ELSEVIER

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring ■ (2017) 1-8

Alzheimer's & Dementia

Blood Based Biomarkers

Nutrients required for phospholipid synthesis are lower in blood and cerebrospinal fluid in mild cognitive impairment and Alzheimer's disease dementia

Q9 Nick van Wijk[a,*], Rosalinde E. R. Slot[b], Flora H. Duits[b], Marieke Strik[c], Egbert Biesheuvel[a], John W. C. Sijben[a], Marinus A. Blankenstein[c], Jörgen Bierau[d], Wiesje M. van der Flier[b], Philip Scheltens[b], Charlotte E. Teunissen[c]

Q1 [a]*Nutricia Advanced Medical Nutrition, Nutricia Research, Utrecht, The Netherlands*
[b]*Alzheimer Center and Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands*
[c]*Department of Clinical Chemistry, VU University Medical Center, Amsterdam, The Netherlands*
[d]*Department of Clinical Genetics, Maastricht UMC+, Maastricht, The Netherlands*

Abstract

Introduction: Synaptic membrane formation depends on nutrients that fuel metabolic pathways for the synthesis of constituent phospholipids. Consequently, insufficient availability of such nutrients may restrict membrane formation and contribute to synaptic dysfunction in Alzheimer's disease (AD). We assessed whether blood and cerebrospinal fluid (CSF) concentrations of nutrients related to phospholipid synthesis differ among patients with AD, mild cognitive impairment (MCI), and control subjects.

Methods: Concentrations of uridine, choline, folate, homocysteine, and other related metabolites were analyzed in paired blood and CSF samples from subjects selected from the Amsterdam Dementia Cohort with AD ($n = 150$; age, 66 ± 7 years; 37% female), MCI ($n = 148$; age, 66 ± 8 years; 37% female), and control subjects ($n = 148$; age, 59 ± 8 years; 38% female).

Results: Age- and gender-adjusted analysis of variance revealed different concentrations of circulating uridine, choline, and folate and CSF uridine, folate, and homocysteine (all $P < .05$) among the three diagnostic groups. Post hoc pairwise comparison showed that subjects with AD had lower CSF uridine, plasma choline and higher CSF homocysteine concentrations, whereas subjects with MCI had lower plasma and CSF uridine, serum and CSF folate, and higher CSF homocysteine concentrations compared with control subjects (all $P < .05$), with differences ranging from −11 to +22%.

Discussion: AD and MCI patients have lower levels of nutrients involved in phospholipid synthesis. The current observations warrant exploration of the application of nutritional strategies in the early stages of AD.

Keywords: Nutritional status; Uridine; Choline; Folate; Homocysteine; Blood; Cerebrospinal fluid; Phospholipid precursors; Mild cognitive impairment; Alzheimer's disease

1. Background

Several interacting processes contribute to the neurodegenerative process of Alzheimer's disease (AD), including abnormal protein processing and neuronal membrane degeneration that lead to synaptic loss and synaptic dysfunction starting early in the disease course [1–3].

Nutrition is increasingly recognized as an important factor in the etiology and progression of AD. Epidemiologic studies have suggested that specific macronutrients and micronutrients are involved in the decline of cognitive function and risk of AD [4,5]. Nutrients can affect normal functioning and maintenance

*Corresponding author. Tel.: +31-30-2095000; Fax: +31-30-2100436.
E-mail address: nick.vanwijk@nutricia.com

http://dx.doi.org/10.1016/j.dadm.2017.04.005

of the brain via various mechanisms [6]. In particular, poor availability of certain nutrients in AD has been suggested to affect synaptic function [7,8]. The synthesis of synaptic membranes is dependent on several nutrients, for example, docosahexaenoic acid, uridine, choline, and folate, vitamin B12, vitamin B6, vitamin E, vitamin C, and selenium, which fuel the metabolic pathways for the formation of constituent phospholipids [9,10]. Consequently, insufficient availability of these nutrients hypothetically limits, among other processes, membrane formation and could contribute to synaptic dysfunction in AD.

Several studies have provided data on nutritional status in AD and results have generally shown lower blood levels of most nutrients that are required for phospholipid synthesis [11–13], but for some of these nutrients results are inconclusive. In addition, there is a lack of information in mild cognitive impairment (MCI), a predementia stage in which the scope for intervention is arguably higher. Most studies have focused only on one nutritional marker instead of a set of nutrients, which allow correlations between nutrients to be studied. Furthermore, only a limited number of studies reported paired blood and cerebrospinal fluid (CSF) nutritional markers. These data are important because blood levels are valuable in assessing nutritional status, whereas CSF levels give specific insights into the availability of nutrients in the brain.

The aims of this cross-sectional study were to assess whether blood and CSF concentrations of nutrients needed for phospholipid synthesis and related metabolites differ among AD, MCI, and control subjects. Concentrations of uridine, choline, betaine, folate, homocysteine, albumin, and bilirubin were measured in paired blood and CSF samples from subjects with MCI or AD and compared with control subjects. Revealing a disease-specific nutritional deficit would lend support to the application of nutritional supplementation in the management of AD.

2. Methods

2.1. Subjects

Subjects for this cross-sectional study were selected from the Amsterdam Dementia Cohort of the Alzheimer Center of the VU University Medical Center (VUmc) [14]. The study included patients with probable AD (n = 150), MCI (n = 148), and control subjects with subjective cognitive decline (n = 148), with all baseline biomaterial available, that is, paired blood plasma, blood serum, and CSF. The three diagnostic groups were matched for gender but not for age, as this was not feasible. All subjects underwent dementia screening at baseline, including physical and neurologic examination, electroencephalography, brain magnetic resonance imaging, and laboratory tests. Cognitive screening included a Mini–Mental State Examination (MMSE) and comprehensive neuropsychological test battery. Diagnoses were made by consensus in a multidisciplinary team, without knowledge of AD CSF biomarker results. Probable AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association up to the beginning of 2012, and subsequently, using the National Institute on Aging-Alzheimer's Association criteria for AD. MCI was diagnosed using "the Petersen criteria" up to the beginning of 2012 and the National Institute on Aging-Alzheimer's Association criteria for MCI after this date [14]. As control subjects, we used subjects who presented with cognitive complaints at our memory clinic, but who performed normal on clinical examinations, that is, the criteria for MCI were not fulfilled, and there were no psychiatric or neurologic diseases contributing to cognitive complaints. In addition, if follow-up diagnosis was available, control subjects were selected only if they remained stable. All subjects gave written informed consent for the use of their clinical data and samples for research purposes, and the study was approved by the medical ethics committee of the VUmc (protocol 00/211).

2.2. Blood and CSF collection

CSF and blood samples were collected from nonfasted subjects during diagnostic workup. CSF was collected by lumbar puncture between the L3/L4 or L4/L5 intervertebral space, using a 25-gauge needle and syringe, and collected in polypropylene tubes (Sarstedt, Nümbrecht, Germany) in agreement with international consensus protocols [15]. Within 2 hours, CSF samples were centrifuged at 1800g for 10 minutes at 4°C. Aliquots were either frozen at −20°C until routine analysis of Alzheimer biomarkers or frozen and stored at −80°C until further analysis. Venous blood was drawn (clotted blood for serum and EDTA blood for plasma), centrifuged at 1800g for 10 minutes at 4°C, aliquoted, and stored at −80°C. Q2

2.3. Blood and CSF analyses

Analyses of CSF amyloid-β 1–42 (Aβ42), total tau, and tau phosphorylated at threonine 181 (p-tau) were routinely Q3 done at the Neurochemistry laboratory of the VUmc Department of Clinical Chemistry using sandwich ELISAs (Innotest, beta-amyloid1–42, Innotest hTAU-Ag, and Innotest Q4 PhosphoTAU-181p; Fujirebio Europe, Gent, Belgium) [16]. The interassay coefficients of variation (CVs) were 10.9% for Aβ42, 9.9% for tau, and 9.1% for p-tau [14].

Concentrations of nutrients needed for phospholipid synthesis and related metabolites were analyzed in paired blood and CSF samples. All compounds, except bilirubin, were measured in CSF. Uridine, choline, betaine, and homocysteine concentrations were measured in blood plasma, whereas folate, albumin, and bilirubin concentrations were measured in blood serum. The Department of Clinical Chemistry of the VUmc, Amsterdam, the Netherlands, performed all analyses except the uridine analyses (plasma and