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Research report

CSF $A\beta_{1-42,}$ but not p-$Tau_{181,}$ differentiates aMCI from SCI

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ABSTRACT

Aim: Individuals with amnestic mild cognitive impairment (aMCI) are at a high risk to develop Alzheimer's disease (AD). We compared CSF levels of biomarkers of amyloidosis ($A\beta_{1-42}$) and neurodegeneration (p-Tau_{181}) in individuals with aMCI and with subjective cognitive impairment (SCI) in order to ascertain diagnostic accuracy and predict the odds ratio associated with aMCI.

Methods: We collected CSF of individuals clinically diagnosed with aMCI (33) and SCI (12) of a memory clinic of Southern Brazil. Levels of $A\beta_{1-42}$ and p-Tau_{181} were measured by immunoenzymatic assay. Participants also underwent neuropsychological testing including the verbal memory test subscore of the Consortium to Establish a Registry for Alzheimer's Disease (VM-CERAD).

Results: CSF concentration of $A\beta_{1-42}$ was significantly lower (p: .007) and p-$Tau_{181}/A\beta_{1-42}$ ratio higher (p: .014) in aMCI individuals than in SCI. However, isolate p-Tau_{181} levels were not associated with aMCI (p: .166). There was a statistically significant association between $A\beta_{1-42}$ and p-Tau_{181} (R^2: 0.177; β: −4.43; p: .017). ROC AUC of CSF $A\beta_{1-42}$ was 0.768 and of the p-$Tau_{181}/A\beta_{1-42}$ ratio equals 0.742. Individuals with $A\beta_{1-42}$ < 823 pg/mL levels were 6.0 times more likely to be diagnosed with aMCI (p: .019), with a 68.9% accuracy. Those with p-$Tau_{181}/A\beta_{1-42}$ ratio > 0.071 were at 4.6 increased odds to have aMCI (p: .043), with a 64.5% accuracy. VM-CERAD was significantly lower in aMCI than among SCI (p: .041).

Conclusion: CSF $A\beta_{1-42}$, but not p-$Tau_{181,}$ level was significantly associated with aMCI.

1. Introduction

Mild cognitive impairment (MCI) is a disorder situated in the continuum between normal cognition and dementia. According to National Institute on Aging and the Alzheimer's Association (NIA-AA), the clinical characterization of MCI requires the presence all items below: (1) self- or informant -reported cognitive complain, (2) objective cognitive impairment, (3) preserved independence in functional abilities, and (4) no dementia. Individuals with MCI ascertained according to these core clinical criteria could be further sub classified into two categories: amnestic MCI (aMCI) if performance on neuropsychological tests of episodic memory is poor, and non-amnestic MCI (naMCI) in the case of poor performance on tests covering cognitive domains other than memory (Petersen et al., 2014).

Only a proportion of individuals with MCI progress to AD (Alzheimer's disease). According to criteria established by NIA-AA, the use of biomarkers may aid in identifying etiological MCI subtypes by differentiating between MCI due to AD (i.e.: prodromal AD) and MCI that is unlikely to be due to AD (Albert et al., 2011; Dubois et al., 2014).

Many biomarkers have been studied to support the clinical diagnosis of AD. Nonetheless, few have successfully defined AD signature. The most consistent ones have been related to compounds of neuritic plaques such as the β-amyloid protein ($A\beta_{1-42}$) and the main constituent of the neurofibrillary tangles, i.e., the hyperphosphorylated Tau protein (p-Tau_{181}) (Blennow et al., 2014). They are reported to be altered at least 5–10 years before dementia diagnosis (Jack et al., 2013). However, diagnostic accuracies of CSF biomarkers in MCI are still to be defined.

Although aMCI is a well-defined entity, it may be more difficult for non-specialists to proper diagnose this condition in their practice. In this sense, an exam that helps to discriminate normal aging from aMCI would be welcomed (Brandt, 2001). Moreover, accurate identification of prodromal AD would become crucial when a disease-modifying drug becomes a reality (Cavedo et al., 2014).

Based on core criteria above we measured and compared the concentration of ($A\beta_{1-42}$ and p-Tau_{181}), in individuals clinically diagnosed with aMCI and with subjective cognitive impairment

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(SCI) in a manner to ascertain the diagnostic accuracy and verify the odds ratio to have aMCI.

2. Results

Table 1 compares the demographics characteristics and neuropsychological scores between aMCI and SCI groups. Mean age was 67.9 ± 5.4 years and the majority was women (71.1%). There was a significant difference in median verbal memory test subscore of the Consortium to Establish a Registry for Alzheimer's Disease (VM-CERAD) (Bertolucci et al., 1998) between aMCI and SCI groups (p: .041). No differences were found when we analyzed scores of Geriatric Depression Scale (GDS) (Almeida and Almeida, 1999) (p: .724) and Clock-Drawing Test (CDT) (Shulman et al., 1993) (p: .825) between aMCI and SCI. Our sample was composed mostly of a Caucasian population, as which reflects the demographics of the Southern Brazilian population. Only one individual in each group was African-Brazilian.

Table 2 describes CSF biomarkers concentration between aMCI and SCI. CSF concentration of $A\beta_{1-42}$ protein (p: .007), but not p-Tau protein (p: .166), was significantly different between the two groups. The p-Tau_{181}/$A\beta_{1-42}$ ratio displayed significant difference between groups (p: .014). A linear regression analysis demonstrated significant association between $A\beta_{1-42}$ and p-Tau_{181} protein (R^2: 0.100; β: 95.19; p: .034), even when adjusted for age (R^2: 0.177; β: −4.43; p: .017). When the two outliers showed in the Fig. 1 were removed, the analysis remains significant (R^2: 0.171; β: 1.77; p: .023, adjusted for age).

$A\beta_{1-42}$ ROC AUC was 0.768 (CI 95%: 0.618–0.918; p: .007), as shown at Table 3. Cutoff value determined by the Youden index, that stretches the maximum potential effectiveness of a biomarker, was 823 pg/mL, with sensibility of 66.7% (CI 95%: 49.6–80.2), specificity of 75% (CI95%: 46.7–91.1) and predictive positive value of 88% (CI95%: 73.67–95.05%). The logistic linear regression analysis revealed that individuals with $A\beta_{1-42}$ < 823 pg/mL were 6.0 increased odds (p: .019) to have aMCI. When adjusted for age, the odds ratio almost did not change (6.2; p: .022). At this cutoff level, 31 of 45 individuals (68.9%) were correctly classified. ROC AUC of the ratio p-Tau_{181}/$A\beta_{1-42}$ was 0.742 (CI 95%: 0.589–0.896; p: .014). The optimal cutoff value was 0.071, with sensibility of 60.6% (CI 95%: 43.6–75.3), specificity of 75% (CI95%: 46.7–91.1) and predictive positive value of 87% (CI95%: 71.60–94.63%). Individuals with the ratio p-Tau_{181}/$A\beta_{1-42}$ > 0.071 were at 4.6 increased odds (p: .043) to have aMCI. At this cutoff 29 of 45 individuals (64.5%) were correctly classified, but all of them were also adequately classified according to $A\beta_{1-42}$ levels alone.

Table 1
Demographics characteristics and neuropsychological scores.

	aMCI	SCI	ρ value
n	33	12	
Age (years): median (min-max)	68 (61–78)	63.5 (60–76)	0.053
Education (years): median (min-max)	11 (1–18)	11 (5–18)	0.211
Gender, (male/female): n	10/23	3/9	0.120
GDS: median (min-max)	2 (0–5)	1 (0–5)	0.724
VM-CERAD: median (min-max)	27 (18–37)	31 (23–40)	0.041
CDT: median (min-max)	4 (1–5)	4 (1–5)	0.825

†aMCI: amnestic Mild Cognitive Impairment; CDT: Clock Drawing Test; GDS: Geriatric Depression Scale; SCI: Subjective Cognitive Impairment; VM-CERAD: Verbal Memory test subscore of the Consortium to Establish a Registry for Alzheimer's Disease. ‡Mann-Whitney test was used, except for sex (Chi-Square Test).

Table 2
CSF biomarkers features.

	aMCI	SCI	ρ value
n	33	12	
$A\beta_{1-42}$ (pg/mL): median (P25–P75)	677.82 (493.72–913.35)	985.99 (757.67–1096.57)	0.007
p-Tau_{181} (pg/mL): median (P25–P75)	64.94 (50.32–85.08)	55.26 (48.54–69.87)	0.166
p-Tau_{181}/$A\beta_{1-42}$ ratio: median (P25–P75)	0.075 (0.059–0.167)	0.059 (0.051–0.074)	0.014

†aMCI: amnestic Mild Cognitive Impairment; SCI: Subjective Cognitive Impairment. P25: percentile 25; P75: percentile 75. ‡Mann-Whitney test was used.

3. Discussion

As expected, the concentration of $A\beta_{1-42}$ protein was significantly diminished in aMCI subjects than among SCI. However, p-Tau_{181} protein was not different between groups. These results are in accord with the recently proposed biomarker behavior hypothetical model of AD (Jack et al., 2010). According to this model, CSF $A\beta_{1-42}$ levels declines before the p-Tau_{181} increases. It is possibly that CSF p-Tau_{181} levels only start to increases expressively as neurodegeneration advances. Considering this model, we can infer that at the moment the markers were measured at our sample, CSF p-Tau_{181} concentration in aMCI may not have raised expressively yet. In fact, p-Tau_{181} only increase in the CSF later than $A\beta_{1-42}$ starts to decrease (Buchhave et al., 2012).

Although we found no significant difference in levels of p-Tau_{181}, we verified a linear association of this protein with $A\beta_{1-42}$, suggesting that they could be influenced by common mechanisms and/or influence each other. p-Tau_{181}/$A\beta_{1-42}$ ratio displayed significant difference between groups at our study. This coefficient is frequently utilized because it presumes a link between β-amyloid and p-Tau pathways (Shaw et al., 2009). Indeed, p-Tau_{181}/$A\beta_{1-42}$ ratio was already reported (1) to predict cognitive decline in cognitively normal elderly (Fagan et al., 2007), (2) to differentiate patients with AD from individuals without objective cognitive impairment (Ferreira et al., 2014), and (3) to predict MCI progression to AD (Ferreira et al., 2014).

Patients with AD dementia tends to have lower levels of CSF $A\beta_{1-42}$ and higher levels of CSF p-Tau_{181} than individuals without cognitive impairment (Blennow et al., 2010). It has been reported $A\beta_{1-42}$ levels are reduced in about 50% among individuals with AD relatively to age-matched people without cognitive impairment (Holtzman, 2011). Although there are no established cutoff values for these CSF biomarkers general acceptable, some studies suggests cutoffs for CSF $A\beta_{1-42}$ positivity in AD, which below 650 pg/mL when utilizing immunoenzymatic assays (Blennow et al., 2015). p-Tau_{181} thresholds usually vary above 60 and 80 pg/mL at the demential phase of the disease(Tang et al., 2014b).

Cutoff points for $A\beta_{1-42}$ and p-Tau_{181} are still scarce and even unclear for aMCI individuals. A recent meta-analysis described that the levels of $A\beta_{1-42}$ in aMCI individuals ranged from 172.6 ± 53.5 to 622.9 ± 275.6 pg/mL, whereas among healthy cognitively people they vary between 383.5 ± 101.8 and 1020 ± 230 pg/mL. However, none of these studies have direct compared aMCI to SCI. This meta-analysis suggests that there is no established threshold which can distinguish AD or aMCI from healthy cognitively individuals (Mo et al., 2015). Although this study does not differentiate aMCI from SCI, some older studies compared CSF $A\beta_{1-42}$ levels in general MCI individuals and healthy cognitively people (Herukka et al., 2005; Maruyama et al., 2001). One reported that CSF $A\beta_{1-42}$ levels did not differ significantly between cognitively normal subjects and MCI groups (Maruyama et al., 2001), and other showed that values of CSF $A\beta_{1-42}$ were significantly lower in progressive MCI group than in progressive and stable MCI groups (Herukka et al., 2005).

The broad variation at the measurements of these biomarkers between studies and laboratories is only one of the difficulties in