# Frontotemporal Dementia

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Frontotemporal dementia (FTD) is a heterogeneous group of neurodegenerative disorders characterized by a combination of behavioral changes, social cognitive impairment, language and memory impairments, and executive function deficits. These clinical symptoms result from the prominent degeneration of neurons in the frontal and temporal lobes associated with diverse underlying pathology.

Keywords: neurofilaments ; blood biomarkers ; behavioral frontotemporal dementia ; neuropsychiatry ; diagnosis ; single molecular array

## 1. Introduction

FTD is divided into three major clinical syndromes: The behavioral variant (bvFTD) [1] and the two language variants referred to as semantic or non-fluent primary progressive aphasias [2]. The diagnosis of bvFTD is challenging because cognitive impairment may be absent or subtle in the early stages, and initial symptoms, including behavioral disinhibition, apathy, lack of empathy, dietary changes, and compulsions, may be suggestive of primary psychiatric disorders (PPD). This clinical overlap with late-onset PPD leads to a high rate of misdiagnosis at the initial stages of bvFTD. Indeed, in a large retrospective study, about 50% of bvFTD patients received a prior diagnosis of a psychiatric disorder [3]. This led international experts to recently publish consensus recommendations to distinguish bvFTD from PPD [4].

Thus, biomarkers with the potential to accurately discriminate between late-onset PPD and bvFTD are needed to help early diagnosis and to initiate appropriate patient management. CSF and blood neurofilament proteins, which are axonal structural proteins, have emerged as biomarkers of axonal damage in various neurological disorders [5]. Moreover, neurofilament light chains' (NfL) detection from peripheral blood samples is now possible with ultrasensitive analytic platforms [6]. This convenient and less invasive option than CSF assessments could be especially suited for neuropsychiatric differential diagnostic.

## 2. Biomarkers to Support the Diagnosis

Apart from genetically proven cases, definitive biomarkers for the diagnosis of bvFTD are lacking. Routine CSF biomarkers (amyloid-β, t-tau, and p-tau) are helpful to distinguish FTD from AD and are listed in the exclusionary criteria of bvFTD [1]. Currently, as no specific CSF biomarker pattern has been identified in FTD [7], they are of no help to distinguish FTD from PPD.

The 2011 consensus criteria [1] introduced imaging biomarkers (structural or functional imaging) as possible tools to increase diagnostic probability. Disproportional atrophy in the medial frontal, orbital–insular, and anterior temporal regions on brain MRI are observed in bvFTD patients [8]. However, a neuropathologically confirmed cohort showed that 50% of bvFTD patients were lacking these typical MRI features, reflecting the low sensitivity of structural brain imaging in bvFTD patients, especially at the early stages of the disease [9]. This is in line with the idea that clinical and functional abnormalities may precede structural imaging changes in the disease course, as shown by brain functional imaging. However, a study assessing the added value of [18 F]-FDG-PET in patients with suspected bvFTD and normal structural MRI reported a sensitivity of only 47%, while the specificity was high (92%) [10]. A report from the Late-Onset Frontal Lobe Syndrome Study (an observational prospective follow-up of patients with late-onset frontal behavioral change consisting of apathy, disinhibition, or compulsive/stereotypical behavior) found that the specificity of [18 F]-FDG-PET might be lower in bvFTD patients with initial psychiatric presentation [11].

### Neurofilaments as Emerging Biomarkers in Neurological Disorders and Frontotemporal Dementia

Neurofilaments (Nf) are neuronal-specific cytoskeleton filaments. They are composed of heteropolymers of three subunits, namely, neurofilament heavy, medium, and light (NfH, NfM, and NfL) that assemble to form long and thin intermediate filaments. Nf are expressed throughout the whole cell and are especially enriched in the axonal region. Thus, axonal injury causes the release of Nf proteins into the extracellular fluid, the amount depending on the extent of damage [12]. Interestingly, Nf subunits levels can be measured in CSF and, more recently, in peripheral blood using high-sensitivity detection techniques such as the single molecule array (Simoa™) assays [13].

Consequently, numerous studies have demonstrated that levels of Nf proteins, especially NfL in CSF and plasma, are increased in a wide range of neurological diseases [5]. Both CSF and serum NfL, for instance, have been extensively studied in multiple sclerosis in which they revealed to be interesting biomarkers for assessment of disease activity, prognosis, and drug response [14][15]. CSF NfL have also been studied in various neurodegenerative disorders. Two cohort studies demonstrated that CSF NfL levels can effectively differentiate Parkinson's disease from atypical parkinsonian disorders [16][17]. In ALS, CSF NfL levels are especially high, which aids differential diagnosis and correlates with disease extent and prognosis [18][19][20]. Among neurocognitive degenerative disorders, a mild elevation of NfL has been reported in Alzheimer's disease [21], but levels are consistently higher in FTD [22]. In addition, both CSF and serum NfL levels seem to correlate with the severity of the disease, either measured by survival rates [23] or frontal lobe atrophy rate [24] in FTD patients.

## 3. Conclusions

Due to a significant symptomatic overlap, differentiating bvFTD from PPD is a frequent diagnostic challenge. Biomarkers used currently in clinical practice to facilitate this diagnostic process have limited sensitivity. Misdiagnosis of bvFTD leads to ineffective and potentially harmful treatments, delays in organizing proper support, and increased family stress [25]. Disease-modifying treatments for FTD are currently in the research pipeline and some are already under investigation in clinical trials. Thus, there is an urgent need for earlier and more accurate diagnosis of bvFTD, especially when the initial presentation is equivocal. In late-onset neuropsychiatric presentation, the level of CSF and/or serum neurofilaments could be a convenient measure to assess whether or not a neurodegenerative process is already in progress.

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