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Fluid biomarkers for frontotemporal dementias

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Abstract

Frontotemporal dementias (FTDs) are clinically, genetically and pathologically heterogeneous neurodegenerative disorders that affect the frontal and anterior temporal lobes of the brain. They are relatively common causes of young-onset dementia and usually present with behavioural disturbance (behavioural variant FTD) or language impairment (primary progressive aphasia), but there is also overlap with motor neuron disease and the atypical parkinsonian disorders, corticobasal syndrome and progressive supranuclear palsy. At *post mortem*, neuronal inclusions containing tau, TDP-43 or infrequently FUS protein are seen in most cases. However, a poor correlation between clinical syndrome and underlying pathology means that it is difficult to diagnose the underlying molecular basis using clinical criteria. At this point, biomarkers for the underlying pathology come into play. This paper provides a brief update on fluid biomarkers for FTDs that may be useful to dissect the underlying molecular changes in patients presenting with signs of frontal and/or temporal lobe dysfunction. The hope is that such biomarkers, together with genetics and imaging, would be useful in clinical trials of novel drug candidates directed against specific pathologies and, in the long run, helpful in clinical practice to select the most appropriate treatment at the right dose for individual patients.

Introduction

Frontotemporal dementias (FTDs) are clinically, genetically and pathologically heterogeneous neurodegenerative disorders that preferentially affect the frontal and anterior temporal lobes of the brain [1]. FTDs usually present with behavioural disturbance (behavioural variant FTD, bvFTD) or language impairment (primary progressive aphasia, PPA) but there is also overlap with motor neuron disease (MND) and the atypical parkinsonian disorders, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) [2].

Pathologically, FTDs are characterized by degeneration of cortical grey matter and axons in the frontal and/or temporal lobes, along with neuronal and/or glial inclusions containing abnormally folded tau or TAR DNA-binding protein 43 (TDP-43) [3]. In some patients, there are also inclusions containing FUS protein, but this is much less common [3]. Around a third of cases are inherited in an autosomal dominant mode, caused by mutations in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) or chromosome 9 open reading frame 72

(*C9orf72*) [4], and in these cases the type of pathology can reliably be predicted during life (TDP-43 in *GRN* and *C9orf72*, tau in *MAPT* mutation carriers). Whilst there is a fairly good correlation between clinical syndrome and underlying pathology in some sporadic cases, *e.g.*, semantic variant PPA (svPPA) and TDP-43, for the most common syndrome, bvFTD, there is poor phenotype/pathological correlation [5].

Biomarkers

Broadly speaking, a biomarker is a measurable indicator of a biological state or pathological condition. In FTDs, the poor phenotype/pathological correlation makes it hard to sub-classify patients according to the underlying molecular pathology during life. This makes biomarkers particularly relevant for this condition. Additionally, therapies for FTD are likely going to be directed towards a specific protein target/pathology and therefore identification of the correct patient population using fluid biomarkers will likely be essential for human clinical trials. Imaging and genetics are covered in other papers of this volume. This overview paper gives an updated account of current fluid biomarkers of relevance to the disease (Figure 1).

Biomarker fluids

Cerebrospinal fluid (CSF) is a clear fluid that surrounds the brain and provides mechanical support. It also carries nutrients and signalling molecules to neurons and helps disposing metabolites that are further cleared into the blood via arachnoid villi, as well as through meningeal lymphatic vessels [6] and along paravascular spaces that open up during deep sleep [7]. The total CSF volume is around 150 mL with a turnover rate of 15-25 mL per hour. This volume can be sampled in clinical practice through a lumbar puncture, which is a safe procedure with post-lumbar puncture headache as the only relevant complication (incidence is 2-20%) [8]. An advantage of CSF as a matrix in which to measure biomarkers for neurodegenerative dementias is that the fluid is on the brain side of the blood-brain barrier and communicates freely with the brain interstitial fluid; neuronally derived molecules are present at higher concentrations in CSF compared with blood. There are additional issues with the measurement of CNS-related biomarkers in blood. If the biomarker is not CNS-enriched but also expressed in peripheral tissues, it may be challenging to determine if an altered concentration actually reflects what is happening in the brain. This is relevant to several FTD-related biomarkers, *e.g.* TDP-43 that is expressed in most tissues of the body. Further, the high amount of other proteins in blood (*e.g.*, albumin and immunoglobulins) may interfere in the assays [9]. Blood may also contain specifically interfering substances, *e.g.*,

heterophilic antibodies (endogenous antibodies directed against the non-human monoclonal antibodies of the assay) [10]. Finally, the analyte of interest may undergo proteolytic degradation by various proteases in plasma [11]. This seems to be a problem for tau, which is stable in CSF but has a very short (~10 hours) half-life in blood [12]. A few years ago, there was a lot of scepticism in regard to blood-based biomarkers for CNS disorders. However, the advent of highly sensitive and specific immuno- and mass spectrometry-based assays has changed this view and made the biomarker field much more hopeful [13]. Below, we provide an updated account of fluid-based biomarkers in CSF and plasma/serum. Other potential biomarker matrices, including saliva and urine, are not discussed due to lack of data.

FTD-related fluid biomarkers

NfL

Neurofilaments are structural proteins of the axonal cytoskeleton. In FTDs, the CSF concentration of the neurofilament light (NfL) subunit has been shown to be higher compared with Alzheimer's disease (AD) [14-16]; a result that was recently confirmed in a large retrospective analysis of data from the Swedish Dementia Registry [17]. Although CSF NfL is considered a general biomarker for neurodegeneration [18], a recent evaluation of its usefulness in a memory clinic setting suggests that it can be used to positively identify FTD, particularly so bvFTD [19]. Higher concentrations of CSF NfL are associated with shorter survival in FTD, which suggest that it is a marker of disease intensity/severity [20]. Plasma concentrations of NfL correlate strongly with CSF [21, 22] and recent data show that serum or plasma levels of NfL are increased in FTD, reflect disease intensity and predict future clinical deterioration and brain volume loss on magnetic resonance imaging [23-25]. Consistent with this, NfL concentration only seems to become raised during the symptomatic period with pre-symptomatic levels being similar to controls [26]. However, care should be taken when interpreting CSF and plasma NfL concentrations; diseases like PSP, CBS and vascular dementia typically also have high concentrations [17, 27, 28].

TDP-43

Aggregates positive for TDP-43 are seen in about 50% of FTD patients and are found in FTD-MND, in most svPPA patients and only rarely in nonfluent variant primary progressive aphasia (nfvPPA) or CBS. TDP-43 can be measured in CSF but, unfortunately, most of the

protein appears to be blood-derived and its CSF concentration does not reflect neuropathology in FTD [29, 30]. No difference in lumbar CSF TDP-43 concentration was seen between patients with neuropathologically confirmed FTD-tau vs. FTD-TDP [31]. Regarding its plasma concentration, there is a paucity of data, but one study reported higher levels of phosphorylated TDP-43 in both CSF and plasma in patients carrying the *C9orf72* repeat expansion or a *GRN* mutation than in patients with other types of FTD and healthy controls [32].

Progranulin

Progranulin is a ubiquitously expressed pleiotropic growth factor that is known to play important roles in normal tissue development, proliferation and regeneration [33]. CSF and plasma progranulin concentrations have been shown to be reduced in progranulin (*GRN*) mutation carriers [34]. This progranulin deficiency is accompanied by complement activation in the brain tissue, which is reflected in the CSF as increased concentrations of C1qa and C3b as the disease progresses [35], which suggests that complement activation may be involved in the neurodegenerative process in FTD caused by progranulin deficiency. The progranulin deficiency in *GRN* mutation carriers has been confirmed recently by several studies [36] and suggests progranulin determination as an alternative to genetic testing for the identification of *GRN* mutation carriers. This can be particularly helpful for identifying both the presence of mutations not found on standard genetic screening (*e.g.*, large deletions) and the pathogenicity of certain mutations (*e.g.*, missense *GRN* mutations) [37]. In a clinical setting, CSF progranulin concentration has been shown to be low in svPPA and bvFTD (*i.e.*, mainly attributed to TDP-43 pathology) compared to nfvPPA (mainly tau pathology) [38].

Tau and amyloid β

bvFTD is the neurodegenerative disease with the smallest proportion of patients with positive AD biomarkers, i.e. increased CSF total-tau (T-tau) and phospho-tau (P-tau) and reduced amyloid β 42 (Aβ42) [39]. Combining the classical AD biomarkers (all normal) with NfL (increased) results in diagnostic sensitivities of 75-86% and specificities of 94-100% for FTD as compared to AD and cognitively normal controls [14]. In a more recent, memory clinic-based study, CSF Aβ42/40 (the most accurate Aβ pathology fluid biomarker [40]) and T-tau/Aβ42 ratios had high diagnostic utility in distinguishing AD from both bvFTD and semantic dementia (SD, sensitivities and specificities of 80-90%) [41]. Irrespective of

subgroup (except logopenic variant primary progressive aphasia [lvPPA], which is associated with underlying AD pathology), FTD patients appeared to have a lower ratio of P-tau to T-tau in CSF [42]. Interestingly, FTD patients, irrespective of subgroup, have lower levels of the secreted form of the Aβ precursor protein (sAPPβ) in CSF compared with both AD patients and controls [43]. The molecular mechanisms underlying this finding are currently unknown and the result needs replication. In plasma, there is currently no validated P-tau test but for T-tau, higher plasma concentrations were seen in bvFTD and PPA (irrespective of subgroup) compared with controls [44]. However, the overlap was large, which negates diagnostic usefulness on a case-by-case basis, and there were no significant correlations with cross-sectional or longitudinal brain volume changes or disease duration [44]. Recent data suggest that a reduced Aβ42/40 ratio in plasma reflects AD-associated brain Aβ pathology with fair diagnostic accuracy (80-90%) [40]. Whether this could be used to exclude AD in FTD remains to be examined.

Dipeptide repeats

Pathogenic repeat expansions in *C9orf72* are the most common genetic cause of autosomal dominant FTD and amyotrophic lateral sclerosis (ALS) [45]. These expansions result in the production of abnormal dipeptide repeat (DPR) proteins. For one of these, a reliable immunoassay for detection in CSF has been developed [46, 47]. CSF poly(GP) is detectable in mutation carriers only (100% specificity), and particularly so in symptomatic carriers, but with limited correlation to neurodegeneration biomarkers [48]. CSF poly(GP) is thus a potential marker for target engagement in clinical trials aimed at silencing DPR expression (potentially in combination with NfL as a marker of disease activity).

sTREM2

The protein triggering receptor expressed on myeloid cells 2 (TREM2) is an innate immune receptor expressed on microglia and on myeloid cells outside the brain [49]. TREM2 is upregulated on activated microglia and involved in microglial phagocytosis, survival and chemotaxis and response to neuronal injury [49]. Homozygous *TREM2* mutations lead to Nasu-Hakola disease, which is associated with an early-onset FTD-like dementia [49], and homozygous *TREM2* variants are associated with FTD-like syndromes without bony involvement [50]. TREM2 undergoes cleavage of its ectodomain to release a soluble TREM2 (sTREM2) fragment into the extracellular space [50]. This fragment is measurable in CSF and blood [51, 52]. CSF sTREM2 levels are increased in AD and associated with grey matter

volume increases and reduced diffusivity, particularly so in pre-dementia stages of the disease [51-53]. In a recent study of FTD, CSF sTREM2 levels were similar in clinical FTD subgroups and controls but were increased in a small (n=3) cohort of *GRN* mutation carriers [54]. Additionally, like in AD, CSF sTREM2 levels are positively associated with CSF tau levels. Thus, CSF sTREM2 may be a marker of microglial activation also in FTD, although more studies are needed to examine this.

Conclusions and future perspectives

Recent years have seen a rapid development of fluid biomarkers for FTD. CSF and serum/plasma levels of NfL seem to be reliable biomarkers for the intensity of the neurodegenerative process in FTDs across subtypes. CSF AD biomarkers (tau and Aβ) can effectively exclude AD pathology in FTD and help differentiate frontal AD from FTD and promising results have recently been reported regarding their diagnostic accuracy for AD pathology as blood tests. CSF and plasma progranulin levels may be used to detect *GRN* mutation carriers; restoration of progranulin concentration could be an important biomarker readout in clinical trials in this form of the disease. CSF poly(GP) concentration could be a target engagement marker in clinical trials in *C9orf72* mutation carriers. The most problematic FTD biomarker at present is TPD-43. Its ubiquitous expression pattern makes it very hard to develop a fluid-based test for TDP-43 pathology. Ultrasensitive assays for inclusion-specific forms of the protein are probably the way forward. A similar approach should probably be explored for FUS, a protein inclusion associated with some forms of FTD for which there is currently no fluid biomarker.

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Figure Legend

Schematic illustration of an inclusion- and tangle-bearing neuron with para-synaptic amyloid β (Aβ) plaques, a microglial cell and a blood vessel. Arrows indicate candidate CSF and plasma biomarkers for frontotemporal dementia-related processes. NfL, neurofilament light; TDP-43, TAR DNA-binding protein 43; T-tau, total tau; P-tau, phospho-tau; Aβ, amyloid β; sAPPβ, soluble Aβ precursor protein; poly(GP), dipeptide repeats of glycine and proline; sTREM2, soluble triggering receptor expressed on myeloid cells 2.

Figure 1