Imaging and fluid biomarkers in frontotemporal dementia

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Abstract

Frontotemporal dementia (FTD), the second most common type of presenile dementia, is characterized by progressive behavioral and/or language problems. It is a heterogeneous neurodegenerative disease, and includes a range of clinical, genetic and pathological subtypes. This heterogeneity hampers the diagnostic process, which is becoming increasingly important for future clinical trials on disease-modifying treatments. Reliable biomarkers will enable us to better discriminate FTD from other forms of dementia and predict disease progression in the clinical setting. As different underlying pathologies probably require specific pharmacological interventions, robust biomarkers are essential to select patients with specific FTD subtypes. This review emphasizes the increasing availability and potential applications of imaging (structural and functional) and fluid biomarkers (CSF and blood) in sporadic and genetic FTD. The relevance of new MRI modalities such as VBM, DTI and ASL in the early stages of FTD is discussed, together with their ability to classify FTD subtypes. We highlight promising new fluid biomarkers for staging and monitoring FTD, underlining the importance of large, multicenter studies of presymptomatic FTD subjects. Crucial for the implementation of new biomarkers in clinical practice, is the harmonization in collecting and analyzing across different centers, which will become a great challenge for the next years.

Introduction

Frontotemporal dementia (FTD) is the second most common form of dementia in people aged under 65 and encompasses two main clinical manifestations: behavioral changes with executive dysfunction ('behavioral FTD', bvFTD) or predominant language impairment ('primary progressive aphasia', PPA) (Text Box 1).[1,2] PPAs can be further divided in the semantic variant (svPPA), non-fluent variant (nfvPPA) and logopenic variant (lvPPA).[2] Patients may develop concomitant parkinsonism or motor neuron disease (MND) at an early or late stage, resulting in a broad clinical phenotype ranging from amyotrophic lateral sclerosis (ALS) to progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) (Figure 1).[3]

Patients presenting with nfvPPA may develop characteristic features of PSP or CBS over time, while lvPPA is frequently associated with underlying Alzheimer's disease (AD).

Postmortem examination of the brain shows frontotemporal lobar degeneration (FTLD) with either tau (FTLD-tau), TAR DNA-binding protein 43 (FTLD-TDP), or fused in sarcoma inclusions (FTLD-FUS).[3] Correlation between the clinical presentation and specific underlying pathology is poor in bvFTD and better in svPPA and FTD-MND, both associated with TDP pathology.[4] Patients who develop symptoms consistent with PSP or CBS, often exhibit FTLD-tau at post-mortem examination. In contrast to sporadic FTD, the underlying pathology in genetic FTD can accurately be predicted (Figure 1).

FTD is highly heritable and 10-20% of all cases are caused by mutations in three genes: microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), and chromosome 9 open reading frame 72 (*C9orf72*).[3] Other, rare, FTLD genes include charged multivesicular body protein 2B (*CHMP2B),* valosin containing protein *(VCP),* sequestosome 1 *(SQSTM1),* transactive response DNA-binding protein *(TARDP),* and the more recently identified TANK-binding kinase 1 gene (*TBK-1).*[5]Although some phenotypes are associated with specific mutations, e.g. the co-occurence of MND with *C9orf72* mutations, genotype-phenotype correlations are generally poor, even within families.[3]

Sensitive biomarkers are crucial for FTD because of its heterogeneity. Great efforts to identify these biomarkers have been made over the last two decades, with a predominant focus on fluid biomaterial and neuroimaging features. The ideal biomarker should meet the following criteria, according to previous consensus: 1) able to detect a fundamental pathological feature of the disease, 2) validated in pathological proven cohorts, 3) precise, 4) reliable, 5) non-invasive, 6) simple to perform, and 7) inexpensive (Text Box 2).[6] Different biomarkers can be used for specific purposes (Text Box 2), and therefore the value of a biomarker depends on its application. In FTD, diagnostic biomarkers should discriminate FTD from controls and other neurodegenerative diseases, or differentiate between clinical, genetic or pathologic subtypes. Staging biomarkers should allow us to assess disease severity and to discriminate between

presymptomatic, prodromal, and early or late symptomatic stages. Pharmacodynamic biomarkers are important for evaluating the biological and clinical effect of future therapeutic interventions. Predicting the underlying pathology in FTD (tau versus TDP-43) is one of the greatest challenges, as this will be essential when specific disease-modifying interventions become available. Ideally, these interventions should be applied at an early stage when only minimal neuronal damage is present, underpinning the need for early biomarkers; at-risk subjects from families with genetic FTD form the ideal study population for detecting these earliest changes.

In this review we focus on fluid and neuroimaging biomarkers in FTD. We discuss previous work on biomarkers with its current application in clinical practice and we highlight the development of new, promising biomarkers.

Neuroimaging biomarkers

Most FTD imaging studies have focused on structural changes by assessing grey matter atrophy, while more recent studies have been directed towards studying white matter integrity using diffusion tensor imaging (DTI), which is probably more sensitive for the earliest changes in FTD. In neurodegenerative diseases in general, structural abnormalities are often preceded by functional changes, and in the following section, we describe both the structural and functional changes found with different imaging modalities.

Structural changes

Grey matter

The majority of imaging studies in FTD have used volumetric T1 MRI to investigate changes in grey matter structure.[7–10] This technique is used to measure brain volume (and longitudinally, changes in that volume i.e. the rate of brain atrophy) as well as the volume of specific regions of interest within the brain, for example the frontal lobe or hippocampus. Several post-processing analytic techniques have also been

applied to T1 imaging e.g. investigation of changes at the voxel level (e.g. voxel-based morphometry) or measurement of cortical thickness (e.g. Freesurfer), each providing an alternative way of investigating grey matter loss in the brain.

On an individual patient level, semi-quantitative assessment of atrophy by visual rating scales performed by experienced dementia experts, has provided a good diagnostic performance to discriminate FTD from AD (where more posterior cortical involvement is seen) with a specificity of 81%.[11]

Also clinical, genetic and pathological syndromes of FTD can to some degree be distinguished by distinct and dissociable patterns of grey matter atrophy at group level (Figure 2). Clinically, bvFTD is associated with frontal, temporal, insula and anterior cingulate atrophy, with earliest involvement of frontal paralimbic cortices and insula in mild bvFTD.[12–14] Cluster analyses suggest that there may be four anatomical forms of bvFTD with frontal-dominant, temporal-dominant, frontotemporal and distributed temporofrontoparietal subtypes.[15,16] However, these analyses have underplayed the involvement of subcortical structures in bvFTD, and it is clear that as the disease progresses, atrophy of the hippocampus, amygdala, basal ganglia and thalamus occurs.[14,17] In the PPA syndromes, svPPA is associated with (commonly left-sided) asymmetrical anteroinferior temporal lobe atrophy, nfvPPA with left-sided predominant inferior frontal and insula involvement, and lvPPA with left temporo-parietal junction loss.[18,19] Over time the extent of atrophy progresses not only within the same hemisphere but also starts to involve the opposite hemisphere in each of the PPA syndromes.[20–22] In the genetic forms of FTD, *GRN* mutations are associated with asymmetrical fronto-temporo-parietal atrophy, *MAPT* mutations with relatively symmetrical involvement of the anteromedial temporal and orbitofrontal lobes, and *C9orf72* expansions with a symmetrical more widespread pattern of atrophy together with involvement of the thalamus and superior cerebellum.[16,23–26] As with the clinical and genetic subtypes, whilst there are group-level patterns, it has been difficult to distinguish individuals with specific pathological forms of FTD purely using structural T1 imaging, nor has it been possible to distinguish those with FTLD-TDP from

FTLD-tau.[9] Patients with FUS pathology generally present with prominent caudate atrophy, accompanied by orbitofrontal, anteriomedial temporal, anterior cingulate, and insula atrophy.[27,28]

Across clinical, genetic and pathological forms of FTD, less work has been done on longitudinal changes in grey matter loss. However it is clear that there are variable rates of atrophy in different groups, with some being relatively fast (e.g. those with *GRN* mutations), and some very slow (a subgroup of patients with *C9orf72* repeat expansions).[29] If longitudinal structural imaging would be used for monitoring in clinical trials, sample size estimations show that focal atrophy rates, e.g. temporal lobe in svPPA, would allow a smaller sample than whole brain atrophy rates (reviewed elsewhere).[7]

Findings from a number of small studies of those at-risk for genetic FTD have been inconsistent, with some showing grey matter atrophy prior to onset of symptoms and others not. However, a recent large multicenter analysis from the GENFI study reported the presence of atrophy at least 10 years prior to expected symptom onset (Figure 3a), with different genetic groups showing different patterns: in *MAPT* mutations, atrophy was noted first in the hippocampus and amygdala, followed by the temporal lobe and later the insula; in *GRN* carriers differences started in the insula, followed by temporal and parietal lobes and thereafter the striatum; in the *C9orf72* group, changes were found very early (25 years before expected onset) in the subcortical areas (including thalamus), insula and occipital cortex, then the frontal and temporal lobes and later the cerebellum.[30] Prominent asymmetry was found in *GRN* mutation carriers at five years before expected onset, but not in the other genetic subgroups. It is important to look at changes over time in this cohort, as small-scale longitudinal studies have shown more sensitivity, as illustrated by a significant reduction of left temporal cortical thickness in presymptomatic *GRN* carriers, without differences between presymptomatic- and non-carriers at baseline.[31]

Diffusion tensor imaging

DTI is a valuable non-invasive imaging technique for assessing white matter structure of the brain. It measures white matter microstructural integrity by determining the rate of diffusion (motion of water

molecules) in different directions. Specific DTI metrics are thought to reflect different pathological changes in microstructure: a decrease in axial diffusivity (AxD) correlates with axonal degeneration; an increase in radial diffusivity (RD) indicates myelin breakdown; and a decrease of fractional anisotropy (FA), as a composite measure of both AxD and RD, represents more general nonspecific white matter integrity loss.[32] Abnormalities in white matter diffusivity have been found to be more widespread and to grey matter atrophy in FTD, supporting the importance of white matter involvement in FTD.[33–38] DTI may become a valuable biomarker as it has at least four potential applications, although currently, it has only been investigated at group level and not at single-subject level.

Firstly, DTI is highly sensitive to differentiate FTD from controls and from other types of dementia, such as AD.[32–36,38–45] White matter microstructure has shown to be more widespread affected in FTD compared with AD,[32,34,39,40] with a high sensitivity (78%) and moderate specificity (68%) to discriminate these conditions by whole brain mean FA.[34] White matter degradation co-occurs with frontal, temporal and insular atrophy in FTD, and is probably due to axonal degeneration associated with grey matter neuronal loss. It includes the anterior corpus callosum, bilateral anterior and descending cingulum and uncinate fasciculus tracts,[42] which are part of motor, executive and language neural networks.

Secondly, although white matter damage on DTI largely overlaps between subtypes, some distinctive DTI changes have been found in clinical, pathological and genetic FTD subtypes.[33,35,36,38,40,42–44,46] The uncinate fasciculus, cingulum bundle and genu of the corpus callosum appear to be key tracts involved in the bvFTD disease process.[34,41,44] PPA subtypes have shown different spatial patterns of white matter damage: left orbitofrontal and anterior temporal white matter (superior longitudinal fasciculus) in nfvPPA; asymmetric (mostly left) changes in the anterior and inferior temporal white matter (including the inferior longitudinal fasciculus), and bilateral uncinate fasciculi in svPPA; and more posterior abnormalities such as the posterior region of the left inferior longitudinal fasciculus in lvPPA.[33,35,36,38,42–44] DTI may have the potential to differentiate FTLD-tau from FTLD-TDP *in vivo*, as two studies have found more severe white matter integrity loss in FTLD-tau than FTLP-TDP.[33,46] This parallels postmortem

findings where tau-pathology is associated with marked axonal loss and glial tau-inclusions, and TDP-pathology with greater grey matter neuronal loss than white matter pathology.[46] Larger studies are needed for more conclusive observations before this can be used in individual patients. DTI studies have shown different patterns across genetic FTD patients subtypes: *MAPT* patients show consistent alterations in the uncinate fasciculus and right parahippocampal cingulum,[34,41] whereas *C9orf72*-FTD patients tend to have more dorsal white matter tract pathology located in the cingulum, corpus callosum and the superior cerebellar peduncles.[34,41]

Thirdly, though studies so far are limited, longitudinal DTI changes may be used to monitor the disease process and evaluate therapeutic effects in future clinical trials.[41] Over time, DTI changes have been found to be more widespread than progression of grey matter atrophy, and have shown distinct patterns between clinical and genetic FTD subtypes which reflect different propagation of the neurodegenerative process within large scale brain networks.[35] The bilateral uncinate fasciculus and paracallosal cingulum have shown the largest FA reduction in bvFTD,[35,41] while left-to-right sided progression is seen in both svPPA and nfvPPA.[35,43] In svPPA, longitudinal DTI changes extended to bilateral frontotemporal tracts, whereas changes in nfvPPA appeared to remain relatively focal.[35,43]

Lastly, DTI as a biomarker may even be able to detect pathological changes before the onset of clinical symptoms and before grey matter atrophy in FTD. Decreased FA and increased RD in bilateral uncinate fasciculi (and forceps minor) have been found in a group of presymptomatic *MAPT* or *GRN* mutation carriers without grey matter atrophy (Figure 3b).[37,47]

In conclusion, DTI appears to be a promising imaging biomarker for early diagnosis, and possibly to monitor the effect of pharmacological interventions in the future. To use DTI in the individual patient, reference data are essential to identify abnormal changes in white matter integrity, alike the use of automated quantitative MRI.[48] The assembly of such normative data is however challenging due to variability across scanners and field strengths, as well as choice of DTI metric, tract, and method of

analyzing (e.g. tracking or skeletonized). Region of interest analyses of specific tracts, such as the uncinate fasciculus, inferior – and superior longitudinal fasciculus, are likely to provide the best opportunity to move forward from the current group level studies to a single-subject analysis.

Functional changes

FDG-PET

Positron emission tomography with [^{18}F]fluorodeoxyglucose as tracer (FDG-PET) allows the visualization of alterations in brain metabolism, which precede grey matter atrophy in FTD and different forms of dementia.[49–52] Distinct regional hypometabolism patterns on FDG-PET contribute to an accurate clinical diagnosis at an individual patient level, both by visual inspection and especially by quantitative assessment.[53] Lower glucose metabolism, often asymmetric, in the orbitofrontal, dorsolateral and medial prefrontal cortex, anterior temporal poles and basal ganglia, is highly specific for bvFTD, with a sensitivity and specificity ranging between 80 and 95% for the differentiation from other dementia types and healthy controls.[50,51,53–56] These patterns of hypometabolism are early features in the symptomatic stage, but also a few years before patients fulfill the criteria for probable bvFTD.[50] As false-positive FDG-PETs have been found in primary psychiatric disorders mimicking FTD, future quantitative assessment of metabolism patterns on PET may further increase its diagnostic value.[54]

The patterns of focal hypometabolism vary between PPA subtypes and between genetic forms, and mirror the structural changes described above. svPPA is characteristically associated with asymmetrical bilateral temporal hypometabolism, while nfvPPA shows larger variability in hypometabolic patterns of the left inferior frontal gyrus, dorsolateral frontal cortex, anterior cingulate cortex, insula, and, occasionally, of the parietal cortex.[57] Distinct FDG-PET patterns in PPAs may predict progression to specific dementia subtypes: bilateral temporo-parietal hypometabolism predicted conversion to AD, parietal hypometabolism to CBS, and involvement of basal ganglia, midbrain and cerebellum to PSP.[57] Longitudinal changes on FDG-PET may provide additional information on the patterns and speed of

pathological spread.[31,56] For example, svPPA patients show bilateral reduction of glucose metabolism in temporal lobes over time, which further extends to the anterior cingulate cortex and the posterior temporal lobes.[58] When looking at genetic subtypes, *GRN* mutations are associated with asymmetric hypometabolism in frontal and temporal brain regions,[31,59] ALS and/or FTD patients with *C9orf72* expansions with hypometabolism in the limbic system, basal ganglia and thalamus,[60] and *MAPT* mutations with hypometabolism in the medial temporal lobe, frontal and parietal cortices.[24]

Interestingly, FDG-PET already reveals abnormalities in the presymptomatic stage, and may serve as a surrogate endpoint in future therapeutic trials; asymmetric hypometabolism was found in frontal and temporal lobes in asymptomatic *GRN* carriers preceding the onset of clinical symptoms and of grey matter atrophy.[31,59]

Arterial spin labeling

Arterial spin labeling MRI (ASL) measures brain perfusion non-invasively by magnetically labeling water protons in arterial blood, which creates an endogenous tracer of cerebral blood flow (CBF).[61] Brain perfusion measured by ASL correlates very well with metabolism measured by FDG-PET,[51,53] but has several advantages over FDG-PET: it can be combined with other MRI techniques in a single session, it is non-invasive, has no radiation exposure, is widely available and is less costly.[62]

ASL has shown hypoperfusion in the insula, the amygdala and several parts of the medial frontal lobes, including the anterior cingulate, in FTD patients.[51,53,63–65] It differentiated bvFTD from AD at an early phase, with areas under the curve of up to 0.87 for CBF in specific frontal or parietal regions.[51,53,63] In two comparative studies, the regions of hypoperfusion of ASL-MRI largely overlapped with those of hypometabolism on FDG-PET scans,[51,53] and diagnostic performance when distinguishing bvFTD from AD and controls, was similar for both modalities.[53]

ASL may also be an early biomarker in the preclinical stage of genetic FTD. Presymptomatic *GRN* and *MAPT* mutation carriers have showed significantly stronger CBF decrease over time than controls (Figure

3c), independent of grey matter atrophy, in widespread frontal, temporal, parietal, and subcortical regions, with the strongest perfusion decline in subjects who converted to the disease stage.[62] Some regional ASL changes may be specific for particular gene defects, as hypoperfusion may extend into posterior temporal and parietal regions in *GRN* mutation carriers.[62]

Resting-state fMRI

Resting-state functional MRI (RS-fMRI) is a potential biomarker for early diagnosis and disease staging as it measures intrinsic functional connectivity between brain regions on MRI, which can be detected as synchronous patterns of spontaneous low frequency fluctuations in blood-oxygen-level-dependent signals. RS-fMRI is a safe, non-invasive, and repeatable tool, which is sensitive to detecting changes in brain functional connectivity before the onset of clinical symptoms or atrophy on group-level.[37,66,67] Decreased connectivity between the frontoinsula and anterior cingulate cortex, as part of the salience network, is the most consistent finding in FTD,[67–71] while other studies found normal or increased connectivity.[72–74] Inconsistent differences (both increased and decreased connectivity) were found for the default mode network in FTD.[67–69] The discrepancies in functional connectivity may partly be explained by cohort and scanner differences and the wide variation in analytical methods, such as independent component analyses, seed- or region-of-interest approaches, or regional homogeneity analyses.[66,68,72,74,75]

Specific network alterations are also found between clinical and genetic subtypes of FTD. Reduced left temporal lobe connectivity is found in svPPA,[76,77] attenuated connectivity in both salience and sensorimotor networks in *C9orf72* bvFTD-patients,[26] and reduced left frontal connectivity in *GRN* mutations.[78] In the presymptomatic phase, RS-fMRI may be sensitive to detecting connectivity differences, as altered (both reduced and increased) frontoinsula and/or ACC connectivity have been reported in presymptomatic mutation carriers.[37,66,78,79]

Amyloid and Tau PET tracers

Several other tracers may serve as diagnostic biomarkers in the differential diagnosis of FTD and AD, and between different pathological subtypes of FTD. PET with an amyloid tracer such as Pittsburgh compound B (PiB) tracer is a robust and sensitive biomarker for detecting amyloid-β deposits, indicating AD pathology, *in vivo*,[80] and bvFTD, svPPA and nfvPPA are mostly PiB-negative. Most lvPPA cases represent atypical AD with a PiB binding pattern similar to that of AD,[81–83] while lvPPA with negative PiB-PET is accompanied by structural and FDG-PET abnormalities supporting underlying FTLD pathology.[83,84] Unexpected positive PiB-PET in FTD cases may result from mild co-incidental AD pathology, not related to the clinical FTD presentation.[85]

Several tracers have been developed to visualize tau pathology *in vivo* however the ideal ligand that captures the wide range of tau pathology has not yet been developed. Distinct ligand selectivity to the different tau isoforms and their intracellular aggregation requires probably the application of different tau ligands.[86] Tau PET with the ^{18}F-AV-1451 ligand has shown increased uptake in the temporal cortex, frontal cortex, and basal ganglia in FTD patients with an R406W *MAPT* mutation, which is associated with both 3-repeat- and 4-repeat-tau pathology. In these patients, higher regional ^{18}F-AV-1451 uptake correlated with lower glucose metabolism and with postmortem burden of tau pathology.[87] However, binding of ^{18}F-AV-1451 appears poorer in conditions with only 4-repeat-tau, as shown by a lack of correlation with postmortem tau pathology in PSP.[88,89] A recent study using postmortem material reported that ^{11}C-PBB3 was more robust for capturing wide-range tau pathologies, including both 3- and 4-repeat-conditions.[90] Also the ^{18}F-THK-5351 ligand showed promising results in the 4-repeat-diseases PSP and CBS both on postmortem tissue as *in vivo*.[91,92] Once validated, tau PET may become effective in diagnosing underlying tau pathology as well as providing a surrogate marker for trials with anti-tau therapeutics.[86]

Summary of imaging biomarkers

Grey matter atrophy and FDG-PET hypometabolism are validated diagnostic biomarkers showing relatively consistent changes at group level between studies, and are clinically applied at an individual level for the differentiation between FTD and AD or controls (Table 1). More work needs to be done on the use of imaging modalities in distinguishing FTD subtypes at an individual level, with larger studies of longitudinally acquired imaging data, before this can be used as an outcome measure to monitor disease progression in clinical trials.

We expect new modalities like DTI, ASL and RS-fMRI to become valuable biomarkers in clinical practice, especially due to their sensitivity, enabling early diagnosis and their potential use in longitudinal monitoring (Table 1). Crucial to their implementation is the harmonization across different centers, as there is considerable variation across scanners and protocols. For example in ASL, the diversity of scanning protocols influences perfusion quantification, which may be overcome by proposed international standardization of protocols.[61] Additionally, integrating different types of information by combining imaging modalities holds great promise for the future, as demonstrated by multimodal analyses that have improved the classification between FTD and AD, [40,45,52,65,93,94] and between clinical FTD subtypes. [94]

Fluid biomarkers

Alterations in specific protein concentrations in different human fluid compartments may reflect pathophysiological changes of disease processes. The close vicinity of CSF to the brain offers a high chance of revealing disease-specific biomarkers. Subsequent validation in blood of such biomarkers would be of great value, being minimally invasive and enabling repeated measurements over time. Recent studies have demonstrated that brain specific proteins in neurodegenerative disorders can reliable be detected in blood by novel ultrasensitive assays (e.g. Single Molecule Array technology). The progress of these developments in the following years, offers a new window of opportunities for diagnosing, staging and monitoring FTD patients. In the next section, we will first review the currently applied CSF

markers for differentiating FTD from AD, and then highlight promising (also blood-derived) biomarkers in sporadic and genetic FTD.

CSF amyloid-β and tau

The core CSF biomarkers for AD are phospho-tau$_{181}$ (p-tau), total-tau (t-tau), and amyloid beta$_{1-42}$ (Aβ_{1-42}); these represent the pathological changes in AD, being accumulation of hyperphosphorylated tau in neurofibrillary tangles, neuronal loss, and amyloid beta (Aβ) depositions in senile plaques respectively.[95] These biomarkers have comprehensively been validated to exclude AD in the diagnostic work-up of FTD, both in clinical cohorts and small pathologically confirmed case series, with higher p-tau and t-tau, and lower Aβ_{1-42} levels in AD than FTD patients.[96] A high Aβ_{1-42}:p-tau or Aβ_{1-42}:t-tau ratio gives an especially good diagnostic performance when distinguishing FTD from AD (Aβ_{1-42}:p-tau: specificity 80% and sensitivity 87%; Aβ_{1-42}:t-tau: specificity 79%, sensitivity 89%). The use of ratios of other Aβ isoforms may improve diagnostic accuracy, especially when differentiating AD from vascular dementia and LBD, but also for distinguishing AD from FTD.[97,98]

The core AD biomarkers are also valuable when differentiating between underlying AD or FTLD pathology in the differential diagnosis of PPA, in which an AD profile is often found in clinically diagnosed lvPPA patients as opposed to svPPA and nfvPPA patients.[99–102] An AD CSF profile occasionally occurs in FTD cases, even in pathology proven cases; this may partly be explained by the co-occurrence of AD pathology.[103] Moreover, decreased Aβ_{1-42} levels were found in up to 25% *C9orf72* patients in a Finish cohort, but not in *GRN* patients, and to elucidate its pathophysiological significance, more clinicopathological and genetic studies are required.[104–106]

Tau levels in CSF are not increased in FTD with underlying tau-pathology nor in patients with *MAPT* mutations, compared to tau-negative or sporadic FTD.[107,108] Reduced p-tau:t-tau ratios have been found to be a specific biomarker to distinguish FTLD-TDP from FTLD-tau, although this appears to be driven by concomitant MND.[109–112] Whether the increase of t-tau as abnormal axonal biomarker or reduction of p-

tau determines the reduced ratio, is not completely clear. In line with this hypothesis of axonal damage, the association of a reduced p-tau:t-tau ratio with survival is an interesting finding in one study.[111]

Neurofilament proteins

Neurofilament light chain (NfL) is probably the most promising fluid biomarker in FTD in the short term for disease monitoring and prognosis. Neurofilaments are the major constituent of the neuroaxonal cytoskeleton and play important roles in axonal transport and in the synaps.[113] NfL is the most abundant and soluble neurofilament-subunit, and increased levels are thought to reflect axonal damage.

NfL levels are 2.5-11 times higher in FTD than in controls and its clinical value especially lies in the correlation with disease severity and progression, survival, and cerebral atrophy (Figure 4).[114–116,111,117–119] CSF NfL is also increased, although to a lesser extent, in several other neurodegenerative diseases (e.g. ALS, AD, PSP, and vascular dementia), and should therefore be combined with disease specific biomarkers.[114,117,120–122] NfL levels are equally elevated among FTD subtypes bvFTD, nfvPPA and svPPA, and are strongly increased in FTD with MND.[111,114–116,118] High CSF NfL levels were found in patients with TDP pathology compared with tau pathology, which was largely driven by ALS co-occurrence.[111,118] In particular, high NfL levels were found in FTD patients with *GRN* mutations, a large variation was found in *C9orf72* patients (ranging from high levels in concomitant MND to low levels in patients who slowly progress), and *MAPT* patients had relatively low levels (Figure 4b).[115] Interestingly, presymptomatic genetic FTD carriers show normal NfL levels in CSF and blood, with a sharp increase reported after conversion to the disease stage in two converters (Figure 4b).[115] It is unknown whether and how NfL levels fluctuate over time in FTD, but available longitudinal data in ALS have shown stable NfL levels or a minor increase over time.[120,123] The recent finding of the strong correlation of NfL levels between CSF and serum makes this biomarker measurable in blood and especially suitable for repeated measurements.[115,119]

In mouse models of neurodegenerative diseases (tau, Aβ, and α-synuclein), NfL increase coincided with the onset and progression of brain pathology, and blocking Aβ lesions attenuated the NfL increase.[124] This observation suggests that we can use NfL to monitor treatment response in neurodegenerative diseases. In conclusion, NfL is a promising, non-invasive biomarker for disease staging, monitoring, and prognosis in FTD. Longitudinal studies in FTD need to be conducted to gain insights into the role of NfL as a progression marker.

Genetic-specific biomarkers

Progranulin

Progranulin (PGRN), a multifunctional protein, plays an important role in neurite outgrowth and inflammation.[125] Due to haploinsufficiency, pathogenic loss of function mutations in *GRN* reduce blood and CSF PGRN to 25-40% of normal levels.[125–129] Blood or CSF PGRN are diagnostic biomarkers for pathogenic *GRN* mutations, as they discriminate (presymptomatic and symptomatic) carriers from non-carriers with a sensitivity and specificity of up to 100% (Figure 5a).[128,129] In line with this, blood PGRN levels can help to assess the pathogenicity for unclassified variants in *GRN*. Currently, therapeutic trials are focusing on enhancing PGRN expression, for example by histone deacetylase inhibitors.[130] In these trials, target engagement is assessed using blood PGRN levels, as they appear to be constant over time.[129,131] However, blood and CSF PGRN are differentially regulated, as demonstrated by the moderate correlation between these compartments in *GRN* mutation carriers, and therefore CSF should be sampled as well.[129] PGRN levels thus provide a good pharmacodynamic biomarker, but do not reflect the extent of neurodegeneration in the brain, wherefore different additional biomarkers are needed as surrogate endpoints.

Dipeptide-repeats in C9orf72

C9orf72 repeat expansions are known to be transcribed to expanded G_4C_2 RNA, which forms RNA foci and in parallel is translated into proteins of repeating dipeptides (dipeptide-repeats, DPRs) by repeat-associated non-ATG translation.[132] Both RNA foci and DPRs are believed to have a key role in the pathophysiology of this disorder.[132–134] An elevated poly(GP) level, one of the DPRs, has been found in the CSF of patients with *C9orf72* repeat expansions, and also in presymptomatic mutation carriers (Figure 5b+c).[134,135] Moreover, poly(GP) levels remained relatively constant over time, which support the use of poly(GP) as a potential pharmacodynamic biomarker in future therapeutic trials.[135] Antisense oligonucleotides binding to G_4C_2 RNA have been shown to reduce extracellular poly(GP) in human cell models and to reduce RNA foci and DPRs, as well as CSF poly(GP) levels, in mice harboring a G_4C_2 expansion.[133–135] This implicates that poly(GP) may be a potential target engagement biomarkers to measure biochemical responses to treatment with these agents.[134,135] As poly(GP) levels did not correlate with age at onset, disease duration, severity or survival, future clinical trials in patients with *C9orf72* repeat expansions may benefit from the combination of poly(GP) levels as pharmacodynamic marker and NfL as a prognostic marker.

Potential future fluid biomarkers

As FTLD with phosphorylated TDP-43 (pTDP-43) aggregates constitutes one of the major pathological subgroups of FTLD, pTDP-43 protein levels in CSF or blood would be an interesting biomarker, but to date, results have been contradictory. Strongly elevated CSF pTDP-43 levels have been found in a small series of *C9orf72* and *GRN* patients, but did not differ between FTD with TDP-43 and tau pathology in a pathology-proven cohort.[112,136] Quantification in CSF is challenging due to low concentrations, various isoforms and antibodies,[112,137] and the development of better TDP-43 assays is warranted.

Neuroinflammation plays an important role in FTD and other neurodegenerative diseases, as it represents both a consequence of and a trigger for pathology.[138] Microglia are the major immune component of the central nervous system, and are activated by damaged neurons and misfolded proteins resulting in the

initiation of a chronic inflammatory response.[138] In a study on sporadic FTD (and AD) patients, reduced levels of soluble triggering receptor expressed on myeloid cells 2 (sTREM2, a protein involved in inflammation and phagocytosis and mainly expressed by microglia) were found.[139] CSF levels of YKL-40 (chitinase-3 like-1, cartilage glycoprotein-39), an inflammatory protein produced by astrocytes, have been found to be elevated in pathologically proven FTD, but also in AD, vascular dementia, normal aging and other neurological disorders such as multiple sclerosis.[140–142] This is also true for glial fibrillary acidic protein, an astrocytic cytoskeletal protein, which was found to be increased in both FTD and other dementia types.[143] Recently, a strong link between *GRN* mutations and microglial activation has been established, with excessive complement production leading to synaptic pruning.[144] Promising data suggest that proteins involved in complement activation are potential biomarkers to track disease progression in *GRN* mutation carriers.[144]

Various changes in cytokines (primarily pro-inflammatory, e.g. MCP-1, IL-6, TNF-α) have been found in FTD, but these also reflect aspecific mechanisms, as they are also present in AD.[145–150] The role of several neuropeptides has been extensively reviewed elsewhere,[151] for example neurogranin, a postsynaptic protein involved in synaptic plasticity, which was lower in FTD patients than in controls and AD patients.[141] Larger, pathologically proven and genetically determined cohorts are needed for validation of these cytokines and neuropeptides.

Novel approaches are focusing on enriched protein fractions and microRNAs (miRNAs) in exosomes. Exosomes are vesicles secreted from cells; they facilitate intercellular communication and are enriched sources of biomolecules. The value of examining exosomes is supported by a small study reporting reduced synaptic protein levels in blood-derived exosomes in FTD.[152] miRNAs regulate gene expression, and seem to play a role in TDP-43 and FUS pathology, but have not yet been studied as biomarkers in FTD.[153]

Summary of fluid biomarkers

Several fluid biomarkers provide currently usable (e.g. core AD biomarkers) or promising biomarkers in FTD (e.g. NfL) (Table 1). It is likely that combinations of CSF metabolites will yield more information than single markers alone, for example a biomarker panel achieved a high sensitivity to differentiate TDP43- from tau-pathology.[145] In general, more validation and longitudinal data is needed to determine the full potential of these and other candidates. Lastly, it is important to harmonize collection and analysis of fluid biomarkers, as their levels can be influenced by multiple pre-analytical and analytical factors, including sampling and storage methods, and choice and implementation of assays.[154] Multicenter standardization of these procedures and quality control programs will facilitate collaborative research and the implementation of new fluid biomarkers in clinical practice.

Conclusions

Neuroimaging and fluid biomarkers are becoming increasingly important in the context of future therapeutic interventions in both sporadic and genetic forms of FTD. Several imaging and CSF biomarkers are already established (e.g. grey matter atrophy, FDG-PET and CSF AD biomarkers) and being used in clinical practice, often in the differential diagnosis of FTD. The field is moving forward in identifying gene-specific markers and finding new biomarkers for staging, predicting underlying pathology and monitoring treatment responses. For example, DTI has shown a good performance in discriminating FTD from AD, as well as demonstrating early pathological changes; NfL can differentiate FTD from controls and is a promising staging and prognostic biomarker for FTD; and genetic specific biomarkers (PGRN and DPRs) may be valuable for assessing target engagement in therapeutic trials. Importantly, combinations of biomarkers will add value in order to accurately define the FTD subtype, disease onset, as well as to monitor progression and eventually treatment response. For example, in a PGRN-enhancing trial, target engagement can be assessed by PGRN levels, but additional surrogate endpoints are needed to assess the physiological effect (i.e. reduction of neurodegeneration).

Most alterations of these novel biomarkers have currently been demonstrated on group level and need to be validated for individual subjects, which is challenging due to the relative rarity of FTD. Multicenter research can help to increase statistical power and prove clinical utility; prime examples of longitudinal observational cohorts include GENFI (Genetic Frontotemporal Dementia Initiative), ARTFL (Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium), LEFFTDS (Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects), and a collaboration including these consortia in the FPI (FTD Prevention Initiative). Research in genetic FTD provides a unique window to study the earliest disease effects and therefore offers a high chance to identify valuable biomarkers. Despite similarities between genetic and sporadic FTD, the use of biomarkers identified in genetic cases requires validation in sporadic cohorts as biomarker profiles and trajectories may differ, alike in AD.[155]

Interestingly, it is increasingly emphasized that FTD, classically considered as an early-onset dementia, frequently manifests after the age of 65 years and may include clinical features suggestive of AD.[156,157] This stresses the need of diagnostic biomarkers specific for FTD, as the co-occurrence of Alzheimer pathology increases with age. The value of FTD biomarkers in different age groups with comorbidities remains to be elucidated. Additionally, future research should focus on combining biomarkers (both fluid and imaging) to make optimal use of these modalities, as well as on harmonization of collection and analysis protocols to facilitate dissemination in research and clinical practices.

Key points

- Most of the validated biomarkers in frontotemporal dementia (FTD) (e.g. grey matter atrophy, FDG-PET and CSF amyloid beta$_{1-42}$, phospho-tau$_{181}$, and total-tau) are used to differentiate FTD from Alzheimer's disease or controls
- New imaging biomarkers, like arterial spin labeling and diffusion tensor imaging, appear to be more sensitive to show subtle changes that precede grey matter atrophy in FTD, providing a potential role in diagnosis and monitoring

- Promising upcoming fluid biomarkers are neurofilament light chain for staging, monitoring, and prognosis in all FTD subtypes, and dipeptide and progranulin proteins for target engagement in gene-specific forms
- There is still a need of reliable biomarkers to differentiate between tau- and TDP-pathology in light of trials on disease-modifying treatments
- Future research should focus on the multimodal combination of fluid and imaging biomarkers, as well as on the harmonizing of collection and analysis protocols

Display items:

Text Boxes:

Text Box 1. Main clinical characteristics of FTD

- **BvFTD (behavioral variant FTD)**:
  - Personality and behavioral changes (including disinhibition, apathy, loss of sympathy, perseverative behavior, abnormal appetite), and executive dysfunction
- **Primary progressive aphasia (PPA)**: progressive prominent language difficulties that impair daily living. Subtypes:
  - **Semantic variant PPA (svPPA)**: fluent speech characterized by anomia and impaired single word comprehension
  - **Non-fluent variant PPA (nfvPPA)**: non-fluent speech with agrammatism and/or apraxia of speech
  - **Logopenic variant (lvPPA)**: non-fluent speech with word-finding difficulties in spontaneous speech and in repetition

Text Box 2. Biomarkers – requirements and applications

Requirements: *(adjusted from [6])*

- Able to detect fundamental feature of FTD pathology
- Validated in neuropathological confirmed FTD
- Precise
- Reliable
- Non-invasive
- Simple to perform
- Inexpensive

Applications:

- Prediction

- Diagnostic
- Staging
- Monitoring:
  - Disease progression
  - Treatment response (surrogate endpoint, target engagement)
- Prognostic

Figure legends:

Figure 1. Clinical, pathological and genetic spectrum of FTD. Genetic forms have predictable pathology: *GRN* and *C9orf72* mutations show TDP pathology whereas *MAPT* mutations show tau pathology. In contrast, across the clinical spectrum of FTD variable underlying pathologies and genetic forms can be found. ALS and FTD-MND phenotypes is infrequently caused by FTLD-FUS pathology or *FUS* mutations, for simplicity this is not included in the figure. Adapted with permission from Seelaar et al.[158] ALS: amyotrophic lateral sclerosis, bvFTD: behavioral variant FTD; *C9orf72*: *C9orf72* repeat expansions; CBD: corticobasal degeneration; FTD: frontotemporal dementia; FTLD: frontotemporal lobar degeneration; FUS: fused in sarcoma; *GRN*: progranulin gene mutations; *MAPT*: microtubule-associated protein tau mutations; MND: motor neuron disease; nfvPPA: non-fluent variant PPA; PPA: primary progressive aphasia; PSP: progressive supranuclear palsy; svPPA: semantic variant PPA; *TARDP*: transactive response DNA-binding protein gene; *TBK-1*: TANK-binding kinase 1 gene; TDP-43: transactive response DNA-binding protein 43; *VCP:* valosin containing protein

Figure 2. Characteristic patterns of grey matter atrophy (highlighted) in different clinical and genetic subtypes of FTD. bvFTD patients show prominent frontal, insular and anterior cingulate atrophy; typical temporal atrophy in svPPA is asymmetrical (most often left); nfvPPA patients show left frontal and insular atrophy; in patients with underlying FUS-pathology, nucleus caudatus atrophy is pronounced; *GRN* patients often show asymmetrical fronto-temporo-parietal atrophy; *C9orf72* present mostly with a generalized symmetrical atrophy; and *MAPT* patients show marked symmetrical temporal atrophy.

bvFTD: behavioral variant FTD; *C9orf72*: *C9orf72* repeat expansions; FTD: frontotemporal dementia; FUS: fused in sarcoma underlying pathology; *GRN*: progranulin mutations; *MAPT*: microtubule-associated protein tau mutations; nfvPPA: non-fluent variant PPA; PPA: primary progressive aphasia; svPPA: semantic variant PPA;

Figure 3. Imaging abnormalities in the presymptomatic stage of genetic FTD. (a) Grey matter changes adopted from the GENFI study: standardized difference between all (presymptomatic + symptomatic) mutation carriers and non-carriers in cortical grey matter volumetric imaging measures (Y-axis) versus estimated years from expected symptoms onset (X-axis); (b) DTI changes: decreased fractional anisotropy in presymptomatic *GRN* and *MAPT* mutation carriers versus controls in the uncinate fasciculus; and (c) ASL changes: lower cerebral blood flow in presymptomatic *GRN* mutation carriers than in controls cross-sectionally at follow-up. Reproduced with permission from (a) Rohrer et al.,[30] (b) Dopper et al.,[37] and (c) Dopper et al.[62]

Figure 4. CSF neurofilament light chain levels. (a) CSF NfL levels in clinical FTD subtypes and other neurodegenerative disease; horizontal lines represent medians and filled squares represent patients with concomitant MND; (b) CSF NfL levels in presymptomatic and symptomatic genetic FTD of the three major genes (*GRN, C9orf72* and *MAPT*), including two subjects who converted from the presymptomatic to symptomatic stage (connecting line), filled squares represent patients with concomitant MND; and (c) Kaplan-Meier survival curves stratified for CSF NfL levels in tertiles; upper light-grey line represents low CSF NfL levels, middle dark-grey line represents intermediate CSF NfL levels, and lower black line represents high CSF NfL levels. Adapted with permission from (a) Scherling et al.,[114] and (b+c) Meeter et al.[115] *Permission obtained from Scherling and Meeter; permission necessary from (a) Annals of Neurology, and (b+c) Annals of Clinical and Translational Neurology.*

AD: Alzheimer's disease; bvFTD: behavioral variant FTD; *C9orf72*: *C9orf72* repeat expansions; CBS: corticobasal syndrome; CSF: cerebrospinal fluid; *GRN*: progranulin mutations; *MAPT*: microtubule-

associated protein tau mutations; MND: motor neuron disease; NC: normal controls; NC2: healthy at risk for a genetic mutation subjects; NfL: neurofilament light chain; nfvPPA: non fluent variant PPA; PD: Parkinson's disease; PPA: primary progressive aphasia; PSP: progressive supranuclear palsy; svPPA: semantic variant PPA.

Figure 5. Genetic specific fluid biomarkers. (a) plasma PGRN levels are significantly lower, without overlap, in carriers of *GRN* mutations (presymptomatic carriers, ASX GRN+, and symptomatic carriers, SX GRN+) than in controls (GRN-), [(b+c) ***confidential panels****, will be published in March]* (b) CSF poly(GP) levels are significantly higher in *C9orf72* repeat expansion carriers (C9+) than non-carriers (C91), (c) already in the presymptomatic stage (ASX) when compared to the symptomatic stage (SX). Adapted with permission from (a) Meeter et al.,[129] and (b+c) adopted from Gendron et al.[135] Horizontal red lines represent the sample medians in a given group. *This figure is optional; in our opinion it is very illustrative, however it exceeds the maximum of 7 display items. Lay-out, including terminology, can be adjusted once the poly(GP) figures are published and permission to adapt is obtained.*

ASX: asymptomatic (presymptomatic) carrier; C9+: *C9orf72* repeat expansion carrier; C9-: non-carriers of a *C9orf72* repeat expansion; CSF: cerebrospinal fluid; *GRN+*: *progranulin* gene mutation carrier; *GRN-*: non-*GRN*-carriers; PGRN: progranulin protein; poly(GP): glycine-proline repeating protein; SX: symptomatic carrier

Tables

Table 1. Potential biomarkers in FTD and their application in clinical practice

Biomarker	Application					
	Diagnosis		Staging and monitoring disease progression		Prognosis	Monitoring treatment response
	FTD vs AD	*FTD subtypes (clinical/genetic /pathologic)*	*Symptomatic*	*Presymptomatic*		
Imaging biomarkers						

Grey matter atrophy	++	++	+	+		+
DTI	++	+	+	+		+
FDG-PET	++	++	+	+		+
Tau-PET	+	+				
ASL	++	+	+	+		
RS-fMRI	+	+	+	+		
Fluid biomarkers						
p-tau, t-tau and $A\beta_{1-42}$	++	+			+[a]	
NfL	+	+	++	+	++	+
PGRN		++				+
Poly(GP)		+				+

Summary of current or potential biomarkers and their applications that are reported thus far. ++ = robust biomarker, replicated in independent cohorts, + = potential biomarker.
[a]p:t-tau ratio. *$A\beta_{1-42}$: amyloid beta$_{1-42}$; AD: Alzheimer's disease; ASL: arterial spin labeling; DTI: diffusion tensor imaging; FDG-PET: [18F]fluorodeoxyglucose positron emission tomography; FTD: frontotemporal dementia; NfL: neurofilament light chain; PGRN: progranulin protein; poly(GP): glycine-proline repeating protein; p-tau: phospho-tau$_{181}$; RS-fMRI: resting-state functional magnetic resonance imaging; tau-PET: tau positron emission tomography; t-tau: total-tau*

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Authors contributions

LHM, LDK, JDR and JCvS performed the literature review and drafted and revised the manuscript and figures.

Competing interests

The authors declare no competing financial interests.

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Laura Donker Kaat is a neurologist and resident in clinical genetics; she has a special interest in the genetics of adult onset neurological diseases. During her PhD, she worked on the clinical and genetic aspects of Progressive Supranuclear Palsy. In addition to her work as a resident in clinical genetics, she is involved in scientific projects on hereditary FTD at the Alzheimer Center in Rotterdam.

Jonathan D. Rohrer: Dr Rohrer's research focuses on the neuroimaging and neuropsychology of FTD, particularly in relation to their underlying genetic causes. Research in the field of FTD has led to the publication of over 120 Pubmed-referenced papers and he has spoken at a number of international conferences about the work. Since 2011 he has co-ordinated the Genetic FTD Initiative, GENFI, a multicentre cohort study of presymptomatic genetic FTD, and has been the clinical lead for the International FTD GWAS Consortium. He has also set up FTD UK, an annual scientific meeting of UK researchers who work in the FTD field (running since 2011), and runs a website dedicated to providing research updates to the general public about FTD: FTD talk.

John C. van Swieten: Dr. John van Swieten’s research focus has been on FTD since his first paper on hereditary FTD linked to chromosome 17q21-22 in 1996. He was involved in the identification of *MAPT* mutations, and his work includes clinical, pathological and genetic aspects of dementia and related

disorders (> 200 papers). He currently coordinates research on neuroimaging and fluid biomarkers in a large Dutch cohort of presymptomatic carriers, and takes part in the European GENFI initiative. Dr. John van Swieten has identified for the first time mutations in two genes (*PRKAR1B, FGF14*) in families with hereditary dementia-parkinsonism and with cerebellar degeneration.

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