Neuropsychiatric Contributions to Alzheimer's Disease

Cerebrospinal fluid biomarker examination as a tool to discriminate behavioral variant frontotemporal dementia from primary psychiatric disorders

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Abstract

Introduction: To prospectively determine the diagnostic value of cerebrospinal fluid (CSF) levels total-tau (tau) to amyloid-β_{1-42} ratio ($A\beta_{1-42}$) ratio (tau/$A\beta_{1-42}$ ratio), phosphorylated-tau (p-tau) to tau ratio (p-tau/tau ratio), neurofilament light chain (NfL) and YKL40 in the late-onset frontal lobe syndrome, in particular for the differential diagnosis of behavioral variant frontotemporal dementia (bvFTD) versus primary psychiatric disorders (PSY).

Method: We included patients with a multidisciplinary 2-year-follow-up diagnosis of probable/definite bvFTD ($n = 22$) or PSY ($n = 25$), who underwent a detailed neuropsychiatric clinical examination, neuropsychological test battery, and magnetic resonance imaging at baseline. In all cases, CSF was collected through lumbar puncture at baseline. We compared CSF biomarker levels between the two groups and measured the diagnostic accuracy for probable/definite bvFTD, using the follow-up diagnosis as the reference standard.

Results: The best discriminators between probable/definite bvFTD and PSY were the levels of CSF NfL (area under the curve [AUC] 0.93, $P < .001$, 95% confidence interval [CI] 0.85–1.00), p-tau/tau ratio (AUC 0.87, $P < .001$, 95% CI 0.77–0.97), and YKL40 (AUC 0.82, $P = .001$, 95% CI 0.68–0.97). The combination of these three biomarkers had a sensitivity of 91% (95% CI 66%–100%) at a specificity of 83% (95% CI 65%–95%) with an AUC of 0.94 ($P < .001$, 95% CI 0.87–1.00) for bvFTD. CSF tau/$A\beta_{1-42}$ ratio was less accurate in differentiating between bvFTD and PSY.

Discussion: We found a good diagnostic accuracy for higher levels of CSF NfL and YKL40 and reduced p-tau/tau ratio in distinguishing bvFTD from PSY. We advocate the use of these CSF biomarkers as potential additional tools to neuroimaging in the diagnosis of bvFTD versus PSY.

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Keywords: Frontotemporal dementia; Psychiatric disorders; Cerebrospinal fluid; Biomarker; Neurofilament; p/t ratio; YKL40

1. Introduction

Clinical differentiation between behavioral variant frontotemporal dementia (bvFTD) from primary psychiatric disorders such as major depressive disorder, bipolar disorder (BD), or schizophrenia (SZ) forms a great challenge due to symptomatic overlap [1,2]. These disorders share clinical features that are generally characterized by changes in the regulation of social, interpersonal, and personal conduct and cognitive impairment. For example, the neuropsychiatric feature apathy is frequently present in

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both bvFTD and primary psychiatric disorders [3]. Although bvFTD and primary psychiatric disorders can often be discriminated through imaging techniques, these investigations have a relatively low sensitivity (magnetic resonance imaging [MRI]) or specificity ([^{18}F]-fluorodeoxyglucose–positron emission tomography ([^{18}F]FDG-PET)) [4]. Therefore, ancillary biomarkers that are able to distinguish between bvFTD and primary psychiatric disorders at a higher accuracy are needed. Apart from patient management perspectives, this is becoming even more important in light of future treatment development in both bvFTD and primary psychiatric disorders.

Cerebrospinal fluid (CSF) biomarkers are of great potential because they are considered to reflect pathological processes taking place in the brain. CSF biomarkers have proven to be of great diagnostic value in the diagnosis of Alzheimer's disease (AD), whereby levels of CSF total-tau (CSF tau) and phosphorylated-tau (CSF p-tau$_{181}$) are increased, and levels of CSF amyloid-β_{1-42} (CSF Aβ_{1-42}) are decreased reflecting amyloid plaque load and severity of neurodegeneration, respectively [5].

For bvFTD, several studies investigated the utility of CSF biomarkers. However, in contrast to AD, the pathology of the clinical phenotype bvFTD is heterogeneous and consists of either TAR-DNA binding protein 43 (TDP43) inclusions or tau pathology in most cases, whereas a smaller proportion (<10%) has fused in sarcoma protein pathology [6]. Because most CSF studies in FTD rely on clinically diagnosed cases, various results have been found regarding the conventional biomarkers (CSF tau, p-tau$_{181}$, and Aβ_{1-42}). More recently, however, a decreased phosphorylated-tau to total-tau ratio (p-tau/tau ratio), increased CSF neurofilament light chain (NfL), and YKL40 have been identified as markers of underlying TDP43 pathology in FTD [7–10], whereas these markers have also been found to be accurate for subjects with underlying tau pathology and correlated with survival [9]. In addition, NfL is a marker for axonal dysfunction or degeneration and YKL40 (chitinase-3 like-1, cartilage glycoprotein-39) is a glycoprotein that is produced by activated microglia and reflects inflammatory processes [11,12].

Although primary psychiatric disorders are considered to lack neuropathological changes, several CSF biomarkers have been investigated in psychiatric illnesses based on the persistence of cognitive impairment in euthymic or remitted patients [13] or on morphological abnormalities of the brain [14]. For example, in patients with BD, levels of CSF NfL and YKL40 were found to be higher than in healthy controls [15,16], whereas levels of CSF Aβ_{1-42}, tau and p-tau$_{181}$ were found to be similar compared with healthy controls [17]. In SZ, CSF Aβ_{1-42} was found to be significantly lower with equal levels of tau and p-tau$_{181}$ compared to healthy controls [18]. Thus, although there is some evidence of axonal dysfunction in primary psychiatric disorders, it is unknown to what extent levels of CSF biomarkers are elevated or decreased compared to bvFTD patients.

Therefore, in the present study, we aim to prospectively determine the diagnostic value of CSF levels of total-tau to amyloid-β_{1-42} ratio (tau/Aβ_{1-42} ratio), p-tau/tau ratio, NfL, and YKL40 in a cohort presenting with a late-onset frontal lobe syndrome, in particular for the differential diagnosis of bvFTD versus primary psychiatric disorders. By selecting bvFTD and a heterogeneous group of primary psychiatric disorders, this study resembles a daily clinical practice where different primary psychiatric disorders can overlap with bvFTD.

2. Methods

2.1. Participants

All subjects were participants of the late-onset frontal lobe (LOF) study, a multicenter prospective study conducted between April 2011 and June 2015 [19]. In the LOF study, 137 patients who presented with behavioral changes consisting of apathy, disinhibition, and/or compulsive/stereotypical behavior between 45 and 75 years of age were included. Patients were included in the study when they had a score ≥11 on the Frontal Behavioural Inventory [20] or a score ≥10 on the Stereotypy Rating Inventory [21]. All patients received full neurological and psychiatric examination at baseline and at 2-year follow-up. Cognitive screening tests included the Mini–Mental State Examination [22], the frontal assessment battery [23], and a neuropsychological battery concerned the domains of attention/concentration, memory, language, visuospatial, executive, and social functioning. Psychiatric evaluation included an interview by a psychiatrist, the Montgomery Aberg Depression Rating Scale [24] for depressive symptoms, the positive and negative symptom scale for psychotic symptoms [25], and the MINI-PLUS Diagnostic interview [26] to assess primary psychiatric disorders. A consensus diagnosis between the neurologist and the psychiatrist was made at baseline based on the clinical information and additional investigations, including results of conventional CSF biomarkers (CSF tau, p-tau$_{181}$, and Aβ_{1-42}; ratio was not used), MRI, and [^{18}F]FDG-PET. After 2 years of follow-up, the neuropsychiatric examination, neuropsychological tests, and the MRI of the brain were repeated, followed by establishment of the final multidisciplinary diagnosis. Diagnoses were based on the consensus guidelines for various types of dementia including the frontotemporal dementia consensus criteria, and the psychiatric diagnoses were based on current psychiatric criteria [27–32].

From the original LOF cohort of 137 cases included at baseline, a total of 21 patients were excluded at follow-up. Three patients were excluded from the final analysis with a 2-year follow-up diagnosis of possible bvFTD, whereas three patients died without postmortem verification or a clear clinical diagnosis. Fifteen patients were lost to follow-up.

For the present study, we included participants with a final multidisciplinary diagnosis at 2-year follow-up who had undergone a diagnostic lumbar puncture at baseline with either