Decreased sAβPPβ, Aβ38, and Aβ40 Cerebrospinal Fluid Levels in Frontotemporal Dementia.

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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, Aβ42, sAβPP, and sAβPPβ. This study conducted in two centers included...
patients with FTD (n = 34), AD (n = 52), as well as a control group of persons without dementia (CTRL, n = 42). Identical clinical criteria and pre-analytical conditions were used while CSF biomarkers were measured using commercial single and multiplex quantitative immunoassays. Thorough statistical analyses, including ROC curves, logistic regressions, and decision trees, were performed. We validated in AD the specific increase of p-Tau levels and the decrease of Aβ40 levels, two biological hallmarks of this disease. Tau concentrations were highest in AD and intermediate in FTD when compared to CTRL. The most interesting results were obtained by focusing on amyloid biomarkers as we found out in FTD a significant decrease of sAβ42, Aβ40, and Aβ38 levels. Aβ42 in particular was the most useful biomarker to differentiate FTD subjects from the CTRL population. Combining p-Tau and Aβ42 led us to correctly classifying FTD patients with sensitivity at 85% and specificity at 82%. Significant changes in amyloid biomarkers, particularly for Aβ42, are therefore seen in FTD. This could be quite useful for diagnosis purposes and it might provide additional evidence on the interrelationship between Tau and αβPP biology which understanding is essential to progress towards optimal therapeutic and diagnostic approaches of dementia.

Keywords: Alzheimer’s disease, frontotemporal dementia, CSF biomarkers, CSF amyloid peptides, Aβ42

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 diagnosis 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 (sAβPP) 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 sAβPPβ, Aβ40, and Aβ42 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, sAβPPβ, and Aβ40, Aβ42, 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 sAβPPα, Aβ40, 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 AβPP 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.
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, electrophysiological, and neuroimaging exams were also in favor of each diagnosis included in the CTRL (e.g., for hydrocephalus all exams point to the diagnosis) or 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 commercial 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 Innogenetics 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)
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 Aβ40. 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 Ab\textsubscript{42} values ($p<0.0001$, not shown).

Concentration of sA\beta\textsubscript{PP42} but not of sA\beta\textsubscript{PP40} 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 sA\beta\textsubscript{PP} might be a valuable diagnosis marker of AD. The closest measurement of the different A\beta peptides allowed us to calculate ratios (Table 1, Figs. 2B-D). Both A\beta\textsubscript{42}/40 and A\beta\textsubscript{38}/42 ratios were significantly altered in AD as already reported [28-30]. We also computed the ratio A\beta\textsubscript{40}/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 pathological variation, or misclassifications, were detected. However these outliers did not significantly affect the statistical significance of our results (e.g., in Fig. 1D, A\beta\textsubscript{42} 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 A\beta\textsubscript{42}/40 ratio and the IATI (AUCs = 0.87). However, A\beta\textsubscript{38}/42 ratio or A\beta\textsubscript{42} 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. A\beta\textsubscript{42}/40, sA\beta\textsubscript{PP42}, sA\beta\textsubscript{PP40}, and A\beta\textsubscript{38}/42 ratios were also clearly less efficient for differentiating FTD from AD.

For FTD versus CTRL, A\beta\textsubscript{42} and the ratio A\beta\textsubscript{40}/38 were the best biomarkers (AUCs = 0.81). Interestingly, these biomarkers were better than A\beta\textsubscript{40} (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 A\beta\textsubscript{42} with a couple sensitivity/specifity (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, A\beta\textsubscript{42}, and A\beta\textsubscript{38}) and new CSF neurochemical biomarkers such as soluble forms of amyloid precursor proteins (sA\beta\textsubscript{PP40}, sA\beta\textsubscript{PP42}) and A\beta peptides (A\beta\textsubscript{40}, A\beta\textsubscript{42}) 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 (panels C and D) to discriminate FTD from AD (panel A and C) and FTD from CTRL (panel B and D).

A: Gabelle et al. / CSF Biomarkers in FTD

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 Aβ38/42, 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
ROC curve area for single variable, selection of the best sensitivity and specificity values

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1Receiver 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).

Table 3A
Logistic regression

| Variable       | Tau | p-Tau | A    | H9252 | 38 | A | H9252 | 40 | A | H9252 | 42 | IATI | A | H9252 | 38/42 | A | H9252 | 40/42 | A | H9252 | 40/38 | A | H9252 | 40/38 |
|----------------|-----|-------|------|-------|----|---|-------|----|---|-------|----|------|---|-------|------|---|-------|------|---|-------|------|---|-------|------|---|
| Sensitivity    | 80  | 81    | 42   | 71    | 60 | 66 | 69    | 67 | 57 | 76    | 59 | 69   |   |       |      |   |       |      |   |       |      |   |       |      |   |
| Specificity    | 81  | 74    | 64   | 57    | 87 | 79 | 69    | 67 | 57 | 69    | 59 | 76   |   |       |      |   |       |      |   |       |      |   |       |      |   |
| Cut-off        | >300| >43   | ≤1470| ≤7148 | ≤1111| ≤18 | ≤119  | <65 | <129| >693  | >5.93| >5.28|   |       |      |   |       |      |   |       |      |   |       |      |   |
| AUC            | 0.62| 0.53  | 0.81 | 0.63  | 0.78| 0.69| 0.57  | 0.74| 0.81|       |   |       |   |       |      |   |       |      |   |       |      |   |       |      |   |

2Logistic 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.

Table 3B
Logistic regression

| Variable       | Tau | p-Tau | A    | H9252 | 38 | A | H9252 | 40 | A | H9252 | 42 | IATI | A | H9252 | 38/42 | A | H9252 | 40/42 | A | H9252 | 40/38 | A | H9252 | 40/38 |
|----------------|-----|-------|------|-------|----|---|-------|----|---|-------|----|------|---|-------|------|---|-------|------|---|-------|------|---|-------|------|---|
| Sensitivity    | 86  | 90    | 42   | 71    | 60 | 66 | 69    | 67 | 57 | 76    | 59 | 69   |   |       |      |   |       |      |   |       |      |   |       |      |   |
| Specificity    | 89  | 74    | 64   | 57    | 87 | 79 | 69    | 67 | 57 | 69    | 59 | 76   |   |       |      |   |       |      |   |       |      |   |       |      |   |
| Cut-off        | >300| >43   | ≤1470| ≤7148 | ≤1111| ≤18 | ≤119  | <65 | <129| >693  | >5.93| >5.28|   |       |      |   |       |      |   |       |      |   |       |      |   |
| AUC            | 0.62| 0.53  | 0.81 | 0.63  | 0.78| 0.69| 0.57  | 0.74| 0.81|       |   |       |   |       |      |   |       |      |   |       |      |   |       |      |   |

3Multiple logistic regression indicating the resulting sensitivity and specificity (left part) for detection FTD vs AD + CTRL. The variables with significant ROC areas were selected to be considered in the model. Variables no retained based on their resulting p values after regression (p > 0.1) were indicated on the last lane (no or Yes).

4Multiple logistic regression indicating the resulting sensitivity and specificity (left part) for detection AD vs FTD + CTRL. The variables with significant ROC areas were selected to be considered in the model. Variables no retained based on their resulting p values after regression (p > 0.1) were indicated on the last lane (no or Yes).
The presence of lower CSF small series [39]. In fact, A

controls [16]. The specific decrease of A

revealed an interesting new finding with a significant decrease of Aβ40, Aβ42, and sAβPPβ in this diagnosis (Figs. 1D, 1E, 3B). 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, s131, and Aβ42) 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 Aβ40, Aβ42, and sAβPPβ in this diagnosis (Figs. 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, Aβ40 appeared to be as relevant as Aβ42, 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 2A).

This Aβ40/42 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 Aβ40 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 58 pg/mL for p-Tau). Out of the 77 remaining, 31 could be classified as FTD (Aβ40 under 1470 pg/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 conservation of the samples.

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, Aβ40, and Aβ42 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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