November 9, 2020
Sysmex Corporation
Eisai Co., Ltd.

Sysmex Presents Academic Report with a View to Creating a Simple Method of Diagnosing Alzheimer's Disease Using Blood

- The Content Presented at the 13th Clinical Trials on Alzheimer's Disease (CTAD) Conference -

Sysmex Corporation (HQ: Kobe, Japan; Chairman and CEO: Hisashi Ietsugu; "Sysmex") and Eisai Co., Ltd. (HQ: Tokyo, Japan; CEO: Haruto Naito; "Eisai") announced that the most recent data from the project to develop a method of diagnosing Alzheimer's disease (AD) using blood plasma was presented at the 13th Clinical Trials on Alzheimer's Disease (CTAD) conference, held virtually from November 4 to 7, 2020. Sysmex demonstrated on behalf of the two companies the performance of the amyloid beta (Aβ) in plasma measured on Sysmex's HISCL™ fully automated immunoassay analyzers in predicting amyloid pathology as defined by amyloid positron emission tomography (PET) imaging on the centiloid scale.[1]

Clinical trials: biomarkers including plasma LP10	Plasma Aβ ratio measured on a fully automated immunoassay predicts amyloid positivity defined by amyloid PET centiloid Poster presentation: November 4 (Wed.) to November 7 (Sat.)

Our group has hitherto used the visual read method[2], which is commonly used for clinical trials, to confirm amyloid pathology by amyloid PET scan. Meanwhile, an increasing number of recent research projects quantify amyloid PET images with the index called SUVR (Standard Uptake Value Ratio) and correct with a standardized technique called the centiloid method to assess amyloid pathology quantitatively.[3] Accordingly, to assess the performance of the plasma $A\beta_{1-42}/A\beta_{1-40}$ (Aβ ratio) as measured on a fully automated immunoassay system HISCL in predicting amyloid pathology, we used both the visual read method and centiloid method to determine amyloid pathology for 149 cases clinically diagnosed as having MCI (Mild Cognitive Impairment) and mild AD to ascertain the difference in their predictive performance.

The results confirmed that the centiloid method exhibited a better performance in determining amyloid pathology with sensitivity and specificity measuring at 78% (AUC = 0.82), whereas sensitivity and specificity was 72% and 71% (AUC = 0.74), respectively, for the visual read method. Also, a correlation (Spearman's rank correlation coefficient (r_s)[4] = -0.57, $p < 0.0001$) was determined between the plasma Aβ ratio and the centiloid values, indicating more strongly than ever the potential to predict amyloid pathology in the brain with the plasma Aβ ratio. Furthermore, it was observed that many instances where there was a mismatch between the decisions by the plasma Aβ ratio and the centiloid method were false-positive cases (positive by the plasma Aβ ratio, negative by amyloid PET centiloid). Other research groups have also reported on such mismatches, suggesting that these false-positive subjects are more likely to test positive in amyloid PET imaging than the negative subjects.[5] It follows from these findings that there is a possibility that the plasma Aβ ratio measured on a fully automated immunoassay system HISCL reflects earlier amyloid pathology in the brain, which amyloid PET imaging cannot detect.

To further assess clinical utility of our assay system, we will evaluate additional sample sets.

The total number of those living with dementia across the world is projected to reach 82 million in 2030 and 152 million in 2050, with the total global societal cost of dementia stemming from direct medical and social care costs and lower productivity being estimated to reach 2 trillion USD in 2030.[6] In Japan, the number of those with dementia is thought to have reached approximately 4.62 million in 2012 and is projected to grow to 7.30 million in 2025[7], with the total societal cost of this disease being estimated to be equivalent to 4.1%[8] of the gross domestic product (GDP) in 2025 (25.8 trillion yen[9]). Of these sufferers, those living with AD are thought to account for more than 60% of those living with dementia.[7]

It is conceivable that AD is a disease that results in synaptic dysfunction and neuronal cell death due to tau deposition in neurons triggered by Aβ aggregation on the outside of neurons. These brain changes cause cognitive impairment and psychological and behavioral symptoms, suggesting that the Aβ aggregation and accumulation inside the brain is caused by AD before the presence of cognitive impairment appears, thus, it is believed that early diagnosis and early intervention is more effective in therapies targeting Aβ. Currently, amyloid PET and Aβ ratio in cerebrospinal fluid (CSF) are used for detecting amyloid aggregates in the brain, but this puts significant burden on patients in terms of access, costs, and their physical wellbeing.[10]

Sysmex and Eisai are working to create new diagnostic technologies for the prevention and treatment of dementia. Accordingly, the overarching aim is to contribute to the advancement of healthcare and improve the quality of life for those living with the disease and their families.

Terminology

1 A standardization scale for integration analysis of PET SUVR values as measured by different amyloid PET imaging probes.
2 Trained doctors qualitatively distinguish amyloid PET positive from amyloid negative subjects by visually reading images.
3 Klunk WE *et al*, Alzheimer's Dementia (2014)
4 Assesses how correlated two sets of data are based on two quantitative data distributions. For the purpose of this analysis, Spearman's rank correlation coefficient (r_s), which is a correlation index as determined by the rankings of the two variables, was calculated.
5 Schindler SE *et al*, Neurology (2019)
6 World Alzheimer Report 2018
7 Promotion of Comprehensive Measures against Dementia, Ministry of Health, Labour and Welfare
8 Study on Economic Impact of Dementia in Japan, 2014 Health Labour Sciences Research Grant Annual Report
9 Estimated by Sysmex based on Japan's Medium-term Economic Outlook (February 2018), Daiwa Institute of Research
10 Aβ is a peptide made of amino-acid residues removed from amyloid precursor protein. Many of them are $Aβ_{1-40}$, which is comprised of 40-residues, and the $Aβ_{1-40}$ level does not fluctuate significantly as AD progresses. Comprised of 42-residues, $Aβ_{1-42}$, on the other hand, is highly cohesive and decreases in cerebrospinal fluid (CSF) from the early stages of AD. It is believed that Aβ's absolute values show individual and intrinsic variability but that the plasma $Aβ_{1-42}/Aβ_{1-40}$ ratio remains unchanged. It has also been reported that the plasma $Aβ_{1-42}/Aβ_{1-40}$ ratio in CSF shows a high correlation with amyloid PET.

About the collaboration between Sysmex and Eisai

In February 2016, Sysmex and Eisai signed a comprehensive non-exclusive agreement aimed at the development of new diagnostic tests in the field of dementia. By leveraging each other's technologies and knowledge, the objective has been to discover next-generation diagnostic reagents that will enable early diagnosis of dementia, selection of the most appropriate treatment options, and regular monitoring of the effects of such treatments. At the 12th CTAD held in December 2019, the two companies reported on the performance of the plasma Aβ ratio measured on a fully automated immunoassay system HISCL in predicting the amyloid PET scan results (sensitivity: 73%, specificity: 71% [AUC = 0.74]), thus demonstrating the potential to predict amyloid pathology in the brain using the plasma Aβ ratio.* This finding was expected to lead to the development of a simple method of diagnosing Alzheimer's disease using blood.

*https://www.sysmex.co.jp/en/news/2019/191209.html
https://www.eisai.com/news/2019/news201990.html

Contacts for inquiries

IR & Corporate Communication Sysmex Corporation Tel：078-265-0500	Public Relations Department Eisai Co., Ltd. Tel：03-3817-5120