Alzheimer's & Dementia 10 (2014) 485–502

Review Article

Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis

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Abstract

Background: Alzheimer disease (AD) patients are at risk of nutritional insufficiencies because of physiological and psychological factors. Nutritional compounds are postulated to play a role in the pathophysiological processes that are affected in AD. We here provide the first systematic review and meta-analysis that compares plasma levels of micronutrients and fatty acids in AD patients to those in cognitively intact elderly controls. A secondary objective was to explore the presence of different plasma nutrient levels between AD and control populations that did not differ in measures of protein/energy nourishment.

Methods: We screened literature published after 1990 in the Cochrane Central Register of Controlled Trials, Medline, and Embase electronic databases using Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for AD patients, controls, micronutrient, vitamins, and fatty acids, resulting in 3397 publications, of which 80 met all inclusion criteria. Status of protein/energy malnutrition was assessed by body mass index, mini nutritional assessment score, or plasma albumin. Meta-analysis, with correction for differences in mean age between AD patients and controls, was performed when more than five publications were retrieved for a specific nutrient.

Results: We identified five or more studies for folate, vitamin A, vitamin B12, vitamin C, vitamin D, vitamin E, copper, iron, and zinc but fewer than five studies for vitamins B1 and B6, long-chain omega-3 fatty acids, calcium, magnesium, manganese, and selenium (the results of the individual publications are discussed). Meta-analysis showed significantly lower plasma levels of folate and vitamin A, vitamin B12, vitamin C, and vitamin E ($P < .001$), whereas nonsignificantly lower levels of zinc ($P = .050$) and vitamin D ($P = .075$) were found in AD patients. No significant differences were observed for plasma levels of copper and iron. A meta-analysis that was limited to studies reporting no differences in protein/energy malnourishment between AD and control populations yielded similar significantly lower plasma levels of folate and vitamin B12, vitamin C, and vitamin E in AD.

Conclusions: The lower plasma nutrient levels indicate that patients with AD have impaired systemic availability of several nutrients. This difference appears to be unrelated to the classic malnourishment that is well known to be common in AD, suggesting that compromised micronutrient status may precede protein and energy malnutrition. Contributing factors might be AD-related alterations in feeding behavior and intake, nutrient absorption, alterations in metabolism, and increased utilization of nutrients for AD pathology-related processes. Given the potential role of nutrients in

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http://dx.doi.org/10.1016/j.jalz.2013.05.1771

the pathophysiological processes of AD, the utility of nutrition may currently be underappreciated and offer potential in AD management.

Keywords: Vitamin A; Vitamin B1; Vitamin B6; Folate; Vitamin B12; Vitamin C; Vitamin D; Vitamin E; Omega-3 fatty acids (DHA and EPA); Calcium; Copper; Iron; Magnesium; Manganese; Selenium; Zinc

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder of unknown origin and the leading cause of dementia. Age is the primary risk factor for AD [1,2], whereas a family history of AD (in familial AD) and the presence of the ApoE4 genotype (in sporadic AD) are the most important inherited determinants known for this disease [3,4]. Other risk factors for AD include gender, education, and potentially modifiable lifestyle factors including diet and physical activity [5,6]. Diet-related disorders such as obesity, hypertension, hypercholesterolemia, and diabetes have consistently been shown to be associated with AD [7–9]. Risk factors of nutritional origin are extensively analyzed for their possible role in AD onset and progression [3,10–13]. Epidemiological studies have suggested a positive correlation between AD and the consumption of a diet rich in saturated fatty acids and alcohol and low in antioxidants and vitamins. However, adherence to a diet rich in fruits, vegetables, and unsaturated fatty acids and low in saturated fat and refined sugar seems to reduce the risk of dementia and cognitive decline [10,14–17].

The first nutrients identified to be of pivotal importance for neuronal functioning and cognition were the B vitamins [18]. They were discovered at the beginning of the 20th century as being essential nutrients able to relieve beriberi and pellagra, deficiency diseases affecting the nervous system [19]. In 1929, Frederick Gowland Hopkins [20] and Christiaan Eijkman were awarded the Nobel Prize in Physiology for this discovery. Since then, several nutrients, including antioxidants, choline, and omega-3 fatty acids, have been suggested to influence cerebral functioning (reviewed in Bourre [21] and in Smith and Blumenthal [22]).

Therefore, it is no surprise that these nutrients have been postulated to play roles in the pathophysiological processes in AD. For example, antioxidants reduce reactive-oxygen-species-induced damage and stabilize membranes; the fatty acid docosahexaenoic acid (DHA) affects abnormal protein processing (amyloid-β, tau); and DHA, choline, and uridine modulate neuronal membrane formation [23]. Recent evidence suggests that a multinutrient intervention comprising DHA, eicosapentaenoic acid (EPA), uridine monophosphate (UMP), choline, folate, vitamin B6, vitamin B12, vitamin C, vitamin E, selenium, and phospholipids (PLs) modulated functional connectivity measures (assessed by electroencephalography) in AD, indicative of preserved synaptic function [24]. Therefore, increasing specific nutrient levels may modulate synaptic function and prevent neurodegeneration and eventually neuronal loss. Despite the potential importance of nutrient availability for brain function in AD, evidence on its systemic availability in AD is not conclusive. The results of the many studies that examined plasma nutrient levels in AD are not fully consistent, and systematic reviews are lacking.

The primary objective of the current systematic review is to evaluate the presence of differences in the systemic availability of nutrients between AD patients and cognitively intact elderly controls. Because protein/energy malnutrition may be present more among patients with AD than among control subjects and can potentially be associated with differential micronutrient and fatty acid status, the secondary objective was to compare plasma nutrient levels of AD patients and controls that were reported not to differ in measures of protein/energy malnourishment. All relevant literature published after 1990 in Medline, Embase, and the Cochrane Central Register of Controlled Trials was reviewed using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines recently published by Moher and colleagues [25].

2. Methods

2.1. Search strategy and selection criteria

The literature published from 1990 to March 26, 2012 was systematically screened in the Cochrane Central Register of Controlled Trials, Medline, and Embase electronic databases according to PRISMA guidelines [25] using the following search terms in the title, abstract, or descriptors:

(Alzheimer* and [humans or patients or inpatients or outpatients or persons or volunteers or participants or subjects] and [nutrition or nutritional or nutrient or nutrients or micronutrient or micronutrients or diet or diets or dietary or vitamin or vitamins or mineral or minerals or trace-element or trace-elements or fatty-acid or fatty-acids or pufa or pufas])

The search in the Cochrane Central Register of Controlled Trials, Embase, and Medline resulted in 4768 published studies that were imported into Endnote. Duplicate references (684) were automatically removed, followed by manual examination, which retrieved another 687 duplicate references. The title and abstract of the remaining 3397 publications were evaluated according to predefined exclusion and inclusion criteria.