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Cerebrospinal Fluid A β 40 Improves the Interpretation of A β 42 Concentration for Diagnosing Alzheimer's Disease

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The combination of decreased amyloid β 42 (A β 42) and increased total tau proteins (T-Tau) and phosphorylated tau (P-Tau) in cerebrospinal fluid (CSF) has recently been considered as a biological diagnostic criterion of Alzheimer's disease (AD). Previous studies showed significant heterogeneity in CSF A β 42 levels to discriminate AD from non-AD patients. It was also suggested that the CSF amyloid peptide β 42/ β 40 ratio has better diagnostic performance than A β 42 alone. The objective of the present study was to investigate the potential added value of determining CSF amyloid β 40 peptide (A β 40) for biological diagnosis of AD when CSF A β 42 levels failed. CSF AD biomarkers were run in 2,171 samples from 1,499 AD and 672 non-AD patients. The following pathologic thresholds were used to define an AD-positive CSF biomarker profile: T-Tau \geq 400 ng/L, P-Tau181 \geq 60 ng/L, and A β 42 \leq 700 ng/L. CSF A β 40 was assayed in AD patients with CSF A β 42 levels above 700 ng/L and non-AD patients with CSF A β 42 levels below 700 ng/L. CSF A β 40 levels were higher in AD than non-AD patients. The receiver operator characteristic curves of CSF A β 40 and the A β 42/A β 40 ratio defined AD cut-off values at 12,644 ng/L and 0.06, respectively. In AD patients with non-pathological CSF A β 42, CSF A β 40 concentration was able to correct 76.2% of cases when expressed as CSF A β 42/A β 40 ratio and 94.7% of cases when used alone. Using CSF A β 42 and then CSF A β 40, the percentage of misinterpreted AD patients fell to 1.0%. CSF A β 40 concentration improved interpretation of A β 42 level for the diagnosis of AD. CSF A β 40 alone showed better diagnostic performance than the amyloid peptide A β 42/A β 40 ratio. The added value of determining CSF A β 40 in AD diagnosis now needs confirming in a cohort of definite AD patients and to be completed with novel amyloid cascade biomarkers.

Keywords: dementia, Alzheimer, A β 42, A β 40, cerebrospinal fluid

INTRODUCTION

According to the revised criteria for Alzheimer's disease (AD), definite diagnosis is founded on neuropathology as gold standard, when patients meet the clinical and cognitive criteria for AD dementia (1). Diagnosis of AD onset during the patient's lifetime is said to be "possible" or "probable." Amyloid β 42 (A β 42), total Tau (T-Tau), and phosphorylated Tau proteins (P-Tau) assay in cerebrospinal fluid (CSF) is recommended to increase the level of diagnostic certainty for AD in atypical clinical phenotypes, for inclusion of patients in clinical trials and to improve AD diagnosis at the earliest stages of the disease (1–5). A positive AD CSF biomarker profile was defined as increased CSF Tau and/or P-Tau181 and decreased CSF A β 42 concentrations (1, 6–8). However, researchers and clinicians continue to debate the sensitivity and specificity of various biomarkers, and especially CSF A β 42. A recent meta-analysis highlighted significant heterogeneity in CSF A β 42 values between different disease groups (9), reporting sensitivity and specificity ranging from 71 to 91% and 44 to 82%, respectively. Moreover, Rosen et al. showed that "normal" CSF A β 42 levels were observed in AD patients, leading to misinterpretation of the AD CSF biomarker profile in 23.2% of AD patients (10).

One of the crucial challenges to improve screening in clinical trials is to identify an accurate CSF biomarker reflecting amyloid pathology. There is now strong evidence that CSF A β 42 levels depend not only on impaired brain clearance in Alzheimer's pathophysiology, but also on the total load of amyloid peptides, which shows large interindividual variability (11–14). Gamma-secretase cleaves amyloid precursor protein (APP) at several sites, resulting in different C-terminally truncated A β variants: amyloid β 40 (A β 40) is the most abundant amyloid peptide in CSF (15), while A β 42 accounts for only about 10% of the total A β peptide population (12, 16–18). Total A β concentration was found not to vary significantly between various dementia disorders (11, 18, 19), and A β 40 concentration did not differ between AD (or presymptomatic AD) patients, healthy controls, and non-AD dementia patients (19–23). CSF A β 40 concentration could, therefore, be considered to most closely reflect total A β load in the brain (13). Previous studies showed that the A β 42/A β 40 ratio in CSF is reduced in AD patients, and its assessment improves AD diagnostic accuracy (21–25). More recently, a few studies demonstrated added value for CSF A β 40 or CSF A β 42/A β 40 ratio for differential diagnosis of AD using CSF P-Tau181 levels or in ambiguous AD CSF biomarker profiles (26–28). Therefore, the objective of the present study was to investigate whether determining CSF A β 40 level and CSF A β 42/A β 40 ratio could improve diagnosis in AD patients without low CSF A β 42 levels.

MATERIALS AND METHODS

Cerebrospinal fluid samples were collected between October 2010 and January 2013 from 2,171 patients who underwent lumbar puncture (LP) for routine clinical diagnosis of AD in the Neurochemistry Unit and Biochemistry Department of the

University Hospital of Lyon (France). Patients were included in a multicenter memory clinic and had at least 2 years' follow-up. They were classified into two groups: 1,499 AD and 672 non-AD patients. The non-AD group consisted of 259 patients with probable frontotemporal lobar degeneration (FTLD), 119 with probable dementia with Lewy bodies (DLB), 159 with normal pressure hydrocephalus (NPH), and 135 with psychiatric disorders.

The patients' age, gender, and mini mental state evaluation (MMSE) score were recorded when the LP was performed. At that time, initial diagnosis was based on medical history, caregiver interviews, neurologic examination, neuropsychological battery evaluation, and brain imaging. Clinical diagnosis was made in multidisciplinary team meeting, comprising neurologists, neuropsychologists, and radiologists, and confirmed on follow-up. Dementia was defined according to DSM IV-TR criteria (29), and all AD patients were classified as having AD dementia with evidence of the AD pathophysiological process (1). Patients with mild cognitive impairment were excluded. The non-AD patients diagnosed with FTLD and DLB met the international criteria (30, 31). The non-AD patients with psychiatric disorders or NPH with cognitive complaints unrelated to AD or other degenerative disease were age matched with AD patients, and showed no progression of cognitive impairment within 2 years after CSF analysis.

This study, based on routine biological analyses, was not considered as "biomedical research" under French regulations, and therefore did not require informed consent. Samples were, however, stored in a biobank with authorization from the French Ministry of Health (Declaration number DC-2008-304). Authorization for handling personal data was granted by the French data protection commission [*Commission Nationale de l'Informatique et des Libertés* (CNIL)].

All patients underwent LP to collect CSF using a standard procedure. CSF collection, sampling, and storage were performed according to the international consensus (32, 33). All CSF samples were collected in Sarstedt polypropylene tubes (ref. 62.610.201) showing low adsorption of amyloid peptides (7). CSF biomarker analyses were performed, blind to clinical diagnosis, in the Neurochemistry Unit and Biochemistry Department of the University Hospital of Lyon. This department is involved in two external quality control schemes, one at French national level (working group of the French Society of Clinical Biology: *Société Française de Biologie Clinique*) and the other with the Alzheimer's Association QC program (34). CSF concentrations of A β 42, T-Tau, and P-Tau181 were measured using the standardized commercially available sandwich ELISA kit (INNOTEST®) according to the manufacturer's procedures (Fujirebio, Ghent, Belgium).

For each CSF sample, A β 42, T-Tau, and P-Tau181 biomarkers were simultaneously analyzed. As previously described (7), the cut-off values defining positive AD CSF biomarker profile were: T-Tau \geq 400 ng/L, P-Tau181 \geq 60 ng/L, and A β 42 \leq 700 ng/L.

A β 40 level in CSF was quantified using ELISA tests [Human Amyloid b (1–40) (N) Assay kit, IBL, Japan] in AD patients with CSF A β 42 levels above 700 ng/L and in non-AD patients with CSF A β 42 levels below 700 ng/L.

Statistical Analysis

Chi-square test, Mann–Whitney U test, Kruskal–Wallis test, and receiver operator characteristic (ROC) analyses were performed using MedCalc version 11.3.1.0 (<http://www.medcalc.be>). Differences were considered statistically significant at $p < 0.05$. ROC curves were applied to define optimal biomarker cut-off values to discriminate between AD and non-AD groups. The cut-off value was defined as the value corresponding to the highest average for sensitivity and specificity. Accuracy was calculated as the sum of true positives and true negatives in the total number of patients (35).

RESULTS

Cerebrospinal fluid data according to diagnostic group are summarized in **Table 1** and **Figure 1**.

About 81.3% of AD patients (1,218/1,499) fulfilled the pathological CSF A β 42 criteria; the remaining 18.7% (281/1,499) presented CSF A β 42 levels above cut-off (>700 ng/L). 63.7% of non-AD patients (428/672) presented CSF A β 42 levels above 700 ng/L; 36.3% (244/672) had CSF A β 42 levels below 700 ng/L (**Figure 2**). CSF A β 40 levels were then determined in these 525 patients: 281 AD patients (>700 ng/L) and 244 non-AD patients (≤ 700 ng/L).

The ROC curves of CSF A β 40 level and the A β 42/A β 40 ratio determined AD cut-off values of $\geq 12,644$ ng/L and ≤ 0.06 , respectively (**Figure 3**).

In the overall population, the percentage of patients in whom amyloid pathology was misinterpreted fell from 24.2% (525/2,171) using CSF A β 42 alone to 7.8% (169/2,171) when it was followed by CSF A β 42/A β 40 ratio, and to 1.7% (37/2,171) when followed by CSF A β 40 (**Figure 2**). In patients in whom CSF A β 40 level was determined ($n = 525$), sensitivity and specificity for AD diagnosis were 76.2 and 58.2%, respectively (accuracy, 0.678) using the CSF A β 42/A β 40 ratio, and 94.7 and 91.0%, respectively (accuracy, 0.930) using CSF A β 40 determination.

About 58.2% of the 244 non-AD patients with CSF A β 42 levels below 700 ng/L (142/244) had CSF A β 42/A β 40 ratios higher than 0.06 and 91.0% (222/244) had CSF A β 40 levels below 12,644 ng/L.

About 76.2% of AD patients (214/281) had CSF A β 42/A β 40 ratios below 0.06 and 94.7% (266/281) had CSF A β 40 levels higher than 12,644 ng/L. In the overall AD population, percentage misinterpretation fell from 18.7% (281/1,499) with CSF A β 42 alone to 4.5% (67/1,499) using CSF A β 42 and then CSF A β 42/A β 40 ratio and 1.0% (15/1,499) using CSF A β 42 and then CSF A β 40 (**Figure 2**).

DISCUSSION

We investigated the potential added value of CSF A β 40 assay to improve the interpretation of A β 42 level. The main finding was that CSF A β 40 appeared to be an interesting complementary biomarker. CSF A β 40 levels were higher in AD than non-AD patients. Thus, determining CSF A β 40 concentrations corrected biological diagnosis in AD patients with non-pathological CSF A β 42 levels in 76.2% of cases using the CSF A β 42/A β 40 ratio and in 94.7% using CSF A β 40 alone; using CSF A β 42 and then CSF A β 40, percentage misinterpretation fell to 1.0%.

Cerebrospinal fluid A β 42 concentrations led to misinterpretation of the AD CSF biomarker profile in 24.2% of our total population and notably in 18.7% of AD patients. This low performance of CSF A β 42 is in perfect agreement with previous reports (7, 10, 18, 20, 36, 37). The presence of CSF A β 42 concentrations ≤ 700 ng/L in non-AD patients could reflect low total CSF amyloid load, while CSF A β 42 >700 ng/L in AD patients could result from high amyloid load. This concept justifies CSF A β 40 assay to complete amyloid pathway interpretation.

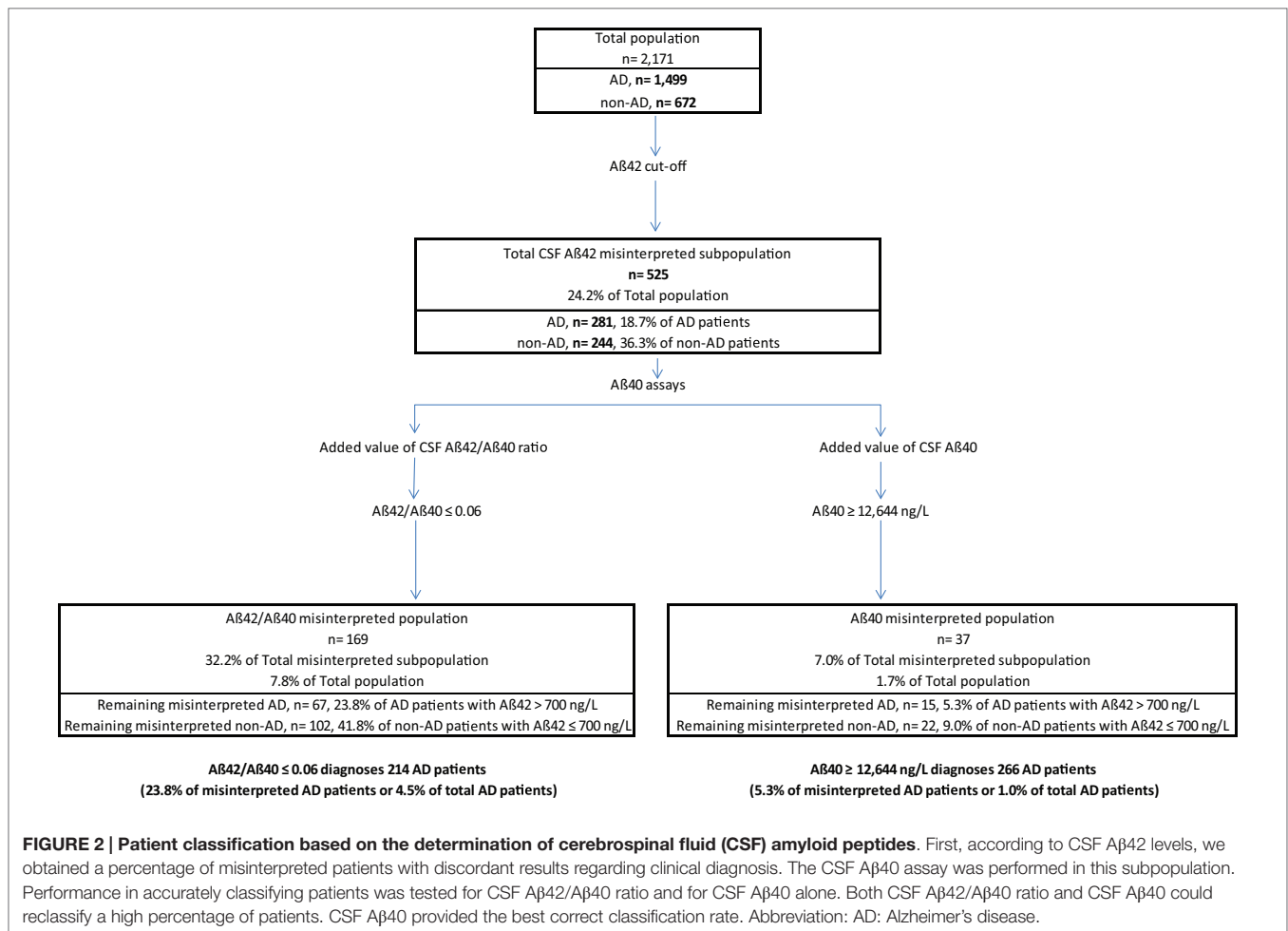
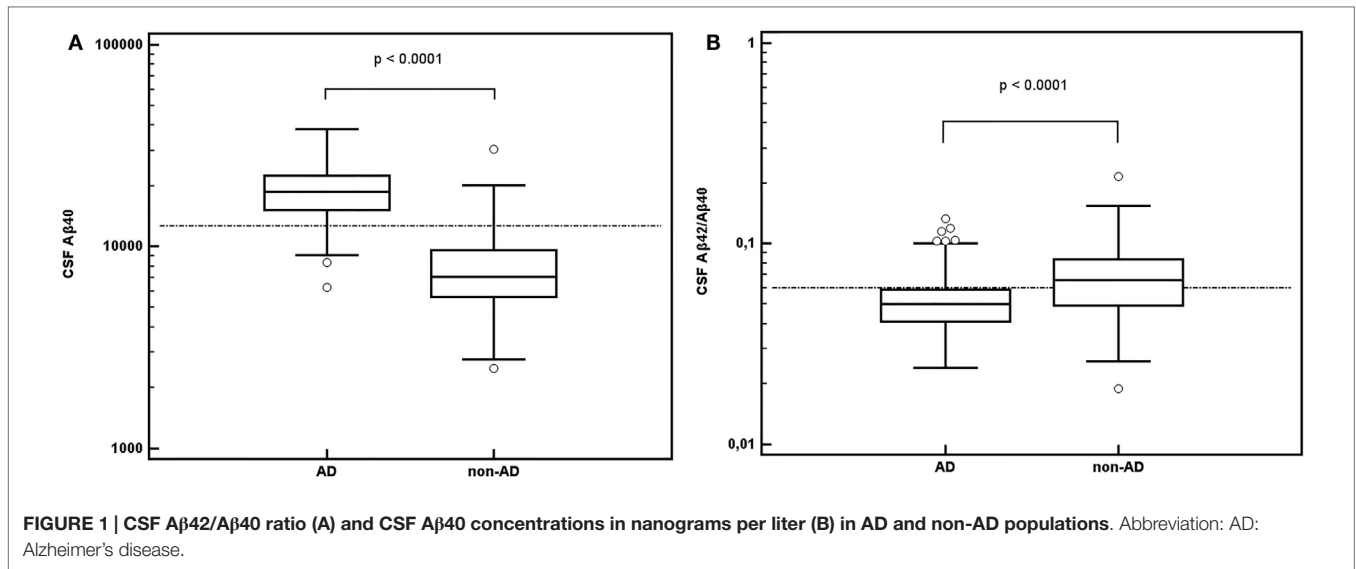
As reported in various studies (20, 26, 27, 36), the CSF A β 42/A β 40 ratio showed better diagnostic performance than CSF A β 42 alone. The CSF A β 42/A β 40 ratio cut-off value at 0.06 was identical to that reported by Lewczuk et al. (36). The discrepancy with Hansson et al.'s (20) 0.095 cut-off might be due to the Genetics Company ELISA kit halving the range of CSF A β 40 levels. We found an increase in the rate of correct interpretation from 75.8% with CSF A β 42 alone to 92.2% when CSF A β 42 assay was followed by determining the CSF A β 42/A β 40 ratio, similarly to other reports (20, 28, 36).

The type of sampling and storage tubes is an important source of variability because of amyloid adsorption (33, 37, 38). CSF sample selection from biological banks should, therefore, be performed rigorously. There is parallel adsorption of CSF A β 42 and A β 40 onto the sampling tube surface, regardless of the type of plastic (personal data). Systematic use of the CSF

TABLE 1 | Demographic, pathologic, and biological parameters of study populations.

		AD	Non-AD
Gender	<i>n</i>	1,499	672
	M/F	643/856	358/314
Age (years)	<i>n</i>	1,499	672
	Mean	71.6	70.0
	SD	9.5	10.6
MMSE score (/30)	<i>n</i>	1,093	488
	Mean	20.2	21.6
	SD	5.6	5.5
T-Tau (ng/L)	<i>n</i>	1,499	672
	Median	650	230
	25th–75th P	487–913	168–311
P-Tau ₁₈₁ (ng/L)	<i>n</i>	1,499	672
	Median	83	38
	25th–75th P	68–109	30–48
A β 42 (ng/L)	<i>n</i>	1,499	672
	Median	539	807
	25th–75th P	443–663	570–1,056
A β 40 (ng/L)	<i>n</i>	281	244
	Median	19,198	7,112
	25th–75th P	15,162–22,409	5,643–9,636
A β 42/A β 40 ratio	<i>n</i>	281	244
	Median	0.053	0.066
	25th–75th P	0.041–0.059	0.049–0.084

AD, Alzheimer's disease; MMSE, mini mental state evaluation; M, male; F, female; SD, standard deviation; P, percentile.



Aβ42/Aβ40 ratio would provide complete interpretation of CSF amyloid biomarker results, integrating the impact of plastic tube type. In the present study, however, samples were analyzed

sequentially, leading to higher between-run imprecision for the CSF Aβ42/Aβ40 ratio than for CSF Aβ42 alone [coefficient of variation (CV), 13.3 and 10.2%, respectively]. One solution

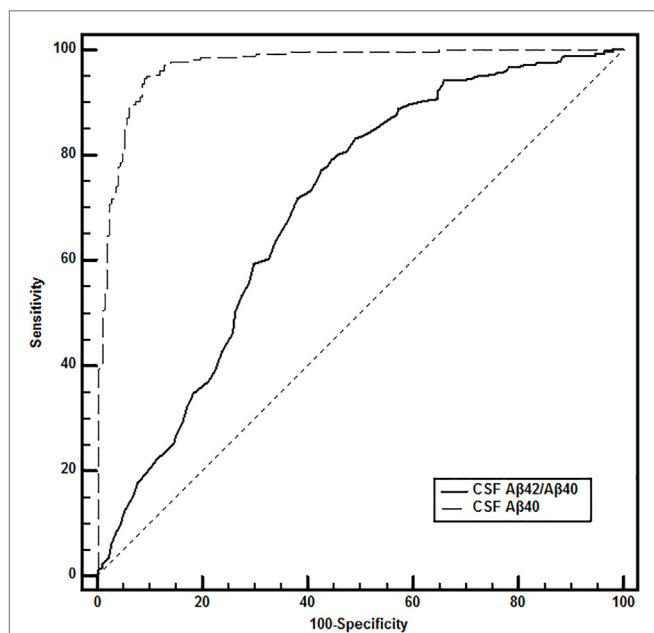


FIGURE 3 | Receiver operating characteristic curve comparison for AD diagnosis in the “discordant CSF A β 42 values” subpopulation.

DeLong et al.’s (1988) method was used to compare the values of the area under the curve (AUC). In the 525 selected patients, accuracy of diagnostic performance was significantly higher for CSF A β 40 compared to CSF A β 42/A β 40 ratio, with 94.7% sensitivity and 91.0% specificity for CSF A β 40 $\geq 12,644$ ng/L (AUC, 0.969) compared to 76.2 and 58.2%, respectively for CSF A β 42/A β 40 ratio ≤ 0.06 (AUC, 0.700).

to decrease the CV of the CSF A β 42/A β 40 ratio would be to use multiplex assays to analyze both amyloid peptides simultaneously. Unfortunately, at the moment, there is no analytical validation available for CSF A β 42 and CSF A β 40 in multiplex assays for *in vitro* diagnostic use.

In the present study, CSF A β 40 was determined only in AD patients with CSF A β 42 levels above 700 ng/L and in non-AD patients with levels below 700 ng/L. CSF A β 40 concentrations were significantly higher in AD than non-AD patients. The optimal CSF A β 40 cut-off value was 12,644 ng/L. To our knowledge, there is currently no effective CSF A β 40 cut-off value to discriminate AD from non-AD patients reported in the literature; only a slight increase in CSF A β 40 was found in two other studies (20, 24), and a recent study focusing on AD-MCI patients found a significant increase in CSF A β 40 values compared to a control group (36). However, the present data contrasted with those reported in another study (26) including AD and non-AD dementia. Selection of the non-AD patient population to compare with the AD population was probably one of the major differences. Another difference may be the biological factor used for the patients’ initial classification, CSF P-Tau181 concentrations in intermediate levels (26). Similarly, Sauvee et al. suggested using the CSF A β 42/A β 40 ratio when data for CSF A β 42 combined to CSF P-Tau181 are inconclusive (27). In these particular cases, adding the CSF A β 42/A β 40 ratio improved their proportion of

interpretable biological profiles from 68 to 89% (27). Moreover, in confirmation of our sequential approach, Sauvee et al. showed that adding CSF A β 40 peptide concentration and CSF A β 42/A β 40 ratio did not change their conclusions when CSF A β 42 and CSF P-Tau181 were concordant.

In the present study, it was also interesting that 36.3% of non-AD patients presented pathological CSF A β 42 levels. One hypothesis could concern the heterogeneity of the non-AD population, which included patients with psychiatric disorders and NPH and demented patients with neurodegenerative diseases (FTLD and DLB). CSF A β 42 was previously reported to be less effective for differential diagnosis of the main neurodegenerative dementia than CSF Tau proteins (39–41). To discriminate AD and FTLD, CSF A β 42 assay could then be combined with Tau proteins and expressed as T-Tau/A β 42 and P-Tau181/A β 42 ratios (42, 43). Typical CSF AD profiles including CSF A β 42 and Tau proteins were reported in 47% of patients meeting clinical diagnostic criteria for DLB and in 30% of FTLD patients (41), suggesting coexisting pathologies, as strongly highlighted by postmortem studies (44, 45). NPH patients also have lower CSF amyloid peptide and Tau protein concentrations than controls (46, 47). To validate our hypothesis and strategy regarding differential diagnosis, postmortem confirmation on autopsy-proven patients should be carried out.

The diagnostic performance of CSF A β 42 is increasingly questioned. It should be noted that biological diagnosis as performed in specialized memory clinics is also founded on the second pathway of AD pathophysiology, reflected by CSF Tau protein levels. Nevertheless, a more accurate evaluation of CSF amyloid biomarkers is important to include patients in therapeutic trials involving the amyloid cascade, using added A β peptides or other amyloid cascade biomarkers. For example, the soluble peptide APP β (sAPP β) and CSF A β 40 come from the same enzymatic digestion of APP, and it would be interesting to assess sAPP β to complete this study. Increased CSF sAPP β levels were already reported in AD patients as compared to non-AD demented patients (48) and FTD patients (49).

In conclusion, the present study offers an improvement in biological diagnosis of AD focusing on the amyloid pathway. In the misinterpretation using CSF A β 42 levels, classification based on the CSF A β 42/A β 40 ratio gives good results. More interestingly, CSF A β 40 assay alone also provides better results: the misinterpretation rate using CSF A β 42 and then CSF A β 40 alone falls to 1.7%. Sequential assessment of CSF A β 40 would also provide a better cost-effectiveness ratio than systematic determination of the CSF A β 42/A β 40 ratio. Finally, these results need to be confirmed in a prospective study including autopsy-proven AD patients, and completed with novel amyloid cascade biomarkers.

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