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Abstract: To improve the etiological diagnosis of neurodegenerative dementias like Alzheimer’s disease (AD) or frontotemporal dementia (FTD), we evaluated the value of individual and combined measurements of the following relevant cerebrospinal fluid (CSF) biomarkers: Tau, 181p-Tau, Aβ38, Aβ40, sAβPPβ, and sAβPPβ. This study conducted in two centers included
INTRODUCTION

Cerebrospinal fluid (CSF) biomarkers analysis is an important tool for the early and etiological differential diagnosis of dementia. Accurate diagnosis is now becoming mandatory to optimize patient’s therapeutic care, alleviate the burden of caregivers, and conduct clinical trials. Based on the revised Alzheimer’s disease (AD) diagnosis criteria [1, 2], our routine clinical practice now includes the dosage in the CSF of the Tau protein, its phosphorylated form phospho-tau181 (p-Tau) and the Aβ peptides 1–42 (Aβ42). The relevance of using a combination of these three CSF biomarkers has been validated for the diagnosis of AD and its prodromal forms [3–7]. However, their pertinence is limited for the etiological diagnosis of dementia and for related diseases like frontotemporal lobar degeneration (FTLD) and its subtype with predominant behavioral impairments called frontotemporal dementia (FTD). The presence of depressive or behavioral disorders in the early stage of the disease could in fact mislead the clinician. In 50% of these clinical presentations, the diagnosis happens at a late stage and remains doubtful. To date, no satisfactory set of CSF biomarkers have been thoroughly validated to discriminate FTLD from AD and other neurological disorders. Increased Tau levels were initially selected as specific to this diagnosis [8, 9], but further studies showed normal or decreased levels [10-13]. Additional discrepancies were observed for the combined measurement or ratio of Tau and Aβ42 which was either not relevant [14] or had no diagnostic usefulness [12, 15]. Recently, the value of CSF Aβ42 was pointed out to discriminate FTD from control non-demented subjects [16]. However, in this same study the value of this analyte to distinguish FTD from AD was limited.

Other CSF biomarkers like the soluble amyloid-β protein precursor (sAbPP) α and β isoforms, as well as additional Aβ peptides have been identified as potentially pertinent to detect AD and its prodromal states, but also for differential AD diagnosis [17, 18]. In a recent work, we investigated the biological relationship between these biomarkers and underlined the strong correlations between sAbPP, Aβ42, and Aβ40 CSF levels [19]. Our results suggested that in the presence of an amyloid pathology such as AD, the various Aβ peptides would have different evolutions, which could be interesting for differentiating AD from other neurodegenerative disorders in particular FTD. To test this hypothesis, we evaluated here the diagnostic significance of individual and combined levels (ratios) of Tau, p-Tau, sAbPP/β, and Aβ42, Aβ40, and Aβ42 peptides in FTD, AD, and a control population (CTRL) without dementia. We first confirmed the usefulness of p-Tau and Aβ42 in AD detection. In FTD, Tau concentrations were intermediate between AD and CTRL and we observed for this diagnosis significant decreased levels of sAbPP, Aβ42, and Aβ40. These results were used to optimize FTD detection using both p-Tau and Aβ40 levels. We also interpreted the changes of amyloid biomarkers in FTD as an additional evidence of the interrelationship between Tau and AbPP biology, its understanding being essential to progress towards optimal therapeutic care and diagnostic methods for dementia.

MATERIALS AND METHODS

Study design and subjects

A total of 128 CSF samples were collected from patients referred to our neurological and Clinical Research Memory Centers for cognitive or behavioral disorders (Biobank officially registered # DC-2008-417). All the patients gave their written informed consent to participate in this research.
study. CSF dosages of Tau, p-Tau, Aβ42, Aβ40, and Aβ40 were performed for all subjects. The CSF sAbPbb assay was only done on the 86 AD and FTD patients. All patients underwent a standardized clinical investigation including anamnestic, clinical, neuropsychological, screening laboratory tests, brain morphological (computed tomography (CT) scans, and/or magnetic-resonance imaging (MRI)) or functional (single photon emission tomography 99m Tc-ECD-SPECT scans (SPECT)) imagining evaluations. The standardized neuropsychometric battery for patients with cognitive alterations included the mini-mental status examination (MMSE) [20], the Mattis dementia rating scale [21], the Frontal Assessment Battery [22], and the Free and Cued Recall Test [23]. AD patients met the diagnosis criteria of NIN CDS/ADRDA [24] and the DSM IV. In these patients, the neuropsychological tests reflected an amnestic syndrome with a hippocampal deficit associated to aphasia and agnosia. The morphological and functional imaging displayed global cortical atrophy or temporal and parietotemporal atrophy, such as hypometabolism in these regions on SPECT data.

The diagnosis assessment of patients with clinically validated FTD included full medical history, thorough neurological examination and evaluation by at least two independent and experimented reviewers. The diagnosis was based on the Lund and MacHester criteria established in 1994 and revised by Neary and McKhann [25]. Only patients with a full consensus agreement by the experts were recruited. We selected patients with neuropsychological tests reflecting dysexecutive deficit with behavioral disorders such as apathy, disinterest, loss of self-awareness, social inappropriateness, and clinical frontal signs (perseverative behavior, grasping). We excluded patients with language troubles (verbal fluency or semantic) such as progressive primary aphasia (PPA) or semantic dementia (SD). The morphological and functional imaging displayed global cortical atrophy or frontal and frontotemporal atrophy such as hypometabolism in these regions on the SPECT data. No predominant anterior temporal lobe lesion was observed. No clinical parkinsonism sign was underlined in these patients. No clinical or electrophysiological sign of motoneuron disease was observed in our FTD group of patients. To detect familial FTD cases we relied on the algorithm for genetic testing by Goldman et al. [26], which excluded in most cases these forms in patients above the age of 50 and without any familial history. Furthermore, FTD diagnosis in our population was based on a 3 to 5-year clinical follow-up.

Various control patients (CTRL) without cognitive impairments, memory, or behavioral complaints were included: 14 patients with chronic hydrocephalus, 12 with peripheral neuropathy, 11 with mild depression, and 5 with multiple sclerosis. For each diagnosis, the criteria were validated by multidisciplinary teams. Each clinical investigation, e.g., biological, electro-physiological, and neuroimaging exams were also in favor of each diagnosis included in the CTRL (e.g., for hydrocephalus all exams point to the diagnosis) of course the results of the exams correspond to the raised diagnosis.

**CSF samples and assays**

Lumbar puncture (LP) was performed in standardized conditions preferentially between 11:00 and 13:00 to minimize diurnal variation of CSF Aβ levels [27]. CSF were transferred to the laboratories in less than 4 hours, centrifuged (1000 × g, 10 min, at 4–8°C, without breaks), and aliquoted in polypropylene tubes before storage at −80°C. The three routine CSF biomarkers were determined using standardized commercially available ELISA Kits (InnoTest β-amyloid 1–42, hTau, and Phospho-Tau (181P), Innogenetics, Ghent, Belgium). The IATI score was calculated using the formula IATI = Aβ42(240 + 1.18 × Tau) as described [5]. Detection of CSF sAbPbb was performed independently in the two laboratories using multiplex kits from MSD (Meso Scale Discovery ref: K11120E, K11148E). Common quality controls ensured that the inter-laboratory variability was similar to the inter-assay variability. All reagents were provided with the kits along with antibody precoated 96-well plates. The detailed procedures of the assays, very similar to classical ELISA but with a final quantitation on the MSD Sector Imager 6000 plate reader, are provided elsewhere [19]. Aβ42 peptide levels assessed with Inno- genetics kits were identified in the text as "Inno-Aβ42".

**Statistical analysis**

Statistical analyses were performed with the software MedCalc (7.3). Graphic results were presented as medians and interquartile ranges (Figs. 1–3). Statistical analysis of the characteristics of the three clinical groups (Table 1) was performed with the one-way ANOVA and the chi-2 tests. Unpaired Student’s t tests and Mann-Whitney tests were used to evaluate the significance of the difference between two sample groups (Figs. 1–3). Receiver Operating Characteristic (ROC)
Fig. 1. Box/dot plots showing median values and quartiles of individual biomarkers in AD, FTD, and CTRL populations. Non-parametric Mann-Whitney tests were used to calculate the indicated p values. The red solid squares indicated outliner values defined as values larger than the upper quartile plus 1.5 times the interquartile range.

curves and logistic regression were used to select the most relevant diagnosis biomarkers (see description of the tests in Tables 2–3).

RESULTS

General characteristics of our population

As reported in Table 1, AD, FTD, and CTRL groups did not differ in gender, CSF total protein or Aβ42. They globally differed in age (ANOVA, p = 0.003) but the only pairwise statistical difference was between AD and CTRL (Student’s t test, p < 0.001) and no statistical difference (p = 0.1) was observed between FTD and CTRL patients. Moreover, there was no significant correlation between age and any other parameters (data not shown). The mean MMSE score was lower in the AD than in the FTD groups (Student’s t test, p < 0.005) while CTRL had, as expected, much higher and significantly different values (Student’s t test, p < 0.001).

Mean values of routine CSF biomarkers

Pairwise comparisons of Tau, p-Tau, Inno-Aβ42 (Table 1 and Figs. 1A–C), and Innogenetics Aβ/Tau index (IATI) (Fig. 2A) were done for the three clinical groups. Tau concentrations were the highest in the AD group and intermediate in the FTD group when compared with the CTRL population (Fig. 1A). p-Tau was also statistically higher in AD than in CTRL or FTD (Fig. 1B). Inno-Aβ42 values were clearly decreased in AD and intermediate in FTD, which was a first indication that this pathology also had an impact on amyloid biomarkers (Fig. 1C). IATI which has been designed to amplify the opposite variation of Tau and Aβ42 in AD followed the same pattern as Aβ42 (Fig. 2A).

All together, these results validated known differences between the values of these routine biomarkers in different clinical situations.

Mean values of amyloid CSF biomarkers measured with multiplex assays

Aβ42 multiplex value variations (Fig. 1F) were comparable to those of the Inno-Aβ42 discussed above (correlation, p < 0.0001). Interestingly, CSF concentrations of both Aβ38 and Aβ40 were significantly lower in FTD than in AD or CTRL (Figs. 1D–E). Since our CTRL population was heterogeneous, when we restricted the comparison with FTD to “healthy”
Fig. 2. Box/dot plots showing median values and quartiles of individual biomarkers in AD, FTD, and CTRL populations. Non-parametric Mann-Whitney tests were used to calculate the indicated p values. The red solid squares indicated outlier values defined as values larger than the upper quartile plus 1.5 times the interquartile range.

Fig. 3. Box/dot plots showing median values and quartiles of sAβPPα and β in AD and FTD. Non-parametric Mann-Whitney tests were used to calculate the indicated p values.
patients (i.e., with no active neurological disease), we still obtained highly significant differences in Aβ112 values (p < 0.0001, not shown).

Concentration of sAβPPβ but not of sAβPPα was also significantly higher in AD than in FTD (Figs. 3A-B). This result was in accordance to previous works by our team and others [18, 19], suggesting that sAβPPβ might be a valuable diagnosis marker of AD.

The combined measurement of the different Aβ peptides allowed us to calculate ratios (Table 1, Figs. 2B-D). Both Aβ42/40 and Aβ38/42 ratios were significantly altered in AD as already reported [28-30]. We also computed the ratio Aβ40/38 that interestingly was the only one that differentiated clearly CTRL subjects from FTD subjects, while not being significant between AD and FTD. A few outlier samples (see isolated dots on Figs. 1, 2), probably linked to pre-analytical differences, analytical variation, clinical phenotypical variation, or misclassifications, were detected. However these did not significantly affect the statistical significance of our results (e.g., in Fig. 1D, Aβ42 remained significantly different between AD and FTD after removing the two AD outliers).

Receiver operating characteristic (ROC)

ROC curves were computed for each biomarker or ratio in relevant differential diagnostic situations (Table 2 and Fig. 4). For FTD versus AD diagnosis, the best AUCs for amyloid biomarkers were the Aβ40/42 ratio and the IATI (AUCs = 0.87). However, Aβ40/42 ratio or Aβ42 alone had very close and statistically undifferentiated AUC values. It is interesting to note that p-Tau outperformed all these single biomarkers or ratios with an AUC at 0.95. Aβ40, sAβPPα, sAβPPβ, and Aβ40/38 ratios were also clearly less efficient for differentiating FTD from AD.

For FTD versus CTRL, Aβ142 and the ratio Aβ40/142 were the best biomarkers (AUCs = 0.81). Interestingly, these biomarkers were better than Aβ40 (AUC = 0.63) which was identified in a previous study while comparing FTD and normal controls [16].

Logistic regression analysis

To combine the diagnosis power of several biomarkers we performed a multiple logistic regression analysis (Table 3). To identify FTD from AD+CTRL, the only two variables retained in the model were p-Tau and Aβ134 with a couple sensitivity/specificity (Se/Sp) 56%/89% (mean 72.5%; Table 3A). This result was relatively low validating the difficulty to differentiate FTD. To discriminate AD vs. FTD+CTRL, only two variables were also kept: p-Tau and the IATI with an excellent Se/Sp = 86%/96% (mean 91%; Table 3B).

DISCUSSION

In this report, we presented the results of classical (Tau, p-Tau, Aβ142, and Aβ40) and new CSF neurochemical biomarkers such as soluble forms of amyloid precursor proteins (sAβPPα, sAβPPβ) and Aβ peptides (Aβ14, Aβ40) and their relevance in the differential diagnosis between AD, FTD, and control patients (CTRL) without dementia. Biological data were collected in two independent laboratories using similar
Fig. 4. Receiver Operating Characteristic (ROC) curves plot the true positive rate in function of the false positive rate at different cut-off points. A good estimation of the value of a biomarker is given by the area under the curve (AUC) of the ROC (see also table 3) which tends to be higher while the curve is closer to the upper left corner, where the values of the specificity and the sensitivity are the highest. ROC curves were plotted for the different individual biomarkers (panel A and B) and their ratios (panel C and D) to discriminate FTD from AD (panel A and C) and FTD from CTRL (panel B and D).

and controlled pre-analytic and analytic conditions [31]. Moreover, a recent investigation on sAβPPs CSF levels already supported the specificity of the detection assays used in the present study [18]. All clinical diagnoses were validated independently by a multidisciplinary and expert team blinded to all the CSF neurochemical outcome measures. Unfortunately, neuropathological data were not available, which represents a limitation of the study. The AD diagnosis was however corroborated by the classical CSF profile (Tau, p-Tau, Aβ42) with higher Tau, p-Tau, and lower Aβ42 compared to CTRL and FTD patients. In particular, p-Tau reached very high sensitivity (Se) and specificity (Sp) values that outperformed the other biomarkers. The Aβ18/42, 40/42 and the IATI ratios were also better than individual biomarkers to identify AD therefore justifying their clinical relevance [5, 32].

The focus of our study was the variation of CSF neurochemical biomarkers in FTD. We first observed that FTD Tau levels were higher than those in CTRL, but lower than those in AD as validated by previous reports [12, 13, 33]. CSF Tau is regarded as a marker of both neuronal degeneration and Tau pathology in the brain [34, 35]. FTD are, however, not always associated to high CSF Tau in particular when linked to
Table 2

| Table 2A | FTD vs AD Tau p-Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 |Tau A/H9252 |
|----------|-----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Sensitivity | 88 91 91 91 79 88 88 79 76 59 67 | 88 80 34 62 86 86 76 44 64 71 |
| Specificity | ≤448 ≤58 ≤1394 ≤896 ≤646 ≤666 ≤2400 ≤111 ≤63 ≤333 ≤360 |
| AUC | 0.88 0.95 0.64 0.61 0.75 0.87 0.87 0.85 0.51 0.61 0.67 |

Table 2B

| Table 2B | FTD vs CTRL Tau p-Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 |Tau A/H9252 |
|----------|-----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Sensitivity | 50 42 94 71 88 79 63 85 91 | 81 74 64 57 67 57 59 69 76 |
| Specificity | >300 >43 ≤1470 ≤7148 ≤1111 ≤150 ≤129 ≤63 ≤2888 |
| AUC | 0.62 0.53 0.81 0.63 0.78 0.69 0.57 0.74 0.81 |

Receiver Operating Characteristic (ROC) curve plots the true positive rate in function of the false positive rate at different cut-off points (see Fig. 3). A good estimation of the value of a biomarker is given by the area under the curve (AUC) of the ROC (last lane of each table below). The indicated sensitivity and specificity corresponded to the values obtained at the cut-off selected at the highest accuracy point (minimal false negative and false positive results).

Table 3

| Table 3A | FTD vs AD + CTRL p-Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 |Tau A/H9252 |
|----------|-----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| ROC | 0.71 0.70 0.63 0.77 0.66 0.59 | Sensitivity 56
| Retained | Yes Yes no no no no-

Table 3B

| Table 3B | AD vs FTD + CTRL Tau p-Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 | Tau A/H9252 |Tau A/H9252 |
|----------|-----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| ROC | 0.93 0.97 0.88 0.92 0.89 0.90 | Sensitivity 86
| Retained | no Yes no Yes no-

Logistic regression is a technique for analyzing problems in which there are one or more independent variables (here the biomarkers) which determine an outcome that is measured with a dichotomous variable in which there are only two possible outcomes (FTD or not FTD for example). Sensitivity (upper case) and specificity (lower case) indicated in the tables for each combination were obtained by logistic regression using a backward model. The backward method consists at entering all selected variables into the model and next removing the non-significant variables (P > 0.1) sequentially.

Motoneuron variants are also characterized by specific features, but here we really focused on the behavioral variant of Fronto-Temporal Degeneration (FTLD) with behavioral form of frontotemporal syndrome (FTD) with no language or semantic difficulties. If total Tau in our cohort was higher in FTD than in CTRL, p-Tau 181 levels were however similar suggesting that we did not have a significant number of AD patients misdiagnosed for FTD. Tau aggregation in the brain is strongly linked to Tau abnormal tau mutations or in specific regional forms with lobar localization predominant on the frontal or temporal lobe [14, 36, 37]. The correlation between CSF Tau levels and lobe localization was recently researched [33], showing that higher CSF Tau levels were significantly associated to a greater atrophy in the language areas, namely the left middle temporal gyrus and left inferior parietal lobule. Such a correlation was not the objective of our study but an increased Tau in some patients could be related to the regional distribution of the pathology. In addition, FTD forms exist without a defined Tau pathology [38]. In conclusion, it is apparent that FTD regroups both clinical and biological entities that are different but one could be mistaken for the others. Familial FTD forms linked to mutation are probably the easiest to regroup and were avoided in our study. Motoneuron variant are also characterized by specific features but here we really focused on the behavioral variant of Frontal-Temporal Lobar Degeneration (FTLD) with behavioral form of frontotemporal syndrome (FTD) with no language or semantic difficulties. If total Tau in our cohort was higher in FTD than in CTRL, p-Tau 181 levels were however similar suggesting that we did not have a significant number of AD patients misdiagnosed for FTD. Tau aggregation in the brain is strongly linked to Tau abnormal...
phosphorylation [34, 35], but in FTD patients, normal or sub-normal levels of p-Tau have been already described [33, 37, 39]. This might be due to specific histological forms [36] or to the sequestration of p-Tau in the filamentous inclusions. This situation is similar to pathologies like prion diseases characterized by a high Tau/p-Tau ratio [40]. The results of the “classic” CSF biomarkers (Tau, p-Tau, and AβPP) validated the high diagnostic value of p-Tau for AD and the moderate changes of Tau in FTD when compared to CTRL. A clear CSF profile of FTD that would significantly improve the diagnosis of this pathology was nevertheless not seen with this set of biomarkers.

The focus on the CSF amyloid status of FTD revealed an interesting new finding with a significant decrease of Aβ38, Aβ40, and sAβPPβ in this diagnosis (Fig.s 1D, 1E, 3B). The presence of lower CSF Aβ40 levels in FTD confirmed previous results using Aβ-SDS-PAGE/immunoblot techniques [17] or using the same multiplex assays as in our study, but in smaller series [39]. In fact, Aβ38 appeared to be as relevant as Aβ40, a biomarker pointed out as useful in a recent study comparing FTLD subjects and normal controls [16]. The specific decrease of Aβ40 in FTD was not only a way of differentiating this diagnosis from CTRL, it was also quite relevant when combined to Aβ42 to differentiate FTD from AD with an excellent 88% sensitivity and 86% specificity (Table 2). This Aβ38/42 ratio appeared more pertinent than Aβ42 alone or than the Aβ40/42 ratio as already pointed out in a previous analysis [32].

Finally, when all biomarkers and ratios where considered to help define a specific FTD CSF profile (Table 3), it was not surprising that both Aβ38 and p-Tau were selected using backward multiple logistic regression. If we used these biomarkers sequentially using the ROC cut-off (Table 2), starting from 128 samples, 51 could be classified as AD (above 58g/mL for p-Tau). Out of the 77 remaining, 31 could be classified as FTD (Aβ38 under 1470pg/mL). Taken together, these two simple criteria reached an 85.3% Se and 81.9% Sp for FTD diagnosis. This “decision tree” classification might be used by other laboratories with the same detection kits and/or after adjusting cut-off values.

The fact that amyloid biomarkers were modified in FTLD/FTD as reported in our study and others [16; 39] raised many questions on the relationship between Tau and amyloid biology. The effect of Aβ on Tau phosphorylation [41] has been demonstrated in different models [42] and appeared essential for amyloid-induced neurotoxicity [43]. On the other hand, elevation of Tau levels seemed to have a general inhibitory effect on anterograde trafficking and especially on vesicles carrying AβPP [44, 45]. This could alter AβPP trafficking and amount to a possible decrease in AβPP processing and Aβ generation [46]. Finally, another relationship between AβPP and Tau relates to GSK3β [47], an enzyme able to both phosphorylate Tau and interact with the γ-secretase cleavage of AβPP [48]. An analysis of our results suggested that FTD pathological processes involved both amyloid and Tau pathways, but in a different manner than in AD. The decrease of sAβPPβ, Aβ38, and Aβ40 levels in FTD suggested that AβPP processing or availability was modified. This might be a consequence of the pathology or linked to its etiology. Longitudinal studies could help differentiate these two possibilities. sAβPPβ could also represent a key element between tau- and amyloidopathies. The specific fate of Aβ38 may be related to its lower aggregation tendency when compared to Aβ40 or Aβ42, as well as its distinct production pathway by the γ secretase [49, 50], which might be modulated by sAβPPβ and/or Tau. Anyway, it is quite difficult to conclude on the effect of these modifications since Aβ38 has, to our knowledge, no specific physiological effects.

Taken together, these data represent additional evidence for the interrelationship between Tau and AβPP biology. They could promote the development and follow-up of optimal therapeutic strategies for different types of dementia, as well as helping in their diagnosis as illustrated by our decisional algorithm based on p-Tau and Aβ38.

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