

## ORIGINAL ARTICLE

# Correlation between CSF biomarkers of Alzheimer's disease and global cognition in a psychogeriatric clinic cohort

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**Objective:** The relationship between biomarkers of amyloid-beta aggregation ( $A\beta_{1-42}$ ) and/or neurodegeneration (Tau protein) in cerebrospinal fluid (CSF) and cognitive decline is still unclear. We aimed to ascertain whether CSF biomarkers correlate with cognitive performance in healthy and cognitively impaired subjects, starting from clinical diagnoses.

**Methods:** We tested for correlation between CSF biomarkers and Mini-Mental State Examination (MMSE) scores in 208 subjects: 54 healthy controls, 82 with mild cognitive impairment (MCI), 46 with Alzheimer's disease (AD), and 26 with other dementias (OD).

**Results:** MMSE correlated weakly with all CSF biomarkers in the overall sample ( $r = 0.242$ ,  $p < 0.0006$ ).  $A\beta_{1-42}$  and MMSE correlated weakly in MCI ( $r = 0.247$ ,  $p = 0.030$ ), and moderately in OD ( $r = 0.440$ ,  $p = 0.027$ ). t-Tau showed a weak inverse correlation with MMSE in controls ( $r = -0.284$ ,  $p = 0.043$ ) and MCI ( $r = -0.241$ ,  $p = 0.036$ ), and a moderate/strong correlation in OD ( $r = 0.665$ ),  $p = 0.0003$ . p-Tau correlated weakly with MMSE in AD ( $r = -0.343$ ,  $p = 0.026$ ) and moderately in OD ( $r = -0.540$ ,  $p = 0.0005$ ). The  $A\beta_{1-42}/p$ -Tau ratio had a moderate/strong correlation with MMSE in OD ( $r = 0.597$ ,  $p = 0.001$ ).

**Conclusion:** CSF biomarkers correlated best with cognitive performance in OD. t-Tau correlated weakly with cognition in controls and patients with MCI. In AD, only p-Tau levels correlated with cognitive performance. This pattern, which has been reported previously, seems to indicate that CSF biomarkers might not be reliable as indicators of disease severity.

**Keywords:** Mild cognitive impairment; dementia; Alzheimer's disease; cerebrospinal fluid biomarkers

## Introduction

Alzheimer's disease (AD) is the most common neurodegenerative cause of dementia, affecting more than 35 million people worldwide, with its prevalence expected to double every 20 years due to population aging.<sup>1</sup> AD is known to have a long preclinical phase<sup>2</sup> during which its pathophysiological processes could be detected by molecular and neuroimaging biomarkers.<sup>3</sup>

One of the best-established molecular biomarkers in dementia is the "AD signature" in cerebrospinal fluid (CSF), a decreased concentration of amyloid-beta peptide ( $A\beta_{1-42}$ ) with increased total tau protein (t-Tau) and hyperphosphorylated tau (p-Tau).<sup>4</sup> This CSF profile has been already incorporated as supporting diagnostic criteria in international guidelines.<sup>4,5</sup> Most research efforts are directed towards defining its level of accuracy in determining AD pathology as the underlying etiology of dementia and its power to predict conversion rates from mild cognitive impairment (MCI) or even asymptomatic (preclinical) stages to AD,<sup>4</sup>

as a means to contribute to the differential diagnosis of dementia.<sup>6-8</sup>

It has been reported that levels of these biomarkers correlate with cognitive performance, especially in patients within the MCI-AD continuum,<sup>9,10</sup> but this association is still controversial,<sup>11</sup> and it is unclear whether this correlation is also found in non-AD dementias.

Our study aimed to correlate CSF levels of  $A\beta_{1-42}$ , t-Tau, p-Tau, and  $A\beta_{1-42}/p$ -Tau ratio with cognitive performance in healthy and cognitively impaired subjects (MCI, AD, and non-AD dementias), starting from clinical diagnoses. To the best of our knowledge, no similar studies have been conducted in Brazilian populations.

## Methods

### Participants

Participants were recruited from a cohort of older adults who are regularly followed up at a university-based

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psychogeriatric clinic in São Paulo, Brazil. This facility receives patients referred from other hospitals due to suspected cognitive decline and those spontaneously seeking medical attention related to cognitive complaints or worries about developing dementia (for instance, individuals with one or more relatives who experienced cognitive decline in the old age). All participants were interviewed and evaluated by a multidisciplinary team of psychiatrists, neurologists, geriatricians, neuropsychologists, and occupational therapists. Clinical history and general and neurological examinations were performed before the cognitive diagnosis, which was obtained through a full neuropsychological and functional assessment that included the Fuld object memory evaluation (FOME),<sup>12</sup> the Rivermead Behavioral Memory Test (RBMT),<sup>13</sup> tasks A and B of the Trail Making Test (TMT),<sup>14</sup> the Revised Wechsler Adult Intelligence Scale Vocabulary and Block Design subtests,<sup>15</sup> and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).<sup>16</sup> Depressive symptoms were ruled out through the 21-item Hamilton Depression Rating Scale,<sup>17</sup> with euthymia considered for scores < 8. The Mini-Mental State Examination (MMSE)<sup>18,19</sup> was also administered. All participants were screened for treatable causes of dementia (complete blood count, liver enzymes, serum vitamin B<sub>12</sub>, HIV serology, VDRL, and kidney and thyroid function), as well as by neuroimaging (MRI) studies.

Exclusion criteria for all participants were: a) history or current neurological and/or psychiatric comorbidities (including major depression) which might lead to inaccurate cognitive assessment; b) uncompensated systemic diseases; and c) recent introduction or dose adjustment of medications that interfere with cognitive performance.

After the selection process, 208 participants were divided into four groups: AD, MCI, other dementias (OD), and control. Eighty-two participants were clinically diagnosed with MCI and 46 with AD according to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria.<sup>4,20</sup> Twenty-six participants were diagnosed with non-AD dementias; frontotemporal lobar degeneration (FTLD) was most prevalent, and was diagnosed according to the Frontotemporal Dementia Consortium (FTDC) revised criteria.<sup>21</sup> Fifty-four participants with no evidence of cognitive impairment nor of any psychiatric disorders at the time of evaluation were defined as controls. Neither MMSE scores nor CSF biomarkers were used as diagnostic criteria for any groups.

### Cerebrospinal fluid analyses

All participants underwent morning lumbar puncture in the L3/L4 or L4/L5 intervertebral space, using a 23-gauge needle. CSF samples containing 12-15 mL each were collected into polypropylene tubes, centrifuged at  $3,200 \times g$  for 10 minutes at 4 °C, split into 0.5-mL aliquots in cryotubes (Sarstedt), immediately frozen and stored at -80 °C until analysis. No samples were thawed or refrozen. Concentrations of A $\beta$ <sub>1-42</sub>, t-Tau, and p-Tau were then measured in duplicate using the INNO-BIA AlzBio3 immunoassay kit (Innogenetics, Ghent, Belgium).

A suspension of microspheres carrying the capturing antibodies (AT120, AT270, and 4D7A3 for t-Tau, p-Tau,

and A $\beta$ <sub>1-42</sub>, respectively) was added to a pre-wetted filter plate with a wash buffer. A mixture of 75  $\mu$ L of CSF or standards along with biotinylated detection monoclonal antibodies designed for each of the capturing antibodies (HT7 for t-Tau and p-Tau and 3D6 for A $\beta$ <sub>1-42</sub>) was then added to the plate and incubated overnight in the dark. The plate was then washed, a detection conjugate (phycoerythrin-labeled streptavidin) added, and incubated for 1 hour at room temperature. The plate was washed again and, after addition of a reading solution (phosphate-buffered saline), the assay was finally analyzed in a Luminex 100IS platform (Luminex, Austin, TX, USA).

Standard curves were constructed for each biomarker by a sigmoidal curve-fitting method, and the mean fluorescence values for the duplicate CSF samples were used to determine the concentration of A $\beta$ <sub>1-42</sub>, t-Tau, and p-Tau.

### Statistical analyses

Demographic and clinical characteristics were analyzed by comparison of means  $\pm$  standard deviation or frequency of distribution among groups. One-way analysis of variance (ANOVA) was used for normally distributed variables, and the Kruskal-Wallis test for nonparametric variables. For the categorical variable sex, we used the chi-square test. Analyses to assess between-group differences were followed by Student's *t*-tests. Pearson correlation coefficients were calculated to determine the association between MMSE scores and biomarkers, adjusted for age and education.

In all tests, we considered *p*-values below 0.05 as statistically significant.

### Standard protocols, registrations, and patient consent

The institutional ethics committee of Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, and a national ethics committee (Plataforma Brasil) approved this study. All subjects or their legal guardians provided written consent prior to enrollment in the assessment protocol.

### Data availability statement

All raw data not published within the article are publicly available through the Open Science Framework (OSF) at doi:10.17605/OSF.IO/WXFTG.

## Results

There were no statistically significant differences among groups regarding age and sex. Controls had significantly more years of schooling than the other groups. They also had significantly higher MMSE scores, as expected. Regarding CSF biomarkers, patients in the AD group had significantly lower levels of A $\beta$ <sub>1-42</sub>, higher levels of t-Tau, and a lower A $\beta$ <sub>1-42</sub>/P-tau ratio when compared to the control and MCI, but not OD, groups; P-tau levels were highest in the AD group as compared to all remaining groups (Table 1).

**Table 1** Demographic characteristics, cognitive performance, and concentrations of biomarkers ( $A\beta_{1-42}$ , t-Tau, and p-Tau) in cerebrospinal fluid according to baseline diagnosis

Variable	C (n=54)	MCI (n=82)	AD (n=46)	OD (n=26)	p	Multiple comparison p < 0.05
Age (years)	71.3 (5.0)	72.8 (6.2)	73.4 (7.2)	70.8 (6.3)	0.220	N/A
Schooling (years)	11.5 (5.8)	8.9 (5.4)	8.7 (4.8)	8.4 (5.3)	0.035	C $\neq$ MCI, AD & OD
Sex, M/F	35/19	51/31	24/22	21/5	0.114	N/A
MMSE	27.4 (3.7)	26.1 (3.2)	22.5 (5.0)	22.9 (6.0)	< 0.0001	C $\neq$ MCI, AD & OD
$A\beta_{1-42}$ (pg/mL)	461.6 (170.5)	450.0 (178.6)	365.3 (126.3)	434.0 (182.3)	0.022	AD $\neq$ C & MCI
t-Tau (pg/mL)	91.1 (57.7)	103.1 (73.8)	133.9 (90.8)	100.2 (64.4)	0.029	AD $\neq$ C & MCI
p-Tau (pg/mL)	46.8 (30.9)	45.6 (29.0)	64.6 (39.3)	35.9 (14.6)	0.001	AD $\neq$ C, MCI & OD
$A\beta_{1-42}/p$ -Tau	13.4 (8.6)	13.3 (8.9)	8.3 (7.4)	13.6 (7.9)	0.006	AD $\neq$ C & MCI

Data presented as mean (standard deviation), unless otherwise specified.

$A\beta_{1-42}$  = amyloid-beta peptide; AD = Alzheimer's disease; C = controls; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; N/A = not applicable; OD = other dementias; p-Tau =  $^{181}$ Thr-phosphorylated-tau; t-Tau = total tau.

**Table 2** Correlations (r) between biomarkers in cerebrospinal fluid and MMSE scores for each diagnostic group

MMSE vs.	Total sample	Control	MCI	AD	OD
$A\beta_{1-42}$	0.242 p = 0.0006	0.211 p = 0.132	0.247 p = 0.030	-0.145 p = 0.358	0.440 p = 0.027
t-Tau	-0.325 p < 0.0001	-0.284 p = 0.043	-0.241 p = 0.036	-0.282 p = 0.070	-0.665 p = 0.0003
p-Tau	-0.247 p = 0.0005	-0.206 p = 0.141	-0.092 p = 0.426	-0.343 p = 0.026	-0.540 p = 0.005
$A\beta_{1-42}/p$ -Tau	0.277 p = 0.0001	0.207 p = 0.140	0.137 p = 0.233	0.176 p = 0.262	0.597 p = 0.001

$A\beta_{1-42}$  = amyloid-beta peptide; AD = Alzheimer's disease; p-Tau =  $^{181}$ Thr-phosphorylated-tau; t-Tau = total tau; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; OD = other dementias.

MMSE scores correlated weakly with all CSF biomarkers in the total sample. When considering correlations across diagnostic groups,  $A\beta_{1-42}$  levels and MMSE scores correlated weakly in the MCI group, and moderately in the OD group. t-Tau levels showed a mild inverse correlation with MMSE scores in the control and MCI groups, and this correlation was moderate/strong in the OD group. p-Tau levels correlated with MMSE scores in the AD (weak correlation) and OD (moderate correlation) groups. Finally, the  $A\beta_{1-42}/p$ -Tau ratio had a moderate to strong correlation with MMSE scores in the OD group (Table 2 and Figure 1).

## Discussion

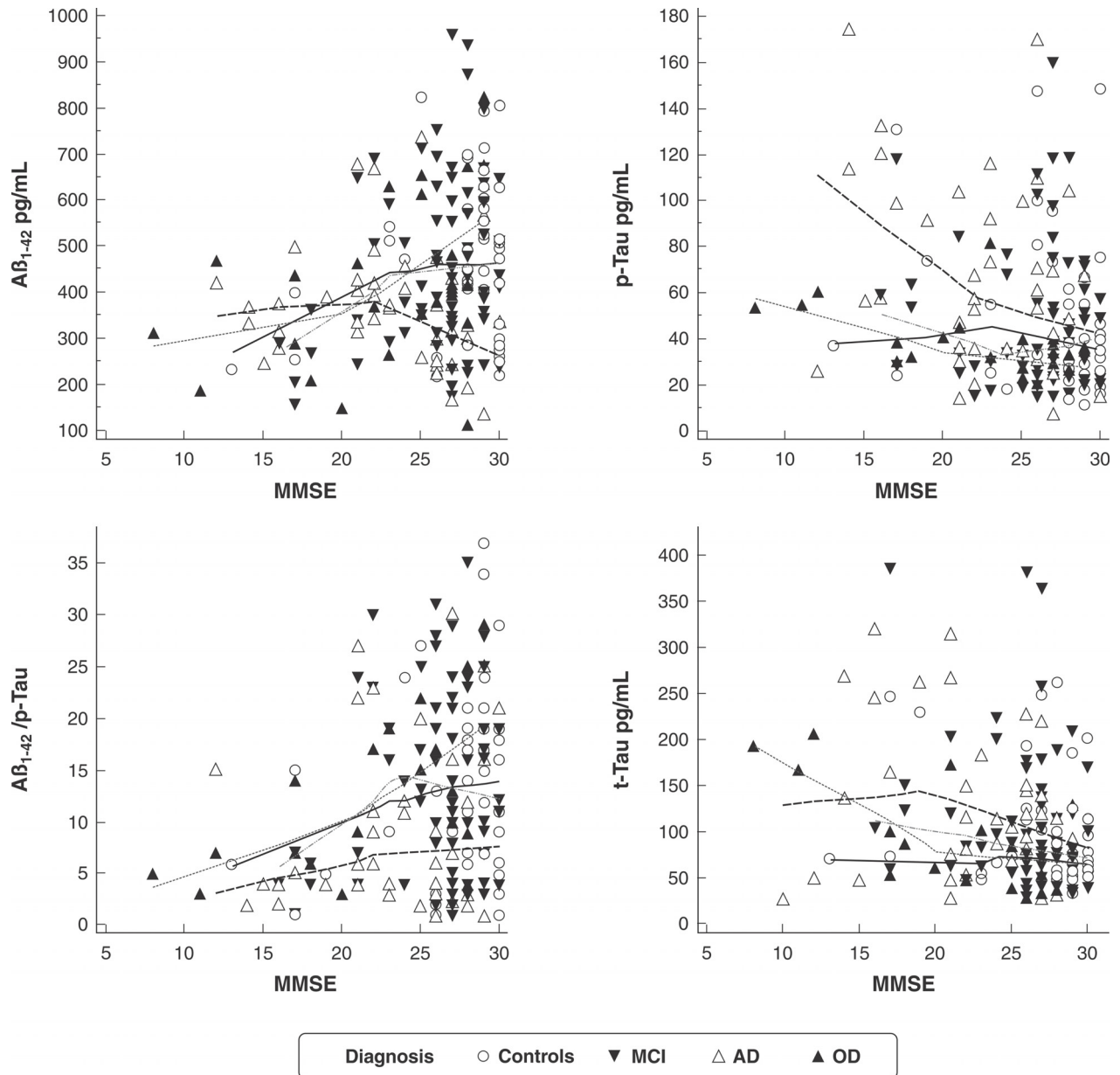
Measurement of biomarkers in CSF is a valuable tool in clinical practice, and its use is becoming increasingly widespread as a means of determining the underlying pathology in dementias of atypical presentation<sup>22</sup> and in predicting the risk of developing dementia in MCI and asymptomatic older adults.<sup>23</sup> Moreover, CSF biomarker levels are useful in the differential diagnosis of dementia.<sup>24</sup> Currently,  $A\beta_{1-42}$ , t-Tau, p-Tau, and combined ratios thereof are the best-studied CSF biomarkers;  $A\beta_{1-42}$  is considered a marker of amyloid deposition, whereas t-Tau and p-Tau are considered markers of neuronal injury.<sup>25</sup>

However, the reliability of these CSF biomarkers in reflecting the rate of cognitive decline over the course of dementing illnesses has yet to be determined. Studies focusing on this issue have reached contradictory results,<sup>11,26</sup> and most recent studies have focused on

the association between the "AD-signature" and impairments in specific cognitive domains, such as memory.<sup>27</sup>

Our results show that patterns of CSF biomarker levels differed in each group, with the AD group exhibiting significantly higher levels of p-Tau and t-Tau, lower  $A\beta_{1-42}$  levels, and, consequently, a lower  $A\beta_{1-42}/p$ -Tau ratio, as expected.<sup>4</sup> In the AD group, cognitive performance correlated only with p-Tau levels. Increased levels of p-Tau are considered to strengthen sensitivity for differential diagnosis of AD<sup>24</sup> and were capable of differentiating AD from OD in our sample. Seppälä et al.<sup>28</sup> described a correlation between decreasing rates of p-Tau and MMSE scores in AD, which was interpreted as a sign of progressive neuronal loss. Rolstad et al.<sup>9</sup> described a more significant impact of CSF  $A\beta_{1-42}$  levels in episodic memory and visuospatial abilities, while t-Tau levels correlated better with episodic memory in patients with dementia. In 2013, Rolstad et al.<sup>26</sup> replicated their study and confirmed that  $A\beta_{1-42}$  and t-Tau levels in CSF were associated with semantic and working memory performance, with the effect size of t-Tau levels being larger than that of  $A\beta_{1-42}$ . Rami et al.<sup>27</sup> also found a correlation between memory performance and CSF  $A\beta_{1-42}$  levels in AD. However, negative reports have also been published.<sup>11,29</sup> More recently, Mandacka et al.<sup>30</sup> described an association between the severity of verbal memory impairment and the degree of CSF abnormalities in AD.

In the MCI group, there was a statistically significant negative correlation between MMSE scores and t-Tau levels in CSF, as well as a positive correlation with  $A\beta_{1-42}$  levels. Memory performance has been associated with higher t-Tau and p-Tau levels in MCI populations,<sup>27</sup>



**Figure 1** Correlations between cerebrospinal fluid biomarkers and MMSE scores in each diagnostic group.  $A\beta_{1-42}$  = amyloid-beta peptide; AD = Alzheimer's disease; p-Tau =  $^{181}$ Thr-phosphorylated-tau; t-Tau = total tau; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; OD = other dementias.

as well as with  $A\beta_{1-42}$  levels.<sup>30,31</sup> Rolstad et al.<sup>9,26</sup> found a more widespread pattern of correlation across all cognitive domains. Nathan et al.<sup>32</sup> recently described a relationship between sustained attention and memory performance and higher t-Tau and p-Tau levels in CSF. Such findings, in association with those described for AD patients, led to the currently accepted notion that, in the continuum from healthy aging to AD, CSF biomarker levels can reflect cognitive decline. This association, however, seems to obey a temporal pattern, in which cognitive performance first correlates with  $A\beta_{1-42}$  levels, then with t-Tau and p-Tau levels, and finally becomes independent from biomarkers in fully developed dementia. Thus, the combination of neuropsychological examination and analysis of the CSF biomarker

profile seems promising in predicting conversion to dementia,<sup>33,34</sup> especially AD.

In the control group, we found a negative correlation between t-Tau levels and cognitive performance. Studies focusing on CSF biomarker levels in cognitively healthy subjects have demonstrated that a proportion of such subjects exhibit both evidence of amyloid deposition (as indicated by low CSF levels of  $A\beta_{1-42}$ ) and/or neurodegeneration (as shown by high levels of t-Tau and p-Tau). This proportion tends to increase through the aging process and is affected by presence of the APOE4 genotype.<sup>25,35</sup> Subjects who show evidence of neurodegeneration, but not of amyloid deposition, known as the "suspected non-Alzheimer pathology" (SNAP)

category,<sup>36</sup> represent those who not display underlying AD pathology and would probably develop non-AD dementias.<sup>35</sup> Studies in cognitively preserved individuals have disclosed an association between  $A\beta_{1-42}$  levels in CSF and episodic, semantic, and working memory performance, although most cases assessed individuals with subjective memory complaints (SMC).<sup>9,27,30</sup> Only one study<sup>26</sup> reported an impact of t-Tau levels in executive functions in SMC. As noted in the Methods section, although our control group was composed of cognitively healthy subjects (as defined through standard cognitive and functional assessment), they might be considered as an SMC group, as they presented with mild memory complaints (“forgetfulness”).

Lastly, the group in which the strongest correlations between CSF levels and cognition occurred was the non-AD dementia group, where most patients had FTLD (either behavioral variant or primary progressive aphasia). We found only two studies describing a correlation between CSF  $A\beta_{1-42}$  levels and general cognitive function<sup>37</sup> and memory performance (both learning and recall)<sup>38</sup> in FTLD. Tau levels have already been associated with survival rates in FTLD,<sup>39</sup> but we did not find any reports of association between neuronal injury biomarkers and cognition in this population.

In summary, we observed that all CSF biomarkers correlated to some extent with overall cognitive performance when considering the sample as a whole. A more thorough analysis revealed that  $A\beta_{1-42}$  levels were associated with cognitive performance in the MCI and OD groups. Several studies have established this association in MCI, although focusing on isolated cognitive domains.<sup>10,28,29</sup> Tau levels correlated with cognitive performance in the control, MCI, and non-AD dementia groups. As already noted, t-Tau levels are markers of neuronal injury, which may explain why they correlate more consistently with diagnostic status in earlier (oligo-symptomatic) stages of cognitive decline, reaching a “ground effect” once the dementia is fully developed (in AD). p-Tau levels correlated more specifically with cognition in the AD group, which probably reflects the greater specificity of this biomarker for AD diagnosis.<sup>25</sup> Recently, Koychev et al.<sup>40</sup> described a pattern of correlation between CSF levels of t-Tau (but not of  $A\beta_{1-42}$ ) and cognitive decline assessed through the ADAS-Cog, which is also suitable for measuring global cognition. Bouallègue et al.<sup>41</sup> reported a similar correlation (CSF t-Tau, but not  $A\beta_{1-42}$ , levels vs. cognitive performance) in a cross-sectional cohort assessed with the ADAS-Cog, MMSE, and CDR; longitudinal observation found that t-Tau levels were associated with cognitive worsening as measured by a decrease in MMSE scores only (and not in ADAS-Cog or CDR), while p-Tau levels were associated with baseline diagnosis (control, MCI, or AD). However, Joachim et al.<sup>42</sup> found a significant decrease in cognitive performance using the ADAS-Cog in patients with MCI who had lower levels of  $A\beta_{1-42}$  and higher levels of t-Tau, despite treatment with acetylcholinesterase inhibitors. Such heterogeneous results raise some questions regarding the optimal outcome measure for primary clinical settings, as the association between CSF

biomarker levels and global measures of cognition seems to reach a “steady state” close to the initial stages of fully developed AD.

Finally, t-Tau levels and t-Tau/A  $A\beta_{1-42}$  ratios are considered useful for differential diagnosis between AD and non-AD dementias, especially FTLD, although their accuracy is highly variable across studies. t-Tau concentrations are significantly higher in FTLD than in controls, but significantly lower than in AD. p-Tau concentrations show good capacity to differentiate AD cases from FTLD.<sup>43</sup> Unfortunately, the lack of data on the association between cognitive performance and CSF biomarkers in FTLD hampers comparison with our data.

The main limitations of this study are its cross-sectional design, which is not the best suited to verify changes in biomarker levels across the natural history of disease, and the fact that the MCI group was not subdivided into amnesic (AD-MCI) and nonamnesic subjects, as these two populations are prone to developing dementia of different etiologies. Regarding the use of the MMSE (a screening test) as the cognitive outcome measure, it was our purpose to verify the association of CSF biomarkers with global cognition rather than with specific domains, in a study design with both an ecological and practical focus. We understand that further studies using more refined global cognitive measures, larger samples (especially for non-AD dementias), and, most of all, a longitudinal design are necessary to establish the mechanisms that ultimately lead to clinically significant neuronal injury, which is pivotal in developing disease-modification therapies. However, to the best of our knowledge, this is the first study to address such correlations in the Brazilian population.

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## Disclosure

The authors report no conflicts of interest.

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