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Reduced plasma desmosterol-to-cholesterol ratio and longitudinal cognitive decline in Alzheimer's disease

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Abstract

Background: We here examined whether plasma desmosterol-to-cholesterol ratio (DES/CHO) is decreased in patients with Alzheimer's disease (AD) and investigated the association between plasma DES/CHO and longitudinal cognitive decline.
Methods: Plasma DES/CHO of AD patients and age-matched controls in a Japanese cross-sectional cohort was determined. Plasma DES/CHO at baseline and follow-up visits was assessed in relation to cognitive decline in Japanese and Swedish longitudinal cohorts.
Results: Plasma DES/CHO was significantly reduced in Japanese AD patients and significantly correlated with Mini-Mental State Examination (MMSE) score. The longitudinal analysis revealed that plasma DES/CHO in AD patients shows a significant decrease at follow-up intervals. The decline in plasma DES/CHO is larger in the AD group with rapid progression than in that with slow progression. The changes in plasma DES/CHO significantly correlated with changes in the MMSE score.
Conclusion: Plasma DES/CHO is decreased in AD patients and may serve as a longitudinal surrogate marker associated with cognitive decline.

Keywords: Alzheimer's disease; Mild cognitive impairment; Blood-based biomarker; Desmosterol; Longitudinal biomarker

1. Introduction

Alzheimer's disease (AD) is one of the most common and debilitating neurodegenerative disorders of the aging population. AD manifests itself as a progressive decline in memory accompanied by other cognitive and functional disabilities [1]. From the viewpoint of clinical practice and therapeutic clinical trials in AD, biomarkers are becoming increasingly important particularly when disease-modifying drugs will become available. Numerous studies have shown that tau, phosphorylated tau, and amyloid-β (Aβ) 42 in cerebrospinal fluid (CSF) are reliable biomarkers for AD diagnosis [2–4]. However, the CSF examination of AD patients has not been broadly applied in general clinical practice because lumbar puncture to obtain CSF is relatively invasive and time consuming. Moreover, these CSF markers do not seem to be associated with longitudinal cognitive decline in patients with AD [5]. Thus, there is a compelling need to establish a noninvasive biomarker for AD that follows the disease progression. Efforts to find reliable blood-based biomarkers for AD have met with little success [6]. Several reports have been published describing altered levels of proteins, peptides, or metabolites in patients with AD, but those blood-based biomarkers have proven difficult to replicate in independent studies [6], highlighting the importance of multiple validations.

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Table 1
Demographic characteristics of AD patients and age-matched cognitively normal controls in the Japanese cross-sectional cohort

Variable	Control (n = 201)	AD (n = 200)
Female (%)	72	75
Age, mean (SD)		
Age at examination (y)	77.6 (4.7)	77.6 (5.4)
Age at onset (y)	n/a	73.5 (5.0)
MMSE, mean (SD)	28.7 (1.5)	17.0 (5.2)**
APOE genotype		
2*3	15	6
2*4	2	1
3*3	151	71
3*4	32	99
4*4	1	23
DES/CHO (10^{-6}), mean (SD)	456 (119)	357 (134)**

Abbreviations: AD, Alzheimer's disease; n/a, not available; MMSE, Mini-Mental State Examination; DES/CHO, desmosterol-to-cholesterol ratio.
**$P < .01$.

In our previous report, we found that the plasma desmosterol-to-cholesterol ratio (DES/CHO) is significantly decreased in Caucasian patients with AD and subjects with mild cognitive impairment (MCI) [7]. Desmosterol is the most abundant precursor but rarely exceeds 1% of total brain sterols because the conversion from desmosterol to cholesterol is tightly regulated by the enzyme 3-hydroxysterol 24-reductase (DHCR24) [8]. A substantially higher desmosterol concentration in the hippocampus could be attributed to neurogenesis and synaptic plasticity that take place in the adult dentate gyrus [9]. Conversely, a decrease in desmosterol level in the hippocampus could at least in part correlate with the reduced number of progenitor cells differentiating into neurons [10]. These reports suggest an important role of desmosterol in the brain.

With this background, we here measured plasma DES/CHO of samples from a large Japanese cohort to extend our previous result that plasma DES/CHO is decreased in patients with AD in a different ethnic group. Furthermore, we performed longitudinal studies to determine the association between plasma DES/CHO and cognitive decline in patients with AD over time.

2. Materials and methods

2.1. Subjects

For cross-sectional analysis, plasma samples of 200 patients with AD and 201 age-matched cognitively normal elderly individuals (older than 65 years) were collected from seven clinical institutions in Japan (Table 1). The diagnosis of AD was made on the basis of the criteria of the National Institute of Neurological and Communicative Diseases and the Stroke–Alzheimer's Disease and Related Disorders Association [11]. Each participant was asked to complete the Mini-Mental State Examination (MMSE) [12]. *APOE* genotyping was performed as previously reported [13].

For longitudinal analysis, we used 17 subjects with AD (Japanese longitudinal cohort collected at Niigata University Hospital) and 28 subjects (Swedish longitudinal cohort consisting of 6 control, 12 MCI, and 10 AD subjects collected at Uppsala University Hospital), whose blood was drawn at two different time points (Table 2). Additional longitudinal plasma samples of 30 subjects at least at 3 different time points were obtained from Uppsala University Hospital (AD, n = 6; MCI, n = 6; control, n = 2) or purchased from PrecisionMed, Inc. (AD, n = 12; control, n = 4) (San Diego, CA, USA). The criteria of Petersen et al. [14,15] were used for the diagnosis of MCI. To be considered as having MCI, the patients had to be free of significant underlying medical, neurologic, or psychiatric illness and meet the following criteria: (1) subjective memory complaint, (2) objective signs of decline in any cognitive domain, (3) intact activities of daily living, and (4) clinical features not fulfilling the DSM-IV/ICD-10 criteria for dementia [16]. The two AD/MCI groups with slow and rapid progression were classified on the basis of

Table 2
Demographic characteristics of subjects in the longitudinal study

Variable	Japanese cohort, AD (n = 17)	Swedish cohort			Combined cohort, MCI/AD (n = 39)
		Control (n = 6)	MCI (n = 12)	AD (n = 10)	
Female (%)	71	75	33	30	56
Age, mean (SD)	68 (8)	67 (9)	62 (8)	66 (10)	66 (9)
Follow-up time, y, mean (SD)	2.0 (1.0)	2.7 (0.8)	1.8 (0.9)	2.2 (0.9)	2.1 (1.0)
MMSE, mean (SD)					
Baseline	20 (5)	30 (1)	28 (2)	25 (3)	24 (6)
Follow-up	16 (7)	30 (0)	28 (2)	22 (3)	21 (7)
ΔMMSE	−4 (4)**	0 (1)	0 (2)	−3 (3)*	−2 (4)**
DES/CHO (10^{-6}), mean (SD)					
Baseline	329 (103)	654 (146)	660 (200)	556 (232)	489 (225)
Follow-up	290 (79)	661 (130)	607 (237)	487 (276)	438 (237)
% Change	−10 (14)*	1.7 (5.1)	−8.3 (21)	−18 (27)	−11 (20)**

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; DES/CHO, desmosterol-to-cholesterol ratio.
*$P < .05$, **$P < .01$.