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RESEARCH ARTICLE

Clinical utility of CSF Aβ38 in Japanese research and clinical cohorts

Tamao Tsukie[1] | **Kensaku Kasuga**[1] | **Masataka Kikuchi**[1] | **Takanobu Ishiguro**[2] | **Akinori Miyashita**[1] | **Osamu Onodera**[2] | **Takeshi Iwatsubo**[3] | **Japanese Alzheimer's Disease Neuroimaging Initiative** | **Takeshi Ikeuchi**[1,‡]

[1]Department of Molecular Genetics, Brain Research Institute, Niigata University, Niigata, Japan

[2]Department of Neurology, Brain Research Institute, Niigata University, Niigata, Japan

[3]Department of Neuropathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Correspondence
Kensaku Kasuga or Takeshi Ikeuchi, Molecular Genetics, Brain Research Institute, Niigata University, 1-757 Asahimachi-dori, Chuo-ku, Niigata City, Niigata 951-8585, Japan.
Email: ken39@bri.niigata-u.ac.jp and ikeuchi@bri.niigata-u.ac.jp

‡The full membership of the Japanese ADNI investigators is listed at https://humandbs.biosciencedbc.jp/en/hum0043-j-adni-authors

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Abstract

INTRODUCTION: Previous studies have reported that cerebrospinal fluid (CSF) amyloid beta (Aβ42/Aβ38) performs comparably to Aβ42/Aβ40 in predicting amyloid positron emission tomography (PET) positivity in White cohorts. However, this finding has not been validated in diverse populations. Moreover, the utility of CSF Aβ38 in diagnosing various neurological diseases has not been fully understood.

METHODS: We analyzed CSF Aβ38, Aβ40, Aβ42, phosphorylated tau181, and neurofilament light chain in Japanese research and clinical cohorts with Alzheimer's clinical syndrome (ACS) or non-ACS.

RESULTS: CSF Aβ42/Aβ38 predicted amyloid PET positivity comparably to Aβ42/Aβ40. The levels of CSF Aβ38 were significantly lower in patients with progressive supranuclear palsy (PSP) and idiopathic normal pressure hydrocephalus (iNPH) than in those with other diseases.

DISCUSSION: We validated the high diagnostic performance of CSF Aβ42/Aβ38 in Japanese patients with AD. CSF Aβ38 reduction may be a characteristic feature of PSP and iNPH.

KEYWORDS
Alzheimer's disease continuum, amyloid beta 38, cerebrospinal fluid, idiopathic normal pressure hydrocephalus, progressive supranuclear palsy

Highlights

- The diagnostic value of cerebrospinal fluid (CSF) amyloid beta (Aβ)38 was examined in Japanese research and clinical cohorts.
- CSF Aβ42/Aβ38 and Aβ42/Aβ40 showed comparable performance to detect brain Aβ deposition.
- CSF Aβ42/Aβ38 and Aβ42/Aβ40 discordant group showed a characteristic profile.

Tamao Tsukie and Kasuga contributed equally to this work

- CSF Aβ38 and Aβ40 were prominently decreased in progressive supranuclear palsy and idiopathic normal pressure hydrocephalus.

1 | INTRODUCTION

The number of patients with dementia, including Alzheimer's disease (AD), is increasing worldwide.[1] The introduction of anti-amyloid beta (Aβ) antibody therapy for AD in Japan has increased the need to use biomarkers in distinguishing AD from other neurocognitive disorders. The Aβ42/Aβ40 ratio (Aβ42/Aβ40) in cerebrospinal fluid (CSF) is decreased in patients with AD and is highly concordant with amyloid positron emission tomography (PET) positivity. CSF Aβ42/Aβ40 is used in differentiating AD from other diseases.[2,3] In fact, a positive CSF Aβ42/Aβ40 finding is considered sufficient to diagnose AD.[4]

Aβ is produced by sequential cleavage of amyloid precursor protein. In addition to the long and toxic Aβ42, short Aβ40 and Aβ38 are produced, which can be detected in the CSF.[5–7] To date, reports of the usefulness of the CSF Aβ42/Aβ38 ratio (Aβ42/Aβ38) in AD diagnosis are limited to White populations. In these reports, the performance of CSF Aβ42/Aβ38 in predicting PET positivity[8–10] and discriminating AD from non-AD dementia[10–17] is comparable to that of CSF Aβ42/Aβ40.

We previously reported that CSF Aβ38 levels are decreased in patients with AD caused by presenilin 1 (*PSEN1*) mutations.[18] Aβ38 levels are also reduced in various neurological diseases, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), frontotemporal dementia, or idiopathic normal pressure hydrocephalus (iNPH).[12,19–28] Most evidence on the utility of Aβ38 in diagnosing dementia has been reported from Europe; however, these findings have yet to be validated in diverse populations.

In this study, we aimed to compare the performance of CSF Aβ42/Aβ38 to that of Aβ42/Aβ40 in the differential diagnosis of dementia in a Japanese population. The diagnostic accuracy of CSF Aβ42/Aβ38 in detecting amyloid PET positivity was examined compared to that of Aβ42/Aβ40 in the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI), a multicenter research cohort of the AD continuum. The utility of CSF Aβ38 in diagnosing dementia across various neurological diseases in a multicenter clinical cohort was also explored. We confirmed the diagnostic utility of CSF Aβ42/Aβ38 and Aβ38 in a non-White population.

2 | METHODS

2.1 | Participants

2.1.1 | Cohort 1 (J-ADNI research cohort)

The J-ADNI study was a multicenter research cohort in Japan and was conducted to discover the fluid and imaging biomarkers for the AD continuum using a harmonized protocol with ADNI.[29,30] Of the 537 participants recruited for the J-ADNI study, 194 underwent lumbar puncture. In the current study, we included 177 participants, including 46 participants without cognitive impairment (CU), 82 patients with mild cognitive impairment (MCI), and 49 patients with AD dementia, for whom CSF Aβ42/Aβ38 could be measured due to sample availability (Figure S1A in supporting information). The demographic characteristics of the participants are shown in Table S1 in supporting information. Of the 177 participants, 88 (49.7%) underwent amyloid PET imaging, of whom 46 (52.3%) were found positive by visual reading (Table 1). The J-ADNI study protocol (UMIN000001374) was approved by

TABLE 1 Demographic characteristics and biomarkers of participants with amyloid PET.

	Amyloid PET negative ($n = 42$)	Amyloid PET positive ($n = 46$)	p value
Age, y	66 (10)	72 (8)	**0.023**
Female	19 (45%)	27 (59%)	0.286
APOE ε4	5 (12%)	32 (70%)	**< 0.001**
Education, y	14 (4)	12.5 (4)	0.219
MMSE	30 (2)	25 (5)	**< 0.001**
ADAS-Cog	7.4 (5.4)	23.3 (10.0)	**< 0.001**
CDR-SB	0 (0.5)	2.0 (3.0)	**< 0.001**
Clinical category			< 0.001
CU	26 (62%)	3 (7%)	
MCI	15 (36%)	23 (50%)	
ADD	1 (2%)	20 (43%)	
CSF Aβ38 (pg/mL)	2333 (779)	2469 (798)	0.207
CSF Aβ40 (pg/mL)	5511 (1854)	5808 (1393)	0.216
CSF Aβ42 (pg/mL)	484.6 (200.3)	244.8 (73.4)	**< 0.001**
CSF Aβ42/Aβ38	0.221 (0.037)	0.101 (0.031)	**< 0.001**
CSF Aβ42/Aβ40	0.091 (0.012)	0.044 (0.012)	**< 0.001**
CSF p-tau181 (pg/mL)	19.1 (8.6)	37.4 (19.7)	**< 0.001**
CSF NfL (pg/mL)	2389 (1709)	3283 (1083)	**< 0.001**

Note: Values are presented as median (interquartile range) unless otherwise specified.
Bold font indicates statistically significant difference.
Abbreviations: Aβ, amyloid beta; ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive subscale; ADD, Alzheimer's disease dementia; *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating Sum of Boxes; CSF, cerebrospinal fluid; CU, cognitively unimpaired subjects; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NfL, neurofilament light chain; PET, positron emission tomography; p-tau, phosphorylated tau.

institutional review committees at each site. Informed written consent was obtained from all participants.

2.1.2 | Cohort 2 (memory clinic cohort)

We included 774 consecutive patients who underwent lumbar puncture for the analysis of AD-related CSF biomarkers assessed at Niigata University from October 2013 to March 2023. Nineteen follow-up samples taken after the initial visit and 14 samples without clinical diagnosis were excluded (Figure S1B). Of the 741 clinically diagnosed cases, those with cerebral amyloid angiopathy (CAA, $n = 30$), which shares Aβ pathology with AD, and heterogenous neurological diseases classified as "other" ($n = 61$) were excluded (Figure S1B). The 650 remaining cases were divided into 277 Alzheimer's clinical syndrome (ACS) cases, including 164 probable AD, 35 possible AD, and 78 MCI due to AD, and 373 non-ACS cases (Figure S1B, Table S2 in supporting information), including 26 vascular cognitive impairment, 66 Lewy body disease, 10 multiple system atrophy, 37 corticobasal syndrome, 33 progressive supranuclear palsy (PSP), 49 frontotemporal lobar degeneration, 101 iNPH, and 51 unclassified cognitive impairment. The patients were clinically diagnosed after a thorough neurological and neuropsychological evaluation without information on CSF biomarkers or amyloid PET imaging. The results of core CSF biomarkers were previously reported.[31] This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Niigata University (2019-0239). All participants or their representatives provided written informed consent.

2.2 | CSF collection and analysis

CSF samples were collected by lumbar puncture at each institution, sent to Niigata University in both cohorts, aliquoted at a volume of 0.5 mL, and then stored at −80°C until the assay.[31,32]

The concentrations of CSF Aβ42, Aβ40, and Aβ38 were measured using V-PLEX Aβ Peptide Panel 1 (6E10; Meso Scale Discovery). The concentration of CSF phosphorylated tau at threonine 181 (p-tau181) was measured using the AlzBio3 kit (Fujirebio) until March 2019. After the supply of the AlzBio3 kit was discontinued, INNOTEST PHOSPHO-TAU (181P; Fujirebio) was used to measure p-tau181 concentration, and the results were converted to AlzBio3 measurements. The concentration of CSF neurofilament light chain (NfL) was measured using the R-PLEX NfL (Meso Scale Discovery). All analyses were conducted in duplicate by experienced laboratory personnel blinded to the clinical diagnosis in accordance with the manufacturer's instructions. The intra-assay and inter-assay coefficients of variation were < 20% for all assays.

Previously, we determined cutoff values for CSF Aβ42/Aβ40 (< 0.072), p-tau181 (> 30.6 pg/mL), and NfL (> 2650 pg/mL) based on the Gaussian mixture model (GMM), which is unbiased in detecting AD pathology and sensitive in detecting biological changes[33] by using CSF samples from the J-ADNI cohort.[31,32]

RESEARCH IN CONTEXT

1. **Systematic review**: Literature was reviewed in PubMed. The excellent accuracy of the cerebrospinal fluid (CSF) amyloid beta (Aβ)42/Aβ38 ratio for predicting amyloid positron emission tomography (PET) positivity and discriminating Alzheimer's disease (AD) from other diseases has been reported from Europe. However, its utility has not been confirmed in Asian countries, including Japan. Limited evidence is also available regarding the utility of CSF Aβ38 in diagnosing non-AD disorders.
2. **Interpretation**: In a research cohort, we showed that CSF Aβ42/Aβ38 performed comparably to CSF Aβ42/Aβ40 in predicting amyloid PET positivity. In a clinical cohort including non-Alzheimer's clinical syndrome (ACS), CSF Aβ42/Aβ38 may reflect AD-related changes more precisely than CSF Aβ42/Aβ40.
3. **Future directions**: In clinical cases including non-ACS, the utility of CSF Aβ42/Aβ38 should be further verified using amyloid PET.

2.3 | Statistical analyses

Statistical analyses were performed using GraphPad Prism (GraphPad Software Inc.) and R (http://www.r-project.org/). For continuous variables, group comparisons were performed using the Mann–Whitney *U* test for two groups and the Kruskal–Wallis test for multiple groups, followed by Dunn multiple-comparison test. For categorical data, group comparisons were performed using χ^2 test or Fisher exact test. Correlations between two datasets were identified using Spearman rank correlation coefficient. The diagnostic accuracy of the CSF biomarkers was assessed through receiver operating characteristic (ROC) analysis. The areas under the curve (AUC) of the biomarkers were calculated and then compared using a DeLong test. Across all analyses, p value < 0.05 was considered statistically significant. The cutoff values of the biomarkers were calculated based on the maximum Youden index and GMM. The percentage of concordance/discordance of the two markers was calculated with 95% confidence intervals (CIs) generated using bootstrap resampling ($n = 1000$).

3 | RESULTS

3.1 | Diagnostic accuracy of Aβ42/Aβ38 in the J-ADNI research cohort

We analyzed 177 CSF samples obtained from the Japanese AD continuum research cohort (J-ADNI). In addition to CSF, amyloid PET status was confirmed in 88/177 cases, of whom 46 (52.3%) were found positive by visual reading. The PET-positive group had significantly lower Aβ42 levels, Aβ42/Aβ38, and Aβ42/Aβ40 and higher p-tau181 and NfL

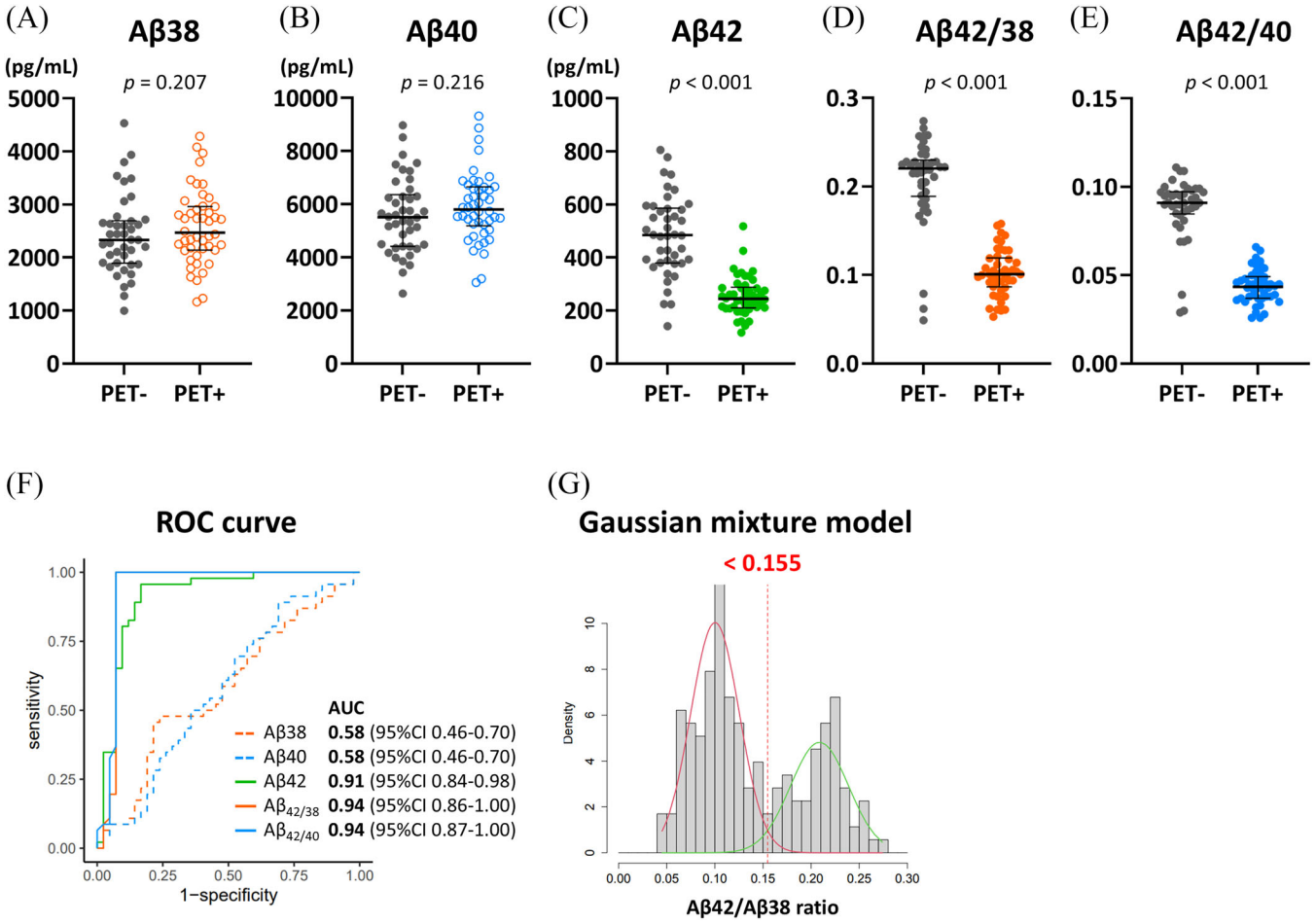

FIGURE 1 CSF Aβ species and ratios in a Japanese AD continuum research cohort. Differences in CSF Aβ species and ratios are shown between participants with negative and positive amyloid PET results (A, Aβ38; B, Aβ40; C, Aβ42; D, Aβ42/Aβ38 ratio [Aβ42/Aβ38]; E, Aβ42/Aβ40 ratio [Aβ42/Aβ40]). Group differences were assessed with Mann–Whitney *U* test. ROC curves of CSF Aβ species and ratios for discriminating amyloid PET positive from negative results (F). In the Gaussian mixture model, the cutoff value of Aβ42/Aβ38 was estimated as the crossing point (vertical red lines) of the prevalence weighted densities (G). Aβ, amyloid beta; AD, Alzheimer's disease; AUC, area under the curve; CI, confidence interval; CSF, cerebrospinal fluid; PET, positron emission tomography; ROC, receiver operating characteristic.

levels than the PET-negative group (Table 1). No significant differences in CSF Aβ38 and Aβ40 levels were found between the PET-positive and -negative groups (Table 1, Figure 1A–E).

We performed ROC analysis with amyloid PET as a reference standard to examine the diagnostic performance of the biomarkers. CSF Aβ42/Aβ38 and Aβ42/Aβ40 predicted Aβ status with AUC values of 0.94 (95% CI: 0.85–1.00) and 0.94 (95% CI: 0.86–1.00), respectively (Figure 1F). The performance of CSF Aβ42/Aβ38 and Aβ42/Aβ40 in predicting amyloid PET positivity was not significantly different (DeLong test, $p = 0.249$; Table S3 in supporting information). However, Aβ42/Aβ38 and Aβ42/Aβ40 predicted Aβ positivity significantly better than Aβ38 and Aβ40 alone and slightly better than Aβ42 alone, but the difference was not statistically significant (Figure 1F, Table S3). Based on the maximum Youden index, the cutoff for CSF Aβ42/Aβ38 was 0.159 with 100% sensitivity and 92.9% specificity.

The cutoff value of Aβ42/Aβ38 was calculated using GMM with whole samples from the 177 J-ADNI participants (Table S1). The GMM-based cutoff value was 0.155 (Figure 1G). Hereafter, this GMM-based value was used as a cutoff value in this study.

3.2 | Concordance of CSF Aβ42/Aβ38 and Aβ42/Aβ40 in the J-ADNI research cohort

We examined the concordance rates between CSF Aβ42/Aβ38 and CSF Aβ42/Aβ40 in the J-ADNI cohort consisting of CU, MCI due to AD, and AD dementia. In the 177 cases, CSF Aβ42/Aβ38 and Aβ42/Aβ40 were strongly correlated ($r = 0.960$, $p < 0.001$; Figure 2A). Aβ38 was strongly correlated with Aβ40 ($r = 0.933$, $p < 0.001$), and Aβ42 was moderately correlated with Aβ38 ($r = 0.382$, $p < 0.001$) and Aβ40 ($r = 0.433$, $p < 0.001$; Figure S2 in supporting information). Overall agreement was observed in 95.5%, and only 4.5% showed discordance. All discordant cases were only positive for Aβ42/Aβ40 (Figure 2A). The discordant group (i.e., Aβ42/Aβ38−/Aβ42/Aβ40+

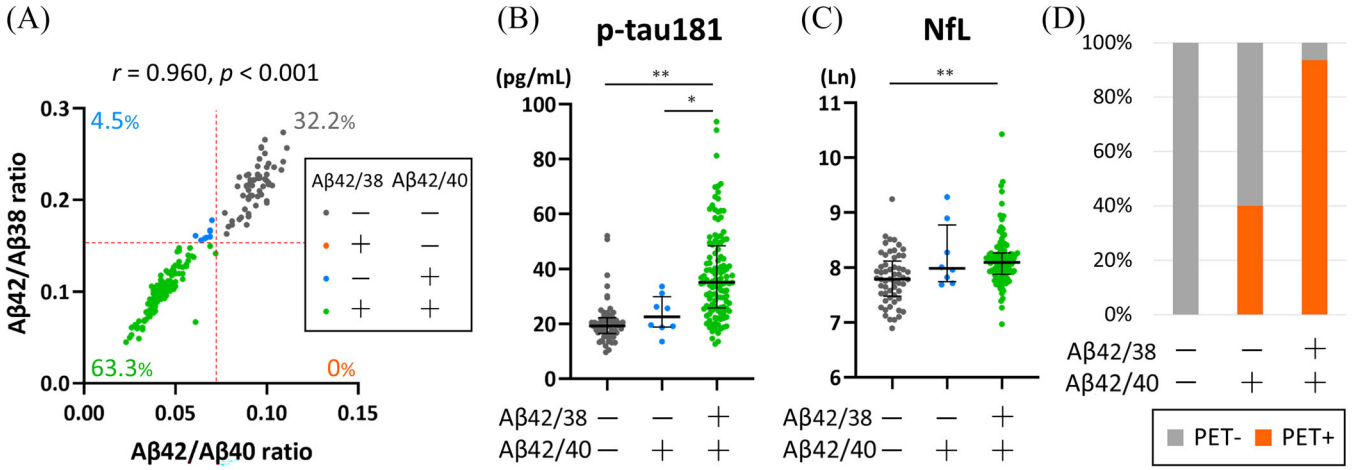

FIGURE 2 Concordance and discordance of CSF Aβ42/Aβ38 and Aβ42/Aβ40 in a Japanese AD continuum research cohort. A scatterplot shows the percentage of subjects with concordant and discordant CSF Aβ42/Aβ38 and Aβ42/Aβ40 ratios (A). Dashed lines indicate the cutoff values. Differences in CSF p-tau181 (B) and NfL (C) are shown among concordant and discordant groups stratified by Aβ ratios. Group differences were assessed with the Kruskal–Wallis test, followed by a Dunn multiple-comparison test; $^{*}p < 0.05$; $^{**}p < 0.001$. The percentages of amyloid PET-positive participants are shown among concordant and discordant Aβ ratios (D). Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; NfL, neurofilament light chain; p-tau, phosphorylated tau.

group) showed clinically intermediate features between the Aβ42/Aβ38−/Aβ42/Aβ40− and Aβ42/Aβ38+/Aβ42/Aβ40+ groups (Table 2). Specifically, the percentage of apolipoprotein E ε4 carriers and the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale Cognitive subscale, and Clinical Dementia Rating Sum of Boxes scores in the Aβ42/Aβ38−/Aβ42/Aβ40+ group were intermediate between the both-negative and both-positive groups. CSF Aβ38 and Aβ40 levels were not significantly different among the Aβ42/Aβ38−/Aβ42/Aβ40−, Aβ42/Aβ38−/Aβ42/Aβ40+, and Aβ42/Aβ38+/Aβ42/Aβ40+ groups. By contrast, Aβ42 levels were significantly lower in the Aβ42/Aβ38+/Aβ42/Aβ40+ group than in the two other groups (Figure S3 in supporting information). CSF p-tau181 levels were significantly higher in the Aβ42/Aβ38+/Aβ42/Aβ40+ group than in the two other groups (Figure 2B). CSF NfL levels were significantly higher in the Aβ42/Aβ38+/Aβ42/Aβ40+ group than in the Aβ42/Aβ38−/Aβ42/Aβ40− group (Figure 2C). The amyloid PET positive rate in the Aβ42/Aβ38−/Aβ42/Aβ40+ group was 40%, which was intermediate between the Aβ42/Aβ38−/Aβ42/Aβ40− (0%) and Aβ42/Aβ38+/Aβ42/Aβ40+ (94%) groups (Figure 2D). Thus, in the J-ADNI cohort including CU, the Aβ42/Aβ38−/Aβ42/Aβ40+ group exhibited clinically and biologically intermediate features between the Aβ42/Aβ38−/Aβ42/Aβ40− and Aβ42/Aβ38+/Aβ42/Aβ40+ groups.

3.3 | Concordance of CSF Aβ42/Aβ38 and Aβ42/Aβ40 in the memory clinic cohort

We compared the utility of CSF Aβ42/Aβ38 to that of Aβ42/Aβ40 in the differential diagnosis of dementia among various neurological diseases. We analyzed 650 CSF samples obtained from 277 cases with ACS and 373 cases with non-ACS that were clinically diagnosed (Figure S1B).

In the ACS group, CSF Aβ42/Aβ38 was significantly correlated with Aβ42/Aβ40 ($r = 0.943$, $p < 0.001$), and the concordance of these ratios was 90.6%. Only 9.4% were discordant, of which 0.4% (95% CI: −0.4%–0.7%) were only positive for Aβ42/Aβ38 and 9.0% (95% CI: 5.8%–12.3%) for Aβ42/Aβ40 alone (Figure 3A). The Aβ42/Aβ38+/Aβ42/Aβ40− group was small ($n = 1$); hence, demographic characteristics were compared among the three remaining groups. No difference in age was found between groups, but more female participants and lower MMSE scores were observed in the Aβ42/Aβ38−/Aβ42/Aβ40+ and Aβ42/Aβ38+/Aβ42/Aβ40+ groups than in the Aβ42/Aβ38−/Aβ42/Aβ40− group (Table 2). CSF Aβ38 and Aβ40 levels were significantly lower in the Aβ42/Aβ38−/Aβ42/Aβ40+ group than in the two other groups (Table 2, Figure S4A, B in supporting information). CSF Aβ42 levels were significantly lower in the Aβ42/Aβ38−/Aβ42/Aβ40+ and Aβ42/Aβ38+/Aβ42/Aβ40+ groups than in the Aβ42/Aβ38−/Aβ42/Aβ40− group (Table 2, Figure S4C). CSF p-tau181 levels were significantly higher in the Aβ42/Aβ38+/Aβ42/Aβ40+ group than in the Aβ42/Aβ38−/Aβ42/Aβ40− and Aβ42/Aβ38−/Aβ42/Aβ40+ groups, whereas no significant differences were found between the Aβ42/Aβ38−/Aβ42/Aβ40− and Aβ42/Aβ38−/Aβ42/Aβ40+ groups (Table 2, Figure 3B). NfL levels did not differ significantly among the three groups (Table 2, Figure 3C). Thus, in the clinical AD continuum cohort consisting only of symptomatic cases without CU, the Aβ42/Aβ38−/Aβ42/Aβ40+ group did not show intermediate characteristics between the Aβ42/Aβ38−/Aβ42/Aβ40− and Aβ42/Aβ38+/Aβ42/Aβ40+ groups.

In the non-ACS group, CSF Aβ42/Aβ38 was significantly correlated with Aβ42/Aβ40 ($r = 0.899$, $p < 0.001$), and the concordance of these ratios was 83.1% (Figure 3D). Interestingly, unlike the ACS group, substantial cases (16.6%, 95% CI: 12.9%–20.4%) were positive

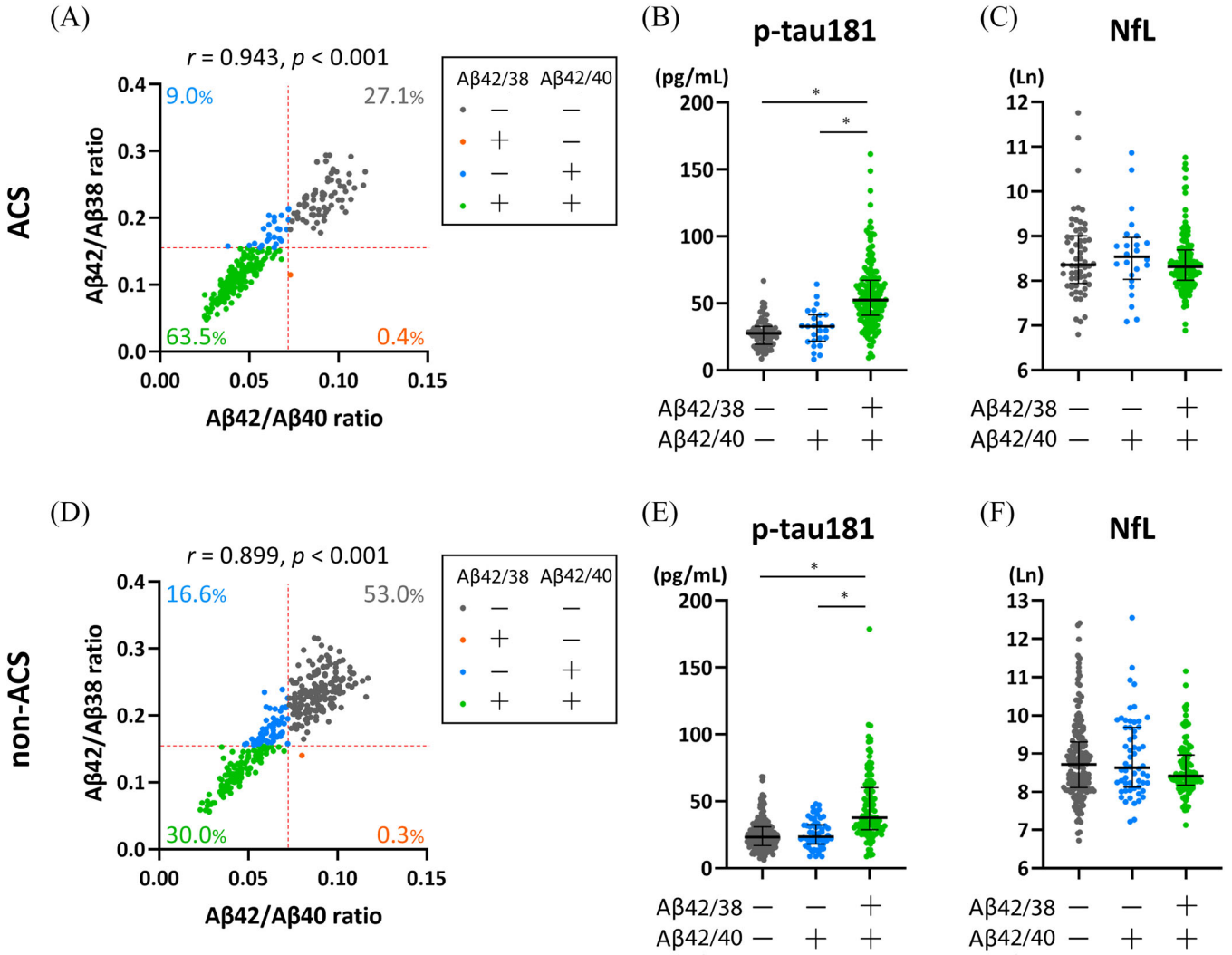

FIGURE 3 Concordance and discordance of CSF Aβ42/Aβ38 and Aβ42/Aβ40 in a Japanese memory clinic cohort. The upper figures (A–C) show data obtained from patients with ACS, and the lower figures (D–F) show data obtained from patients with non-ACS. Scatterplots show the percentage of patients with concordant and discordant groups stratified by CSF Aβ42/Aβ38 and Aβ42/Aβ40 ratios (A, D). Dashed lines indicate the cutoff values. Differences in CSF p-tau181 (B, E) and NfL (C, F) are shown among concordant and discordant groups. Group differences were assessed with a Kruskal–Wallis test, followed by a Dunn multiple-comparison test; *$p < 0.001$. Aβ, amyloid beta; ACS, Alzheimer's clinical syndrome; CSF, cerebrospinal fluid; NfL, neurofilament light chain; p-tau, phosphorylated tau.

for Aβ42/Aβ40 alone, whereas a small number of cases (0.3%, 95% CI: −0.3% to 0.5%) were only positive for Aβ42/Aβ38 (Figure 3D).

Compared to the Aβ42/Aβ38−/Aβ42/Aβ40− group, the Aβ42/Aβ38−/Aβ42/Aβ40+ and Aβ42/Aβ38+/Aβ42/Aβ40+ groups were older, and the Aβ42/Aβ38+/Aβ42/Aβ40+ group had more female participants and lower MMSE scores (Table 2). CSF Aβ38 and Aβ40 levels were significantly lower in the Aβ42/Aβ38−/Aβ42/Aβ40+ group than in the Aβ42/Aβ38−/Aβ42/Aβ40− and Aβ42/Aβ38+/Aβ42/Aβ40+ groups (Table 2, Figure S5A, B in supporting information), and Aβ42 levels were significantly lower in the Aβ42/Aβ38−/Aβ42/Aβ40+ and Aβ42/Aβ38+/Aβ42/Aβ40+ groups than in the Aβ42/Aβ38−/Aβ42/Aβ40− group (Table 2, Figure S5C). CSF p-tau181 levels were higher in the Aβ42/Aβ38+/Aβ42/Aβ40+ group than in the Aβ42/Aβ38−/Aβ42/Aβ40− or Aβ42/Aβ38−/Aβ42/Aβ40+ group, with no significant difference between the Aβ42/Aβ38−/Aβ42/Aβ40− and Aβ42/Aβ38−/Aβ42/Aβ40+ groups (Table 2, Figure 3E). No significant difference in NfL levels was found among the groups (Table 2, Figure 3F).

3.4 | Comparison of Aβ38, Aβ40, and Aβ42 in the memory clinic cohort

We further investigated the clinical utility of Aβ38 in various neurological diseases and compared the concordance and discordance rates between Aβ42/Aβ38 and Aβ42/Aβ40 in the memory clinic cohort. The concordance rates varied among the neurological disease groups (Figure 4A), especially in the PSP and iNPH groups, where the only Aβ42/Aβ40-positive group was not negligible (27% of PSP and 22% of iNPH). Both Aβ42/Aβ38 and Aβ42/Aβ40 were significantly lower in

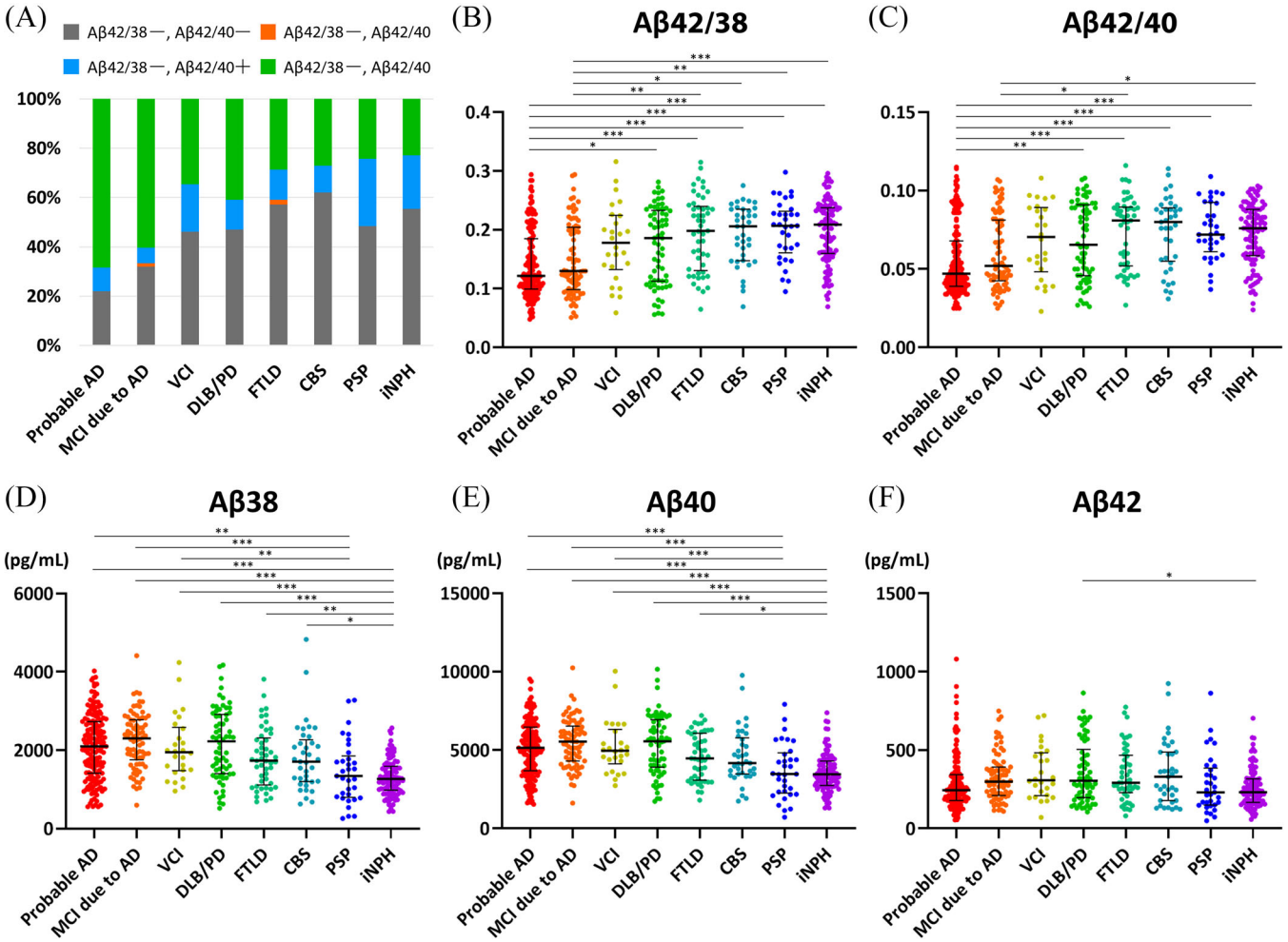

FIGURE 4 Aβ species and ratios by clinical phenotype. Concordance and discordance rates between the Aβ42/Aβ38 ratio (Aβ42/Aβ38) and Aβ42/Aβ40 ratio (Aβ42/Aβ40) for each clinical phenotype are shown (A). Differences in CSF Aβ ratios and species are shown between each clinical phenotype (B, Aβ42/Aβ38; C, Aβ42/Aβ40; D, Aβ38; E, Aβ40; F, Aβ42). Group differences were assessed with a Kruskal–Wallis test, followed by a Dunn multiple-comparison test; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Aβ, amyloid beta; AD, Alzheimer's disease; CBS, corticobasal syndrome; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; iNPH, idiopathic normal pressure hydrocephalus; MCI, mild cognitive impairment; PD, Parkinson's disease; PSP, progressive supranuclear palsy; VCI, vascular cognitive impairment.

the probable AD and MCI due to AD groups than in the other groups (Figure 4B, C).

CSF Aβ38 and Aβ40 levels were significantly lower in the iNPH and PSP groups than in the other groups, including the probable AD and MCI due to AD groups (Figure 4D, E). CSF Aβ42 levels were significantly lower in the iNPH group than the DLB/PD group (Figure 4F). The AUC values for Aβ38 and Aβ40 for distinguishing PSP from ACS were 0.74 (95% CI: 0.64–0.82) and 0.74 (95% CI: 0.64–0.83), respectively, which were not significantly lower than the performance of Aβ42/Aβ38 (AUC 0.76, 95% CI: 0.68–0.83) or Aβ42/Aβ40 (AUC 0.74, 95% CI: 0.66–0.81; Table S4, Figure S6 in supporting information). The AUC for Aβ38 for distinguishing iNPH from ACS was 0.81 (95% CI: 0.76–0.85), which was significantly higher than the performance of Aβ40 (AUC 0.79, 95% CI: 0.73–0.84), Aβ42 (AUC 0.56, 95% CI: 0.50–0.63), and Aβ42/Aβ40 (AUC 0.69, 95% CI: 0.63–0.75) and comparable to that of Aβ42/Aβ38 (AUC 0.75, 95% CI: 0.69–0.80; Table S4, Figure S6).

4 | DISCUSSION

CSF Aβ42/Aβ40 precisely predicts amyloid PET positivity in diverse populations.[2,31,34–38] CSF Aβ42/Aβ38 is similarly useful to Aβ42/Aβ40 in diagnosing AD in White populations;[8–10] however, this finding remains to be verified in other ethnic populations. In the present study, using amyloid PET as a reference standard in a Japanese research cohort, we found that the diagnostic performance of CSF Aβ42/Aβ38 was comparable to that of Aβ42/Aβ40.

The concordance rate between CSF Aβ42/Aβ38 and Aβ42/Aβ40 was high (95.5%) in the J-ADNI cohort and in the ACS (90.6%) and non-ACS groups (83.1%) in our memory clinic cohort. Discordant cases with positive CSF Aβ42/Aβ40 alone were more frequently observed in the non-ACS group (16.6%) than in the ACS groups. In the J-ADNI cohort including CU, discordant cases (i.e., Aβ42/Aβ38−/Aβ42/Aβ40+) showed intermediate characteristics between the Aβ42/Aβ38−/Aβ42/Aβ40−

TABLE 2 Demographic characteristics and biomarkers of concordant and discordant groups of Aβ ratios.

J-ADNI (*n* = 177)	Aβ42/Aβ38−, Aβ42/Aβ40−	Aβ42/Aβ38−, Aβ42/Aβ40+	Aβ42/Aβ38+, Aβ42/Aβ40+
N (%)	57 (32%)	8 (5%)	112 (63%)
Age, y	68 (9)	77 (9)	73 (8)[a]
Female	25 (44%)	3 (38%)	59 (53%)
APOE ε4[b]	4 (7%)	2 (25%)	76 (68%)
Education, y	14 (4)	16 (2)	13 (4)
MMSE	29 (2)	27 (5)	25 (4)[c]
ADAS-Cog	8.3 (9.0)	15.7 (12.2)	23.3 (9.1)[c]
CDR-SB	0 (0.5)	0.5 (0.6)	2 (2.5)[c,d]
Clinical category[b]			
CU	36 (63%)	2 (25%)	8 (7%)
MCI	20 (35%)	5 (63%)	112 (51%)
ADD	1 (2%)	1 (13%)	47 (42%)
PET negative / positive[b]	36 / 0	3 / 2	3 / 44
CSF Aβ38 (pg/mL)	2444 (735)	2379 (558)	2392 (916)
CSF Aβ40 (pg/mL)	5543 (1803)	5924 (1432)	5561 (1906)
CSF Aβ42 (pg/mL)	531.9 (176.1)	390.1 (96.9)	235.3 (79.0)[c,e]
CSF Aβ42/Aβ38	0.216 (0.027)	0.161 (0.007)	0.101 (0.030)[c,e]
CSF Aβ42/Aβ40	0.095 (0.010)	0.068 (0.004)	0.043 (0.011)[c,e]
CSF p-tau181 (pg/mL)	19.3 (5.2)	22.6 (8.5)	36.0 (22.5)[c,d]
CSF NfL (pg/mL)	2425 (1341)	2946 (2349)	3283 (1251)[c]
ACS (*n* = 277)	**Aβ42/Aβ38−, Aβ42/Aβ40−**	**Aβ42/Aβ38−, Aβ42/Aβ40+**	**Aβ42/Aβ38+, Aβ42/Aβ40+**
N (%)	75 (27%)	25 (9%)	176 (64%)
Age, y	70 (16)	74 (15)	76 (17)
Female[b]	35 (47%)	18 (72%)	111 (63%)
MMSE	23 (7)	18 (9)[f]	21 (7)[a]
Clinical category			
Probable AD	36 (48%)	16 (64%)	112 (64%)
Possible AD	14 (19%)	4 (16%)	17 (10%)
MCI due to AD	25 (33%)	5 (20%)	47 (27%)
CSF Aβ38 (pg/mL)	2016 (1126)	1322 (849)[c]	2234 (1186)[c]
CSF Aβ40 (pg/mL)	5109 (2370)	4005 (1812)[a]	5441 (2472)**
CSF Aβ42 (pg/mL)	464.5 (249.0)	244.0 (107.4)[c]	216.5 (123.3)[c]
CSF Aβ42/Aβ38	0.229 (0.038)	0.175 (0.033)[a]	0.107 (0.033)[c,g]
CSF Aβ42/Aβ40	0.091 (0.011)	0.064 (0.008)[f]	0.042 (0.012)[c,g]
CSF p-tau181 (pg/mL)	27.5 (12.8)	32.8 (19.4)	52.4 (25.4)[c,g]
CSF NfL (pg/mL)	4257 (5059)	5103 (3988)	4082 (2887)
Non-ACS (*n* = 373)	**Aβ42/Aβ38−, Aβ42/Aβ40−**	**Aβ42/Aβ38−, Aβ42/Aβ40+**	**Aβ42/Aβ38+, Aβ42/Aβ40+**
N (%)	198 (53%)	62 (17%)	112 (30%)
Age, y	70 (16)	78 (8)[c]	77 (10)[c]
Female[b]	88 (44%)	30 (48%)	69 (60%)
MMSE	25 (7)	24 (12)	22 (8)[f]
Clinical category			
VCI	12 (6%)	5 (8%)	9 (8%)
PD/DLB	31 (16%)	8 (13%)	27 (24%)
MSA	6 (3%)	3 (5%)	1 (1%)
CBS	23 (15%)	4 (6%)	10 (9%)
PSP	16 (8%)	9 (15%)	8 (7%)
FTLD	28 (14%)	6 (10%)	14 (13%)
iNPH	56 (28%)	22 (35%)	23 (21%)
Unclassified	26 (13%)	5 (8%)	20 (18%)
CSF Aβ38 (pg/mL)	1628 (1088)	1172 (632)[c]	1723 (1214)[g]
CSF Aβ40 (pg/mL)	4325 (2528)	3358 (1545)[c]	4402 (2637)[g]
CSF Aβ42 (pg/mL)	373.0 (271.2)	203.7 (97.1)[c]	180.8(129.3)[c]
CSF Aβ42/Aβ38	0.235 (0.040)	0.174 (0.029)[c]	0.118 (0.037)[c,g]
CSF Aβ42/Aβ40	0.088 (0.014)	0.063 (0.009)[c]	0.045 (0.014)[c,g]
CSF p-tau181 (pg/mL)	23.2 (13.7)	23.6 (13.3)	37.7 (31.5)[c,g]
CSF NfL (pg/mL)	6109 (7623)	5583 (12561)	4511 (4179)

Note: Values are presented as median (interquartile range) unless otherwise specified.

Abbreviations: Aβ, amyloid beta; ACS, Alzheimer's clinical syndrome; ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive subscale; AD, Alzheimer's disease; ADD, Alzheimer's disease dementia; *APOE*, apolipoprotein E; CBS, corticobasal syndrome; CDR-SB, Clinical Dementia Rating Sum of Boxes; CSF, cerebrospinal fluid; CU, cognitively unimpaired subjects; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; iNPH, idiopathic normal pressure hydrocephalus; J-ADNI, Japanese Alzheimer's Disease Neuroimaging Initiative; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MSA, multiple system atrophy; NfL, neurofilament light chain; PD, Parkinson's disease; PET, positron emission tomography; PSP, progressive supranuclear palsy; p-tau, phosphorylated tau; VCI, vascular cognitive impairment.

[a]Versus Aβ42/Aβ38−, Aβ42/Aβ40−, $p < 0.05$.

[b]Chi-squared test, $p < 0.05$.

[c]Versus Aβ42/Aβ38−, Aβ42/Aβ40−, $p < 0.001$.

[d]Versus Aβ42/Aβ38−, Aβ42/Aβ40+, $p < 0.05$.

[e]Versus Aβ42/Aβ38−, Aβ42/Aβ40+, $p < 0.01$.

[f]Versus Aβ42/Aβ38−, Aβ42/Aβ40−, $p < 0.01$.

[g]Versus Aβ42/Aβ38−, Aβ42/Aβ40+, $p < 0.001$.

and Aβ42/Aβ38+/Aβ42/Aβ40+ groups. Based on the clinical stages and biomarker profiles, this discordant group may exhibit an early AD pathophysiology. Therefore, Aβ42/Aβ40 change may initially emerge, followed by Aβ42/Aβ38 change in the AD continuum. In the memory clinic cohort including only symptomatic cases, although the Aβ42/Aβ38−/Aβ42/Aβ40+ group had worse cognitive function than the Aβ42/Aβ38+/Aβ42/Aβ40+ group, its p-tau181 and NfL levels were comparable to those of the Aβ42/Aβ38+/Aβ42/Aβ40+ group.

This result suggests that the Aβ42/Aβ38−/Aβ42/Aβ40+ group in the memory clinic cohort may reflect non-AD pathophysiology and that Aβ42/Aβ38 may be more reflective than Aβ42/Aβ40 for detecting AD pathology. When CSF Aβ42/Aβ40 is unexpectedly decreased during the evaluation to exclude AD in cases of suspected non-AD conditions, assessing Aβ42/Aβ38 may be beneficial. A decrease in Aβ42/Aβ38 suggests the presence of Aβ pathology, whereas no decrease suggests that the reduction in Aβ42/Aβ40 is unrelated to Aβ pathology.

In the memory clinic cohort, regardless of the ACS or non-ACS cases, the Aβ42/Aβ38−/Aβ42/Aβ40+ group showed lower CSF Aβ38 and Aβ42 levels, slightly lower Aβ40 levels, and comparable CSF p-tau181 levels to the Aβ42/Aβ38−/Aβ42/Aβ40− group (Table S5 in supporting information). By contrast, in the Aβ42/Aβ38+/Aβ42/Aβ40+ group, Aβ38 and Aβ40 levels were not reduced, whereas Aβ42 levels were remarkably reduced, and p-tau181 levels were elevated compared to those in the Aβ42/Aβ38−/Aβ42/Aβ40− group (Table S5). Furthermore, a quarter of PSP and iNPH cases showed that only Aβ42/Aβ40 was positive, and the CSF Aβ38 and Aβ40 levels in the PSP and iNPH groups were lower than those in the other types of diseases.

CSF Aβ40 and Aβ42 levels are decreased in patients with PSP[39] and iNPH,[21,28] and Aβ38 levels are also decreased in patients with iNPH.[21,28] In this study, we first showed that Aβ38 levels are decreased in the CSF of patients with PSP. Moreover, the CSF Aβ42 levels in the PSP and iNPH groups decreased to levels comparable to those in the probable AD group, and Aβ38 and Aβ40 levels were also significantly reduced compared to those in the other disease groups. This finding suggests that all Aβ species are reduced in patients with PSP and iNPH. In the PSP and iNPH groups, approximately one fourth of the cases showed decreased Aβ42/Aβ40 alone, whereas no cases had decreased Aβ42/Aβ38 alone. This finding suggests that decreased Aβ38 and Aβ42 levels may be more prominent than decreased Aβ40 in these diseases (Table S5). Independent of AD pathology, CSF Aβ42 levels are decreased in autopsy-confirmed PSP.[40] Aβ is produced and secreted in a neural activity-dependent manner.[41] Cortical perfusion is decreased in PSP in association with subcortical tau accumulation.[42] Thus, the reduced levels of all Aβ species in the CSF of patients with PSP may be caused by reduced neural activity. Alternatively, these findings suggest that PSP shares a common pathology with iNPH, which has a similar CSF dynamics and Aβ pattern. Analysis of detailed magnetic resonance imaging findings in neurodegenerative diseases suggests that PSP has the imaging features of iNPH and the presence of transependymal CSF flow.[43] As we found in the present study, Aβ38, 40, and 42 levels are decreased in the CSF of patients with iNPH.[21,28] In patients with iNPH, CSF Aβ42 correlates with brain Aβ burden by biopsy, but CSF Aβ38 and Aβ40 do not.[44] Additionally, shunt surgery increases the levels of these Aβ species.[28] Thus, in iNPH, the reduced levels of CSF Aβ38 and Aβ40 may involve efflux reduction of brain interstitial fluid into the CSF.[45] Isotope labeling analysis of in vivo Aβ kinetics in patients with AD has demonstrated that the turnover of Aβ38, Aβ40, and Aβ42 in the central nervous system slows with age but remains consistent across Aβ species.[5] Future research should investigate whether Aβ38 levels reflect decreased neural production, abnormal CSF dynamics, or both in iNPH and PSP. Taken together, evaluation of CSF Aβ38 reduction together with Aβ40 and Aβ42 may help differentiate PSP and iNPH from AD.

Our study has several limitations. First, we did not confirm the underlying pathology in our clinical cohort through autopsy or amyloid or tau PET. Further studies should analyze the association between CSF Aβ42/Aβ38 and amyloid PET in patients with non-AD disorders, including PSP and iNPH. Second, we did not correct for white matter lesion (WML) volume, which is negatively correlated with CSF Aβ38.[46,47] Individuals with severe ischemic changes were excluded from the J-ADNI cohort; consequently, the effect of WML on CSF Aβ38 may be small. However, the possibility of WML affecting CSF Aβ38 in the clinical cohort cannot be excluded. Third, CSF Aβ38 is inversely correlated with longitudinal cognitive decline.[48] In our clinical cohort, Aβ38 is weakly but significantly correlated with MMSE (ACS, $r = 0.229$, $p < 0.001$; non-ACS, $r = 0.190$, $p < 0.01$), suggesting that Aβ38 may decrease as the disease progresses. The correlation with non-cognitive symptoms such as parkinsonism and with longitudinal changes warrants validation in the future. Fourth, the performance of CSF Aβ38 in the diagnosis of PSP needs validation in an independent larger cohort.

In conclusion, CSF Aβ42/Aβ38 performed comparably to Aβ42/Aβ40 in predicting amyloid PET positivity in the Japanese AD research cohort. Although the concordance rates between CSF Aβ42/Aβ38 and Aβ42/Aβ40 were relatively high, some subgroups, particularly the non-ACS groups, showed reductions in Aβ42/Aβ40 only. Discordant cases in the non-ACS groups were not accompanied by increased p-tau181 levels. Therefore, measuring Aβ42/Aβ38 may help distinguish patients with decreased Aβ42/Aβ40 independent of AD pathology.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All subjects provided informed consent.

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