studies, only neuropsychological measures are monitored and there is hardly any examination of the efficient delivery of the omega-3 products to blood cells, let alone the brain. Even with these limitations, most systematic reviews conclude that omega-3 supplementation may have beneficial effects at the earliest stages of AD-related cognitive brain impairment. With the recognition of promising outcomes for early interventions, several studies examine effects on mild cognitive impairment (MCI). Initial clinical diagnosis used different cognitive assessment scales that are not expected to provide the same sensitivity on the effects of omega-3 intervention. Starting with different clinical phases, using different omega-3 doses, with varied follow-up times, and inadequately powered studies, makes it difficult to ascertain the effects of omega-3 intervention on AD. A combination of brain function, measures of efficient omega-3 incorporation, and monitoring known AD biomarkers are needed to determine efficacy accurately.

Pharmaceutical factors– Studies use omega-3 from different sources, diverse chemical forms (esters, unesterified), and purity without regard of potential limitations in metabolism. Some omega-3s are from algae or fish sources, are not accurately quantified, and are of questionable purity. Quality control aspects, including purity and storage with or without antioxidants may change final composition that is used for interventions. While most studies used omega-3 oils, others are based on the amount of sea food consumed; these inevitably deliver varying amounts of omega-3 supplements. Even in studies using purified oils, variable amounts of omega-3 ranging from 200 mg/day to over 2 g/day are used. With different sources, comes different compositions of omega-3 oils. Some studies use plant oils enriched with omega-3 precursors that may have different metabolic fates and may not be delivered to the brain in the required 20-22 omega-3 EPA or DHA. No attempts are made at monitoring if PUFAs are incorporated at right doses to plasma, or whether they even reach the brain. With varied time of supplementation from months to couple of years, it is unlikely that AD pathology that probably progresses over several years (10-20 years) can be reversed with a few months of intervention.

Conclusions

Omega-3 fatty acid interventions are more likely effective at the earliest preclinical stages of AD. Using high-purity omega-3 oils with defined EPA/DHA contents are highly recommended. Selection of subjects should consider the ApoE genotype and haplotypes of PUFA enzymes to enhance efficient uptake, and should ideally monitor PUFA levels and metabolism to ensure brain delivery. Preferably, surrogate AD biomarkers and disease mechanisms should be identified and

shown to be altered after intervention with an appropriate omega-3 dose for the required time. There is a need for personalized AD intervention because of genetic dependence of omega-3 metabolism [3]. Non-invasive monitor of brain omega-3 contents using PET scans and other functional brain imaging modalities [6] are highly recommended approaches open for future investigation.

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