BMC Neurology

RESEARCH

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Growth associated protein 43 (GAP-43) predicts brain amyloidosis in Alzheimer's dementia continuum: an [^{18} F] AV-45 study

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Abstract

Background Growth-associated protein 43 (GAP-43) is a key protein involved in neuronal growth and synaptic plasticity. Alterations in GAP-43 levels have been associated with Alzheimer's Disease (AD), potentially reflecting synaptic dysfunction. We evaluated the potential of GAP-43 as a biomarker for AD and explored its association with amyloid-beta (Aβ) levels, as well as its correlation with Aβ plaque burden in the brain.

Methods We screened 1,639 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. A total of 226 individuals met the eligibility criteria and were enrolled. Participants were classified into three groups: 77 cognitively normal (CN) individuals, 111 with mild cognitive impairment (MCI), and 38 with a diagnosis of AD. The associations between cerebrospinal fluid (CSF) GAP-43 levels with other biomarkers as well as [^{18}F] AV-45 (Florbetapir) PET Standardized Uptake Value Ratios (SUVR) were investigated.

Results Our findings revealed significantly elevated CSF GAP-43 levels in individuals with AD compared to CN and MCI groups. Furthermore, GAP-43 levels showed a significant positive correlation with tau pathology. Notably, we observed a significant association between GAP-43 and [^{18}F] Florbetapir PET SUVR in the MCI group, suggesting that GAP-43 may serve as a reliable biomarker in the early stages of AD.

Conclusion This study provides evidence supporting the role of GAP-43 as a potential biomarker for AD, particularly in relation to predicting the amyloid pathology pattern in the brain in the MCI stage.

Keywords Alzheimer's disease, Mild cognitive impairment, Growth associated protein 43, Positron emission tomography

#For the Alzheimer's Disease Neuroimaging Initiative.

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Introduction

Dementia is a major global health concern, with approximately affecting 46.8 million people worldwide. This number is projected to increase to 74.7 million by 2030, and to 131.5 million by 2050. The annual incidence of new dementia cases is estimated at 9.9 million globally [1]. Alzheimer's disease (AD), the most common form of dementia, remains a complex disorder, with its exact pathogenesis not fully understood. However, current evidence suggests that AD is strongly associated with the extracellular accumulation of amyloid-beta (Aβ) plaques and the intracellular formation of neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau protein [2, 3]. These protein aggregates lead to neuronal damage and synaptic loss. Early diagnosis of AD is critical, as disease-modifying treatments are most effective during the mild cognitive impairment (MCI) stage [4]. Due to the complexity of AD and its overlapping clinical features with other forms of dementia, particularly in its early phases, identifying reliable early diagnostic markers is crucial.

Aβ, a peptide of 36 to 43 amino acids, is generated by the enzymatic cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase [5–8]. Aβ naturally aggregates in the extracellular space, forming oligomers, protofibrils, and mature amyloid fibrils [9–13]. Plasma Aβ levels and cerebral β-amyloidosis have been shown to correlate with AD pathology and can serve as predictive biomarkers [14–16]. Moreover, Aβ accumulation is sensitive to disease stage, with lower levels of Aβ-42 detected in cerebrospinal fluid (CSF) during the preclinical phase of AD [17, 18].

Growing evidence suggests that Growth Associated Protein 43 (GAP-43) levels are significantly elevated in the brains of AD patients compared to healthy individuals [19–21]. This elevation in GAP-43 levels has been observed in regions affected by AD pathology, including the hippocampus, amygdala, and cerebral cortex [22]. The correlation between GAP-43 levels and the presence of NFT and Aβ plaques suggests that GAP-43 may reflect the extent of disease progression [20]. GAP-43 is a protein involved in synaptic plasticity and axonal growth, and its altered expression is indicative of synaptic dysfunction and neurodegeneration, making it a potential biomarker for AD [23]. Notably, GAP-43 is crucial during early brain development, playing a key role in neurite outgrowth, synaptogenesis, and neuronal plasticity. Given that AD pathology begins years before clinical symptoms manifest, the detection of altered GAP-43 levels in the early stages of the disease suggests its potential as an early biomarker for AD [24].

While [^{18}F] Fludeoxyglucose (FDG) PET is a valuable tool for diagnosing AD, Amyloid PET imaging, specifically [^{18}F] AV45, is considered the gold standard for in vivo detection of amyloid plaques. Florbetapir ([^{18}F] AV45) is a PET ligand that binds specifically to Aβ-42 with high affinity, allowing for the quantification and localization of Aβ deposition in the brain [25]. The association between Florbetapir PET findings and postmortem Aβ burden has been well established, making it a gold standard for evaluating Aβ deposition in vivo [26].

In this study, we aimed to investigate whether GAP-43 levels could serve as an indicator of Aβ pathology, which could potentially explain the mechanisms of synaptic dysfunction and neurodegeneration in AD. Additionally, we hypothesized that GAP-43 levels could predict [^{18}F] AV45 PET standardized uptake value ratio (SUVRs), independent of disease stage and other potential confounding factors. Establishing a relationship between GAP-43 and Aβ depositions could have significant diagnostic implications, contributing to the development of more accurate biomarker panels for AD which could enhance early detection and disease prognostication.

Methodology

Data source

Data for this study was extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, a comprehensive, longitudinal repository of clinical, neuroimaging, genomics, and biomarker data from individuals with AD, MCI, and healthy controls [25, 27]. The ADNI initiative collects and analyzes various data, including PET and MRI scans, genetic materials, cognitive assessments, CSF, blood biomarkers, plasma, serum, urine, and brain tissue, to investigate predictors of AD progression. The data is managed by the Resource Allocation Review Committee (RARC) or the Biospecimen Review Committee (BRC) at the University of Southern California (USC). Participants, aged between 55 and 90 years, are recruited from 59 research centers across Canada and the United States. Informed consent is obtained from all participants, and they undergo a series of baseline tests, which include genetic testing, clinical evaluations, lumbar punctures, neuropsychological assessments, MRI, and PET scans. These assessments are repeated annually for longitudinal analysis.

For this study, only participants with available [^{18}F] AV45 whole brain normalized SUVR, and GAP-43, Aβ, and tau levels, and relevant demographic information were included. A total of 226 participants were selected, categorized into three groups: cognitively normal (CN, $n = 77$), mild cognitive impairment (MCI, $n = 111$), and AD (AD, $n = 38$).

CSF sampling, storage, and measurement

CSF samples were collected via lumbar puncture using either 20- or 24-gauge spinal needles, in accordance with the ADNI procedures manual (http://www.adni-info.org/). Following collection, samples were transferred into

polypropylene tubes within one hour and immediately frozen on dry ice. Aliquots of 0.5 ml were prepared at the ADNI Biomarker Core Laboratory and stored at -80 °C for long-term preservation.

CSF biomarkers were analyzed using the fully automated Cobas e 601 platform, employing electrochemiluminescence immunoassays (ECLIA) to measure Elecsys® Aβ [1–40], Elecsys® Phospho-Tau (181p), and Elecsys® Total-Tau, following the manufacturer's guidelines. For this study, baseline measurements of Aβ, total tau (T-tau), phosphorylated tau (P-tau), and GAP-43 were utilized.

Positron emission tomography (PET)

Imaging data from the ADNI dataset were processed using a standardized preprocessing pipeline, with detailed information on image acquisition available on the ADNI website (http://adni.loni.usc.edu/). For PET scans, [^{18}F] AV45 was used as the tracer to assess amyloid-β (Aβ) burden in the brain. Scans were performed 50 to 70 min after tracer injection. The resulting images were averaged, spatially aligned, interpolated to a standardized voxel size, and smoothed to achieve a uniform resolution of 8 mm full width at half maximum [28]. The whole normalized SUVR was calculated by normalizing the cortical composite region intensity to the FreeSurfer-defined whole brain normalized SUVR, with a threshold set at 1.11 [29, 30].

Statistical methods

All statistical analyses were conducted using SPSS, version 26. For continuous variables with a normal distribution, comparisons were performed using one-way ANOVA, while the Kruskal-Wallis test was applied for non-normally distributed variables. Categorical variables were analyzed using the Chi-square test. Spearman correlation was employed to assess the associations between CSF GAP-43, [^{18}F] AV-45, MMSE, ADAS-Cog 13, and other CSF biomarkers due to the non-normal distribution of the data. To investigate the predictor effect CSF GAP-43 in [^{18}F] AV45, we performed multiple linear regression analysis, adjusting for MMSE, age, sex, and education as covariates. Statistical significance was defined as a p-value < 0.05. Diagnostic capability of CSF biomarkers, specifically GAP-43 was assessed using receiver operating characteristic (ROC) curve analyses, yielding area under the curve (AUC) values.

Ethical considerations

This study utilized deidentified data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, ensuring that no patient-identifying information was accessed by any of the authors. In compliance with ADNI protocols, written informed consent was obtained from all participants at each site prior to their inclusion in the study. All procedures involving human participants were conducted in accordance with ethical standards established by the relevant national and institutional research committees, and in alignment with the principles set forth in the Declaration of Helsinki (1964) and its subsequent amendments. Detailed information regarding the ethical protocols followed in ADNI can be found at adni.loni.usc.edu.

Results

Demographic characteristics

Table 1 summarizes the demographic and clinical characteristics of the study participants across CN ($n = 77$), MCI ($n = 111$), and AD ($n = 38$) groups. The groups did not significantly differ in age ($p = 0.071$) or gender distribution ($p = 0.579$). Education years were significantly lower in the MCI group compared to CN ($p = 0.029$), while no significant differences were observed between CN and AD or between MCI and AD. The MMSE scores were significantly lower in MCI compared to CN ($p < 0.001$) and further declined in AD ($p < 0.001$ for all pairwise comparisons). Similarly, ADAS-Cog 13 scores were significantly higher in MCI versus CN ($p < 0.001$) and further increased in AD ($p < 0.001$ for all comparisons). CDR-SB scores also increased significantly across diagnostic groups ($p < 0.001$ for all comparisons). Total tau (T-tau) and phosphorylated tau (P-tau) levels were significantly elevated in AD compared to both CN and MCI ($p < 0.001$), with MCI showing no significant difference from CN. In contrast, amyloid-β42 (Aβ42) levels were lower in AD compared to both CN and MCI ($p < 0.001$), with a non-significant reduction in MCI versus CN ($p = 0.062$).

Comparison of CSF GAP-43 level and [^{18}F] AV45 in different diagnostic groups

Table 2 presents the levels of CSF GAP-43 and [^{18}F] AV45 metric in the groups. CSF GAP-43 levels showed a significant increase in AD compared to both CN and MCI ($p < 0.001$ for both comparisons). However, no significant difference was observed between CN and MCI ($p = 1.00$). Similarly, cortical amyloid burden, as measured by [^{18}F] AV45 PET, was significantly elevated in AD compared to CN and MCI ($p < 0.001$ for both). No significant difference was detected between CN and MCI ($p = 0.500$).

Correlation of GAP-43 with cognitive, imaging, and biomarker measures

In the CN group, GAP-43 levels showed a strong positive correlation with T- tau ($r = 0.696$, $p < 0.001$) and P-tau ($r = 0.483$, $p < 0.001$). In the MCI group, GAP-43 remained strongly correlated with T-tau ($r = 0.641$, $p < 0.001$) and P-tau ($r = 0.505$, $p < 0.001$), and a moderate

Table 1 Demographic characteristics of participants

	CN (*n* = 77)	MCI (*n* = 111)	AD (*n* = 38)	Comparison	*P* value*	*P* value
Age (years)	71.9 ± 6.7	70.6 ± 7.6	73.1 ± 6.6	CN vs. MCI	0.669	0.071[a]
				CN vs. AD	1.000	
				MCI vs. AD	0.193	
Gender (female)	38 (49.4%)	60 (54.1%)	6 (16.8%)			0.579[b]
Education (years)	17.2 ± 2.2	16.1 ± 2.6	16.5 ± 2.6	CN vs. MCI	0.024	0.029[c]
				CN vs. AD	0.544	
				MCI vs. AD	1.000	
MMSE	29.14 ± 1.11	27.85 ± 1.88	22.11 ± 3.48	CN vs. MCI	< 0.001	< 0.001[c]
				CN vs. AD	< 0.001	
				MCI vs. AD	< 0.001	
ADAS-Cog 13	7.01 ± 3.36	12.44 ± 7.1	28.32 ± 10.35	CN vs. MCI	< 0.001	< 0.001[c]
				CN vs. AD	< 0.001	
				MCI vs. AD	< 0.001	
CDR-SB	1 ± 0.3	1.18 ± 0.92	5.01 ± 1.97	CN vs. MCI	< 0.001	< 0.001[c]
				CN vs. AD	< 0.001	
				MCI vs. AD	< 0.001	
CSF T-tau (pg/mL)	68.9 ± 36.5	77.4 ± 44	151.7 ± 80.6	CN vs. MCI	0.362	< 0.001[c]
				CN vs. AD	< 0.001	
				MCI vs. AD	< 0.001	
CSF P-tau (pg/mL)	39.4 ± 26.7	43.4 ± 24	73.6 ± 36.2	CN vs. MCI	0.559	< 0.001[c]
				CN vs. AD	< 0.001	
				MCI vs. AD	< 0.001	
CSF Aβ42 (pg/mL)	200.6 ± 52.4	182 ± 55.3	132.2 ± 35.2	CN vs. MCI	0.062	< 0.001[c]
				CN vs. AD	< 0.001	
				MCI vs. AD	< 0.001	

Abbreviations: CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; MMSE: Mini-Mental State Examination; CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes; ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive 13; T-tau: total tau; P-tau: phosphorylated tau; Aβ: amyloid-β; CSF: cerebrospinal fluid; [a] ANOVA test; [b] Chi square test; [c] Kruskal-Wallis Test; * Significance values have been adjusted by the Bonferroni correction for multiple tests

Table 2 GAP-43 and [18 F] AV45 alterations across diagnostic groups

	CN (*n* = 77)	MCI (*n* = 111)	AD (*n* = 38)	Comparison	*P* value *	*P* value
GAP-43 (pg/Ml)	5209.87 ± 2872.67	5304.65 ± 2763.97	8073.61 ± 3680.66	CN vs. MCI	1.00	< 0.001[a]
				CN vs. AD	< 0.001	
				MCI vs. AD	< 0.001	
[^{18}F] AV45	1.14 ± 0.26	1.19 ± 0.20	1.42 ± 0.23	CN vs. MCI	0.500	< 0.001[a]
				CN vs. AD	< 0.001	
				MCI vs. AD	< 0.001	

Abbreviations: CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; GAP-43: Growth Associated Protien-43; [a] ANOVA test; * Significance values have been adjusted by the Bonferroni correction for multiple tests

positive correlation was observed with [^{18}F] AV45 ($r = 0.243$, $p = 0.010$). Finally, in AD, GAP-43 continued to show significant correlations with T-tau ($r = 0.485$, $p = 0.002$) and P-tau ($r = 0.409$, $p = 0.011$). However, the correlation with [^{18}F] AV45 did not reach statistical significance ($r = 0.243$, $p = 0.142$). No significant associations were found between GAP-43 levels and Aβ42, MMSE, ADAS-Cog 13, or CDR-SB in all groups (Table 3).

Correlation of [^{18}F] AV45 with cognitive, GAP-43, and biomarker measures

In the CN group, [^{18}F] AV45 showed a significant negative correlation with CSF Aβ42 (r = -0.735, $P < 0.001$) and a positive correlation with T-tau ($r = 0.351$, $P = 0.002$) and P-tau ($r = 0.425$, $P < 0.001$). In the MCI group, [^{18}F] AV45 demonstrated strong negative correlations with CSF Aβ42 (r = -0.743, $P < 0.001$) and positive correlations with T-tau ($r = 0.450$, $P < 0.001$) and P-tau ($r = 0.504$, $P < 0.001$). Additionally, a significant negative correlation was observed between [^{18}F] AV45 and MMSE (r = -0.287, $P = 0.002$). In the AD group, [^{18}F] AV45 was negatively

Table 3 Correlation of GAP-43 with cognitive, imaging, and biomarker measures across diagnostic groups

	CN (*n* = 77)		MCI (*n* = 111)		AD (*n* = 38)	
	r	***P* value**	***r***	***P* value**	***r***	***P* value**
[^{18}F] AV45	0.180	0.118[a]	0.243	0.010[a]	0.243	0.142[a]
Aβ42	-0.019	0.871[a]	-0.110	0.252[a]	-0.185	0.265[a]
T-tau	0.696	< 0.001[a]	0.641	< 0.001[a]	0.485	0.002[a]
P-tau	0.483	< 0.001[a]	0.505	< 0.001[a]	0.409	0.011[a]
ADAS-Cog 13	0.000	0.999[a]	0.144	0.132[a]	-0.103	0.540[a]
MMSE	0.173	0.133[a]	-0.009	0.924[a]	0.117	0.486[a]
CDR-SB	0.043	0.713[a]	-0.161	0.092[a]	0.035	0.836[a]

Abbreviations: CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; MMSE: Mini-Mental State Examination; CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes; ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive 13; T-tau: total tau; P-tau: phosphorylated tau; Aβ: amyloid-β; CSF: cerebrospinal fluid; [a] Spearman correlation

Table 4 Correlation of [^{18}F] AV45 with cognitive and biomarker measures across diagnostic groups

	CN (*n* = 77)		MCI (*n* = 111)		AD (*n* = 38)	
	r	***P* value**	***r***	***P* value**	***r***	***P* value**
Aβ42	-0.735	< 0.001[a]	-0.743	< 0.001[a]	-0.376	0.020[a]
T-tau	0.351	0.002[a]	0.450	< 0.001[a]	0.282	0.087[a]
P-tau	0.425	< 0.001[a]	0.504	< 0.001[a]	0.569	< 0.001[a]
ADAS-Cog 13	0.096	0.405[a]	0.100	0.295[a]	0.169	0.309[a]
MMSE	-0.006	0.956[a]	-0.287	0.002[a]	-0.106	0.528[a]
CDR-SB	0.045	0.701[a]	0.154	0.107[a]	0.146	0.383[a]

Abbreviations: CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; MMSE: Mini-Mental State Examination; CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes; ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive 13; T-tau: total tau; P-tau: phosphorylated tau; Aβ: amyloid-β; CSF: cerebrospinal fluid; GAP-43: Growth Associated Protien-43; [a] Spearman correlation

Table 5 Linear regression analysis of [^{18}F] AV45 and the predictive effect of GAP-43 across diagnostic groups

	CN (*n* = 77)			MCI (*n* = 111)			AD (*n* = 38)		
	Standardized β	**t value**	***P* value**	**Standardized β**	**t value**	***P* value**	**Standardized β**	**t value**	***P* value**
GAP-43	0.264	2.591	0.012	0.220	2.319	0.022	0.381	2.334	0.026
MMSE	-0.126	-1.247	0.217	-0.306	-3.279	0.001	-0.289	-1.694	0.100
Age	0.371	3.661	< 0.001	0.016	0.166	0.869	-0.104	-0.565	0.576
Gender	0.153	1.454	0.150	-0.053	-0.549	0.584	0.075	0.415	0.681
Education	-0.170	-1.623	0.109	0.052	0.514	0.608	0.177	1.074	0.291
Adjusted R^2	0.235			0.103			0.064		
Model p value	< 0.001			0.005			0.216		

Abbreviations: CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; MMSE: Mini-Mental State Examination; GAP-43: Growth Associated Protien-43

correlated with CSF Aβ42 (r = -0.376, P = 0.020) and positively correlated with P-tau (r = 0.569, P < 0.001) (Table 4).

Linear regression analysis of [^{18}F] AV-45 whole brain normalized SUVR and the predictive effect of GAP-43

According to Table 5, linear regression analysis was conducted to assess the predictive effect of GAP-43 on [^{18}F] AV45 normalized SUVR retention in the CN, MCI, and AD groups, adjusting for potential confounders including age, gender, MMSE, and education. In the CN group, GAP-43 was a significant predictor of [^{18}F] AV45 (standardized β = 0.264, P = 0.012, model P < 0.001). In the MCI group, GAP-43 also demonstrated a significant positive association with [^{18}F] AV-45 (standardized β = 0.220, P = 0.022, model P = 0.005). In the AD group, GAP-43 was positively associated with [^{18}F] AV-45, but the association did not reach statistical significance for the model (standardized β = 0.381, P = 0.026, model P = 0.216).

Diagnostic accuracy of CSF biomarkers in differentiating cognitive groups

As shown in Table 6, in the CN vs. MCI comparison, GAP-43 demonstrated a moderate AUC of 0.514. T-tau and P-tau showed stronger diagnostic accuracy with AUCs of 0.567 and 0.566, respectively. In contrast, Aβ42 exhibited minimal diagnostic value, with an AUC of

Table 6 Diagnostic performance of CSF biomarkers

	CN vs. MCI		CN vs. AD		MCI vs. AD	
	AUC	***P* value**	**AUC**	***P* value**	**AUC**	***P* value**
GAP-43	0.514	0.043	0.737	< 0.001	0.736	< 0.001
Aβ42	0.414	0.042	0.168	< 0.001	0.233	< 0.001
T-tau	0.567	0.043	0.839	< 0.001	0.802	< 0.001
P-tau	0.566	0.043	0.843	< 0.001	0.805	< 0.001

Abbreviations: CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; T-tau: total tau; P-tau: phosphorylated tau; Aβ: amyloid-βGAP-43: Growth Associated Protien-43

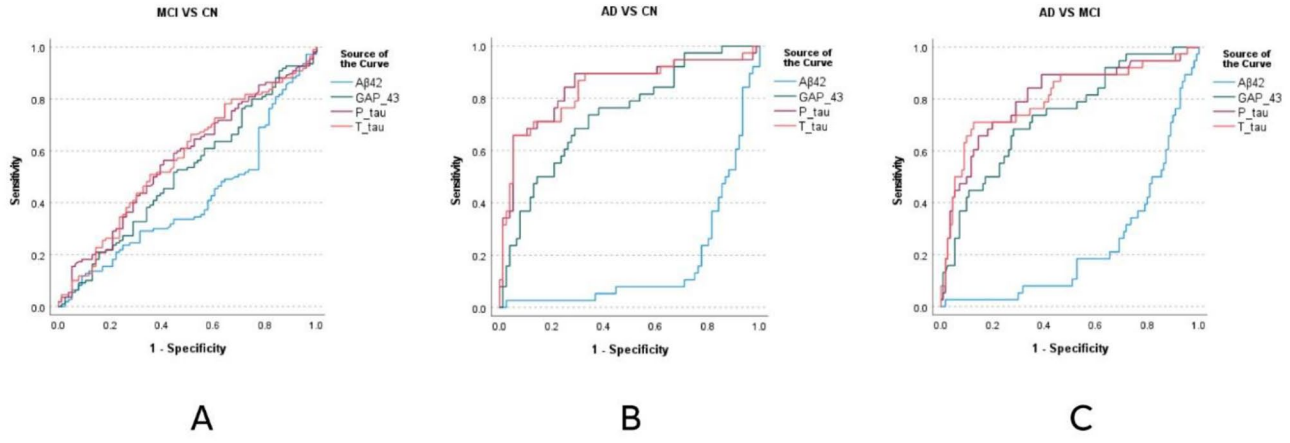

Fig. 1 Receiver operating characteristic (ROC) curves for CSF biomarkers GAP-43, Aβ42, T-tau, and P-tau in differentiating cognitive groups. Abbreviations: MCI vs. CN (**A**). AD vs. MCI (**B**). AD vs. MCI (**C**). CN: cognitively normal; MCI: mild cognitive impairment; T-tau: total tau; P-tau: phosphorylated tau; Aβ: amyloid-β

0.414, showing an inverse association with disease status. For the CN vs. AD comparison, GAP-43 showed moderate discriminatory power with an AUC of 0.737, while T-tau and P-tau demonstrated excellent performance, with AUCs of 0.839 and 0.843, respectively. Aβ42 exhibited a lower AUC of 0.168, further supporting its inverse association with disease progression and its limited utility in distinguishing CN from AD. Finally, in the MCI vs. AD comparison, GAP-43 showed a similar AUC of 0.736, reflecting moderate discriminative ability between MCI and AD. However, T-tau and P-tau again outperformed GAP-43, with AUCs of 0.802 and 0.805, respectively, demonstrating strong diagnostic accuracy. Aβ42 continued to exhibit poor diagnostic capability, with an AUC of 0.233, suggesting an inverse relationship with disease progression, as lower Aβ42 levels were associated with more advanced stages of Alzheimer's disease. This inverse association indicates the limited utility of Aβ42 in distinguishing between MCI and AD (Fig. 1).

Discussion

We explored the association between GAP-43 and brain amyloidosis in AD Continuum using [^{18}F] AV45 PET. Our findings show potential diagnostic implications for GAP-43 in relation to Aβ pathology and provide insights into the mechanisms underlying synaptic dysfunction in AD.

Previous research has demonstrated a close connection between cognitive function and synaptic decline in patients with early AD or MCI, even before the clinical manifestations, which supports monitoring biomarkers reflecting synaptic pathologies, such as the amino acid form of Aβ42, T-tau, P-tau, and GAP-43 [20, 31–33]. However, there is limited research on the role of CSF GAP-43 in the AD continuum. GAP-43 is known for its role in synaptic plasticity and axonal growth and elevated levels of GAP-43 in regions affected by AD pathology hint at its potential involvement in the response to neurodegenerative processes [34, 35].

Our results revealed significant elevations in CSF GAP-43 levels in individuals diagnosed with AD compared to cognitively normal and MCI groups. These findings are consistent with previous reports of elevated levels of GAP-43 in CSF in AD [36]. This finding suggests that GAP-43 might serve as a potential biomarker, aiding in the differentiation of individuals with dementia from those with normal cognition or MCI [20, 37]. Former reports of elevation in CSF GAP-43 levels in MCI and dementia patients at baseline, along with significant increases over time in preclinical, prodromal, and dementia stages of AD, corroborate our initial findings.

This extended validation strengthens the argument for the diagnostic relevance of GAP-43 across various stages of AD [37].

GAP-43 levels in CSF correlate positively with tau levels, supporting a mechanistic model for AD. According to this model, synapse changes are essential for the spread of tau pathology associated with Aβ. This process is a critical factor in the development of neurodegeneration and cognitive decline in AD [38–40]. The theory that Aβ negatively affects synaptic function is supported by evidence from various studies, including in vitro investigations, animal trials, and post-mortem analyses. These studies demonstrate that Aβ influences glutamate reuptake and sensitivity to gamma-aminobutyric acid (GABA), adversely affecting synaptic function [41, 42].

Evidence suggests a correlation between tau spread and hyperexcitatory synaptic changes in AD. In vitro and animal studies have shown increased neuronal activity accelerates tau secretion. This leads to the transsynaptic propagation of seeding-competent tau, which refers to abnormally folded tau proteins capable of initiating pathological aggregation. These seeding-competent tau proteins can travel across synapses between neurons, contributing to tau spread in AD [43, 44].

GAP-43, an enzyme that plays a role in presynaptic vesicle cycling, is overexpressed in AD due to hyperexcitation [21, 45]. The studies provide evidence that when GAP-43 is inhibited, there is a significant reduction in synaptic glutamate release [46]. This finding highlights the critical role of GAP-43 in neurotransmitter release and synaptic activity. Increased glutamate release, can affect overall glutamate, gamma-aminobutyric acid (GABA), dopamine, serotonin, acetylcholine release, and synaptic activity and potentially contribute to AD pathophysiology. Therefore, the increased levels of CSF GAP-43 in AD may indicate hyper excitatory synaptic changes induced by Aβ [47]. Our study findings reveal a significant positive association between GAP-43 and T-tau in all cognitive groups. Unexpectedly, GAP-43 did not significantly correlate with Aβ in any of the three groups. The findings from our study align with previous research, providing additional support to the notion that CSF GAP-43 is more closely linked to tau pathology and neurodegeneration than to Aβ pathology [20, 21, 48].

The observed differences in [^{18}F] AV-45 levels between the CN, MCI, and AD groups provide valuable insights into the progression of amyloid pathology across the Alzheimer's continuum. Notably, the higher [^{18}F] AV-45 levels in the CN group compared to AD indicate that amyloid deposition may initiate early in the disease process, potentially preceding detectable cognitive impairment. This finding is consistent with the amyloid cascade hypothesis, which suggests that Aβ accumulation is one of the earliest pathological events in AD, occurring before the onset of clinical symptoms [49].

A key aspect of our investigation was establishing a link between GAP-43 and Aβ deposition, as detected through [^{18}F] AV-45 PET. We found that a positive correlation observed between GAP-43 and [^{18}F] AV-45 levels in individuals across CN and MCI groups suggests a potential association between synaptic dysfunction and Aβ pathology. This correlation remained consistent even when adjusting for MMSE scores, indicating that the link between GAP-43 and Aβ is independent of the cognitive status. Comparing the diagnostic performance of GAP-43 and [^{18}F] AV-45 with core AD biomarkers. In line with our result, some studies indicate a significant correlation between CSF GAP-43 concentration and [^{18}F] AV45 [37, 50]. These findings emphasize the complementary nature of various biomarkers in understanding the complex landscape of AD pathology. Our study lays the groundwork for further research into the intricate interplay between GAP-43, Aβ pathology, and cognitive decline in AD. Future longitudinal studies should explore the trajectory of GAP-43 alterations in relation to disease progression, considering its potential as an early biomarker. Additionally, investigating the molecular mechanisms linking GAP-43 and Aβ could unveil novel therapeutic targets for mitigating synaptic dysfunction in AD.

Limitations

Incorporating additional imaging techniques and biomarkers in future studies would provide a more comprehensive view of the disease's complexity. Future research with larger sample sizes is needed to confirm our findings and provide more robust evidence of the associations between GAP-43 and Aβ accumulations across different stages of the Alzheimer's continuum.

Conclusions

This study highlights the potential of GAP-43 as an early biomarker for AD. We found significant correlations between GAP-43 levels and key biomarkers of AD, including T-tau, P-tau, and [^{18}F] AV-45 whole brain normalized SUVR, especially in the CN and MCI groups. GAP-43 could predict [^{18}F] AV-45 whole brain normalized SUVR in the CN and MCI groups, suggesting its relevance in early disease stages. Overall, GAP-43 could complement existing biomarkers, offering improved early detection and monitoring of AD. Our findings lay the foundation for future research on GAP-43 and AD progression and the molecular mechanisms linking GAP-43 and Aβ.

Acknowledgements

We would like to acknowledge the Alzheimer's Disease Neuroimaging Initiative (ADNI) for providing the data that were fundamental to our research. Data collection and sharing for the Alzheimer's Disease Neuroimaging

Initiative (ADNI) is funded by the National Institute on Aging (National Institutes of Health Grant U19AG024904). The grantee organization is the Northern California Institute for Research and Education. In the past, ADNI has also received funding from the National Institute of Biomedical Imaging and Bioengineering, the Canadian Institutes of Health Research, and private sector contributions through the Foundation for the National Institutes of Health (FNIH) including generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. A complete list of ADNI investigators is available online (http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf).

Author contributions

RN worked on manuscript preparation and coordination of research activities. MS arranged the research group and contributed to data analysis and interpretation. PS and HN edited the manuscript and supported the technical aspects of data processing. ASA collected data and contributed to the development of the study protocol. SM collected data and assisted in ensuring adherence to ethical standards throughout the study. ASJHA assisted in the technical setup and maintenance of study equipment, contributed to manuscript revisions and data validation. AY participated in data acquisition and preprocessing, and assisted in the review and refinement of the manuscript. AH contributed to participant recruitment and data collection, assisted in the ethical review process and manuscript preparation. NK provided administrative support and coordinated communication between study sites, and assisted in drafting the manuscript. YR supported data management and storage, and contributed to data analysis and interpretation. MM designed the study and provided guidance on its theoretical framework, and assisted in manuscript writing and revised the draft. All authors read and approved the final manuscript.

Funding

No funding was received for this research.

Data availability

The data used in this study are not publicly available as they were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI data are available to qualified researchers upon request and approval from ADNI. Interested researchers can apply for access to the ADNI data through the ADNI website (http://adni.loni.usc.edu/datasamples/access-data/). The authors of this study do not have permission to redistribute the ADNI data directly.

Declarations

Ethics approval and consent to participate

The institutional review boards of all participating centers approved the study procedure (https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf), and all participants or their authorized representatives provided written informed consent. Ethics approval was obtained from the institutional review boards of each institution involved: Oregon Health and Science University; University of Southern California; University of California—San Diego; University of Michigan; Mayo Clinic, Rochester; Baylor College of Medicine; Columbia University Medical Center; Washington University, St. Louis; University of Alabama at Birmingham; Mount Sinai School of Medicine; Rush University Medical Center; Wien Center; Johns Hopkins University; New York University; Duke University Medical Center; University of Pennsylvania; University of Kentucky; University of Pittsburgh; University of Rochester Medical Center; University of California, Irvine; University of Texas Southwestern Medical School; Emory University; University of Kansas, Medical Center; University of California, Los Angeles; Mayo Clinic, Jacksonville; Indiana University; Yale University School of Medicine; McGill University, Montreal-Jewish General Hospital; Sunnybrook Health Sciences, Ontario; U.B.C. Clinic for AD & Related Disorders; and Cognitive Neurology—St. Joseph's, Ontario; Cleveland Clinic Lou Ruvo Center for Brain Health; Northwestern University; Premiere Research Inst (Palm Beach Neurology); Georgetown University Medical Center; Brigham and Women's Hospital; Stanford University; Banner Sun Health Research Institute; Boston University; Howard University; Case Western Reserve University; University of California, Davis—Sacramento; Neurological Care of CNY; Parkwood Hospital; University of Wisconsin; University of California, Irvine—BIC; Banner Alzheimer's Institute; Dent Neurologic Institute; Ohio State University; Albany Medical College; Hartford Hospital, Olin Neuropsychiatry Research Center; Dartmouth-Hitchcock Medical Center; Wake Forest University Health Sciences; Rhode Island Hospital; Butler Hospital; UC San Francisco; Medical University South Carolina; St. Joseph's Health Care Nathan Kline Institute; University of Iowa College of Medicine; and Cornell University and University of South Florida: USF Health Byrd Alzheimer's Institute. This study was conducted using ADNI data. The ADNI study is ethically approved and operated in accordance with the Declaration of Helsinki, 1964.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 30 August 2024 / Accepted: 17 March 2025
Published online: 01 April 2025

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