

Cerebrospinal Fluid Biomarkers

Frontotemporal dementia is the leading cause of “true” A–/T+ profiles defined with $A\beta_{42/40}$ ratio

Hélène Pouclet-Courtemanche^a, Tri-Bao Nguyen^b, Emilie Skrobala^c,
Claire Boutoleau-Bretonnière^a, Florence Pasquier^d, Elodie Bouaziz-Amar^{e,f},
Edith Bigot-Corbel^g, Susanna Schraen^h, Julien Dumurgierⁱ, Claire Paquet^{i,*},
Thibaud Lebouvier^{h,*,*}

^aCHU Nantes, Inserm CIC04, Department of Neurology, Centre Mémoire de Ressources et Recherche, Nantes, France

^bCH Delafontaine, Saint-Denis, France

^cCHU Lille, DISTALZ, Lille, France

^dUniversity of Lille, Inserm U1171, CHU Lille, DISTALZ, Lille, France

^eDépartement de Biochimie et de biologie moléculaire GH Saint-Louis/Lariboisière/Fernand Widal - Site Lariboisière, AP-HP, Paris, France

^fInserm UMR-S 1144 Universités Paris Descartes – Paris Diderot Variabilité de Réponse aux Psychotropes, Paris, France

^gCHU de Nantes, Laboratory of Biochemistry, Nantes, France

^hUniversity of Lille, Inserm U1172, CHU Lille, DISTALZ, Lille, France

ⁱCognitive Neurology Center, Lariboisière - Fernand Widal Hospital, AP-HP, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

Abstract

Introduction: Patients with positive tauopathy but negative $A\beta_{42}$ (A–T+) in the cerebrospinal fluid (CSF) represent a diagnostic challenge. The $A\beta_{42/40}$ ratio supersedes $A\beta_{42}$ and reintegrates “false” A–T+ patients into the Alzheimer’s disease spectrum. However, the biomarker and clinical characteristics of “true” and “false” A–T+ patients remain elusive.

Methods: Among the 509 T+N+ patients extracted from the databases of three memory clinics, we analyzed T+N+ patients with normal $A\beta_{42}$ and compared “false” A–T+ with abnormal $A\beta_{42/40}$ ratio and “true” A–T+ patients with normal $A\beta_{42/40}$ ratio, before CSF analysis and at follow-up.

Results: 24.9% of T+N+ patients had normal $A\beta_{42}$ levels. Among them, 42.7% were “true” A–T+. “True” A–T+ had lower CSF tau^{P181} than “false” A–T+ patients. 48.0% of “true” A–T+ patients were diagnosed with frontotemporal lobar degeneration before CSF analysis and 64.0% at follow-up, as compared with 6% in the “false” A–T+ group ($P < .0001$).

Discussion: Frontotemporal lobar degeneration is probably the main cause of “true” A–T+ profiles.

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Keywords:

Alzheimer’s disease; Cerebrospinal fluid biomarkers; $A\beta_{42/40}$ ratio; $A\beta_{42}/A\beta_{40}$ ratio; Frontotemporal dementia; Suspected non Alzheimer’s disease pathology (SNAP)

1. Introduction

Cerebrospinal fluid (CSF) biomarkers have redesigned Alzheimer’s disease (AD) diagnosis [1–3]. The major interest of CSF biomarkers rests upon their reflection of

brain pathology: several studies have shown that CSF $A\beta_{42}$ levels are inversely correlated with cerebral $A\beta$ load [4–6], whereas increased CSF total tau (T-tau) and phosphorylated tau (tau^{181P}) levels reflect the burden of neurofibrillary pathology [6–8]. Although CSF T-tau is an unspecific marker of neuronal death [9–11], tau^{181P} and $A\beta_{42}$ have a high specificity for AD. Tau^{181P} is not or slightly increased in other tauopathies and was shown to outperform the two other biomarkers taken in isolation for

*Same contribution.

*Corresponding author. Tel.: +333 204 460 21; Fax: +333 204 460 22.

E-mail address: thibaud.lebouvier@chru-lille.fr

differential dementia diagnosis [12–15]. In 2018, the AT(N) classification system proposed by the 2018 National Institute of Aging–Alzheimer's Association (NIA-AA) research framework shifted the definition of AD from a syndromal to a biological construct [16]. This system validates CSF $A\beta_{42}$ and tau^{181P} as suitable markers for amyloid (A) and tau (T) pathology, respectively, while T-tau is considered as a marker of neuronal injury [16,17]. In the AT(N) scheme, AD patients are A+T+ by definition.

According to Jack's model, there is a temporal ordering of biomarker abnormalities in which biomarkers of $A\beta$ deposition become abnormal before biomarkers of tau pathology and neuronal injury [18]. So far, longitudinal studies show that most AD patients fit into this model [19,20]. However, a vast number of patients present with A–T+ CSF profiles, that is, with abnormal tau and normal $A\beta$ biomarkers [21–24]. This possibility of “conflicting” results was anticipated in the 2011 NIA-AA criteria for AD diagnosis. In such instances, biomarkers were deemed “uninformative,” suggesting that results should simply not be taken into account [25,26]. The recent AT(N) classification system goes one step further, as A–T+ patients are now labeled “suspected non-Alzheimer's pathophysiology” (SNAP) [16,27].

In recent years, a growing interest for the mechanisms of amyloid precursor protein cleavage has prompted the development of ELISA kits specific for other $A\beta$ species. In the CSF, the most abundant isoform is $A\beta_{40}$, whose levels show substantial interindividual variations. Because CSF $A\beta_{42}$ concentration may also depend on overall $A\beta$ levels, it was suggested that an imbalance between CSF $A\beta_{42}$ and $A\beta_{40}$ (i.e., a decreased $A\beta_{42/40}$ ratio) could supersede the mere decrease of CSF $A\beta_{42}$ level as a biomarker of amyloid pathology [28–32]. Indeed, $A\beta_{42/40}$ ratio was better correlated than $A\beta_{42}$ with amyloid tracer retention in two positron emission tomography studies [31,32]. Using the $A\beta_{42/40}$ ratio allows to reclassify half of A–T+ patients (hereafter referred to as “false” A–T+, that is, abnormal CSF tau markers and normal $A\beta_{42}$ but abnormal $A\beta_{42/40}$ ratio) into the A+T+ group [33,34]. Despite the relative scarcity of validation studies, the AT(N) system readily recognizes the $A\beta_{42/40}$ ratio as a surrogate marker of amyloid pathology [16].

However, the clinical phenotype of A–T+ patients remains poorly studied. Positing that $A\beta_{42/40}$ is the best CSF amyloid biomarker, “false” A–T+ patients should be clinically indistinguishable from A+T+ patients. Conversely, when using the $A\beta_{42/40}$ ratio instead of $A\beta_{42}$, 10% to 13% of patients still display a “true” A–T+ CSF profile (i.e., abnormal CSF tau markers and normal $A\beta_{42}$ and $A\beta_{42/40}$ ratio) [33,34]. “True” A–T+ patients should have a clinical phenotype that differs from the one of both “false” A–T+ and typical A+T+ patients. In this context, the objectives of this retrospective multicenter study were to (1) determine the proportion of A–T+ CSF profiles in routine clinical care; (2) compare the clinical diagnoses

made before CSF analysis; and (3) compare the clinical phenotype at follow-up in A–T+ patients separated according to the $A\beta_{42/40}$ ratio.

2. Patients and methods

2.1. Subjects

Subjects were recruited between November 14, 2012 and December 31, 2015 from Paris, Lille, and Nantes Memory Resource and Research Centres (MMRC). Inclusion criteria were fivefold: (1) available CSF with AD biomarkers, including $A\beta_{42}$, $A\beta_{40}$, T-tau, and tau^{181P} (quantitative determination of $A\beta_{40}$ and $A\beta_{42/40}$ ratio is routine in the three memory clinics); (2) high CSF tau^{181P} (tau^{181P} \geq 60 pg/mL); (3) mild cognitive impairment (MCI) or dementia; (4) presence of biomarkers of neurodegeneration or neuronal injury (N+) on 18F-fluorodeoxyglucose-PET or MRI, and/or high CSF total-tau [16]; and (5) available medical records and neuropsychological assessments performed before the results of CSF biomarkers were made available. Exclusion criteria were as follows: (1) subjective cognitive decline; (2) unconventional indications of AD CSF biomarkers analysis (e.g., systematic biomarkers analysis following a lumbar puncture [LP] performed for another indication); (3) significant comorbidities, including concomitant nondegenerative and nonvascular neurological disorder.

2.2. Clinical diagnoses

All recruiting centers were tertiary referral memory clinics. These centers use the same clinical and biochemical procedures and international validated criteria for AD and all other dementia. Patients had a thorough examination, including clinical, neurological, and neuropsychological evaluations and brain imaging, as recommended by the Haute Autorité de Santé (French Health Authority). We collected the diagnosis made by the clinician before the LP and the last diagnosis made after the LP at follow-up. To avoid the bias due to the knowledge of CSF biomarkers results, the main analysis was based on the diagnosis evoked by the clinician before the CSF results.

In addition, medical records and neuroimaging studies were analyzed in retrospect by H.P.C., T.B.N., C.P., and T.L., and confronted to current diagnostic criteria. We used the 2011 NIA-AA criteria for probable AD dementia [26]. At the MCI stage, AD diagnosis was only raised when the MCI clinical and cognitive syndrome was consistent with AD, according to the NIA-AA criteria [25]. Vascular cognitive impairment, behavioral variant of frontotemporal dementia (bvFTD), primary progressive aphasia (PPA) syndromes, Lewy body dementia, progressive supranuclear palsy syndrome (PSPS), and corticobasal syndrome (CBS) were defined according to the corresponding criteria [35–40]. In case of discrepancy with the clinician's diagnosis, another diagnosis was suggested.

AD was deemed atypical in case of posterior cortical syndrome, primary logopenic aphasia or frontal/executive variant, as well as in mixed disease (concomitant vascular cognitive impairment and/or Lewy body disease) or when neuroimaging studies were not congruent with AD.

2.3. Cerebrospinal fluid analysis

LPs were performed using a 25-gauge needle, and CSF samples were collected in a 5-mL polypropylene tube in Nantes (catalog number 62.558.201; Sarstedt, Nümbrecht, Germany) or in a 10-mL polypropylene tube in Lille and Paris (catalog number 62.610.201; Sarstedt, Nümbrecht, Germany). Each CSF sample was transferred at 4°C to the corresponding local laboratory within 4 hours after collection and was then centrifuged at 1000 g (Lille and Paris) or 2100 g (Nantes) for 10 minutes at 4°C. A small amount of CSF was used to perform routine analyses, including total cell count, bacteriological examination, and total protein and glucose levels. The CSF was aliquoted in 1.5-mL polypropylene tubes (Lille and Paris) or 2-mL polypropylene tubes (Nantes) and stored at -80°C to await further analysis. CSF A β_{40} , A β_{42} , T-tau, and tau^{181P} were measured in each local laboratory using a commercially available sandwich enzyme-linked immunosorbent assay (INNOTEST; Fujirebio Europe NV, Gent, Belgium) according to the manufacturer's instructions.

2.4. AD biomarker cutoffs

Cutoff values used in clinical routine for P-tau were based on the results of the French multicenter study setting up the harmonization of sampling procedures and collection tubes, to which the three MRRCs involved in the current work participated [41]. Cutoff values for A β_{42} and A $\beta_{42/40}$ were set at, respectively, <800 pg/mL and <0.065 following another French multicenter study involving our two of our three MMRCs [34]. Pathological results were defined as follows: A β_{42} <800 pg/mL, T-tau \geq 350 pg/mL, and tau^{181P} \geq 60 pg/mL.

Although the AT(N) classification system is intended for research and not for clinical practice [16], we chose to use its nomenclature for brevity. A+T+ profiles were defined by tau^{181P} \geq 60 pg/mL and A β_{42} <800 pg/mL. A-T+ profiles were defined by tau^{181P} \geq 60 pg/mL and A β_{42} \geq 800 pg/mL. A-T + CSF profiles were further subdivided into "false" A-T+ profiles (A $\beta_{42/40}$ ratio <0.065, congruent with the presence of amyloid pathology) and "true" A-T+ profiles (normal A $\beta_{42/40}$ ratio \geq 0.065, congruent with the absence of amyloid pathology).

2.5. Statistical analysis

Qualitative variables were expressed as frequencies and percentages. Quantitative variables were expressed as mean \pm standard deviation. Normality of distributions was assessed graphically and using the Shapiro-Wilk test.

"True" and "false" A-T+ patients were compared using chi-square test (or Fisher's exact test when the expected cell frequency was <5) for qualitative variables, and Student t-test (or Mann-Whitney *U* test in case of non-Gaussian distribution) for quantitative variables.

In the "True" A-T+ patient group, different parameters were compared according to diagnosis before CSF results. Qualitative parameters were analyzed using chi-square test or Fisher's exact test. Analysis of variance (or Kruskal-Wallis test in case of non-Gaussian distribution) was used for quantitative parameters.

A sensitivity analysis was systematically performed by including the study site (Lille, Nantes, or Paris) as a covariate, using a logistic regression to compare "true" and "false" A-T+ patients.

Statistical testing was performed at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Study population

The study included 1253 patients who underwent a CSF study for biomarker analysis, among which 509 (40.6%) had pathological levels of tau^{181P}.

The population of the study was further divided according to A $\beta_{42/40}$ ratio. Most of the patients with pathological levels of tau^{181P} were A+T+ (n = 362, 75.1%). One hundred twenty patients were A-T+ (24.9% of patients with pathological tau^{181P}, and 9.8% of all patients). Within this subgroup, 67 (57.3%) had abnormal A $\beta_{42/40}$ ratios ("false" A-T+ profiles) while 50 (42.7%) had normal A $\beta_{42/40}$ ratios ("true" A-T+ profiles) (Fig. 1). Hence, A $\beta_{42/40}$ ratio allowed reclassifying more than half of the A-T+ patients into the AD spectrum.

3.2. CSF biomarkers in "true" and "false" A-T+ patients

CSF biomarker levels were statistically different between both groups (Table 1). "False" A-T+ patients had lower A β_{42} and higher A β_{40} levels (978.3 \pm 216.8 and 20,334.1 \pm 4972.4) as compared with "true" A-T+ patients (1313.3 \pm 329.1 and 15,367.5 \pm 4091.0; *P* < .001 and *P* < .001).

Tau^{181P} and T-tau were significantly higher in the "false" (102.4 \pm 37.6 and 739.9 \pm 405.6) than in the "true" A-T+ group (74.4 \pm 12.3 and 475.2 \pm 147.1; *P* < .001 and *P* < .001). The proportion of patients with concomitant pathological values of T-tau and tau^{181P} was higher in the "false" (94.0%) than in the "true" A-T+ group (80.0%; *P* = .02). Yet in the "true" A-T+ group, tau^{181P} and T-tau levels were far beyond cutoff for a majority of patients (Fig. 2). All results remained highly significant after including the study site as a covariate.

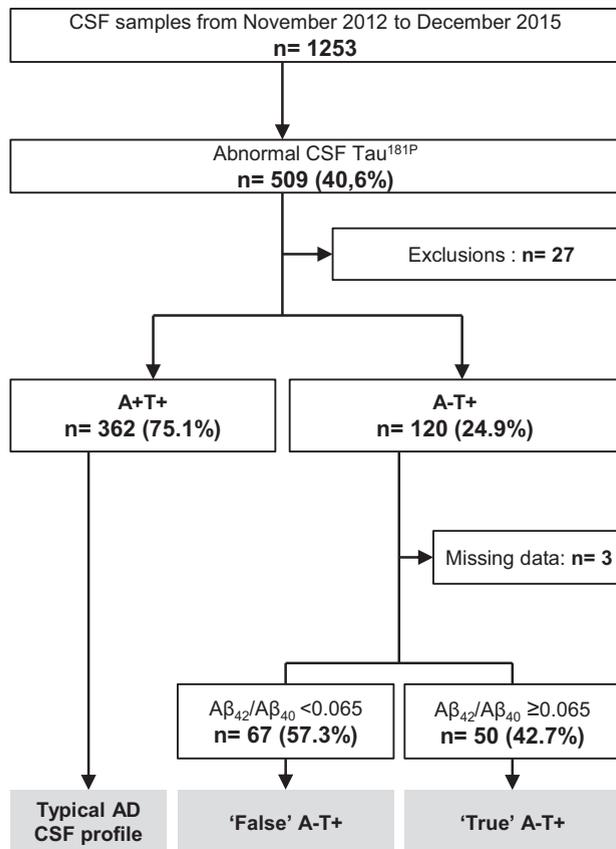


Fig. 1. Flowchart. CSF profiles were determined following the ATN classification system: A+ corresponds to abnormal $A\beta_{42}$, T+ to abnormal tau^{181P}. Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid.

3.3. Clinical diagnoses before biomarkers analysis in "true" and "false" A-T+ patients

A systematic comparison of the clinical data between "true" and "false" A-T+ groups was performed. There was no significant difference regarding age, gender, and MMSE scores (Table 1).

Diagnoses made by the clinician before CSF biomarkers results were differently distributed between groups ($P < .001$). AD diagnosis was significantly more frequent in the "false" A-T+ ($n = 58$, 86.6%) than in the "true" A-T+ group ($n = 20$, 40.0%; $P < .0001$). Among the suspected AD diagnoses, typical amnesic presentations were more frequent among "false" A-T+ patients ($n = 42$, 72.4% of AD diagnoses) than in "true" A-T+ patients ($n = 6$, 30.0% of AD diagnoses; $P = .0008$).

Diagnoses of the frontotemporal lobar degeneration (FTLD) spectrum encompass bvFTD, nonfluent/agrammatic and semantic variants of PPA, CBS, and PSPS [42]. FTLD diagnoses were made for only four patients (6.0%) in the "false" A-T+ group, as opposed to 24 patients in the "true" A-T+ group (48.0%, $P < .0001$). Semantic variant PPA was the leading syndrome (10/24, 41.7%) followed by probable bvFTD (8/24, 33.3%). Four more patients had a

clinical presentation consistent with a pure tauopathy (one with CBS, one with PSPS, two with apraxia of speech, and one with nonfluent/agrammatic PPA). The two remaining patients were classified as possible bvFTD and unclassifiable PPA.

Other etiologies (Lewy body disease, multidomain and executive MCI, VCI, psychiatric) were rarer and were not more represented in the "true" than in the "false" A-T+ group ($P = 1$). Finally, the comparisons of clinical diagnoses remained significant after including the study site as a covariate.

3.4. Follow-up of patients with A-T+ profiles

In the "false" A-T+ group, 58/67 patients (87%) were diagnosed with AD before the LP, and the diagnosis did not change afterward for 50/58 patients (86%). Five of the nine remaining "false" A-T+ patients were diagnosed with AD during follow-up.

Among the 20/50 patients in the "true" A-T+ group diagnosed with AD before biomarker analysis, 7/20 patients fulfilled criteria for FTLD at follow-up (one with possible bvFTD, three with probable bvFTD, two with semantic PPA, and one with unclassifiable PPA). Among the 24/50 patients from the "true" A-T+ group diagnosed with FTLD before biomarker analysis, there was no change in diagnosis at follow-up (Fig. 3 and Supplementary Table 1). In addition, two patients were found to bear a *C9ORF72* gene mutation during follow-up.

Overall, 31/50 (62.0%) "true" A-T+ patients had a clinical diagnosis belonging to the FTLD spectrum after reviewing the clinical files: 12/31 fulfilled the clinical criteria for bvFTD (three possible bvFTD, seven probable bvFTD, two genetically confirmed bvFTD) and 19/31 for one of the FTLD variants (12 svPPA, two unclassifiable PPA, 5 PSP/CBS/nfPPA) (Supplementary Table 1).

4. Discussion

The main results of this retrospective multicenter study are that (1) in a real-life memory clinic setting, A-T+ patients defined by CSF $A\beta_{42}$ were common; (2) the $A\beta_{42/40}$ ratio used instead of $A\beta_{42}$ was able to reclassify half of A-T+ patients (i.e., "false" A-T+ patients) into the A+T+ group; (3) the clinical phenotype of "true" A-T+ patients differed from the one of "false" A-T+ patients, with an overrepresentation of patients whose clinical presentation is congruent with FTLD.

Ever since the first report of its use in 1998 [43], the $A\beta_{42/40}$ ratio was repetitively shown to be superior to $A\beta_{42}$ for AD diagnosis [37,38], including at the prodromal stage [29], as well as for differential dementia diagnosis [30,31,44,45]. In the present study, we showed that the $A\beta_{42/40}$ ratio changes half of previously considered "uninformative" CSF profiles into A+T+, the biological

Table 1
Comparisons between “false” and “true” A–T+ groups

	“False” A–T + $A\beta_{42/40} < 0.065$	“True” A–T + $A\beta_{42/40} \geq 0.065$	P
Demographics			
Patients number	67	50	na
Women (%)	46 (68.7%)	29 (58.0%)	.23
Age (years, mean \pm SD)	69.6 \pm 8.4	67.6 \pm 8.2	.20
MMSE (mean \pm SD)	22.1 \pm 5.9	22.9 \pm 5.2	.55
Clinical diagnosis before LP			
AD	58 (86.6%)	20 (40.0%)	<.0001
Typical amnesic presentations	42 (72.4%)	6 (30.0%)	.0008
FTLD spectrum	4 (6.0%)	24 (48.0%)	<.0001
Probable bv-FTD	0	8	
Possible bv-FTD	1	1	
sv-PPA	1	10	
CBS, PSPS, apraxia of speech	2	4	
PPA	0	1	
Other (LBD, VCI, psychiatric, MCI or dementia without etiology, etc.)	5 (7.5%)	6 (12.0%)	1
CSF biomarkers (mean \pm SD)			
$A\beta_{42}$ (pg/mL)	978.3 \pm 216.8	1313.3 \pm 329.1	<.001
$A\beta_{40}$ (pg/mL)	20,334.1 \pm 4972.4	15,367.5 \pm 4091.0	<.001
T-tau (pg/mL)	739.9 \pm 405.6	475.2 \pm 147.1	<.001
Tau ^{181P} (pg/mL)	102.4 \pm 37.6	74.4 \pm 12.3	<.001

Abbreviations: AD, Alzheimer’s disease; bv-FTLD, behavioral variant of frontotemporal dementia; CSF, cerebrospinal fluid; CBS, corticobasal syndrome; SD, standard deviation; FTLN, frontotemporal lobar degeneration; LBD, Lewy body disease; LP, lumbar puncture; MCI, mild cognitive impairment; MMSE, Mini–Mental State Examination; PPA, primary progressive aphasia; PSPS, progressive supranuclear palsy syndrome; VCI, vascular cognitive impairment.

definition of AD [16]. This result is strikingly similar to the ones of previous studies [33,34,46].

Although the new NIA-AA criteria recently took the leap to a biomarker-based diagnosis of AD, which renders the clinical correlations accessory, our clinical data support the surrogate use of the $A\beta_{42/40}$ ratio. We used a reverse approach, classifying T+ patients into three categories according to CSF $A\beta_{42}$ and the $A\beta_{42/40}$ ratio, and secondarily

tested the classification’s relevance. Previous studies have used this reverse “CSF-to-phenotype” approach, although to our knowledge none used the $A\beta_{42/40}$ ratio [21,22,24]. We herein showed that contrary to “true” A–T+ patients, most “false” A–T+ patients with abnormal $A\beta_{42/40}$ ratios fulfill clinical criteria for amnesic or nonamnesic AD at follow-up.

The case of the “true” A–T + CSF profiles remains an outstanding issue. Considering that CSF tau^{181P} is the most specific marker of AD [12–14,47] opens up two possibilities: (1) despite negative amyloid pathology biomarkers, “true” A–T+ cases belong to the AD spectrum or (2) despite positive tau pathology biomarkers, “true” A–T+ cases are non-Alzheimer’s pathologies.

The first hypothesis raises the possibility of false-negative amyloid biomarkers. However, it seems unlikely that two consecutive—although not independent—amyloid biomarkers, namely $A\beta_{42}$ and the $A\beta_{42/40}$ ratio, yield false-negative results in so many cases. Moreover, the $A\beta_{42/40}$ ratio was shown to have an excellent negative predictive value against amyloid PET status [48]. Alternatively, “true” A–T+ patients may have AD-type tau pathology while displaying few or no amyloid pathology. This situation has been described in young individuals without any cognitive impairment [49] as well in the primary age-related tauopathy (PART) of older individuals [47]. PART is associated with mild episodic and semantic memory impairment as well as attention and executive deficits [50], a phenotype that corresponds only to a minority of our “true” A–T+ patients. The status of CSF tau

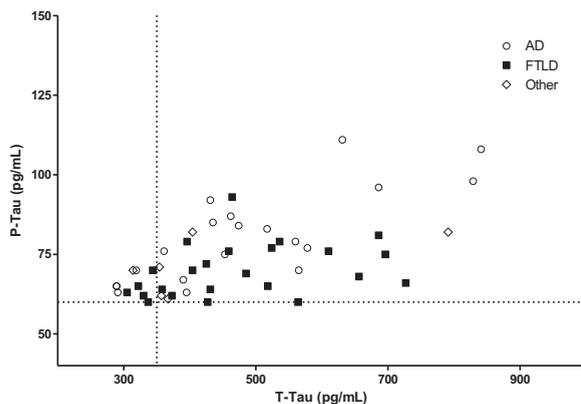


Fig. 2. CSF T-tau and tau^{181P} values in “true” A–T+ patients. Patients diagnosed with AD before the CSF analysis are represented with white circles, patients diagnosed with FTLN with black squares, and others with white diamonds. The vertical dotted line shows the T-tau cutoff (350 pg/mL), and the horizontal dotted line the tau^{181P} cutoff (60 pg/mL). Tau^{181P} and T-tau levels were beyond cutoffs for a majority of patients. Abbreviations: AD, Alzheimer’s disease; CSF, cerebrospinal fluid; FTLN, frontotemporal lobar degeneration.

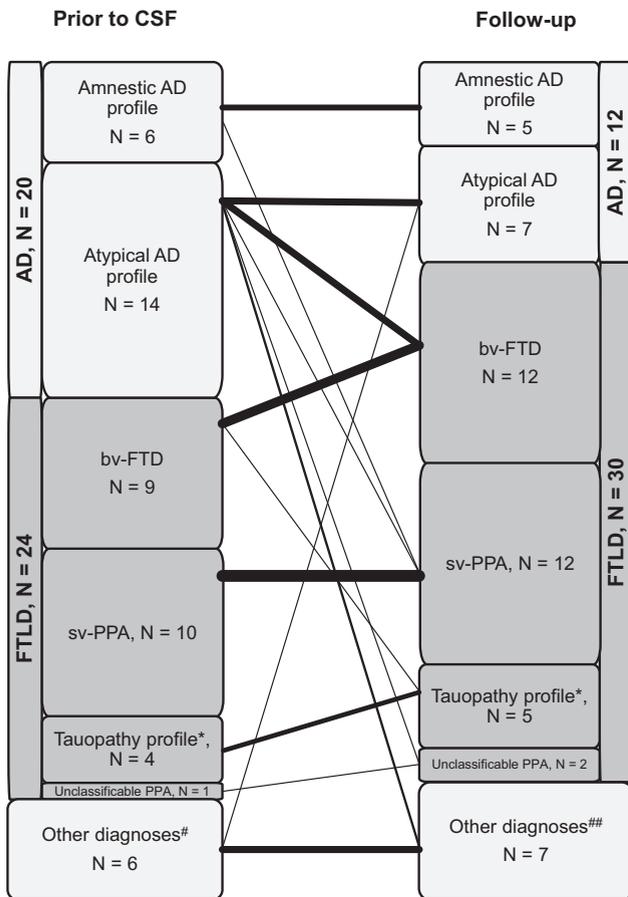


Fig. 3. Diagnoses in “true” A–T+ patients before CSF analysis and at follow-up (last diagnosis). *Tauopathy profiles: corticobasal/progressive supranuclear palsy syndromes, speech apraxia, nonfluent agrammatic primary progressive aphasia. #Other diagnoses before CSF analysis: one vascular cognitive impairment (VCI), one Lewy body disease (LBD), one psychiatric disease, two mild cognitive impairments (MCIs), one unclassifiable dementia. ##Other diagnoses at follow-up: three VCI, one LBD, one psychiatric disease, one MCI, one unclassifiable dementia. Abbreviations: AD, Alzheimer’s disease; bv-FTD, behavioral variant of frontotemporal dementia; CSF, cerebrospinal fluid; FTLD, frontotemporal lobar degeneration; PPA, primary progressive aphasia; sv-PPA, semantic variant of PPA.

biomarkers in PART is currently unknown, and whether PART belongs to the AD spectrum is also a matter of intense debate [49,50].

The second hypothesis raises the possibility of false-positive tau^{181P} results. However, most “true” A–T+ patients had frankly pathological CSF tau^{181P} levels and a concomitant elevation of CSF T-tau, supporting a genuine positivity of tau pathology biomarkers.

Alternatively, “true” A–T+ cases may be non-AD pathologies with positive tau pathology biomarkers. Interestingly 24/50 “true” A–T+ had a clinical phenotype consistent with FTLD before the LP. Among them, nine patients fulfilled bvFTD criteria and four patients had a PSP/CBD phenotype. It would be tempting to assume that such patients correspond to FTLD with neuroglial tau pathology (FTLD-tau) [51]. Consistently in a recent

clinicopathological correlation study, CSF tau^{181P} levels were shown to be positively associated with cerebral tau burden in FTLD, even after exclusion of cases with concomitant AD pathology [52]. However, the other phenotypes in our study (e.g., semantic dementia, n = 10) were suggestive of TDP-43 pathology [53], which was proven in the two cases that bore *C9ORF72* mutations.

In line with the latter, surprising results came from clinical cohorts of patients with *C9ORF72* mutations and available AD CSF biomarkers [54], as well as from clinical cohorts of putative young-onset AD that had a systematic *C9ORF72* mutation screening [55]. Both studies showed that A β_{42} and/or tau^{181P} can be abnormal in a subset of patients bearing *C9ORF72* mutations. Concomitant AD pathology is a possible explanation, although the young age of onset and negative amyloid markers of our “true” A–T+ cases make it unlikely. Overall, although we do not discard that some “true” A–T+ patients may be due to false-negative amyloid biomarkers or false-positive tau biomarkers, most “true” A–T+ cases probably correspond to FTLD (and possibly PART) cases, suggesting that some FTLDs are associated with elevated tau biomarkers.

In a broader perspective, “true” A–T+ cases belong to the SNAPs, a concept forged in 2012 to designate A–T+ and/or N+ cases, that is, cases with positive tau biomarkers and/or neurodegeneration markers in neuroimaging (atrophy and/or hypometabolism) [27,56]. SNAP is not a rare finding in healthy elderly individuals, representing up to 25% of the population, and the relevance of this finding is questionable since SNAP profile does not seem to be associated with cognitive decline [57]. In the population with cognitive decline, the SNAP group is heterogeneous, encompassing cerebrovascular disease, Lewy-body dementia, argyrophilic grain disease, and FTLD or nonspecific hippocampal sclerosis [58]. Within SNAP cases, few studies distinguished A–T+N+ from A+T–N+. A recent survey from a large AD biomarker database showed that 64% of A–N+ cases were T+ [59]. However, this study used high T-tau to define N+, leaving out N+ patients determined by neuroimaging (where atrophy and/or hypometabolism define N+). Furthermore, the A $\beta_{42/40}$ ratio was not used, which overestimates the number of A–T+N+ cases. Altogether, A–T+N+ probably represents a minority of SNAP cases. We show that identification of T+ cases in SNAP is relevant from a clinical point of view because most of them may correspond to FTLD.

The two main limitations of the study are the retrospective methodology and the lack of pathological confirmation of the diagnoses. These limitations however do not outweigh the main interest of this multicenter study, resting in its observational nature. Patients included come from daily care practices, patient groups were established and analyzed in an unbiased way, and the main analysis was based on diagnoses made before the LP. If confirmed by further studies, our results will be easy to generalize to

the general population of memory clinic patients. Even if we cannot provide proof that “true” A–T+ cases are underlain by FTLD pathology, patient follow-up (and in a few cases genetics) strengthened or confirmed the diagnosis made before the CSF biomarker results.

The third limitation of this study lies in the use of what could appear as arbitrary thresholds to define biomarker positivity, raising the possibility that more stringent thresholds would have yielded very different results. This limitation is shared by all biomarker studies. However, the thresholds we used were defined by multicenter harmonization studies [34,41]. While we do not deny that some of our cases may correspond to false-positive tau^{181P} results, tau^{181P} was clearly in the pathological range for most patients and associated with elevated T-tau. Furthermore, the rather homogeneous phenotype of “true” A–T+ patients comforts the relevance of our results.

Finally, the changes in clinical diagnoses following biomarker analysis should be considered with caution because CSF results may influence clinicians, raising a risk of circular reasoning. This is particularly true in the “false” A–T+ group, where pathological A $\beta_{42/40}$ results may have influenced the clinician toward an AD diagnosis. For this reason, our study primarily focused on diagnoses made before the LP. However, changes in diagnoses following biomarker results in the “true” A–T+ group are of particular interest. First, this situation, deemed uninformative in the 2011 criteria, is equivalent to an absence of biomarkers for most clinicians. Second, although the clinician was possibly influenced toward a non-AD diagnosis, the nature of the diagnosis still holds interest.

Overall, our results suggest the A $\beta_{42/40}$ ratio should be systematically calculated in case of discrepancy between normal CSF A β_{42} (A–) and high CSF tau^{181P} (T+) because it will reclassify half of cases as A+T+. FTLD is probably the leading cause of A–T+ profiles when defined by the A $\beta_{42/40}$ ratio, and FTLD should be considered in all SNAP cases.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.dadm.2019.01.001>.

RESEARCH IN CONTEXT

1. Systematic review: The 2018 National Institute of Aging–Alzheimer's Association research framework has validated the A $\beta_{42/40}$ ratio as a surrogate marker of amyloid pathology, which reduces the number of patients with A–T+ profiles. However, the proportion and clinical characterization of T+N+ patients with normal A β_{42} in memory clinics remains poorly studied.
2. Interpretation: In this retrospective multicenter study, we show that the A $\beta_{42/40}$ ratio halves the number of A–T+ patients. “False” A–T+ patients with normal A β_{42} yet abnormal A $\beta_{42/40}$ had higher cerebrospinal fluid tau^{181P} levels and most had a clinical profile congruent with Alzheimer's disease. In sharp contrast, frontotemporal lobar degeneration phenotypes are overrepresented in “true” A–T+ patients.
3. Future directions: Our study supports the systematic use of the A $\beta_{42/40}$ ratio in T+N+ cases with normal A β_{42} . Frontotemporal lobar degeneration should be systematically discussed in “true” A–T+ cases.

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