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Relationship between cortical thickness and cerebrospinal fluid YKL-40 in predementia stages of Alzheimer's disease

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ABSTRACT

Cerebrospinal fluid YKL-40 has been described as a marker of glial inflammation. We aimed to study the relationship between YKL-40 and brain structure and its interactions with core Alzheimer's disease (AD) biomarkers. We measured cortical thickness (CTh) and cerebrospinal fluid biomarkers (amyloid-β 1–42 [Aβ42], total tau, p-tau, and YKL-40) of 80 cognitively normal controls and 27 patients with amnestic mild cognitive impairment. Subjects were classified as Aβ42+ (<550 pg/mL) or Aβ42− (>550 pg/mL). CTh difference maps were derived from the interaction and correlation analyses in the whole sample and within clinical groups. There was a strong correlation between YKL-40 and markers of neurodegeneration (total tau and p-tau). In the whole sample, we found a negative correlation between YKL-40 and CTh in AD vulnerable areas in Aβ42+ subjects but not in Aβ42 participants. Our results suggest that YKL-40 could track the inflammatory processes associated to tau-related neurodegeneration in the presence of the AD pathophysiological process.

1. Introduction

Alzheimer's disease (AD) is a complex disease where multiple pathophysiological processes coexist (Blennow et al., 2006). Different cerebrospinal fluid (CSF) and neuroimaging biomarkers allow us to track these distinct processes (Alcolea et al., 2014a; Fagan and Perrin, 2012). In CSF, the levels of amyloid-β 1–42 (Aβ42) reflect the amyloid deposition in the brain in subjects with AD pathophysiological process (Fagan et al., 2006; Strozyk et al., 2003; Tapiola et al., 2009), whereas the levels of total tau (t-tau) and phospho-tau (p-tau) correlate with neurodegeneration, neuronal loss, and cortical neurofibrillary burden (Buerger et al., 2006; Tapiola et al., 2009). Neuronal loss can also be studied measuring cortical thickness (CTh) with magnetic resonance imaging (MRI) (Dickerson et al., 2009; Fischl and Dale, 2000). Together, these biomarkers have been used to detect biological evidence of the AD pathophysiological process. Therefore, the use of biomarkers allows to stage the preclinical phase of AD (Sperling et al., 2011), to identify patients with mild cognitive impairment (MCI) because of AD (Albert et al., 2011), and to increase the level of certainty in the diagnosis of dementia because of AD (McKhann et al., 2011).

Inflammation is another common factor in the pathogenesis of AD (Akiyama et al., 2000) and can also be studied through

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biomarkers. Several molecules have been investigated in plasma and in CSF as markers of inflammation in AD (Fagan and Perrin, 2012). One of them, YKL-40 (also known as chitinase 3–like 1 protein), has been described as a marker of glial inflammation (Craig-Schapiro et al., 2010; Mattsson et al., 2011). In the previous studies, we and others have found that levels of CSF YKL-40 are higher in AD and in other neurodegenerative conditions than in cognitively normal (CN) controls (Alcolea et al., 2014a; Antonell et al., 2014; Craig-Schapiro et al., 2010; Mattsson et al., 2011; Olsson et al., 2013). Some of these studies also found changes in predementia stages, where YKL-40 has been reported to be higher in subjects with CSF evidence of the AD pathophysiological process (Alcolea et al., 2014a; Antonell et al., 2014). Additionally, the previous studies have reported a strong correlation between CSF YKL-40 and markers of neuronal degeneration (t-tau and p-tau) (Alcolea et al., 2014a; Antonell et al., 2014; Craig-Schapiro et al., 2010; Olsson et al., 2013).

Multimodal studies are essential to disentangle the complex pathophysiological processes that occur in the early stages of AD. In this respect, different studies have explored the relationship between biomarkers in CSF and structural markers in MRI (Desikan et al., 2011; Fagan et al., 2009; Fortea et al., 2014; Mattsson et al., 2014). Specifically, a pattern of atrophy in AD vulnerable areas has been described associated with CSF markers of neurodegeneration (t-tau and p-tau). We described a CSF Aβ42-p-tau interaction affecting brain structure in preclinical AD (Fortea et al., 2014), emphasizing the need to consider interactions to capture pathogenic synergies.

To our knowledge, the relationship between CSF YKL-40 and brain structure has not been previously assessed. In this respect, we hypothesize that YKL-40 in CSF, because of its strong correlation with markers of neurodegeneration, is also associated with structural markers in MRI such as CTh. In particular, our aims were to analyze the relationship between CSF YKL-40 (and markers of neurodegeneration) and CTh in a large cohort of nondemented subjects and to investigate how CSF Aβ42 can affect this relationship.

2. Material and methods

2.1. Study participants and clinical classification

We included 80 CN subjects and 27 patients with amnestic MCI (aMCI) evaluated at Hospital de Sant Pau, Barcelona (HSP, $n = 82$) and Hospital Marqués de Valdecilla, Santander ($n = 25$). All subjects underwent a lumbar puncture and 3-T MRI. CN subjects had a neuropsychological evaluation (Sala et al., 2008) in normal range for age and education, and subjects with aMCI met Petersen criteria (Petersen, 2004). All participants gave their written consent, and the study was approved by the local ethics committee at each center.

2.2. CSF analyses

CSF was obtained through lumbar puncture and collected following international consensus recommendations as described (Alcolea et al., 2014b; Del Campo et al., 2012). Briefly, CSF was collected in polypropylene tubes and immediately centrifuged (1900–2000*g* for 10 minutes) to avoid hematic contamination. All samples were stored in polypropylene tubes at −80 °C and shipped in dry ice to HSP, where they were analyzed. We used commercially available enzyme-linked immunosorbent assay kits to determine the levels of Aβ42 (Innotest β-amyloid$_{1–42}$; Fujirebio Europe), t-tau (Innotest hTAU Ag; Fujirebio Europe), p-tau (Innotest Phospho-Tau$_{181P}$; Fujirebio Europe), and YKL-40 (MicroVue; Quidel) following the manufacturers' recommendations. Our laboratory has experience in CSF biomarker determination and participates in the Alzheimer's Association external quality control program for CSF biomarkers (Alcolea et al., 2014a; Mattsson et al., 2013).

2.3. CSF classification

According to the CSF analysis, participants were classified as Aβ42+ (CSF Aβ42 <550 pg/mL) or Aβ42− (CSF Aβ42 >550 pg/mL). The internal diagnostic accuracy of this cutoff point had been previously assessed in a cohort of 45 patients with dementia of the Alzheimer type and 20 age-matched controls and had a sensitivity of 91.1% and a specificity of 75.0% (Alcolea et al., 2014a).

2.4. MRI acquisition

2.4.1. HSP procedure

The 3-T MRI scanner Philips 3T X Series Achieva was used. A high-resolution 3-dimensional structural dataset was acquired with the following parameters: T1-weighted magnetization-prepared rapid gradient echo; repetition time, 8.1 milliseconds; echo time, 3.7 milliseconds; slices, 160; matrix size, 240 × 234; slice thickness, 1 mm; and voxel size, 0.94 × 0.94 × 1 mm.

2.4.2. Hospital Marqués de Valdecilla, Santander, procedure

The 3-T MRI scanner Philips 3T X Series Achieva was used. A high-resolution 3-dimensional structural dataset was acquired

Table 1
Demographics and biomarker characteristics of the participants

	All	CN	CN Aβ42−	CN Aβ42+	aMCI	aMCI Aβ42−	aMCI Aβ42+
n	**107**[d]	**80**[d]	71	9	**27**[d]	15	12
Age, y	**62.27 (9.10)**[d]	**59.99 (8.57)**[d]	59.6 (8.66)	63.12 (7.53)	**69.02**** **(7.16)**	69.09 (7.97)	68.93 (6.35)
Gender, F (%)	**74 (69.2)**[d]	**55 (68.8)**[d]	49 (69.0)	6 (66.7)	**19 (70.4)**[d]	10 (66.7)	9 (75.0)
Education, y	**12.93 (5.06)**[d]	**13.39 (4.87)**[d]	13.54 (4.76)	12.22 (5.89)	**11.59 (5.43)**[d]	12.53 (5.11)	10.42 (5.82)
APOE ε4+, *n* (%)	**37 (34.6)**[d]	**25 (31.3)**[d]	19 (26.8)	6[a] (66.7)	**12 (44.4)**[d]	4 (26.7)	8[b] (66.7)
MMSE	**28.43 (3.88)**[d]	**28.65 (4.38)**[d]	28.68 (4.64)	28.44 (1.24)	**27.78 (1.53)**[d]	27.73 (1.39)	27.83 (1.75)
CSF Aβ42, pg/mL	**730.57 (204.11)**[d]	**755.94 (182.60)**[d]	793.73 (155.18)	457.78[a] (76.44)	**655.39*** **(246.37)**	839.53 (157.81)	425.21[c] (87.94)
CSF t-tau, pg/mL	**251.1 (176.85)**[d]	**219.79 (148.64)**[d]	214.01 (100.49)	265.33 (356.65)	**343.89**** **(220.04)**	256.3 (112.61)	453.38[c] (273.43)
CSF p-tau, pg/mL	**48.02 (26.09)**[d]	**43.55 (23.30)**[d]	42.88 (15.11)	48.83 (57.70)	**61.26**** **(29.69)**	47.5 (15.50)	78.46[b] (34.59)
CSF YKL-40, ng/mL	**210.39 (50.27)**[d]	**200.37 (47.34)**[d]	202.69 (44.94)	182.12 (63.54)	**240.07**** **(47.64)**	230.32 (44.16)	252.27 (50.90)

Unless otherwise specified, values are presented as mean (standard deviation). *$p = 0.05$ compared with CN and **$p < 0.05$ compared with CN.
Key: aMCI, amnestic mild cognitive impairment; APOE, apolipoprotein E; Aβ42, amyloid-β 1–42; Aβ42−, CSF Aβ42 >550 pg/mL; Aβ42+, CSF Aβ42 <550 pg/mL; CNs, cognitively normal subjects; CSF, cerebrospinal fluid; F, female; MMSE, Mini-Mental State Examination; p-tau, phospho-tau; t-tau, total tau.
[a] $p < 0.05$ compared with CN Aβ42−.
[b] $p = 0.05$ compared with aMCI Aβ42−.
[c] $p < 0.05$ compared with aMCI Aβ42−.
[d] No significant differences compared with CN.