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Article

Depression and Suicide Risk in Mild Cognitive Impairment: The Role of Alzheimer's Disease Biomarkers

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ABSTRACT

Background: Patients with depression and mild cognitive impairment (MCI) are at greater risk of developing dementia. Depression involves a higher risk of suicidal ideation (SI) and suicide attempts (SA). Biomarkers of Alzheimer's Disease (AD) could help to clarify the role of depression and SI in AD. **Method:** Fifty-nine participants aged > 50 with criteria of MCI positive (MCI-AD) (n=22) and negative (MCI-Non AD) (n=24) AD and healthy controls (HC) (n=13) were evaluated. We used the Geriatric Depression Scale (GDS-30) and the GDS-SI factor to measure depression and indirect risk for suicide, respectively. Additionally, AD biomarkers such as amyloid-ß (Aß), hyperphosphorilated tau (P-tau), and total tau (T-tau) in cerebrospinal fluid (CSF) were analyzed. **Results:** No significant differences between the groups were found in depression. However, in the MCI-AD group, lower P-tau and T-tau levels were related to higher GDS-SI scores, suggesting that MCI-AD patients with lower AD pathology are at a higher risk of suicide. **Conclusions:** The result highlights the importance of considering SI in the initial phases of AD, and the potential role of AD biomarkers in early detection of symptoms.

Depresión y Riesgo de Suicidio en el Deterioro Cognitivo Leve: el Rol de los Biomarcadores de la Enfermedad de Alzheimer

Palabras clave:
Depresión
Ideación suicida
Riesgo de suicidio
Deterioro cognitivo leve
β-amiloide
Tau

RESUMEN

Antecedentes: Los pacientes con depresión y deterioro cognitivo leve (DCL) tienen un alto riesgo de desarrollar demencia. La depresión implica un alto riesgo de ideación suicida (IS) e intentos de suicidio (AS). Los biomarcadores de la enfermedad de Alzheimer (EA) pueden clarificar el papel de la depresión e IS en la EA. **Método:** Cincuenta y nueve participantes >50 años con criterios de DCL-EA positivo (DCL-EA; 22) y negativo (DCL-NoEA; 24) y 13 controles sanos. La depresión fue evaluada con la Escala Geriátrica de Depresión (GDS-30) y la IS con el factor GDS-IS. Además, se midieron los siguientes biomarcadores en el líquido cefalorraquídeo: ß-amiloide (ß-A), tau hiperfosforilada (H-tau) y total (T-tau). **Resultados:** No se encontraron diferencias significativas entre los tres grupos de participantes en depresión o en IS. Sin embargo, en el grupo DCL-EA, niveles más bajos de H-tau y T-tau, indicadores de menor patología EA, se relacionaron significativamente con mayor riesgo de suicidio indirecto. **Conclusiones:** Este resultado subraya la importancia de considerar la IS en fases iniciales de EA, y el potencial papel de los biomarcadores de EA para detectar sus síntomas.

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Depression and dementia are the two most prevalent neuropsychiatric diseases in older adults (Beekman et al., 1999; Calderón, 2018). Recent studies highlight depressive symptoms as highly prevalent in early (Atri, 2019) and probably late prodromal stages of asymptomatic (Javaherian et al., 2019; Zhang et al., 2021) Alzheimer´s Disease (AD), the most frequent type of dementia (World Health Organization [WHO], 2020). Moreover, the incidence of depression in dementia varies depending on the different types (Baquero & Martín, 2015). Although recent research emphasizes the importance of considering depression and affective dysregulation as risk factors for dementia (Dafsari & Jessen, 2020; Ismail et al., 2018), they have still not been sufficiently considered (Canevelli et al., 2017).

Furthermore, in the older population, depressive disorder is associated with increased mortality, including suicide attempts (SA) and complete suicide (Goñi-Sarriés et al., 2018; Sekhon et al., 2020). Depression is known to be the main risk factor for suicide in older people (Waern et al., 2003). Suicidal behavior can be considered a continuum from suicidal ideation (SI) to the suicidal act, which includes suicide attempts (SA) and death by suicide (Conejero et al., 2016). Results on the presence of SI and SA in AD patients are heterogeneous (Alphs et al., 2016; Serafini et al., 2016), although a more recent review indicated that patients with AD and other dementias showed a higher risk of suicide (Alejos et al., 2020). Moreover, because completed suicide increases during the initial stages of cognitive impairment (Conejero et al., 2018a), the evaluation of suicide risk is especially recommended in early stages of dementia (Alphs et al., 2016).

Mild Cognitive Impairment (MCI) is considered the stage prior to dementia (Petersen et al., 2009). The prevalence of depression in MCI varies widely, ranging from 3% to 83% in the population (Baquero et al., 2004; Bhalla et al., 2009). In addition, Li et al. (2018) found that older adults with depression showed a high prevalence rate of MCI compared to those without depression. Moreover, Youn et al. (2019) reported that half of older adults with depressive symptoms and concomitant MCI were more likely to suffer from AD. Different studies have also analyzed the relationship between SI and cognitive impairment. Thus, Conejero et al. (2018b) indicated that cognitive impairment is a specific risk factor for SI. Given these results, it is necessary to study this issue in depth and clarify the relationship between depression or suicide and MCI.

Recently, Wiels et al. (2020) concluded that in many patients, depressive symptoms and dementia are related, which may be due to common risk factors, and so more research about predictive biomarkers is required. Thus, in recent years, there has been great interest in analyzing the association between depression and biomarkers involved in AD (Wenzler et al., 2017), and most studies have focused on amyloid-β (Aβ), hyperphosphorilated tau (P-tau), and total tau (T-tau) (Banning et al., 2019; Ng et al., 2021; Showraki et al., 2019). In two different reviews carried out on MCI and AD dementia, Showraki et al. (2019) reported that depression was inversely associated with lower AD pathology, whereas Banning et al. (2019) failed to observe an association between AD biomarkers (Aβ, P-tau, and T-tau) and affective symptoms, including depression. Moreover, a more recent review (Ng et al., 2021) that included preclinical AD and cognitively unimpaired individuals reported that neuropsychiatric symptoms, particularly depressive and anxiety symptoms, were consistently associated with higher Aβ in cross-sectional and longitudinal studies. However, only one study in this review reported that cerebrospinal fluid (CSF) T-tau was linked to an increase in depressive symptoms (Babulal et al., 2016).

These mixed findings might be caused by the large heterogeneity in the methodologies. It has been suggested that the relationship between depressive symptoms and Aβ and tau biomarkers might differ depending on whether there is comorbidity with MCI or not (Lavretsky et al., 2009). Furthermore, in most studies, MCI participants were not classified considering these biomarkers, as recommended by the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework criteria for preclinical AD, described by Ng et al. (2021). Thus, it is important to analyze the association between depression and AD biomarkers by comparing different types of MCI biologically classified as positive and negative AD and to include healthy controls. Furthermore, Conejero et al. (2018a) suggested that Aβ could be a potential risk factor for suicide, given the association between depression and SI observed in initial phases of dementia. However, we have not found any previous study analyzing the relationship between SI and AD biomarkers in MCI patients.

Hence, our first aim was to investigate differences in depression and SI among participants with MCI classified as positive AD (MCI-AD), participants with MCI classified as negative AD (MCI-Non AD), and healthy controls (HC). Our second and main aim was to explore the association between CSF AD biomarkers (Aβ, P-tau, and T-tau) and both depression and SI in each of the three groups. Firstly, we hypothesized that there would be higher depression scores (Krell-Roesch et al., 2019) and the main risk factor for suicide (Waern et al., 2003) in the MCI-AD group, followed by the MCI-Non AD group, and lower scores in the HC group. Secondly, we expected an association between the AD CSF biomarker pattern (lower levels of Aβ and higher levels of P-tau and T-tau) and higher depression and SI scores, especially in the MCI-AD group.

Method

Participants

The final sample was composed of 59 participants of both sexes (30 men and 29 women), ranging in age from 51 to 75 years (M=67.29, SD=6.04). The total sample was classified in three groups: MCI-AD (n=22), MCI-Non AD (n=24), and HC (n=13), according to the criteria for the diagnosis of probable AD of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (Albert et al., 2011; Ekman et al., 2018; McKhann et al., 2011). The inclusion criteria for the study were: age >50 and minimum basic studies (Primary school). Exclusion criteria were: the diagnosis of moderate or severe dementia, neurologic disease, stroke, cancer in the past five years, uncontrolled diabetes or thyroid impairment, hepatitis, surgery with general anesthesia in the past three months, and taking drugs that affect cognition (chemotherapy, radiotherapy, beta-blockers, neuroleptics, glucocorticoids, and substitutive hormonal therapy). The Ethical Committee at the Medical Research Institute of Hospital Universitari I Politècnic La Fe (Spain) approved the study, and all participants agreed to participate in the study and gave their written informed consent.

The characteristics of the study sample are presented in Table 1.

Instruments

Global neuropsychological assessment

The Mini-Mental State Evaluation (MMSE; Folstein et al., 1975) was used as a standardized general screening tool to evaluate cognitive impairment and its severity. The scores on the MMSE range between 0 and 30, with higher scores representing better cognition. An MMSE total score from 21 to 26 indicated MCI, whereas MMSE ≥ 27 indicated an absence of cognitive impairment in the control group.

Functionality

The Barthel Index (Mahoney and Barthel, 1965) is a functional-activities of daily living scale composed of 10 items. The range of possible values of the Barthel Index is between 0 and 100, with intervals of 5 points. A lower score means more dependence; and a higher score, more independence.

Depression and Suicidal Ideation

To assess depression, we used the Spanish version (Fernández-San Martín et al., 2002) of the Geriatric Depression Scale (GDS-30; Yesavage et al., 1982). The internal consistency was .87.

The GDS-30 is a self-report scale designed to distinguish between depressed and non-depressed older people (Brink et al., 1982). The scale includes 30 items formulated as questions about the participant's mood state in the present, with a dichotomous yes/no response. The total number of responses is calculated according to the original scoring for the scale, and there are responses with negative and positive valences. Some items indicate depression when they are responded to positively (items 1, 5, 7, 9, 15, 19, 21, 27, 29 and 30), and the rest indicate depression when they receive a negative response. The total score ranges from 0 to 30, with the following cut-off scores: normal (score: 0-9); mild depression (score: 10-19); and severe depression (score: 20-30) (Yesavage et al., 1982).

In addition, we employed the GDS-SI factor from the GDS-30, which includes five items (3. Do you feel that your life is empty?; 9. Do you feel happy most of the time?; 15. Do you think it is wonderful to be alive?; 17. Do you feel pretty worthless the way you are now?; 22. Do you feel that your situation is hopeless?). A single positive response on items 3, 17, or 22, or a single negative response on items 9 or 15, was considered an indicator of indirect or passive risk of suicide (Heisel et al., 2005; 2010). Desseilles et al. (2012) demonstrated that a dimensional factor derived from a depression scale is a valid approach to evaluate SI. Previously, the SI subscale of the GDS-30 was used to detect passive SI in older people (Heisel et al., 2010; Uncapher & Sandberg, 1998) and in the MCI population (Cheng et al, 2010). We here maintained the SI denomination for this subscale as has usually been employed in the literature.

Table 1.
Characteristics of the study sample (mean and SD or percentages).

	Total sample (n=59)	MCI-AD (n=22)	MCI- Non AD (n=24)	HC (n=13)	F/X^2	Df	*p*
Female	29 (49.2%)	14 (63.6%)	7 (29.2%)	6 (61.5%)	6.480	2	.039
Age	67.29 (6.04)	70.18 (3.62)	67.29 (6.31)	62.38 (5.96)	8.601	2,55	.001
SES	5.24 (1.34)	5.27 (1.20)	5.17 (1.61)	5.31 (1.11)	0.049	2,55	.952
MMSE	26.95 (2.72)	26.00 (2.88)	26.63 (2.58)	29.15 (1.14)	6.976	2,56	.002
Barthel Index	97.74 (4.71)	98.82 (3.76)	96.56 (5.70)	97.78 (4.41)	0.947	2,39	.397
Educational level					14.229	6	.027
Primary school	25 (42.4%)	11 (50.0%)	13 (54.2%)	1 (7.7%)			
High school	17 (28.8%)	4 (18.2%)	5 (20.8%)	8 (61.5%)			
University	17 (28.8%)	7 (31.8%)	6 (25%)	4 (30.8%)			
Psychiatric History depression or/ and anxiety	14 (25%)	5 (25%)	4 (17.4%)	5 (38.5%)	1.967	2	.374
Type of psychiatric pathology					8.452	8	.391
Depression	8 (13.6%)	2 (9.1%)	2 (8.3%)	4 (30.8%)			
Anxiety	2(3.4%)	1 (4.5%)	1 (4.2%)	0 (0.0%)			
Depression and Anxiety	1(1.7%)	0 (0.0%)	1((4.2%)	0 (0.0%)			
Current psychiatric medication	10 (16.9%)	3 (13.6%)	4 (16.7%)	3 (23.1%)	.520	2	.771
Type of psychiatric medication					2.101	6	.910
Antidepressant	5 (8.5%)	2 (9.1%)	2 (8.3%)	1 (7.7%)			
Anxiolytic	2 (3.4%)	1 (4.5%)	1 (4.2%)	0 (0.0%)			
Antidepressant and anxiolytic	2 (3.4%)	0 (0.0%)	1 (4.2%)	1 (7.7%)			
No history of suicide	59 (100%)	22 (100%)	24 (100%)	12 (100%)			
No knowledge about diagnosis	45 (76.3%)	18 (81.8%)	21 (87.5%)	6 (46.2%)	29.091	4	.001

Note: HC= healthy controls; MCI-AD= mild cognitive impairment due to AD; MCI-Non-AD= mild cognitive impairment not due to AD; SES=Socioeconomic-status, MMSE= Mini-Mental State Evaluation

CSF biomarker collection

From 6-8 mL of CSF was collected using a standardized lumbar puncture procedure from 9 to 11 a.m. Aβ (Aβ42), P-tau, and T-tau were rated by the Innotest Elisa kit (Fujirebio Diagnostics, Ghent, Belgium) using a fully automated system (Lumipulse G, Fujirebio).

Procedure

Patients were recruited in the Alzheimer's Disease Research Group from the Neurology Consultation in the Hospital Universitari I Politècnic La Fe (Valencia). The established diagnostic research criteria of the National Institute of Aging-Alzheimer's Association (NIA-AA) for MCI due to AD were used to classify the participants (Albert et al., 2011; Jack et al., 2016; McKhann et al., 2011). The criteria included a neurological examination and usual diagnostic blood tests to rule out other causes of cognitive decline. After, CSF biomarkers for AD were determined (Jack et al., 2018) and neuroimaging (magnetic resonance imaging, MRI, and/or computerized axial tomography, CAT) was performed. Additionally, a global cognition assessment was carried out with the MMSE to categorize the participants' cognitive status. Finally, an interdisciplinary workgroup classified the participants in three groups based on the aforementioned criteria: MCI-AD, MCI-Non AD, and HC.

The MCI-AD group included participants with cognitive impairment (MMSE total score from 21 to 26), and positive biomarkers for AD (CSF Aβ < 725 pg.mL−1, P-tau > 485 pg.mL−1 and T-tau > 56 pg.mL−1) and neuroimaging. The MCI-Non AD group contained participants with cognitive impairment (MMSE total score from 21 to 26), and negative biomarkers for AD (CSF Aβ > 725 pg.mL−1, P-tau < 485 pg.mL−1 and T-tau < 56 pg.mL−1), and neuroimaging. Finally, the HC group contained participants with unimpaired cognition (MMSE total score ≥ 27), and negative biomarkers for AD. All participants were independent for the basic activities of daily living as informants reported (Barthel Index total > 95) (see Table 1). The participants in the MCI-Non AD group presented other neurological conditions (cognitive impairment unspecified not due to AD, vascular cognitive impairment, cognitive impairment due to Lewy body, frontal-temporal cognitive impairment, among others).

Data analysis

Data on the GDS were obtained for all participants, but there were six missing values for the CSF biomarkers (two in the MCI-Non AD group and four in the HC group).

To investigate differences between the groups (MCI-AD vs MCI-Non AD vs HC) in age, educational level, subjective socioeconomic status (SES), cognitive state (MMSE) and functional dependence (Barthel Index), one-way analyses of variance (ANOVAs) were performed. Group differences in sex, current psychiatric treatment, type of psychiatric treatment, and knowledge about the diagnosis the day of the neuropsychological evaluation were analyzed using Chi-square tests.

Before the statistical analyses were performed, Aβ, P-tau, and T-tau data were checked for normal distribution and homogeneity of variance using Kolmogorov–Smirnov and Levene's test. These analyses revealed significant deviations in the three CSF biomarker values; therefore, Aβ, P-tau, and T-tau data were logarithm 10 (Log10) transformed. Before performing the statistical analyses, participants who scored ± 3 SD from the mean were identified, and z scores were winsorized.

We performed univariate ANOVAs to investigate whether there were differences in depression and in SI between the three groups, including age, sex, SES, current psychiatric treatment, type of psychiatric treatment, and knowledge about the diagnosis as covariates. Then, we performed multivariate ANOVAs to investigate group differences in the three CSF biomarkers (Aβ, P-tau, and T-tau) controlling for the covariates. *Post-hoc* comparisons were performed using Bonferroni adjustments for p values.

Next, to test whether there was an association between depression or SI and the three CSF biomarkers for each group, separate linear regression analyses were performed, adjusted for covariates. To do this, we included depression or SI as the dependent variable; age, sex, SES, current psychiatric treatment, type of psychiatric treatment, and knowledge about the diagnosis as covariates in Step 1; and one CSF biomarker (Aβ, P-tau, and T-tau) as the independent variable in Step 2.

To perform these statistical analyses, version 25.0 of SPSS was used. All p values were two-tailed, and the level of significance was taken as $p \leq 0.05$.

Results

Differences in depression, SI, and CSF biomarkers between groups

Univariate ANOVAs revealed no significant group differences in depression (F (2,49) = 1.622, p = .208). However, the Group factor was significant in GDS-SI (F (2,49) = 3.349, p = .043), although post hoc analyses did not show significant differences between the three groups (all p > .095).

ANOVAs confirmed significant differences in the three CSF biomarkers (Aβ, P-tau, and T-tau) among the three groups (all $p \leq .002$) (Table 2). Specifically, the MCI-AD showed significantly lower Aβ levels and higher P-tau and T-tau than the MCI-Non AD (all $p \leq .002$) and HC (all $p \leq .022$) groups. However, there were no differences in Aβ, P-tau, or T-tau between the MCI-Non AD and HC groups (all p > 0.99).

Relationship between depression or SI and the CSF biomarkers

For the MCI-AD group, non-significant associations between depression and Aβ, P-tau or T-tau (all $p \geq .184$) were found. Moreover, results indicate a non-significant association between SI and Aβ (B=-.018, p=.952), although a significant negative association was observed between SI and both P-tau and T-tau (B=-.549, p=.026 and B=-.644, p=.003, respectively).

For the MCI-Non AD and HC groups, none of the associations between depression or SI and the CSF biomarkers were significant (all $p \geq .103$) (see Table 3).

Table 2.
Differences among the three groups in depression, SI, and CSF biomarkers.

	Total	MCI-AD	MCI-Non AD	HC			
	M (SD)	M (SD)	M (SD)	M (SD)	*F*	Df,e,t, tc	*p*
GDS	7.59 (5.64)	6.41 (5.18)	9.25 (6.016)	6.54 (5.30)	1.622	2,49	.208
GDS-SI	1.41 (1.08)	1.09 (1.02)	1.88 (1.19)	1.08 (0.64)	3.349	2,49	.043
Aβ (Lg)	2.83 (0.17)	2.71 (0.12)	2.91 (0.17)	2.93 (.09)	12,360	2,43,52,51	≤.001
P-tau (Lg)	1.79 (.23)	1.96 (0.17)	1.68 (.20)	1.67 (.19)	7,510	2,43,52,51	.002
T-tau (Lg)	2.54 (.31)	2.79 (0.22)	2.40 (.25)	2.31 (.21)	9,542	2,43,52,51	≤.001

Note. GDS= Geriatric Depression Scale; SI= Suicide Ideation; CSF= Cerebrospinal Fluid; Aβ = Amyloid-β; P-Tau= Hyperphosphorilated tau; T-tau = Total tau; MCI-AD = Mild Cognitive Impairment Alzheimer´s Disease; MCI-Non AD = Mild Cognitive Impairment Non Alzheimer´s Disease; HC= Healthy Controls; Lg = Logarithm 10.

Table 3.
Regression analyses with the CSF biomarkers as predictors and depression or SI as dependent variables after controlling for covariates for each group.

	MCI-AD			MCI-Non AD			HC		
	ΔR^2	*B*	*p*	ΔR^2	*B*	*p*	ΔR^2	*B*	*p*
				GDS					
Aβ	.075	.452	.184	.045	-.288	.363	.012	-.518	.548
P-Tau	.031	-.244	.400	.021	.215	.537	.027	-.575	.103
T-Tau	.011	-.150	.627	.001	-.038	.923	.016	-.436	.447
				GDS-SI					
Aβ	.000	-.018	.952	.108	-.462	.142	.002	-.129	.443
P-Tau	.208	-.644	.003	.008	.137	.701	.000	-.021	.889
T-Tau	.135	-.549	.026	.010	-.171	.666	.001	-.079	.544

Note. GDS= Geriatric Depression Scale; GDS-SI= Suicide Ideation; CSF= Cerebrospinal Fluid; Aβ = Amyloid-β; P-Tau= Hyperphosphorilated tau; T-tau = Total tau; MCI-AD = Mild Cognitive Impairment Alzheimer´s Disease; MCI-Non-AD = Mild Cognitive Impairment Non-Alzheimer´s Disease; HC= Healthy Controls.

Discussion

The first aim of this study was to assess differences in depression and SI between the MCI-AD, MCI-Non AD, and HC groups. We found no significant differences between the three groups in depression. However, we observed differences in SI between the three groups, although post-hoc analyses did not reach statistical significance. The second and main aim of this study was to analyze the association between depression or SI and the CSF AD biomarkers (Aβ, P-tau, and T-tau) in the three groups. Our results showed that in the MCI-AD group, higher SI was related to lower P-tau and T-tau levels. However, no association was observed between depression or SI and the AD biomarkers in the MCI-Non AD or HC groups.

Contrary to our hypothesis, we did not find significant differences between the three groups in depression. In this line, previous studies comparing the occurrence of psychiatric disorders across different dementia subtypes also found a lower incidence of depression and suicidal behavior in AD compared to other dementias (Lai et al., 2018; Rao et al., 1997). Similarly, our results also showed significant differences in SI, assessed by the GDS-SI, among the three groups. The MCI-AD group obtained similar SI scores than HC group and lower SI scores than the MCI-Non AD group, although post-hoc analyses were not significant. Future studies with larger samples and statistical power must confirm this result.

Regarding differences among the three groups in the three CSF biomarkers, as expected, the MCI-AD group showed lower Aβ and higher P-tau and T-tau levels, compared to the MCI-Non AD and HC groups as was hypothesized by several authors (Albert et al., 2011; Ekman et al., 2018; Jack et al., 2016). Moreover, the associations between depression or SI and the CSF biomarkers were only observed in the MCI-AD group. In a review, Banning et al. (2019) failed to observe an association between affective symptoms, including depression, and Aβ. Supporting this idea, López et al. (2003) reported that depression was less frequent in patients with severe cognitive deficits than in those with mild/moderate cognitive deficits. Therefore, these authors suggested that the progression of AD pathology, which gradually encompasses all the cortical structures, may limit the patients' insight and ability to communicate depressive symptoms (López et al., 2003). In this line, Conejero et al. (2018a) concluded that late-stage dementia could protect against SI and SA, whereas the risk of complete suicide would increase during the early phases of cognitive decline.

In addition, in the MCI-AD group, we did not observe an association between depression and P-tau or T-tau. Supporting this finding, two recent reviews reported that most of the studies failed to observe an association between depression and tau pathology (Banning et al., 2019; Ng et al., 2021). Furthermore, the fact that an association has been observed between depression and Aβ, but not with tau (Ng et al., 2021), could be because Aβ changes occur before increases in tau in CSF (Braak et al., 2013). Thus, it has been hypothesized that depression is a sign of early AD pathology before significant tau deposition exists. However, although Ng et al. (2021) reported that most of the studies did not observe an association between neuropsychiatric symptoms and tau pathology, only one study measured AD biomarkers in CSF (Babulal et al., 2016). Specifically, these authors demonstrated that higher baseline CSF T-tau levels were not related to neuropsychiatry symptoms, but they predicted changes in mood in normal older adults (Babulal et al., 2016), demonstrating that an association between CSF tau levels and neuropsychiatry symptoms exists.

Our results showed that GDS-SI scores or indirect risk of suicide was negatively related to tau levels only in the MCI-AD. Although Conejero et al. (2018a) highlighted the importance of analyzing

the association between SI and AD biomarkers in initial phases of dementia, to our knowledge, this association has not yet been analyzed. However, significant associations between suicide and AD biomarkers have been reported in some postmortem studies (Dean et al., 2020; Stepien et al., 2021) but not in other (Yoshida et al., 2019). We observed that higher SI were related to lower levels of P-tau and T-tau, indicating lower AD pathology. As increases in tau in CSF occur in later stages of AD than Aβ changes (Braak et al., 2013), our results could suggest that SI appears in a more advanced stage of MCI when tau pathology is detectable. However, we did not observe an association between SI and Aβ in the MCI-AD group. Thus, our results could be supported by the dual pathway model of AD, which suggests that these two AD biomarkers may follow independent mechanisms (Small & Duff, 2008).

However, when we considered the MCI-Non AD group, we did not find an association between depression or SI and CSF AD biomarkers. In previous research, other dementia syndromes have also been associated with altered CSF Aβ and tau levels, although to a lesser degree than AD (Schoonenboom et al., 2012). Our results suggest that tau levels are related to SI in MCI-AD, but not in other MCI subtypes. Hence, these results highlight the importance of analyzing these associations in each type of MCI. Previous studies have included the different MCI subtypes together, which could explain the heterogeneous findings observed in the literature (Banning et al., 2019).

Finally, in the HC group, the three CSF biomarkers were not significantly related to depression or SI. In contrast to this result, Pomara et al. (2012) observed that, in healthy older adults, those with major depression showed lower CSF Aβ compared to participants without depression, but no differences were observed in their CSF P-tau and T-tau levels. However, Babulal et al. (2020) reported that higher CSF and PET biomarkers were associated with mood changes in cognitively normal older adults. Thus, it is possible that with a larger sample and greater statistical power, associations between CSF AD biomarkers and both depression and SI could be observed.

Our results could have important practical implications. Depression is the most recognized neuropsychiatric symptom in MCI (Martin & Velayudhan, 2020). However, depression is misinterpreted as a normal process in aging (Linnemann & Leyhe, 2015), and so it is underdiagnosed and not appropriately treated in a variety of comorbid medical conditions such as AD or MCI (Hussain et al., 2020). Nevertheless, depression strongly affects patients, families, and caregivers' quality of life (Conde-Sala et al., 2014). Therefore, professionals should include more extended protocols for the evaluation of factors associated with depression and suicide risk such as hopelessness and psychological pain in MCI patients, in order to achieve the early detection and management of this symptomatology in this vulnerable population (Pérez-Rodríguez et al., 2017). Moreover, biomarkers could help to detect patients at higher risk of suicide. In this study, in the MCI-AD group, tau biomarkers were related to indirect risk of suicide. Thus, some CSF biomarkers may be considered in the early detection of these neuropsychiatric symptoms in MCI-AD patients.

Some limitations should be considered. First, it is important to note the correlational nature of the results, and so we cannot claim causal relationships. In addition, the sample size is relatively small, which could increase the changes type II error. Nevertheless, it is important to highlight the effort made to recruit not only clinical samples but also HC, incorporating both neurology consultation and lumbar punction to obtain the three CSF biomarkers. Moreover, this study also has other strengths, such as the fact that AD biomarkers were assessed in CSF, which is considered the best approach to identify them (Blennow et al., 2018). Finally, participants were classified as MCI-AD, MCI-Non AD, or HC by considering the biomarkers, as it is recommended by the NINCDS-ADRDA. Thus, this study may help to shed light on the association between depression and SI and AD biomarkers in patients with MCI.

In conclusion, our results showed that the MCI-AD group did not present significant differences in depression and SI in comparison to the MCI-Non AD and HC groups. However, only in the MCI-AD group, lower AD pathology (lower P-tau and T-tau) was related to higher indirect risk of suicide. This result highlights the importance of considering the potential role of some AD biomarkers in the early detection of these symptoms.

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