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Featured Article

Two-level diagnostic classification using cerebrospinal fluid YKL-40 in Alzheimer's disease

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Abstract

Introduction: We assessed the diagnostic accuracy of cerebrospinal fluid (CSF) YKL-40 in discriminating (1) clinical Alzheimer's disease (AD) from cognitively healthy controls (HCs) and frontotemporal dementia (FTD) (level I) and (2) patients stratified by different pathophysiological profiles from HCs and FTD following a novel unbiased/descriptive categorization based on CSF biomarkers, independent of cognitive impairment severity (level II).

Methods: YKL-40 was compared among HCs (n = 21), mild cognitive impairment (n = 41), AD (n = 35), and FTD (n = 9) (level I) and among HCs (n = 21), AD pathophysiology (tau and amyloid β) negative (n = 15), tau positive (n = 15), amyloid β positive (n = 13), AD pathophysiology positive (n = 33), and FTD (n = 9) (level II).

Results: Level I: YKL-40 discriminated AD from HC and FTD (area under the receiver operating characteristic curves [AUROCs] = 0.69, 0.71). Level II: YKL-40 discriminated tau-positive individuals and AD pathophysiology–positive individuals from HC, AD pathophysiology–positive patients from FTD (AUROCs = 0.76, 0.72, 0.73).

Discussion: YKL-40 demonstrates fair performance in distinguishing tau-positive patients from HCs, suggesting it may aid clinical diagnosis and support a biomarker-guided pathophysiological stratification.

Keywords: Alzheimer's disease; Biomarkers; Biomarker-based diagnosis; Cerebrospinal fluid; Clinical diagnosis; Dementia; Diagnostic biomarkers; Frontotemporal dementia; Mild cognitive impairment; Neurodegeneration; Neuroinflammation; YKL-40

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1. Introduction

Alzheimer's disease (AD) is a genetically, biologically, and clinically heterogeneous multifactorial disease [1–3]. The primary pathological hallmarks are amyloid plaques consisting of aggregated amyloid β (Aβ) and neurofibrillary tangles containing hyperphosphorylated and aggregated tau protein [3]. However, in most of patients, AD-related brain changes are combined with other types of pathologies [4,5]. Currently, three core, feasible cerebrospinal fluid (CSF) biomarkers have shown to track pathophysiological mechanisms in vivo in preclinical, prodromal, and AD dementia [6,7]. In particular, (1) CSF concentrations of the Aβ 1–42 ($A\beta_{1–42}$) peptide are considered a biomarker of brain amyloid deposition, (2) total tau (t-tau) protein is considered a marker of neuronal injury in several brain diseases (not pathognomonic for AD), and (3) hyperphosphorylated tau (p-tau) protein is considered a marker reflecting hyperphosphorylation of tau leading to the formation of paired helical filaments and ultimately neurofibrillary tangles [8]. Although neuroinflammation has been consistently suggested with accumulating evidence to contribute as an additional pathophysiological mechanism to AD [1,9], a clinically validated and standardized CSF inflammation biomarker for both diagnosis and as an indicator of mechanism of action in trials has not yet been developed.

In particular, YKL-40, a glycoprotein belonging to the chitinase-like proteins group, represents a promising candidate inflammation biomarker in progressive clinical development for AD. However, its pathophysiological functions are not yet fully clarified [10]. YKL-40 is a differentiation marker of macrophages [11–13] and is expressed in microglia and astroglia within the central nervous system [14].

Recently, in first clinical investigations, statistically significant elevated CSF concentrations of YKL-40 were reported in AD compared with cognitively healthy controls (HCs), in agreement with reported increased concentrations at the prodromal and preclinical stages [15–28].

The main objective of this study was to assess the diagnostic accuracy of CSF YKL-40 in diagnosing and categorizing individuals with cognitive impairment.

In a first step (level I), we tested the performance of YKL-40 in discriminating clinically diagnosed patients with AD dementia from both HC subjects and patients with frontotemporal dementia (FTD).

In a second step of analysis (level II) [4], we evaluated the classificatory performance of YKL-40 across the spectrum of AD pathology by adopting a recently published unbiased descriptive categorization system based on biomarker-guidance only, namely the "A/T/N" scheme, using AD core biomarkers. The A/T/N system comprises three binary components: A = Aβ pathology, T = tau pathology, and N = neurodegeneration for characterizing features of AD pathology/pathophysiology (independently from the severity of cognitive impairment). To this end, we determined the discriminatory performance of CSF YKL-40 in distinguishing HCs from (1) AD pathology patients (presenting both decreased CSF concentrations of $A\beta_{1–42}$ peptide and increased t-tau or p-tau protein [7]), (2) patients showing tau pathology only, and (3) patients with Aβ pathology only. In addition, we explored the ability of CSF YKL-40 to discriminate AD pathology patients from FTD cases.

2. Methods

2.1. Population

A total of 135 individuals from a convenience sample were examined. Of these participants, 27 were excluded because of missing data in one or more CSF biomarkers and the remaining 108 were included in the present study. Clinical and biological data from these 108 individuals (AD = 35, FTD = 9, MCI = 41, and cognitively HC = 23) were retrospectively collected in a multicenter cross-sectional study involving three independent academic AD research centers and expert memory clinics. Thirty-five subjects were recruited at the Institute of Memory and Alzheimer's Disease (IM2A) at Pitié-Salpêtrière University Hospital in Paris (France); 57 at the German Center for Neurodegenerative Diseases (DZNE) in Rostock (Germany); 16 at the Institute of Neuroscience and Physiology at Sahlgrenska University Hospital in Göteborg (Sweden).

The study was conducted according to the provisions of the Declaration of Helsinki. All participants or their representatives gave written informed consent for the use of their clinical data for research purposes and the local ethical committees at the respective universities approved the study. We followed the Standards for Reporting Diagnostic Accuracy Studies (STARD) criteria for the reporting of diagnostic test accuracy studies (available at http://www.equator-network.org/reporting-guidelines/stard/).

2.2. Patient stratification

2.2.1. Level I (purely clinical diagnostic approach)

The first group was composed of 23 cognitively HC subjects. Two individuals from the Göteborg cohort were identified as asymptomatic at-risk of AD [7] or preclinical AD [29] showing high CSF t-tau concentrations. Although tau positivity is a criterion which pertains purely to level II, we decided to exclude two asymptomatic subjects showing positivity to CSF t-tau from the HC group to perform both level I and level II analyses on identical populations. The second group included 41 subjects with MCI [6]. The third group included 35 patients with AD dementia [30]. Finally, the fourth group included nine patients with FTD [31] (Fig. 1). The clinical diagnosis of AD dementia was performed according to the National Institute of