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【Overview presentation】

15th Clinical Trials on Alzheimer's Disease (CTAD)

Age dependency of plasma β-amyloid measured by fully automated and highly specific immunoassays in a Japanese cohort study (SESSA)

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Overview presentation	**Backgrounds** In recent years, blood-based plasma β-amyloid (Aβ) has been increasingly studied as a potential biomarker of Alzheimer's disease (AD) because it is less invasive, more cost-effective, and easily accessible. Mounting evidence shows that the ratio of plasma $Aβ_{1-42}$ to $Aβ_{1-40}$ (Aβ42/Aβ40) is highly concordant with amyloid PET status, suggesting that it may reflect the brain Aβ pathology. Besides amyloid pathology in the brain, other risk factors for AD development are known, most notably age. Considering the use of plasma Aβ for the enrollment of subjects for clinical trials or for diagnostic adjunct purposes, it is important to understand the association between age and plasma Aβ. Because many disease-modifying therapies currently under development target the early stages before the onset of AD, it is necessary to understand the age dependency of plasma Aβ in older adults with normal cognitive function. However, several studies have reported conflicting results regarding the age dependence of plasma Aβ levels. Aβ is known to be unstable in the blood, and various factors at the time of blood collection are known to influence levels of blood Aβ. Such factors may influence the contralateral results on age dependency so far. Currently, the technique of canceling the effect by taking the ratio as Aβ42/ Aβ40 is often used. On the other hand, when trying to understand the age-dependency of Aβ40 and Aβ42 alone, the handling of samples during blood collection requires rigor.

Objectives

In this study, we aimed to examine the age-dependency of plasma Aβ40 and Aβ42 in a general Japanese male population using samples collected under a uniform protocol.

Methods

The Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) is an ongoing epidemiological study in a general population randomly selected from Kusatsu City (Japan) residents at baseline (2006–2008). The second survey was performed between 2010 and 2014 and a total of 853 men aged 46–83 participated in medical examination. We collected blood samples by venipuncture and stored them at -80 degrees Celsius until measurement. For sample collection, blood collected in a collection tube containing EDTA was mixed by gently inverting several times, then stored on ice until centrifugation. Plasma Aβ40 and Aβ42 were measured using a fully automated immunoassay platform (HISCL^{TM} series) in 2021. Both Aβ40 and Aβ42 were measured twice, and the average was used for analysis. We evaluated the age-dependency of Aβ40 and Aβ42 based on the measurement results of 822 participants, excluding 31 participants for whom measurements could not be performed. For this purpose, we divided participants into 5 age groups at 10 years intervals and examined the age dependency of Aβ40, Aβ42, and Aβ42/Aβ40 ratio by the Kruskal-Wallis test.

Results

The mean age of the participants was 69 years. There were significant differences in both Aβ40 and Aβ42 across the age groups, but not for Aβ42/Aβ40 ratio. The change per year of age for Aβ40 and Aβ42 were showing a significant increase by age. On the other hand, the change per year of age for Aβ42/Aβ40 ratio was showing a significant decrease by age.

Conclusion

Our results showed that plasma Aβ40 and Aβ42 increase in an age-dependent manner, while the Aβ42/Aβ40 ratio decreases in an age-dependent manner. This age-related change in plasma Aβ levels may be due to changes in production or functional changes in the blood-brain barrier. However, compared with the age-dependent changes in Aβ40 and Aβ42, the age-dependency of Aβ42/Aβ40 ratio was more gradual, with no significant differences found in the analysis divided into 5 age groups. It may suggest that age dependence may be reduced by using the Aβ42/Aβ40 ratio.

Although the present results were based only on men and limited to the Japanese

	population, they suggest that using appropriate sample handling protocols and measurement methods may be able to assess the relationship between plasma Aβ and other factors. To further our understanding of plasma Aβ, an assessment of the association with cognitive function and other AD risk factors, as well as in women and other races, is warranted in the future.
Session	Poster, Clinical Trials: Biomarkers including plasma（LP68）