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Differential Appearance of Serum A β 43 and A β 42 in the Patients with Alzheimer's Disease

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Abstract

A longer amyloid-β protein (Aβ), Aβ43, deposits in amyloid plaques more frequently than Aβ40 in both sporadic and familial Alzheimer's disease (AD) brains, which shares a similar feature of Aβ42 [1,2]. A recent study reported that Aβ43 is more amyloidogenic and neurotoxic than Aβ42 in vitro and is abundant in the brain of patients with Alzheimer's disease [3]. These studies indicate that Aβ43 could be another key molecule for AD etiology other than Aβ42. Reduced Aβ42 levels and Aβ42/Aβ40 ratio in plasma and cerebrospinal fluid (CSF) were related with cognitive decline and AD [4,5]. However, Aβ43 levels in biological fluid and their relationship with Aβ42 and Aβ40 in living patients with AD remain unclear. Here we examined Aβ43, Aβ42 and Aβ40 levels in the serum of patients with AD and normal controls, and we found differential appearance of serum Aβ43 and Aβ42 in AD patients.

Methods

We examined 26 patients with AD (10 males and 16 females) and 18 age-matched normal controls (10 males and 8 females) at the Iwate Medical University Hospital, Japan. The average age of the subjects of the AD group was 75.1±1.8, and that of the subjects of the control group was 75.4±1.1 (means ± SEM). The clinical diagnosis of AD was based on NINCDS-ADRDA Alzheimer's Criteria. The mean Mini-Mental State Examination (MMSE) score (means ± SEM) of AD patients was 18.6 ± 1.0.

A venous blood sample was collected and serum was separated using standard methods. The serum samples were aliquotted and stored at -80°C until analyses. Serum Aβ42 and Aβ40 were measured using ELISA kits from WAKO (Osaka, Japan). Aβ43 was measured using a newly developed Aβ43-full-length ELISA kit by IBL (Takasaki, Japan). All samples were measured in duplicate. The Aβ values and ratios were compared by nonparametric analysis (Mann-Whitney U-test).

Results

No significant difference was found in serum Aβ40 between control (96.9 ± 7.6 pM, mean ± SEM) and AD (101.5 ± 7.1 pM, mean ± SEM) subjects. However, serum Aβ42 levels were significantly decreased in the AD group (10.2 ± 1.1 pM, mean ± SEM) compared with the control group (17.5 ± 1.8 pM, mean ± SEM, $p<0.001$, Mann-Whitney U-test) (Figure 1A). The Aβ42/40 ratio in the control group was 1.8 fold higher than that in the AD group (n=18, control; n=26, AD; $p<0.001$, Mann-Whitney U-test, data not shown). These results are consistent with previous findings that a lower plasma Aβ42/40 ratio is associated with greater cognitive decline [5]. In contrast to Aβ42, the serum Aβ43 in the AD group (1.32 ± 0.3 pM) was not decreased, and even showed a slight increase compared with the control group (1.04 ± 0.18 pM) (Figure 1B). The serum Aβ43 levels are about 10% of the serum Aβ42 levels. The Aβ43/42 ratio in the AD group was 2.5 fold higher than that in the control group ($p=0.08$, Mann-Whitney (U-test) (Figure 1B).

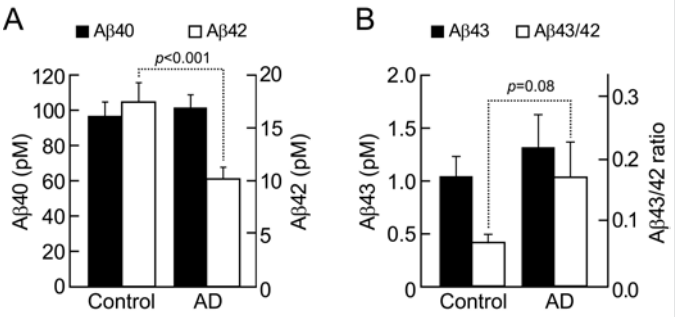

Figure 1: (A, B) The levels of serum Aβ40, Aβ42 and Aβ43 were measured using ELISA kits. All samples were measured in duplicate. A, ■ Aβ40, □ Aβ42; B, ■ Aβ43, □ Aβ43/ Aβ42. Aβ42 decreased in the serum of patients with AD compared with control subjects ($p<0.001$), whereas Aβ43 did not change or slightly increased, which resulted in a higher Aβ43/42 ratio in patients with AD ($p=0.08$). Data represent mean ± SEM; p was determined by the Mann-Whitney U-test. Control subjects, n=18; AD, n=26.

Discussion

AD patients were shown to have lower serum Aβ42 levels compared with control subjects, leading to a higher Aβ40/Aβ42 ratio, which is in agreement with previous findings [4-6]. A recent meta-analysis revealed that AD patients had marginally but non-significantly lower plasma Aβ42 levels compared with cognitively normal individuals, suggesting that lower plasma Aβ42 was not a constant feature of AD patients and that there is a limit to use lower plasma Aβ42 as a blood diagnostic marker [7]. We demonstrated that, in contrast to Aβ42, Aβ43 was not changed or rather increased in the serum of AD patients, suggesting that the clearance of serum Aβ43 or the deposition of Aβ43 in brain may be regulated in a distinct manner from Aβ42. Previous study revealed that the inhibition of Aβ40 and Aβ42 generation using a γ-secretase inhibitor, DAPT, accompanied the accumulation of Aβ43, supporting this notion [8,9]. An increase in serum Aβ43 and a significant decrease in serum Aβ42 in AD patients leaded to a 2.5 fold higher Aβ43/42 ratio compared with control subjects. The increase of serum Aβ43/42 ratio

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(2.5 fold) is bigger than that of Aβ40/42 ratio (1.8 fold) in AD patients. Taking the blood biomarkers of AD into account, it is important to examine whether a higher serum Aβ43/42 ratio in AD patients is a constant feather in further studies. In addition, the differential serum appearance of Aβ43 and Aβ42 in AD patients suggests that Aβ43 may play a different role from Aβ42 in AD pathogenesis.

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