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ASSOCIATION OF ALPHA-SYNUCLEIN CO-PATHOLOGY WITH BETA-AMYLOID AND PHOSPHORYLATED TAU LEVELS IN ALZHEIMER'S DISEASE

Abstract

Misfolded α-synuclein (α-syn) aggregates can be present in the cerebrospinal fluid (CSF) of individuals with Alzheimer's disease (AD), even in the absence of clinical signs of synucleinopathy. This co-pathology may influence AD progression at the molecular level. Detection of α-synuclein aggregates using seed amplification assay (SAA) enables stratification of AD patients beyond classical biomarkers included in the AT(N) framework. The AT(N) framework allows biological classification of AD based on its core pathological processes: β-amyloid aggregation (A), tau accumulation and hyperphosphorylation (T), and non-specific neurodegeneration (N). This study aimed to explore whether α-syn co-pathology, detected by SAA, is associated with altered concentrations and longitudinal trajectories of CSF β-amyloid 42 (Aβ42) and phosphorylated tau 181 (p-tau181) in the biomarker-defined AD group. Data from A+T+ participants (N = 609) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) were analysed, using Roche Elecsys electrochemiluminescence immunoassay (ECLIA) and SAA results. Substantial discrepancies between clinical diagnosis and AT profiles were observed. Twenty-nine percent of A+T+ participants were α-syn-positive (S+), indicating a high prevalence of α-syn co-pathology in biologically defined AD. Cross-sectional comparisons revealed that S+ individuals had lower baseline Aβ42 concentrations compared to α-syn-negative (S−) participants. Linear mixed-effects models (LMEMs) showed a significantly steeper decline in Aβ42 over time in the S+ group, supporting the hypothesis that misfolded α-syn aggregation accelerates amyloid aggregation. However, p-tau181 levels increased more slowly in S+ than in S− individuals, contrary to expectations. These associations remained significant after adjustment for age, sex, diagnosis, and APOE-ε4 genotype. These findings suggest that α-syn co-pathology may affect AD progression through its interaction with Aβ42 and support its integration into biomarker-based classification frameworks.

Keywords: Alzheimer's disease, synucleinopathy, co-pathology, α-synuclein, β-amyloid 42, phosphorylated tau 181, cerebrospinal fluid, AT(N) classification.

Introduction

Alzheimer's disease is the most prevalent cause of dementia worldwide, accounting for up to 80% of cases [1]. It was estimated that approximately 416 million individuals are affected globally, resulting in a significant economic and social burden [2]. AD is characterised by the extracellular neuritic plaques and intercellular neurofibrillary tangles formed by β-amyloid and hyperphosphorylated tau, respectively [3]. More than 98% of clinical trials for AD treatments have failed, mainly due to the high rate of misdiagnosis [4]. Advances in biomarker

* Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.Pdf

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Table 1

AT(N) classification for AD and corresponding cognitive stages. Modified from [7-9]

AT(N) Profile	Cognitive stage			Pathology
	CN	MCI	Dementia	
A–T–(N)–	Normal AD biomarkers			Normal aging
A+T–(N)–	Preclinical AD pathological change	AD pathological change		Alzheimer's continuum
A+T+(N)–	Preclinical AD	Alzheimer's disease		
A+T+(N)+	Preclinical AD	Alzheimer's disease		
A+T–(N)+	AD and concomitant suspected non-AD pathologic change			
A–T+(N)–	Non-AD pathological change			Cerebrovascular disease, prion disease, and early tauopathies
A–T–(N)+	Non-AD pathological change			Limbic-predominant age-related TPD-43 encephalopathy
A–T+(N)+	Non-AD pathological change			Vascular dementia, tauopathies, dementia with Lewy bodies, primary age-related tauopathy

Footnote:

1. The AT(N) framework enables classification of AD based on the presence (+) or absence (–) of amyloid (A), tau (T), and neurodegeneration (N) pathologies.
2. CN – cognitively normal; MCI – mild cognitive impairment.

research have enabled a shift from the clinical diagnosis of AD, traditionally based on cognitive symptoms, to a more accurate biological definition through the AT(N) framework (Table 1) [5,6].

The AT(N) classification can be based on various biomarker sources, including positron emission tomography (PET) neuroimaging and cerebrospinal fluid (CSF) assays [10]. The fully automated Roche Elecsys electrochemiluminescence immunoassay (ECLIA) provides an accessible and cost-effective method, offering high concordance with PET and neuropathological findings [11-13]. Established quantitative cut-offs for CSF β-amyloid 42 (Aβ42) and phosphorylated tau at threonine 181 (p-tau181) measured with Roche Elecsys ECLIA allow accurate and precise categorisation into AD-positive and AD-negative profiles [14-16].

Despite the utility of the AT(N) framework in defining AD biologically, the disease rarely exists in its pure form. In 56% to 94% of cases, it co-occurs with other neuropathological processes that may influence disease progression [17-19]. The most common comorbidities include cerebrovascular pathologies, tauopathies, and synucleinopathies, such as Parkinson's disease (PD) and Lewy-body dementia (LBD), which are characterised by misfolded α-synuclein (α-syn) aggregation. Animal studies suggest that α-syn promotes β-amyloid aggregation and tau accumulation via prion-like spreading [20-22], but translation to humans remains limited [23,24]. Biomarkers offer an alternative for modelling these processes. The seed amplification assay (SAA) allows *in vivo* detection of misfolded α-syn aggregates in CSF. This study aims to investigate the association between misfolded α-syn aggregates and core AD biomarkers CSF Aβ42 and p-tau181 using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Materials and methods

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. Its original goal was to assess whether serial MRI, PET, biomarkers, and clinical assessments could track AD progression. Current aims include biomarker validation for clinical trials and improving diagnostic accuracy across diverse populations. All ADNI study procedures were approved by local ethics committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consents were obtained from all participants.

This study included participants from the ADNI who had CSF samples analysed for Aβ42, p-tau181, and α-synuclein. Demographic variables (age, sex, ethnicity, race), clinical diagnosis, APOE genotype, and biomarker results were retrieved from the ADNI database. CSF Aβ42 and p-tau181 concentrations were measured using automated ECLIA on the Roche Elecsys platform at the ADNI Biomarker Core Laboratory (University of Pennsylvania Medical Center). Samples with values outside the validated detection ranges (Aβ42: 200-1700 pg/mL; p-tau181: 8-120 pg/mL) were excluded. Participants were classified into AT profiles using established cut-offs: A+ if Aβ42 < 1026 pg/mL and T+ if p-tau181 > 22 pg/mL [15].

Misfolded α-synuclein aggregates were detected using the SAA at the Amprion Clinical Laboratory under CLIA certification. Only samples classified as "Detected-1" (LBD-type) or "Not Detected" were included; those labelled as "Detected-2" (MSA-type), "Intermediate", and visibly discoloured due to hemoglobin contamination were excluded. Participants with "Detected-1" results were assigned to the S+ group, and those with "Not Detected" to the S− group. APOE genotyping was based on two SNPs (rs429358, rs7412) and performed via restriction fragment length polymorphism (RFLP) analysis. Only the presence or absence of the APOE ε4 allele was considered in this study.

All statistical analyses were conducted in R version 4.3.2. A p-value < 0.05 was considered statistically significant.

Contingency tables were used to assess the distribution of AT profiles across clinical diagnoses, and the distribution of α-synuclein (S) profiles within each AT group. Pairwise group comparisons between S− and S+ participants within the A+T+ group were performed to assess differences between demographic, clinical and biomarker. The chi-squared test or Fisher's exact test was applied for categorical variables. The Wilcoxon rank sum test was used for continuous variables. Baseline differences in log-transformed CSF Aβ42 and p-tau181 levels were assessed using analysis of covariance (ANCOVA), adjusted for age, sex, clinical diagnosis, and APOE-ε4 carrier status.

Participants with two or more measurements of CSF Aβ42 and p-tau181 were included in the longitudinal analysis. Linear mixed-effects models (LMEMs) were used to assess whether α-syn SAA (S) status predicted the rate of change in log-transformed Aβ42 and p-tau181 levels over time within the A+T+ group. Each model included fixed effects for time (months since baseline), S status, their interaction, and covariates age, sex, clinical diagnosis, and APOE-ε4 carrier status. Random intercepts were included to account for individual baseline differences. Random slopes were estimated at the group level due to the limited number of repeated measures per participant. Two LMEMs were fitted: (1) prediction of Aβ42 change based on S status; (2) prediction of p-tau181 change based on S status. These models were used to evaluate: the change in biomarker levels over time in S− individuals; the change in biomarker levels over time in S+ individuals; the difference in rate of change between S+ and S− groups. All models were fitted using restricted maximum likelihood (REML) estimation, with Satterthwaite's method used to approximate degrees of freedom.

Results and discussion

The final dataset included 1444 ADNI participants: 508 CN, 679 with MCI, and 257 with dementia due to AD. They were classified in four biomarker groups based on AT profiles derived from CSF Aβ42 and p-tau181 levels: amyloid-negative and tau-negative (A–T–), amyloid-negative and tau-positive (A–T+), amyloid-positive and tau-negative (A+T–), amyloid-positive and tau-positive (A+T+). A substantial mismatch was observed between clinical diagnoses and AT profiles (Fig. 1). Only 78% of clinically diagnosed AD cases were A+T+, 14% were A+T–, 3% were A–T+, and 5% had normal CSF Aβ42 and p-tau181 levels. This is consistent with a previous autopsy study showing 76% agreement between clinical and confirmed AD diagnosis [25]. In the MCI group, only 47% were A+T+; 22% were A+T–. Notably, 22% were A–T–, showing no AD pathological change. These participants may have non-AD cognitive impairment due to other causes, such as sleep disorders or depression [26]. Among CN participants, 17% were already A+T+, suggesting preclinical AD; 25% were A+T–, indicating amyloid accumulation without tau pathology. These individuals are at high risk for progression. A PET study in CN individuals reported similar findings, with 9.1% A+T+ individuals who showed the fastest cognitive decline [27].

Misfolded α-synuclein was detected in all AT profiles (Fig. 2). The highest prevalence of S+ individuals was observed in the A+T+ group (29%), followed by A+T– (24%), A–T+ (20%), and A–T– (15%). Similar prevalence of comorbid synucleinopathy among AD cases has been reported in neuropathological studies. For example, postmortem data from the Mayo Clinic Brain Bank revealed that 33% of clinically diagnosed pure AD cases showed Lewy body co-pathology [28].

Clinical, demographic, and biomarker characteristics were compared between S– (N = 431) and S+ (N = 178) participants within the A+T+ group and summarised in Table 2. The distribution of clinical diagnoses was significantly different ($p = 0.002$), with a higher frequency of AD (42%) and a lower frequency (9%) of CN in the S+ group. These findings suggest that α-synuclein co-pathology may be associated with more advanced AD clinical stages. No significant differences were found in age, sex, race, ethnicity, or APOE-ε4 carrier status between S+ and S– individuals. The ADNI cohort represented the limited racial and ethnical diversity with most participants being White and non-Hispanic. Overall, the demographic profile was typical for late-onset AD [29].

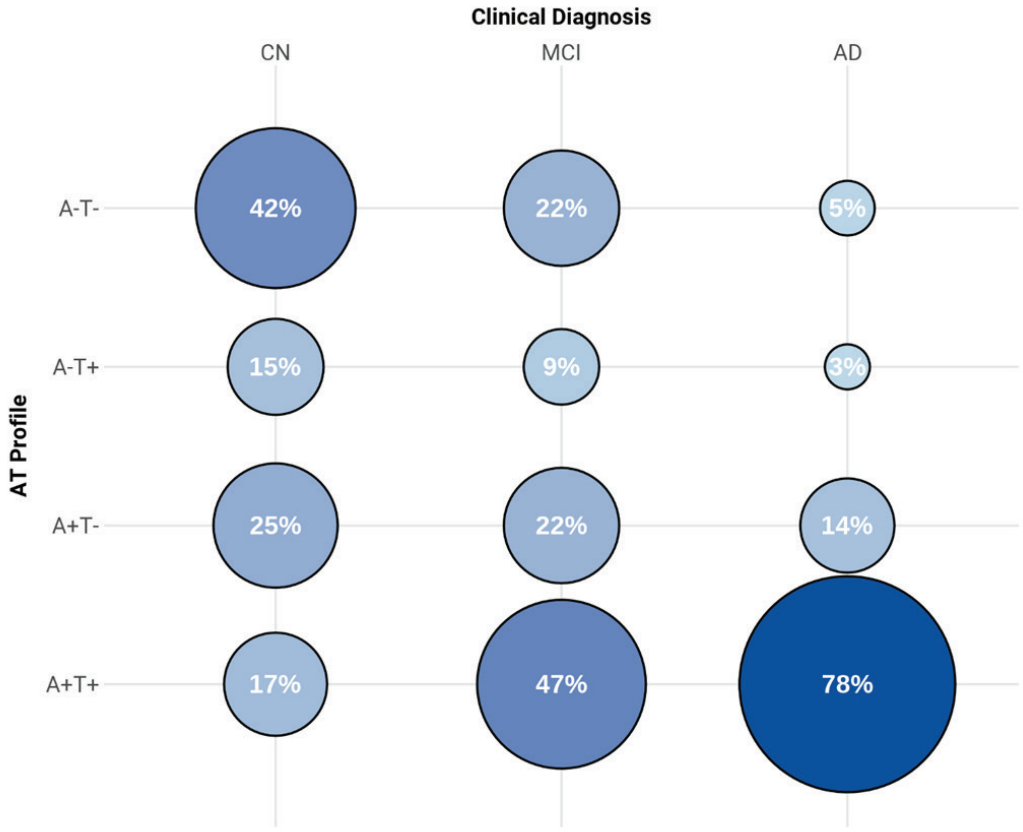

Fig. 1. Distribution of AT biomarker profiles across clinical diagnostic groups. The size and colour intensity of the circles represent the proportion of participants within each clinical diagnosis group: CN – cognitively normal; MCI – mild cognitive impairment; AD – Alzheimer's disease dementia. Participants were classified into one of four biomarker profiles based on CSF Aβ42 and p-tau181 levels: A–T– – amyloid-negative and tau-negative; A–T+ – amyloid-negative and tau-positive; A+T– – amyloid-positive and tau-negative; A+T+ – amyloid-positive and tau-positive.

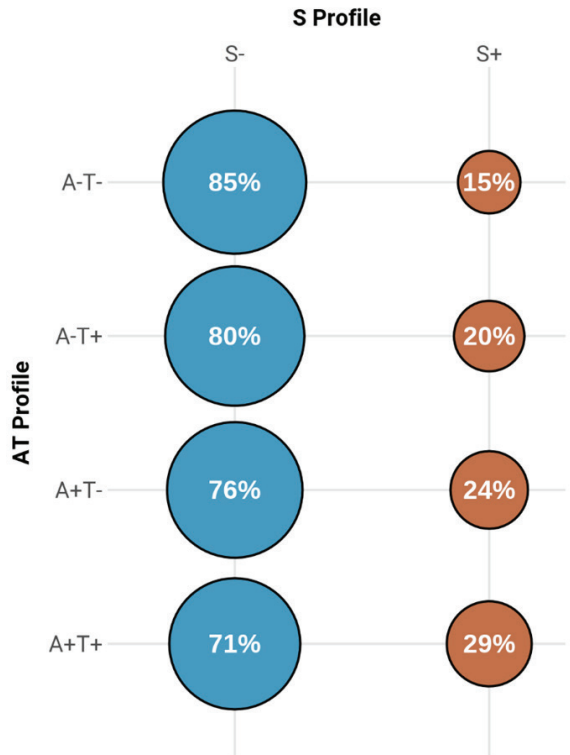

Fig. 2. Distribution of α-synuclein SAA positivity across AT biomarker profiles. Each circle represents the proportion of α-synuclein profiles within each AT biomarker group: S– – α-synuclein-negative; S+ – α-synuclein-positive; A–T– – amyloid-negative and tau-negative; A–T+ – amyloid-negative and tau-positive; A+T– – amyloid-positive and tau-negative; A+T+ – amyloid-positive and tau-positive. Blue circles show the percentage of S– individuals; red circles show the percentage of S+ individuals. Circle size corresponds to the proportion of patients in each subgroup.

Table 2

Clinical, demographic, and biomarker characteristics of A+T+ participants stratified by α-synuclein SAA status

Characteristic	Categories	A+T+ group		P-value
		S– (N = 431)[1]	S+ (N = 178)[1]	
Clinical Diagnosis				0.002[2]
	CN	72 (16.7%)	16 (9.0%)	
	MCI	234 (54.3%)	87 (48.9%)	
	AD	125 (29.0%)	75 (42.1%)	
Age (years)		74 [69–78]	75 [70–79]	0.054[3]
Sex				0.6[2]
	Female	200 (46.4%)	79 (44.4%)	
	Male	231 (53.6%)	99 (55.6%)	
Ethnicity				>0.9[4]
	Not Hispanic or Latino	418 (97.0%)	174 (97.8%)	
	Hispanic or Latino	10 (2.3%)	3 (1.7%)	
	Unknown	3 (0.7%)	1 (0.6%)	
Race				0.8[4]
	White	411 (95.4%)	173 (97.2%)	
	Black	11 (2.6%)	2 (1.1%)	
	Asian	3 (0.7%)	1 (0.6%)	
	Other	6 (1.4%)	2 (1.1%)	
APOE-ε4 Carrier Status				0.5[2]
	Non-carrier	125 (29.0%)	47 (26.4%)	
	Carrier	306 (71.0%)	131 (73.6%)	
CSF Aβ42 (pg/mL)		652 [511–776]	616 [493–744]	0.07[5]
CSF p-tau181 (pg/mL)		34 [28–46]	34 [28–45]	0.5[5]

Footnote:

1. N (%); median [Q1-Q3]
2. Pearson's Chi-squared test
3. Wilcoxon rank sum test
4. Fisher's exact test
5. ANCOVA adjusted for age, sex, clinical diagnosis, and APOE-ε4 carrier status

Lower CSF Aβ42 concentrations were observed in the S+ group (616 pg/mL, IQR: 493–744) compared to the S− group (652 pg/mL, IQR: 511–776), showing no statistical significance after adjustment (p = 0.07). This trend is consistent with prior findings suggesting that α-synuclein aggregation may enhance amyloid deposition [30]. In contrast, p-tau181 levels were nearly identical in both groups (median 34 pg/mL, IQR: 28–46 in S–, IQR: 28-45 in S+), with no significant difference (p = 0.5). These results suggest that α-syn co-pathology is associated with amyloid burden rather than with tau pathology.

Participants with ≥2 CSF measurements (N = 699) were analysed to explore AT profile stability over time. Most individuals (79.5%) retained a stable AT profile. The remaining 21.5% (N = 150) showed at least one AT profile change (Fig. 3). Among them, 125 showed different profiles between baseline and final timepoints (Fig. 4). The remaining 25 showed intermediate transitions but reverted to their initial AT profile. Most profile changes followed a typical amyloid-first pattern of AD progression. For example, 62.5% of A–T– participants converted to A+T–, and all baseline A–T+ participants progressed to A+T+. Profile reversions were observed in 14 A+T+ and 17 A+T– individuals among CN and MCI participants only, suggesting instability during early disease stages. Two subgroups of A+T+ participants demonstrated distinct reversion patterns. The first subgroup (N = 5) transitioned from A+T+ to A–T+, accompanied by a rise in Aβ42 median from 963.2 pg/mL (IQR: 935.3–976.6) to 1082.0 pg/mL (IQR: 1081.0–1099.0). The second subgroup (N = 9) reverted from A+T+ to A+T–, with a decrease in p-tau181 median from 23.7 pg/mL (IQR: 22.8–24.7) to 21.6 pg/mL (IQR: 20.6–21.7). These reversions occurred with biomarker values near diagnostic cut-offs, suggesting that slight fluctuations around threshold levels may drive profile instability. Similar atypical progression patterns have been reported previously, including tau- or neurodegeneration-first patterns and reversals to normal biomarker status [31,32].

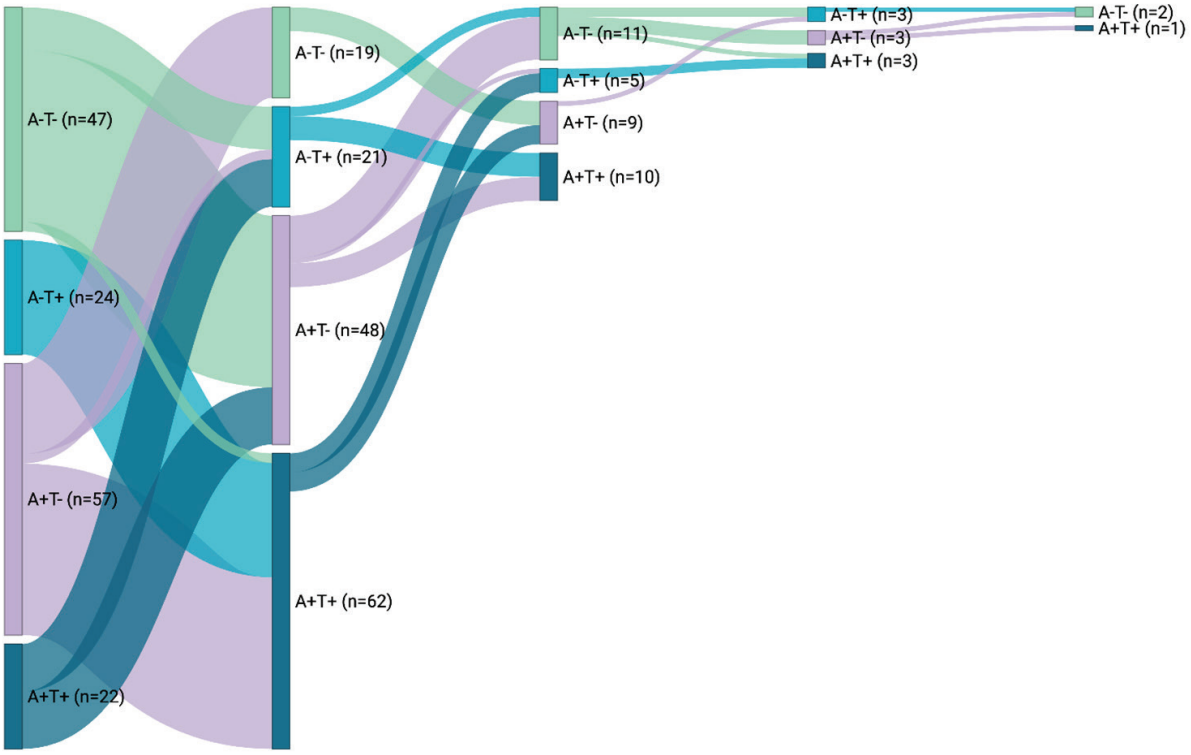

Fig. 3. Sankey diagram of intermediate AT profile transitions across multiple visits in participants with ≥ 3 AT timepoints and ≥ 2 different profiles. The first node represents the AT profile and baseline visit. The following nodes represent the nest AT profile transition at any given time point after baseline. Links represent direction and frequency of transitions.

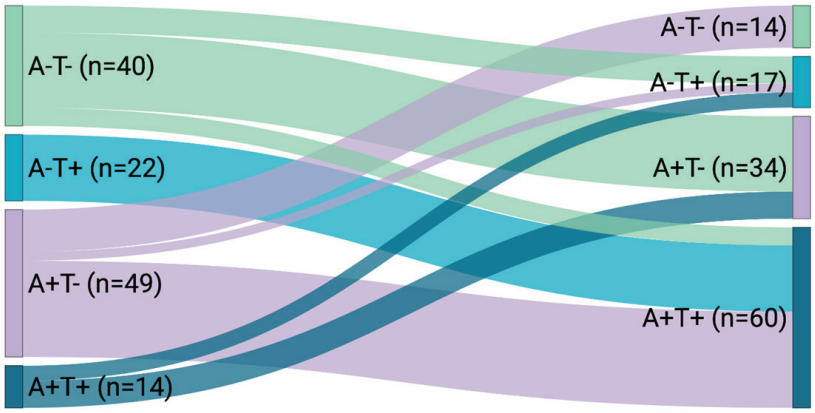

Fig. 4. Sankey diagram of transitions between AT profiles from the first to the last biomarker assessment among participants with at least two CSF Aβ42 and p-tau181 measurements. Each flow represents the number of individuals moving between profiles. Left and right nodes represent the first and the last AT profile. Node sizes reflect the number of individuals in each profile at each time point. Links represent direction and frequency of transitions.

In the model for log-transformed Aβ42 (Table 3), S+ status was not significantly associated with baseline Aβ42 levels (β = –0.042). In the S− group, Aβ42 levels did not change significantly over time (β = 0.0008, p = 0.25). However, a significant interaction between time and S status was observed (β = –0.0016, p < 0.01), indicating a faster decline in Aβ42 levels among S+ participants. Male participants had significantly higher Aβ42 levels (β = 0.089, p < 0.001). APOE-ε4 carriers showed significantly lower Aβ42 levels (β = -0.09, p < 0.001). Participants diagnosed with AD had lower baseline Aβ42 compared to CN (β = –0.059, p = 0.03), while those with MCI did not differ significantly (β = 0.008, p = 0.74). The random intercept for participants showed substantial inter-individual

variability (variance = 0.066), while the lower residual variance (0.016) reflected relatively small within-subject variation. The marginal R^2 for the model was 0.078, meaning 7.8% of variance was explained by fixed effects. The conditional R^2 was 0.816, indicating that the full model accounting for both fixed and random effects explained approximately 82% of the variance in Aβ42 levels.

In the model for log-transformed p-tau181 (Table 4), time was significantly associated with increasing concentrations ($\beta = 0.0039$, $p < 0.001$). A significant interaction between time and S status was also observed ($\beta = -0.002$, $p < 0.001$), indicating that S+ individuals exhibited a slower rate of increase in p-tau181 concentrations over time compared to S− individuals. S status alone was not associated with baseline p-tau181 levels ($\beta = -0.0081$, $p = 0.78$). Male sex was significantly associated with higher p-tau181 concentrations ($\beta = 0.076$, $p = 0.004$). MCI participants had higher baseline levels than CN ($\beta = 0.048$, $p = 0.03$). No significant difference was found for participants with AD compared to CN ($\beta = 0.031$, $p = 0.22$). APOE-ε4 carrier status was not associated with p-tau181 ($\beta = 0.0082$, $p = 0.78$). The random intercept variance was 0.095, with the residual variance of 0.01, suggesting higher between-subject variability than within-subject variability. The marginal R^2 for the model was 0.026, meaning 2.6% of variance was explained by fixed effects. The conditional R^2 was 0.909, indicating that the full model accounting for both fixed and random effects explained 90.9% of the variance in p-tau181 levels.

Predicted biomarker trajectories showed different longitudinal patterns of CSF Aβ42 and p-tau181 in A+T+ individuals depending on the presence of misfolded α-syn aggregates (Figs. 5 and 6). While baseline Aβ42 concentrations were not significantly different ($p = 0.1$) between S+ and S− groups, the rate of decline over time was significantly greater in S+ individuals ($p = 0.001$). This supports the hypothesis that α-synuclein co-pathology accelerates amyloid aggregation in the brain. In contrast, no progressive increase in p-tau181 was observed across the full cohort. Instead, S+ individuals displayed a stable trajectory of p-tau181 over time, while S− individuals exhibited a moderate

Table 3

Linear mixed-effects models were fitted to evaluate longitudinal changes in log-transformed CSF Aβ42 levels in A+T+ participants

Fixed Effect	β	SE	DF	t-value	p-value
(Intercept)	6.42	0.05512	676.4	116.466	< 0.001
Time (months)	0.0008	0.0007087	583.5	1.159	0.25
S+	-0.042	0.02573	632.1	-1.625	0.1
Time × S+	-0.0016	0.0005037	567.7	-3.233	0.001
Male	0.089	0.02311	587.0	3.831	< 0.001
MCI vs. CN	0.008	0.0247	1067.0	0.338	0.74
AD vs. CN	-0.059	0.02713	1078.0	-2.174	0.03
APOE4 Carrier	-0.09	0.0258	585.6	-3.477	< 0.001

Footnote:

1. The table reports the estimated β coefficients for each fixed effect, their standard errors (SE), degrees of freedom (DF), t-statistics (t-value), and the associated p-values.

Table 4

Linear mixed-effects models were fitted to evaluate longitudinal changes in log-transformed CSF p-tau181 levels in A+T+ participants

Fixed Effect	β	SE	DF	t-value	p-value
(Intercept)	3.458	0.06151	651.0	56.22	< 0.001
Time (months)	0.0039	0.0005592	532.9	6.978	< 0.001
S+	-0.0081	0.02917	598.3	-0.279	0.8
Time × S+	-0.002	0.02648	577.5	2.861	< 0.001
Male	0.076	0.0223	889.8	2.148	0.004
MCI vs. CN	0.048	0.02512	957.2	1.23	0.03
AD vs. CN	0.031	0.02957	576.6	0.276	0.2
APOE4 Carrier	0.0082	0.0003952	519.0	-5.028	0.8

Footnote:

1. The table reports the estimated β coefficients for each fixed effect, their standard errors (SE), degrees of freedom (DF), t-statistics (t-value), and the associated p-values.

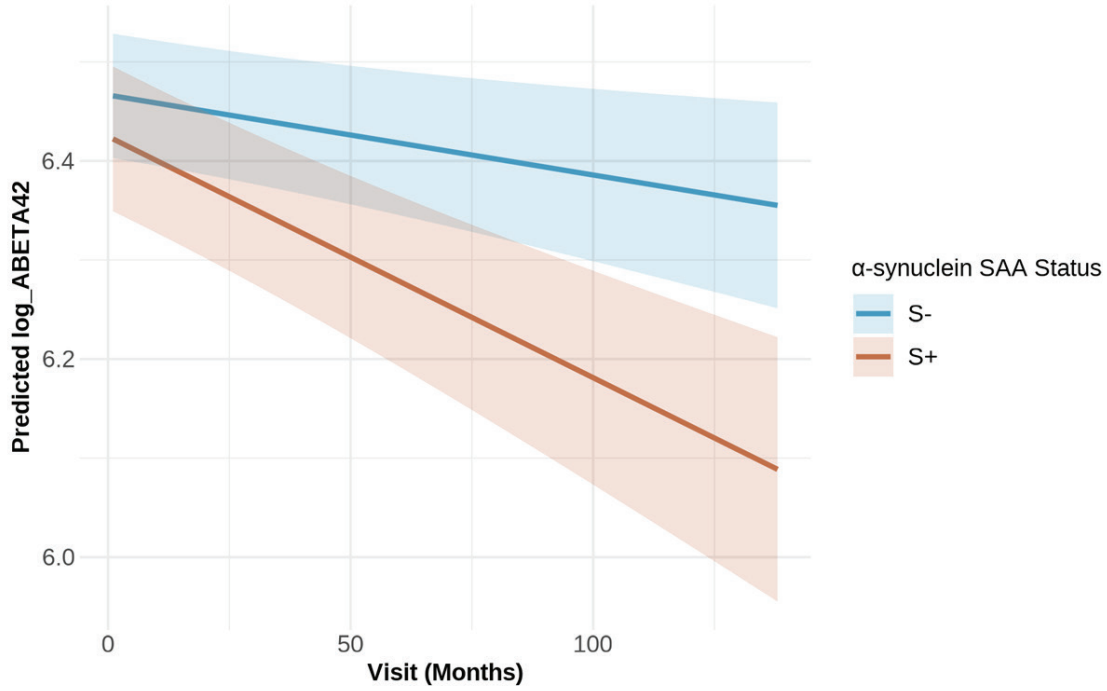

Fig. 5. Predicted longitudinal trajectories of log-transformed CSF Aβ42 levels over time in A+T+ participants, stratified by α-synuclein seeding activity status. Shaded ribbons represent 95% confidence intervals. Adjusted for age, sex, diagnosis, APOE-ε4 carrier status.

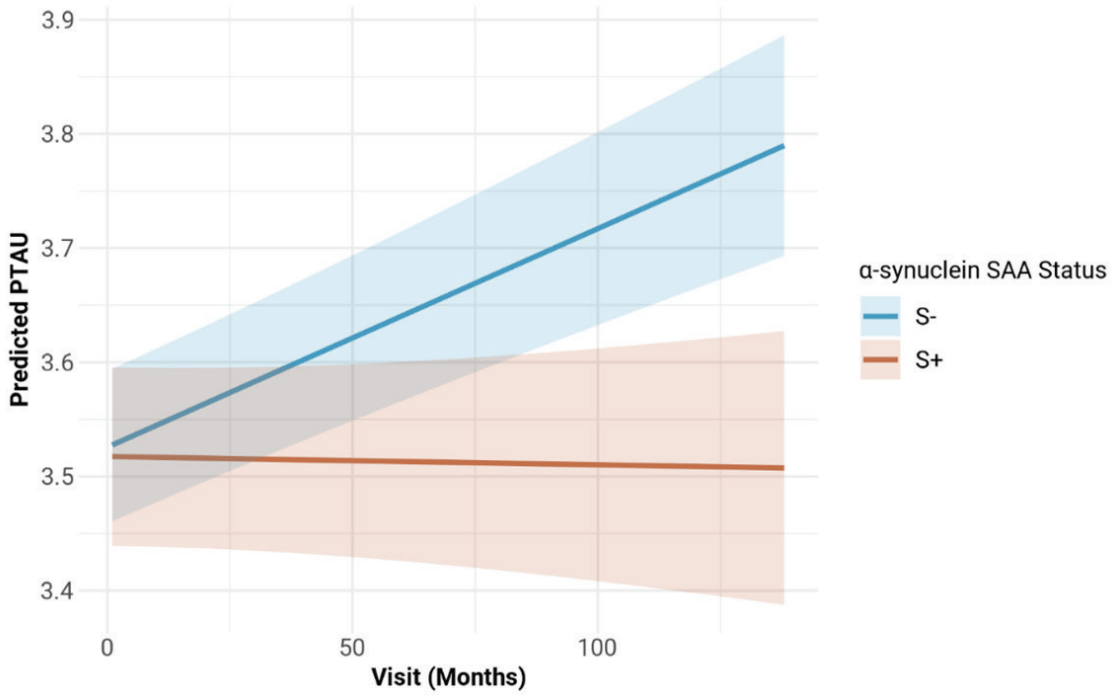

Fig. 6. Predicted longitudinal trajectories of log-transformed CSF p-tau181 levels over time in A+T+ participants, stratified by α-synuclein seeding activity status. Shaded ribbons represent 95% confidence intervals. Adjusted for age, sex, diagnosis, APOE-ε4 carrier status.

upward trend. The predicted p-tau181 rate of change was significantly slower in the S+ group compared to the S− group ($p < 0.001$). These findings differ from the typical pattern of steadily increasing tau pathology in AD and may reflect limitations in measuring tau dynamics using CSF p-tau181.

Similarly, Pichet Binette et al. [33] reported stronger associations between α-synuclein and Aβ PET signal, but not with tau PET trajectories. Franzmeier et al. [34] demonstrated that S+ exacerbates Aβ-related tau accumulation, as measured by tau PET, and accelerates cognitive decline. Tosun et al. [30,35], using ADNI CSF biomarker data, found no significant longitudinal differences in Aβ42 or p-tau181 by S status, but reported earlier symptom onset and faster clinical progression in S+ participants.

Conclusions

Misfolded α-synuclein aggregates were detected in 29% of A+T+ individuals. S+ status was associated with a significantly faster decline in CSF Aβ42 but not with baseline levels. In contrast, p-tau181 levels increased more slowly in the S+ group. Approximately 20% of ADNI participants showed changes in AT profiles over time, occurring only in CN and MCI individuals near diagnostic cut-offs. SAA status did not influence baseline biomarker concentrations independently. Sex, clinical diagnosis, and APOE-ε4 genotype contributed to biomarker variability. Results support the inclusion of α-synuclein status in the AT(N) framework to improve biological stratification of Alzheimer's disease.

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ЗВ'ЯЗОК СУПУТНЬОЇ ПАТОЛОГІЇ АЛЬФА-СИНУКЛЕЇНУ З РІВНЯМИ БЕТА-АМІЛОЇДУ ТА ФОСФОРИЛЬОВАНОГО ТАУ-БІЛКА ПРИ ХВОРОБІ АЛЬЦГЕЙМЕРА

Неправильно згорнуті агрегати α-синуклеїну (α-syn) можуть бути в спинномозковій рідині осіб із хворобою Альцгеймера (ХА) навіть без клінічних ознак синуклеїнопатії. Ця супутня патологія може впливати на прогресування ХА на молекулярному рівні. Виявлення агрегатів α-синуклеїну за допомогою методу seed amplification assay (SAA) дає змогу стратифікувати пацієнтів із ХА за межами класичних біомаркерів, що входять до рамки AT(N). Структура AT(N) дає змогу здійснити біологічну класифікацію ХА на основі її основних патологічних процесів: агрегація β-амілоїду (A), накопичення тау-білка і гіперфосфорилювання (T) та неспецифічна нейродегенерація (N). **Мета дослідження** – з'ясувати, чи пов'язана супутня патологія α-syn, виявлена за допомогою SAA, зі зміненими концентраціями та поздовжніми траєкторіями β-амілоїду 42 (Aβ42) та фосфорильованого тау 181 (p-tau181) у групі осіб із ХА, визначеній за біомаркерами. Дані учасників A+T+ (N = 609) Ініціативи нейровізуалізації хвороби Альцгеймера (ADNI) було проаналізовано з використанням результатів електрохемілюмінесцентного імуноферментного аналізу Roche Elecsys (ECLIA) та SAA. Спостерігалися суттєві розбіжності між клінічним діагнозом та профілями AT. 29 % учасників A+T+ були α-syn-позитивними (S+), що свідчить про значну поширеність супутньої патології α-syn у разі біологічно визначеної хвороби Альцгеймера. Перехресні порівняння показали, що в осіб S+ були нижчі вихідні концентрації Aβ42 порівняно з α-syn-негативними (S−) учасниками. Лінійні моделі змішаних ефектів (LMEM) показали значно різкіше зниження Aβ42 з часом у групі S+, що підтверджує гіпотезу про те, що неправильно згорнута агрегація α-syn пришвидшує агрегацію амілоїду. Однак рівні p-tau181 зростали повільніше в осіб S+, ніж у осіб S−, усупереч очікуванням. Ці зв'язки залишалися значними після коригування на вік, стать, діагноз та генотип APOE-ε4. Отримані результати свідчать про те, що супутня патологія α-syn може впливати на прогресування хвороби Альцгеймера через взаємодію з Aβ42, а отже, це дає змогу підтримувати її інтеграцію в класифікаційні рамки на основі біомаркерів.

Ключові слова: хвороба Альцгеймера, синуклеїнопатія, супутня патологія, α-синуклеїн, β-амілоїд 42, фосфорильований тау-181, спинномозкова рідина, класифікація AT(N).

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