Predictors of survival in frontotemporal lobar degeneration syndromes

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Abstract

After decades of research, large scale clinical trials are now underway in patients diagnosed with frontotemporal lobar degeneration (FTLD), across multiple centres worldwide. As such, refining the determinants of survival in FTLD represents a timely and important challenge. Specifically, disease outcome measures need a greater clarity of definition to enable accurate tracking of therapeutic interventions in both clinical and research settings. Multiple factors potentially determine survival, including the clinical phenotype at presentation; radiological patterns of atrophy including markers on both structural and functional imaging; metabolic factors including eating behaviour and lipid metabolism; biomarkers including both serum and CSF markers of underlying pathology; as well as genetic factors, including both dominantly inherited genes, but also genetic modifiers. The present review synthesises the effect of these factors on disease survival across the syndromes of frontotemporal dementia, with comparison to amyotrophic lateral sclerosis, progressive supranuclear palsy and cortico-basal syndrome. A pathway is presented that outlines the utility of these varied survival factors for future clinical trials and drug development. Given the complexity of the FTLD spectrum, it seems unlikely that any single factor may predict overall survival in individual patients, further suggesting that a precision medicine approach will need to be developed in predicting disease survival in FTLD, to enhance drug target development and future clinical trial methodologies.

Introduction

Frontotemporal lobar degeneration (FTLD) is a leading cause of mid-life dementia that encompasses a heterogenous group of disorders. FTLD includes frontotemporal dementia (FTD) subtypes [behavioural variant FTD (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA)], FTD with amyotrophic lateral sclerosis (FTD-ALS), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). These conditions have varied and overlapping clinical phenotypes affecting cognition, behaviour, and motor functions and are associated with significant morbidity and mortality. Neuropathologically, FTLD is also heterogeneous and comprises tau, TAR DNA-binding protein 43 (TDP-43) and FTD-FET which includes fused in sarcoma (FUS) RNA-binding proteinopathy, Ewing sarcoma protein, and TATA-binding protein associated factor with associated phenotypic

characteristics.[1] Significant work has been undertaken in the last two decades to better understand the clinicopathological correlates of FTLD syndromes, including the natural history of these conditions and predictors of survival and disease progression.

Life expectancy in FTLD ranges from 3-14 years from illness onset [2]. Despite early studies suggesting shorter survival in FTLD compared to Alzheimer's disease (AD) [3], a recent meta-analysis has shown similar median survival between the two conditions.[4] Median survival from diagnosis of FTLD was shown to be 7-13 years in multiple clinic cohorts,[5,6] while neuropathological series show shorter survival of 6-8 years.[7] Importantly, survival from disease onset has been shown to differ amongst FTLD syndromes. Survival in FTD-ALS is considerably shorter than in other FTLD syndromes (3-5 years).[4] Survival differences amongst other FTLD syndromes are less well-characterized, although studies suggest shorter survival in PSP and CBS (6-8 years) compared to bvFTD (8-10 years), with PNFA and SD showing the longest survival from disease onset (9-12 years).[8, 9] The most common causes of death in FTLD are respiratory disorders (pneumonia, choking), cardiovascular disorders, cachexia and cancer.[2, 9]

Significant research has been undertaken to understand the factors impacting on survival amongst FTLD syndromes. Predictors of survival can be grouped into those encompassing clinical or phenotypic features, imaging markers, metabolic factors, serum and CSF biomarkers, and genetic factors. This review aims to provide clinicians with a summary of available data to advise patients and their families on the likely progression and prognosis of their illness. The review also aims to examine the role that predictors of survival may play in disease pathogenesis and how they may form targets for disease modifying therapies. Finally, we discuss the role of predictors of survival in clinical trial development, with the first large scale trials for FTLD syndromes commencing recently.

Methods

Medline, Pre-Medline, PubMed, and the Cochrane Database of Systematic Reviews were searched from August 2020 backwards for the following terms in either the abstract or title: "Survival", "prognosis", "mortality", or "death" combined with "frontotemporal lobar degeneration", "frontotemporal

dementia", "progressive supranuclear palsy", "corticobasal degeneration or syndrome", "behavioural variant frontotemporal dementia", "frontal variant frontotemporal dementia", "semantic dementia", "progressive non-fluent aphasia", "primary progressive aphasia". Results were limited to English language journal articles. Titles and abstracts of all references were reviewed and 76 relevant articles were identified. All of these articles were accessed in full and their references were searched manually, yielding another 11 relevant articles. Relevant articles were those that reported mean or median survival time from symptom onset or diagnosis for FTLD subtypes. Letters, comments, and editorials were excluded. Consensus was reached amongst authors regarding article inclusion.

A. Clinical/ phenotypic predictors of survival

Clinical features can be helpful predictors of survival as they are readily available to clinicians conducting assessments of dementia patients. These features include demographic factors such as age, sex, family history, and years of education as well as clinical factors such as initial symptom(s) at onset, cognitive impairment, and phenotypic subtype. In this section, we review the evidence to date exploring the impact of these factors on survival.

Demographic factors

Age appears to be variably related to survival depending on the definition used and on FTLD subtype. Some studies have found no association between age and survival[4], whereas others show an inverse relationship between the two factors.[10] Overall, it would appear that survival is negatively associated with age at diagnosis in that the older a patient is at time of diagnosis, the shorter they will live with their disease.[11] When considering years of life lost to disease however, the younger the age at onset, the greater the absolute and relative years of life lost to disease. In other words, the impact of dying from FTLD increases with decreasing age at symptom onset.[12] The association between age and survival is variably reported amongst FTLD subtypes. Older age appears to portend shorter survival from disease onset in bvFTD[13] and FTD-ALS[14] with variable reports in PSP[15,16,17]. A series of 100 patients with SD found no association between age and survival. [18]

Sex has often been considered a meaningful predictor of survival in dementia, with female sex being more favourable for dementia mortality,[19] although the evidence is conflicting.[4] When considering absolute years of life lost, women appear to lose more years to the disease due to higher life expectancy. When taking life expectancy into account however, the relative years of life lost appear similar between men and women.[10] The effect of sex on survival amongst FTLD subtypes is also conflicting. In PSP, some studies show that male sex is an independent predictor of shorter survival from disease onset[11] whilst others have found no such association.[17, 20, 21] Studies of bvFTD and SD patients have also found no relationship between sex and survival outcomes.[18, 22]

Other demographic factors investigated for their impact on survival include education level and occupational attainment. A potential association between education or occupation and survival could underlie the effect of cognitive reserve capacity on disease trajectory. The majority of studies exploring the impact of years of education on survival have found either no or indeterminate association, including in FTLD as a whole,[4,5,6,12] as well as in specific conditions such as SD and PSP.[17,18] One potential confounding reason for this may be the low variability rates amongst highly educated cohorts.[23, 24]

Cognitive and behavioural factors

It appears that specific cognitive factors namely frontal executive dysfunction and behavioural change carry significant prognostic information in FTLD, whilst overall global cognitive impairment in FTLD as assessed by the Mini-Mental State Exam (MMSE), Addenbrooke's Cognitive Examination – Revised (ACE-R) or more detailed neuropsychological evaluation, at first clinical evaluation did not predict survival.[4, 18, 19, 22] A growing body of literature suggests that behavioural rather than cognitive decline in FTLD syndromes is a marker of progression and predictor of poorer survival.[5] Indeed, where studies have found an association between cognitive decline and reduced survival, it is predominantly in executive dysfunction as measured by tasks such as letter fluency and Trail Making tests in PSP.[17] Similar findings of worse survival predicted by measures of executive dysfunction have been replicated amongst FTLD syndromes overall as well as in bvFTD.[6,13] An interesting study utilising latent profile analysis of behavioural, functional, and neuropsychological data in FTLD identified three discrete phenotypic clusters: 'pseudo-manic behaviour' characterised by disinhibition and abnormal social

conduct, 'cognitive' characterised by executive dysfunction, and 'pseudo-depressed behaviour' characterised by depressive symptoms and subtle behavioural changes despite good performance on neuropsychological testing. The authors found that the pseudo-manic phenotype had the worst survival from symptom onset, followed by the cognitive phenotype and finally longest survival amongst those with the pseudo-depressed behaviour phenotype.[5] A contrasting study found that an apathetic neurobehavioural profile as reported by carers predicted poorer survival in FTLD.[25] These differences may be accounted for by the distinct underlying neurobiology of depression and apathy, with functional decline and poorer outcomes associated more so with the latter[26]. In CBS, a frontal lobe syndrome characterised by apathy, irritability, disinhibition, and frontal release signs, is a predictor of poorer survival.[27] It remains unclear whether the relationship between apathy and mortality is causal or correlational, and further studies are required to elucidate this relationship and to establish if treatment of apathy might improve outcomes including survival.

Language impairment is another domain with significant predictive value for survival in FTLD. Mutism and aphasia present at the time of diagnosis have been shown to portend worse prognosis in FTLD. [28] Amongst patients with bvFTD, the presence of language impairment at diagnosis, including word-finding difficulties and semantic deficits, but not paucity of speech, has been shown to predict shorter survival.[22] Similarly, patients diagnosed with FTD-ALS with language-dominant symptoms at presentation, most commonly progressive non-fluent aphasia but also semantic dementia and logopenic aphasia, had shorter survival compared to those with only behavioural symptoms at presentation.[29] Interestingly, in patients with SD, the severity of dementia as judged by psychometric scores or the degree of anomia on testing did not predict survival.[18] Overall, patients with combined behavioural and language deficits at presentation appear to have poorer prognosis, reflecting more widespread neuropathology involving both frontal and temporal lobes.

Motor features

Motor features throughout the disease course also have significant impact on survival in FTLD. The presence of amyotrophic lateral sclerosis (ALS) at disease onset or at first presentation of FTLD is associated with significantly increased mortality.[6] Initial presentation with motor symptoms in FTD-

ALS leads to faster progression and significantly shorter survival compared to those with initial cognitive symptoms. [30,31] Other motor symptoms associated with poorer survival in FTLD include dysphagia, dysphonia and gait instability. In PSP, early dysphagia has been identified as a predictor of poor survival, particularly when present within the first year from symptom onset. [16, 17, 21] Dysphagia in PSP may relate to impairment of the swallow reflex due to structural brainstem involvement. [28] The PSP-Richardson's syndrome, characterised by early falls, postural instability, and supranuclear vertical gaze palsy is also associated with worse survival from onset compared to the PSP-Parkinson's phenotype. [15, 16, 21, 32] Early falls within the first year of symptom onset are independently associated with poorer survival in PSP, whilst evidence for the prognostic utility of supranuclear vertical gaze palsy is conflicting. [16, 17] The time to onset of the first clinical milestone in PSP has also been shown to predict survival, including both motor milestones such as frequent falling, inability to walk unassisted, and severe dysphagia, as well as non-motor milestones such as urinary incontinence, use of urinary catheters and institutionalisation. [15, 20, 21] In one of the few studies to report on clinical predictors of survival in CBS patients, bilateral bradykinesia and two of three extra-pyramidal symptoms (rigidity, tremor, bradykinesia) at first presentation predicted poorer survival regardless of symptom duration. [27] Interestingly, survival in CBS was not predicted by early falls, gait disturbance, supranuclear vertical gaze palsy, dystonia, pyramidal signs, dysphagia or urinary incontinence.

Physiological features

FTLD is a network disease resulting in degeneration of multiple systems - cognitive and motor as well as physiological. Autonomic symptoms are widely reported by FTLD patients and their carers as a cause of significant distress and they occur with a high prevalence across the FTLD spectrum. Such symptoms include urinary frequency and incontinence, constipation, orthostatic intolerance, changes in sweating patterns, and cold intolerance. [33] Autonomic dysfunction appears to have a variable impact on survival in FTLD. In PSP, early development of some autonomic symptoms, namely constipation and urinary disturbance, but not orthostatic intolerance or erectile dysfunction, was associated with shorter survival. [34] The differential influence of some autonomic symptoms on survival may relate to associated intrinsic morbidity and mortality (e.g. urinary symptoms predisposing to urinary tract infections),

although further work is required to unravel the mechanisms and impact of autonomic dysfunction on survival in FTLD.

A variety of other neurological signs and symptoms predict poorer survival in FTLD syndromes in a single retrospective cohort, including epileptic seizures, primitive reflexes, and Parkinsonian traits.[28] The presence of sleep disorders in patients with PSP increases the likelihood of death significantly, which could reflect progression of disease pathology to involve sleep brainstem structures or alternatively, unidentified sleep apnoea, which is an independent risk factor for mortality in adults.[35]

Psychiatric features

Psychotic symptoms are relatively common in FTLD and portend poorer prognosis when present. [35,36] Visual hallucinations, although rare, may predict poorer survival when present in patients with PSP.[35] A wide variety of delusions have been reported in bvFTD patients, including persecutory and erotomanic delusions, which appear to be particularly common in patients who develop FTD-ALS. As such, the early presence of delusions in bvFTD should lead to an early search for ALS features, which if present, predicts significantly poorer survival and raises suspicion of a Chromosome 9 open-reading-frame 72 (C9*orf*72) gene expansion.[36]

Overall, demographic factors such as age, sex and family history do not appear to have significant predictive value with regards to survival in FTLD. While older age at onset predicts a shorter disease course, years of life lost is greater with younger onset FTLD. Occupational attainment may be one demographic factor with a protective role in FTLD, although this finding requires further confirmation and exploration of putative mechanisms. Amongst clinical factors, behavioural changes, apathy, and language impairment appear to predict poorer survival across FTLD syndromes. Predictors of poorer survival amongst specific FTLD subtypes include early and severe parkinsonism in CBS, falls, early dysphagia, urinary incontinence, sleep disorders, psychotic symptoms and PSP-RS phenotype in PSP, and motor-onset presentations in FTD-ALS.

Measures of functional decline

Currently we have limited measures of functional decline that can be used across the FTLD spectrum. There are measures that can be used in specific diseases e.g. the FTD rating scale (FRS)[37] in FTD, and the Amyotrophic lateral sclerosis functional rating scale (ALS-FRS) in ALS[38], but we are unable to use these across diseases. It has been shown that the ALSFRS can predict survival independent of symptom duration[38] in ALS, however, whilst the FRS can predict disease progression and show deterioration over time in patients with FTD, between clinical phenotypes there is variation in the time taken to reach each stage, and this does not correlate with length of symptoms and overall cognitive function, and its relationship to survival time is not known.[37] Given the overlap across the FTLD spectrum there is an urgent need for the development of scales that can be used across the spectrum and that measures functional decline involving both cognition, motor factors and other clinical factors, and their relationship to overall survival.

B. **Imaging predictors of survival**

Conventional neuroimaging, including both structural and functional imaging, is widely used in the work-up of suspected FTLD cases to exclude other pathologies and to further support the clinical diagnosis. A growing body of literature supports the use of neuroimaging to help evaluate prognosis and survival in FTLD independent of clinical and neuropsychological profiles.

Structural brain imaging

Structural brain imaging utilising magnetic resonance imaging (MRI) has been investigated extensively as a means of improving diagnosis in FTLD, with characterisation of different patterns of brain atrophy in different FTLD syndromes. The presence or absence of brain atrophy on MRI is itself a determinant of survival. An early study assessing the prognostic utility of MRI showed that bvFTD patients with normal MRI findings have a more benign disease course with significantly longer survival compared to those with definite frontotemporal atrophy.[39] Subsequent studies have shown that MRI-normal bvFTD is not merely an early presentation of the disease but rather a 'phenocopy' syndrome with similar clinical features.[22] These patients have normal frontotemporal metabolism on fluorodeoxyglucose-

positron emission tomography (FDG-PET), do not progress to frank dementia, and have prolonged survival.[40] It remains a matter of debate as to whether these phenocopy cases represent an alternative neuropsychiatric or developmental condition. Thus, regional brain atrophy on MRI likely predicts poorer survival in bvFTD due to identification of patients with a neurodegenerative disease rather than phenocopy syndrome. In terms of specific patterns of brain atrophy and survival in bvFTD, greater atrophy in the anterior cingulate cortex, but not orbitofrontal cortex or anterior temporal lobe, was associated with shorter survival time. Interestingly, motor cortex atrophy was identified as an independent predictor of disease progression, potentially due to identification of the subset of patients at greater risk of developing ALS.[13] Indeed, motor cortex atrophy, particularly in the right hemisphere, in FTD-ALS and bvFTD has been shown to increase the risk of death 1.5-fold. [30] The degree of atrophy on MRI is also predictive of survival in bvFTD, with visually-rated diffuse frontal lobe atrophy predicting worse survival than focal or circumscribed atrophy.[41]

In other FLTD syndromes, investigation of MRI as a tool for prognostication has yielded interesting findings. In SD, all patients demonstrate focal atrophy in either one or both anterior temporal lobes, with a predilection for left more than right temporal atrophy.[42] No difference in survival was found between left- or right-predominant atrophy in SD despite different clinical profiles.[18] In PSP, midbrain atrophy is commonly observed and has led to the development of neuroimaging biomarkers such as the midbrain/pons area ratio and the magnetic resonance parkinsonism index. It has been shown that the midbrain/pons area ratio, a relatively simple measure, predicts earlier institutionalisation and poorer survival in PSP.[43]

Functional brain imaging

Functional brain imaging, including FDG-PET is increasingly being utilised in clinical and research settings to diagnose and differentiate amongst neurodegenerative disorders and in determining longitudinal progression. FDG-PET has been shown to be as predictive as longitudinal clinical follow-up in predicting poorer survival amongst patients with PSP and CBS when cortical or subcortical

hypometabolism is detected.[44] Regional perfusion patterns are also found to correlate with specific clinical phenotypes and survival in FTLD. Hypoperfusion in the orbitomesial frontal cortex has been associated with the 'pseudo-manic behaviour' latent class discussed earlier, which is itself associated with poorer survival.[5] The degree of hypoperfusion in bilateral frontal cortices, particularly the right orbitomesial frontal cortex, is further predictive of shorter survival in FTLD. Orbitomesial frontal dysfunction may impact survival through behavioural disturbance and executive dysfunction, with resultant impairment of adaptive behaviour and symptomatic pharmacological treatment that may lead to poorer prognosis.[45] In bvFTD, brainstem hypoperfusion has interestingly also been shown to predict poorer survival. This is in keeping with brainstem involvement in bvFTD in neuropathological studies and may potentially relate to causes of death due to dysphagia and aspiration pneumonia.[46]

To date studies examining the utility of tau imaging in FTLD spectrum disorders has been limited likely secondary to issues with sensitivity and specificity in predicting between those likely to have underlying tau versus TDP-43 pathology.[47]   Potentially as tau imaging is developed it may become useful as a predictor of survival, as a reflection of underlying pathology. Studies have also recently shown that approximately 30- 40% of patients with a clinical and pathological diagnoses of FTD can have underlying amyloid deposition.[48] Further research also required into the role that amyloid PET imaging, as a reflection of underlying amyloid pathology in FTLD syndromes and the effect that this may have on overall survival and progression.

C. Metabolic predictors of survival

Mounting evidence points to a higher prevalence of metabolic changes, including altered eating behaviour, weight fluctuation, insulin resistance, and lipid levels, in FTD compared to the general population. [49] Similar changes have been noted in a variety of other neurodegenerative conditions such as Parkinson's disease and Alzheimer's disease. [50, 51] Whether these changes are a cause or consequence of the neurodegenerative process and their impact on prognosis and survival is largely unknown. A

growing body of literature endeavours to answer these questions, with a particular focus thus far on the FTD-ALS spectrum.

Hyperorality and dietary changes are one of the six core criteria for bvFTD diagnosis, and are present in over 60% of patients at initial presentation.[52] The factors mediating these eating behaviour changes are complex and likely involve cognitive and behavioural changes, altered reward processing, neuroendocrinological changes and regional degeneration in brain pathways responsible for controlling eating behaviour. Interestingly, increasing changes in eating behaviour along the FTD-ALS spectrum were associated with a threefold decreased risk of dying compared to FTD-ALS patients with mild eating behaviour change.[53] Indeed, patients with ALS who develop FTD have a similar eating behaviour profile and increase in BMI as bvFTD patients, which is not seen in ALS alone.[49] Although speculative, this change in eating behaviour may develop as a protective mechanism along the FTD-ALS spectrum, perhaps through modulation of disease pathophysiology via macronutrient intake and energy metabolism. Further research is required to confirm this hypothesis and delineate a specific mechanism. Alterations in eating behaviour and caloric intake do not however seem to correlate with body mass index (BMI), suggesting additional influences on BMI in the FTD-ALS spectrum. Importantly, BMI itself was not associated with survival in FTD-ALS [53], in contradistinction to ALS where a "U"-shaped association is found between BMI and mortality.[54]

Given the prominent changes in eating behaviour amongst patients with FTD/FTD-ALS, it is unsurprising that these patients exhibit significant alterations in metabolic parameters such as insulin resistance, cholesterol, and neuropeptide levels. Both bvFTD and SD are associated with increased insulin and triglyceride levels and lower high-density lipoprotein (HDL), reflecting a state of insulin resistance.[55] These changes increase with disease progression and lead to a higher incidence of diabetes amongst FTD patients. Investigation of the effects of systemic lipid dysregulation on survival in bvFTD has shed further light in this area. Patients with bvFTD have been shown to have significantly reduced concentrations of apolipoprotein A-1 and A-II (apoA-I and II), decreased high-density lipoprotein-cholesterol (HDL) levels, and increased very-low-density-lipoprotein-triglyceride (VLDL) levels compared to healthy controls, confirming manifestation of hypoalphalipoproteinemia and

hypertriglyceridemia in bvFTD. [56, 57] The apoB:apoA-I ratio, a robust marker of cardiovascular disease, was found to be significantly increased in bvFTD. Additionally, triglyceride:HDL-cholesterol and total cholesterol:HDL-cholesterol ratios were also found to be increased in bvFTD. Further research is required into the effect of insulin resistance and lipid levels on survival in FTD.

Metabolic changes in FTD-ALS also appear to impact on survival. Lower total cholesterol levels in FTD-ALS patients were found to be a significant predictor of shorter survival, with an estimated 3.25-fold increased risk of death.[57] Similar findings have been reported in ALS patients without FTD, and while the exact mechanism is yet unclear, effects on survival may be mediated through alterations in muscle and lipid metabolism.[58] Other biomarkers identified through lipidomics, such as cardiolipin, acylcarnitine, lysophosphatidylcholine, and acrolein, have been shown to be significantly altered in FTD, with consequent effects on mitochondrial dysfunction, increased inflammatory activity, and oxidative stress, although the direct impact on survival has not been elucidated. [59]

Further analyses of survival in FTLD combining assessment of metabolic changes such as eating behaviour, BMI, lipid profiles, and other biomarker levels with central neuropathophysiological and neuroendocrinological changes will enable better understanding between these factors and potentially lead to disease-modifying therapies.

D. Serum and CSF biomarkers as predictors of survival

Fluid-based biomarkers have evolved as a promising tool in the diagnosis and prognostication of neurodegenerative diseases, including as predictors of disease progression and survival. Such biomarkers include neurofilament light chain, tau, and amyloid beta, which can be measured in both serum and cerebrospinal fluid (CSF). The utility of each of these biomarkers in predicting survival amongst FTLD syndromes will be discussed separately here.

Neurofilament light chain

Neurofilament light chain (NfL) is increasingly recognised as a marker of underlying neurological diseases. NfL levels in serum and CSF are increased in a variety of neurological disorders characterised by damage to white matter tracts and subcortical structures, including multiple sclerosis[60], vascular dementia, Alzheimer's disease, and FTLD.[61] Indeed, CSF NfL levels are highest amongst FTLD syndromes compared to other dementia subtypes, perhaps relating to the degeneration of large-calibre axon-rich regions in the frontotemporal lobes and to the underlying neuropathological disease processes at a cellular level leading to neuronal death and CSF leakage. [62] Unsurprisingly, CSF NfL levels have been shown to positively correlate with disease severity and predict shorter survival time in FTLD. [61] Five-year survival in a cohort of patients with FTD, including bvFTD, SD, PNFA, PSP, and CBS subtypes was approximately 73% in patients with low CSF NfL levels (NfL <1,989 pg/mL), 55% in moderate levels (NfL 1,989–3,675 pg/mL), and 36% in high levels (NfL >3,675 pg/mL).[63] Correlation between CNS NfL levels and survival has been further demonstrated in bvFTD, CBS, PSP and FTD-ALS. [63, 64, 65 , 66, 67] In SD, CNS NfL levels were associated with greater semantic deficits and smaller parahippocampal volumes, but did not appear to predict survival.[68] The invasive nature and reduced patient acceptability of lumbar puncture has led to interest in blood-based assays for the quantification of NfL, which are highly correlated with CSF levels, and have similarly been shown to correlate with disease severity and predict survival in FTLD.[69, 70, 71, 72]

Tau

CSF tau is another biomarker with growing utility in the diagnosis and prediction of survival in dementia syndromes, with particularly robust evidence in AD. [73] Results of tau levels in FTLD are more variable, potentially due to the heterogenous neuropathology of FTLD (e.g. FTLD-TDP vs FTLD-tau) as well as underlying pathogenic genetic differences involved in tau expression. Nevertheless, CSF tau is a non-specific marker of axonal damage in neurodegeneration, and as such, has been shown to be elevated in FTLD.[74] Furthermore, higher CSF tau levels (≥400 pg/ml) in FTLD are associated with greater language impairment, more severe temporal atrophy, and shorter survival.[75] Another useful marker in neurodegeneration is the measure of tau hyperphosphorylation with the phospho-tau:total-tau ratio showing promise as a predictor of survival; low phospho-tau:total-tau ratio is associated with

worse survival in FTLD, including in bvFTD and PSP. [63, 66] Reasons for this are not yet clear, and may be driven by increased total tau levels in more severe disease or due to variations in phospho-tau levels amongst pathological subtypes (e.g. lower in FTLD-TDP). [73] As such, CSF and serum tau and phospho-tau levels and their respective ratios may aid in predicting survival in FTLD syndromes.

Amyloid-beta

Whilst amyloid-beta$_{1-42}$ (Aβ_{1-42}) deposition is considered a hallmark of AD, amyloid pathology has been implicated in other neurodegenerative conditions including FTLD. Patients with FTLD can have superimposed amyloid pathology which may interact to facilitate the aggregation of tau.[76] In familial FTD with known genetic mutations, amyloid is associated with worse performance in cognitive tests and greater hypometabolism and atrophy in temporo-parietal regions.[77] Additionally, lower baseline CSF Aβ_{1-42} predicts faster rates of frontotemporal volume loss in bvFTD.[78] It is therefore unsurprising that lower CSF Aβ_{1-42} is associated with higher mortality in FTD. Several potential explanations have been put forward, including amyloid-mediated enhancement of tau aggregation, up-regulation of amyloid-beta deposition through upstream impact of extracellular tau, or additive effects in patients with concomitant pathology.[79] It therefore appears that amyloid-beta analysis may have prognostic utility beyond AD.

E. Genetic predictors of survival

Within the FTLD syndromes, 25-50% of patients have a family history of dementia and approximately 10% have a Mendelian form of the disease with autosomal-dominant inheritance. The most common pathogenic mutations in FTD are found in Microtubule Associated Protein Tau (*MAPT*), Granulin (*GRN*), and hexanucleotide repeat expansion of Chromosome 9 open-reading-frame 72 (*C9orf72*). Additional genes that modulate or increase the risk of FTLD include apolipoprotein E (*APOE*), vascular endothelial growth factor (*VEGF*) and triggering receptor expressed on myeloid cells 2 (*TREM2*). The influence of these genes on survival will be discussed here.

Monogenic mutations in *MAPT* and *GRN* were identified early on as predictors of poorer survival in FTLD. [80]Autosomal dominant mutations are also associated with earlier age at onset and faster disease progression, which may account for the variable effects of age on survival discussed earlier. [76] In bvFTD, the presence of a known mutation is similarly associated with shorter survival from disease onset, with disease duration on average shortest in patients with *C9orf72* expansions, followed by *GRN* and then *MAPT[81]*. The effect on survival of *C9orf72* expansions however, appears to be more complex. Some studies report worse survival amongst carriers of *C9orf72* mutations in FTLD [82], whereas others have found no impact on disease survival in FTD, bvFTD and FTD-ALS, despite seemingly faster rates of progression.[13, 30, 83, 84] Heterogeneous progression in *C9orf72* positive carriers may be further accounted for by the finding that *C9orf72* hypermethylation is widely variable amongst carriers and is associated with slower clinical progression and prolonged survival in FTD, likely due to reduced expression of mutant protein.[85]

In addition to mutations in the *MAPT* gene, tau polymorphisms appear to influence disease development and survival amongst FTLD. Tau H1/H2 haplotype has been shown to influence FTLD presentations. Tau H2 haplotype is associated with an earlier age of onset in FTLD and predicts poorer survival from disease onset;[86] H2 heterozygous carriers have a 2-fold increased risk of death while homozygous carriers have a 3.5-fold increased risk. [87] Within FTLD, both CBS and PSP are associated with higher rates of homozygous H1 genotype (92% and 95% respectively) compared to the general population (60-75%), and while H1 genotype was associated with more severe motor function and a trend towards shorter survival in CBS, no effect of genotype on survival was found in PSP. [88, 89]

Apolipoprotein E (*APOE*) genotype is a well-recognised genetic risk factor for late-onset AD and Lewy-body Dementia (LBD), and is reported to be a modulating risk factor in FTLD. [90] The effect of *APOE* genotype on survival in FTLD is controversial, with a majority of studies reporting no association between genotype and survival in FTD, PSP and CBS, [91, 92] although a few studies do report increased risk of FTLD development with worse prognosis in *APOE* ε4 carriers. [87] Conflicting findings may relate to the complex interaction between APOE genotype and underlying neuropathology in FTLD.

Clinicopathological correlates: Is this the common denominator for predictors of survival?

Based on current research we are unable to say which factor i.e clinical phenotype versus underlying pathology is the major predictor of survival. Intuitively one would expect underlying disease pathology, to hold the greatest influence, but based on clinical and pathological studies to date we are unable to answer this question i.e does pathology influence survival versus clinical phenotype as a reflection of underlying pathology, versus the ability of clinical phenotype eg metabolic factors to modify underlying pathology. We do know that underlying pathology has long been known to influence survival, and indeed may be the common denominator through which all of the abovementioned factors predict survival. Tau-positive pathology is frequently reported to be associated with slower rates of progression and longer survival from symptom onset in FTLD compared to tau-negative cases.[3, 7] Some speculate that poorer survival amongst tau-negative cases is due to the inclusion of ALS patients, who are known to have higher mortality, although one study reported persistently poorer survival amongst tau-negative cases even after ALS patients were excluded.[6] Conversely, some studies report a trend towards poorer survival in tau-positive FTLD.[23] Several reasons could account for these differences and shed further light on the influence of pathology on survival. Firstly, studies reporting poorer survival in tau-positive cases had greater numbers of CBS patients with more extensive tau pathology compared to FTD.[7, 23] Secondly, and importantly, not all tau is equal, with significant clinical and pathological differences between 3-repeat (3R) and 4-repeat (4R) tau. Alternative mRNA splicing results in a different number of repeats of the microtubule binding domain of tau protein, with distinct disease correlates. FTD-tau pathology in bvFTD and PNFA consists primarily of 3R-tau, whereas, CBS and PSP are characterised by abnormal 4R-tau deposition, however a PNFA like syndrome can occur in CBS and PSP. When 3R and 4R-tau pathology were directly compared those with 4-R tau pathology had a shorter survival regardless of the clinical phenotype, suggesting that pathology may be the determining factor of survival.[93] Interestingly among bv-FTD cases, those with 4R tauopathies were more likely to display behavioural underactivity than those with 3R tauopathy,[93] which could be potentially used as a clinical factor to predict underlying pathology.

We can begin to see some pathological underpinnings of clinical and radiological factors that predict poorer survival in FTLD, such as apathy in bvFTD associated with 4R-tauopathies, language impairment in more widespread cortical pathology, and involvement of motor brain regions amongst patients with TDP-43 pathology. Furthermore, genetic mutations impact on survival through direct gain- or loss-of function mutations (e.g. *MAPT*) as well as through modification of specific disease processes (e.g. *APOE ε4* and tauopathies). Finally, CSF and serum biomarkers appear to not only provide prognostic information but also hint at the underlying disease process during life (e.g., phospho-tau:total-tau ratio reflecting tau-negative pathology with associated poorer survival). Further research is required into disentangling the effects of differences in pathology, how this is reflected in clinical phenotype and disease progression and effect on survival.

Future research in survival analyses

Future research into survival in FTLD syndromes will need to focus on large longitudinal survival studies. One of the limitations of this review include the relative paucity of large clinical cohort studies investigating survival in FTLD, relating to the overall rarity of these conditions. Some of the articles included were of small sample size limiting generalisability of the findings. For certain FTLD syndromes, such as CBS, the evidence for predictors of survival is sparse. Many studies did not include neuropathological confirmation of the clinical diagnoses, raising the likelihood of greater clinical heterogeneity and inclusion of patients with alternative disease processes. Furthermore, reviewed articles variably reported on or controlled for factors known to affect mortality, such as comorbid conditions and cause of death. Inconsistency in defining and reporting of disease survival across studies is another significant limitation, with variable reference to mean or median years from symptom onset, initial clinical evaluation, diagnosis, study entry, or death. These measures provide different information regarding prognosis and differ from other methods of reporting survival such as years of life lost relative to matched life expectancy in the general population, a potentially more clinically meaningful yet under-utilised measure.[10] One of the major limitations of the studies examining survival across the FTD spectrum is the lack of functional measures of disease severity and

there correlation with survival. Currently in FTD research there are measures of behaviour, cognition and functional ability via the FTD rating scale (FRS) and Clinical Dementia Rating scale−frontotemporal lobar degeneration (CDR-FTLD, that can show disease progression, but as patients enter the severe stage their ability to detect differences diminishes.[94] Also we do not as yet understand the correlation of these scales with pathology and brain atrophy patterns and overall survival, which requires the development of large scale trials examining clinical phenotype, pathology, brain atrophy patterns and functional decline in order to disentangle these complex interactions. Finally, the predictors of survival discussed in this paper apply to a group of patients with shared clinical and pathological phenotypes, and are not as easily applied to individual patients. This is because survival at the individual level depends greatly on the interactions of many of the discussed factors in a potentially additive or multiplicative manner. For the clinician asked to prognosticate on an individual patient, a useful approach may be to refer to available survival data for specific clinical phenotypes, which is then modulated, either positively or negatively by a factor where available, by the identification of the predictors of survival discussed in this article. (Figures 1) One area in urgent need of research is the development of models/ prediction tools for the clinician that take into account biomarkers of pathology, brain atrophy patterns and clinical phenotype that could be harnessed in order to provide a prediction of survival and progression for individual patients.

Predictors of survival in drug target and clinical trial development

For many years potential drug treatment targets and clinical trials have remained elusive in FTLD spectrum disorders, in part related to the clinical and pathological heterogeneity within the disorder. Recently a number of clinical trials have begun recruiting including those targeting specific genetic mutations. Future clinical trial design will need to include an assessment of variables that potentially modulate prognosis, for example metabolic factors, potential genetic modifiers and imaging markers in order to ascertain the direct effects of the drug. Trial design may also need to stratify patients based on survival factors into those likely to be classified as slow progressors versus fast progressors, as this may potentially affect response to treatment. An examination of predictors of survival along the FTLD

spectrum also provide targets for potential drug treatment development and measures to monitor to determine drug efficacy. Potential drug treatment targets will involve not only genetic and pathological factors but should also include other factors along the FTLD spectrum that can modify disease progression including for example metabolic factors and lipid metabolism. An understanding of survival profiles (Figure 2) also offers the development of individualised precision medicine targeting different aspects for a patient in order to individually improve survival, whilst we await an overall elusive drug treatment. What is clear from an understanding of the clinical and pathological aspects and survival factors along the FTLD spectrum is that there is unlikely to be only one drug target that will stop these devastating diseases, and an individualised precision approach targeting several factors involving phenotypic, genetic, and pathological aspects is likely to be required. .

Conclusion

There are a number of significant predictors of survival across clinical, imaging, metabolic, biomarker and genetic factors within the FTLD spectrum of diseases. Understanding of survival factors in FTLD will undoubtedly help clinicians to identify those patients who are more likely to have a rapidly progressive disease course and hence allow for more proactive and tailored care delivery. It will also allow for more informed delivery of prognostic information to patients with FTLD and their carers. On the research front, insights into predictors of survival will allow the FTLD research community in collaboration with the pharmaceutical industry to design clinical trials that appropriately account for variables that may influence disease progression and survival in addition to the effects of the candidate therapy. Finally, a comprehensive understanding of the factors that influence survival points to new potential treatment targets, particularly metabolic and other genetic factors, that may represent additional mechanisms to slow disease progression.

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Figure Legends

Figure 1. Factors influencing survival in FTLD across clinically-relevant domains. Abbreviations: AAO = age at onset, MAPT = Microtubule Associated Protein Tau, GRN = granulin, APOE ε4 = apolipoprotein ε4, NPY = neuropeptide Y, Aβ$^{1\text{-}42}$ = amyloid beta 1-42, NFL = neurofilament, p-tau:t-tau = phosphorylated tau:total tau ratio, C9orf72 = Chromosome 9 open-reading-frame 72, ACC = anterior cingulate cortex, OFC = orbitofrontal cortex.

Figure 2. Factors influencing poor versus improved survival across the spectrum of FTLD syndromes. Abbreviations: MAPT = Microtubule Associated Protein Tau, GRN = granulin, NPY = neuropeptide Y, CSF = cerebrospinal fluid, Aβ$^{1\text{-}42}$ = amyloid beta 1-42, C9orf72 = Chromosome 9 open-reading-frame 72, NFL = neurofilament, p-tau:t-tau = phosphorylated tau:total tau ratio