Factors associated with survival probability in autopsy-proven frontotemporal lobar degeneration

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ABSTRACT

Objective: To examine the clinical and pathological factors associated with survival in autopsy-confirmed frontotemporal lobar degeneration (FTLD).

Methods: The final analysis cohort included 71 patients with pathologically proven FTLD, excluding patients with clinical motor neuron disease (MND), evaluated at the University of Pennsylvania or at the University of California, San Francisco. We assessed clinical and demographic features; cognitive functioning at presentation; genetic markers of disease; and graded anatomical distribution of tau, ubiquitin and amyloid pathology.

Results: The tau-negative group (n = 35) had a median survival time of 96 months (95% CI: 72–114 months), whereas the tau-positive group (n = 36) had a median survival time of 72 months (95% CI: 60–84 months). Patients with tau-positive pathology across all brain regions had shorter survival than those with tau-negative pathology in univariate Cox regression analyses (Hazard ratio of dying = 2.003, 95% CI = 1.209–3.318, p = 0.007).

Conclusions: Tau-positive pathology represents a significant risk to survival in FTLD, whereas tau-negative pathology is associated with a longer survival time when clinical MND is excluded.

Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative condition that manifests clinically as a disorder of social comportment, personality and executive functioning (ie behavioural change), or as a progressive form of aphasia (ie language change). Although FTLD may progress to death more rapidly than Alzheimer’s disease (AD),1 there has been little consensus on the factors contributing to the rapid decline of these patients. A recent consensus group distinguished between tau-positive and tau-negative pathologies.2 Two reports associate tau-positive pathology with a longer survival,1,3 whereas others have found equal survival in tau-negative and tau-positive pathologies.1,3,4 We examined clinical and pathological characteristics contributing to survival in a relatively large cohort of autopsy-proven FTLD.

METHODS

Study cohort

Inclusion criteria included all patients with FTLD spectrum neuropathology identified at the University of Pennsylvania (UPenn) between 1995 and 2005, following clinical assessments at UPenn or University of California, San Francisco (UCSF), who did not have significant non-neurological co-morbidities such as cancer or pulmonary disease (n = 91). Patients without adequately detailed clinical evaluations were excluded (n = 15), and patients with a clinical diagnosis of motor neuron disease (MND) were excluded due to their known shorter lifespan and known pathology (n = 5). Table 1 summarises the final analysis cohort, including 71 subjects with a pathological diagnosis of FTLD. All subjects in the final analysis cohort had a primary pathological diagnosis related to a disorder of tau. However, four subjects had a secondary pathological diagnosis, suggesting some features of AD. Not all subjects had information for all variables (see table 1 for more details). Some of these patients were previously reported.7

Clinical evaluations and survival time

Clinical diagnosis was based on informant interview, medical history, neurological examination, neuropsychological evaluation, laboratory screening and brain imaging, when available (including MRI, SPECT and/or PET). The clinical diagnosis was consistent with published criteria.2,6

Survival time was computed from the approximated time of symptom onset until the time of death. Symptom onset estimation was based on a family report of the earliest persistently abnormal clinical feature in the domains of language, social function or personality change, memory, executive, visual–spatial functioning, movement disorder or weakness.

Symptoms at presentation included (coded as present or not present): Social/behavioural change; language dysfunction; other cognitive deficits; movement disorder; and focal weakness. Specific clinical signs from the neurological exam included: Social dysfunction; aphasia; extrapyramidal features; and pyramidal signs. A limited battery of cognitive tests was available across the accrual period at the referring sites, including: Mini-Mental State Examination (MMSE); Boston Naming Test; Animal Fluency; Word List Recall; and Digit Span Forward. Family history was coded as: Present or absent. Tau haplotype and Apolipoprotein E genotypic information were also available for analyses.

Pathology evaluation

To establish a neuropathological diagnosis, representative blocks were examined from the brain, as described previously.1 All cases were reviewed by two board-certified neuropathologists (MSF and...
JQT) blinded to clinical diagnosis, and consensus pathological diagnoses were established according to the Workgroup on frontotemporal dementia and Pick’s disease (FTD). Examined brain regions included: mid-frontal gyrus, inferior parietal lobule, superior and middle temporal gyrus, anterior cingulate gyrus, hippocampus, amygdala with entorhinal cortex, thalamus, and basal ganglia. Examined proteins used in the analysis included: tau, amyloid and ubiquitin. Based on the density of immunostained pathology, semi-quantitative grading was assigned (0 = no or rare pathology, 1 = low pathology, 2 = moderate pathology, 3 = high pathology) in each analysed brain region. We considered several summary neuropathology variables, including: average pathology across all regions for each ascertained protein; and average pathology reading across tau, ubiquitin and amyloid for a single brain region. We dichotomised these neuropathology variables into low pathology (grading = 0 or 1) and abundant pathology (grading = 2 or 3) categories. We refer to cases with low tau pathology as tau-negative (average tau pathology rating \( < 1 \)), and cases with abundant tau pathology as tau-positive (average tau pathology rating \( \geq 2 \)).

### Statistical analyses

The Kaplan–Meier method was used to generate survival probabilities. Single and multiple covariate Cox proportional hazards regression models examined factors associated with survival. A forward model selection procedure was used, following model building guidelines. Potential independent variables included demographic features, clinical features at the initial visit, cognitive variables, family history, genetic information and neuropathology features. Statistical analyses used SAS software (SAS Institute, Cary, NC). All statistical tests used two-sided p-values. Statistical significance was set at the 0.05 level.

### Results

The proportion of males and presence of family history, mean years of education, mean age at onset, as well as MMSE score at the initial visit, were similar between tau-negative and tau-positive groups (\( p > 0.05 \), table 1). The discrepancy between estimated symptom onset and initial diagnosis (mean = 59 months, standard deviation = 57 months) differed between tau-positive and tau-negative groups (Wilcoxon rank sum test, \( z = 2.056, p = 0.040 \). Median survival from symptom onset for the entire cohort was 80 months (95% confidence interval (CI) = 72–84 months). The tau-negative group had a median survival time of 96 months (95% CI: 72–114 months), whereas the tau-positive group had a median survival time of 72 months (95% CI: 60–84 months). In the univariate Cox regression analyses, patients with tau-positive pathology had shorter survival than those with tau-negative pathology (Hazard ratio (HR) of dying = 2.003, 95% CI: 1.209–3.318; Wald \( \chi^2 = 7.278, df = 1, p = 0.007 \)). A shorter survival time in the univariate analysis was associated with abundant pathology of any sort in the basal ganglia region (HR = 1.874, 95% CI: 1.054–3.532; Wald \( \chi^2 = 4.569, df = 1, p = 0.033 \)). Shorter survival in the univariate analysis was also associated with abundant pathology of any sort in the anterior cingulate region (HR = 1.782, 95% CI: 1.057–3.062; Wald \( \chi^2 = 4.372, df = 1, p = 0.037 \)).

Finally, shorter survival in the univariate analysis was associated with tau-positive pathology in an averaged cortical region, including midfrontal, parietal, temporal and anterior cingulate regions (HR = 1.637, 95% CI: 1.092–2.565; Wald \( \chi^2 = 3.983, df = 1, p = 0.046 \)). Other characteristics were not significantly associated with the survival probability.

The forward model selection procedure generated a preliminary model with only one significant predictor: status of tau-positive versus tau-negative pathology across all regions. Inspection of the remaining candidate variables revealed that education produced the largest important change to the regression coefficient of the tau pathology factor across all regions (32%). A comparison of higher education levels (>15 years) to lower education levels (<15 years) in FTLD demonstrated a hazard ratio of 0.756 (95% CI = 0.425, 1.274), although this effect did not reach statistical significance. Pathology of any sort in the basal ganglia region also substantially changed the regression coefficient of the model, including both tau pathology status and education (44%). The association between tau pathology status and survival probability was strengthened after adjusting for years of education and pathology of any sort in the basal ganglia region (HR = 3.750, 95% CI: 1.694–8.303;
DISCUSSION

Median survival time from symptom onset in our cohort was 80 months, resembling previous studies of autopsy-proven FTLD, with median survival ranging from 72 months to 104 months.6–8 Tau-positive pathology was associated with shorter survival time in FTLD. Factors contributing to survival included education and disease in the basal ganglia.

Our findings differ from the results of two previous studies charting survival in FTLD.3,4 These investigators reported that tau-negative pathology results in shorter survival time. It is well established that tau-negative pathology—in particular, frontotemporal lobar degeneration with ubiquitin/TDP-43 inclusions (FTLD-U)—is identical to the pathology underlying MND.10,11 However, a second analysis (excluding MND) replicated the basic finding that tau-negative pathology is associated with shorter survival time.3,4 Factors potentially contributing to the discrepancy between these findings and ours include that the pathologies contributing to the cohorts may not be the same across studies. Our cohort had many corticobasal degeneration (CBD) patients, whereas other studies had many tau-positive patients with PiD.3,4 Previous studies performed only univariate analyses, and did not adjust for other covariates. Finally, our study used the actual empirical burden of tau pathology to establish tau-positive and tau-negative patients.15,6 One study compared 19 tau-positive patients primarily with PiD and 24 tau-negative cases found a trend towards more rapid decline in tau-negative cases, but did not exclude clinical MND cases from the tau-negative cohort.1 Another report of 60 autopsy-proven FTLD patients showed a trend toward shorter survival in tau-positive cases.6

In our multivariate survival model, additional factors influencing prognosis in FTLD may include significant basal ganglia pathology. Although this variable did not reach statistical significance in the final multivariate model, it did change the magnitude of the regression coefficient of tau pathology across all regions by >20%, indicating that the burden of basal ganglia pathology may contribute to survival. This may be related, in part, to the large number of CBD patients. Clinical assessments of survival in non-autopsy studies of FTLD have reported that Parkinsonism, a marker of basal ganglia disease, contributes to rapid disease progression.12 Parkinsonism and dementia have independent and additive effects on mortality in Parkinson’s disease13 and in AD.14 We may not have observed the direct contribution of extrapyramidal features to mortality because we ascertained extrapyramidal features only at the onset of disease when all subjects were mildly impaired.

Education also changed the magnitude of the regression coefficient by >20%, although this factor was not significantly associated with survival probability in the multivariate analysis. One previous report found no significant effect of education on survival in FTLD,25 but these investigators did not consider the contribution of demographic factors in a multivariate account of survival in FTLD. It is difficult to assess the effect of education in our highly educated cohort as variance was not sufficiently broad.

Our study did not otherwise demonstrate a relationship between survival and clinical features at presentation. Conclusions about clinical factors such as aphasia or a social disorder have been conflicting.3,4,12 As syndromic subgroup classification may change during the natural history of FTLD,6 we elected to evaluate the presence of a specific clinical abnormality in the model rather than the presence of a particular syndrome.3,4 Although some studies investigated many neuropsychological variables on smaller autopsy samples,4 we evaluated a small number of neuropsychological measures to maximise the size of the autopsy-confirmed cohort. It is unfortunate that inattention and apathy were not ascertained in enough patients because these features may be associated with anterior cingulate disease,15 and pathology in this region may contribute to survival.

Although patients were recruited early in their disease when there is little sense of progression rate, we cannot exclude the possibility that an inadvertent selection bias was introduced because subjects enrolled in an autopsy program may be sicker or have a higher level of education. Because we performed a relatively large number of analyses, the readers should bear in mind that there may exist false-positive findings. With these caveats in mind, our findings indicate that several factors predispose FTLD patients to a limited survival. The principal contributing factor is the presence of tau pathology. This observation emphasises the importance of developing biomarkers that reflect the presence of tau pathology.16

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A note on X linked adrenoleukodystrophy (Addison–Schilder syndrome)

In one of the unsurpassed medical works of the nineteenth century,1 2 Thomas Addison (1793–1860) when investigating a “peculiar form of anaemia” described the classic symptoms of adrenal cortical failure and found pathological changes in both “suprarenal glands”—Addison’s disease. The ill-fated Paul Ferdinand Schilder (1886–1940) in 1913 reported3 three cases of “encephalitis periaxialis diffusa”, characterised by diffuse involvement of the cerebral white matter in children with severe myelin loss, fat-laden phagocytes and gliosis, which resembled multiple sclerosis, and was named Schilder’s disease. The two conditions appeared unrelated until Haberfeld and Spieler reported the combination of bronzed skin with leukodystrophy in 1910, but the findings in the adrenal gland were not reported.4

“A previously normal boy developed disturbances in eye movement and vision at the age of 6 years, became apathetic, and his schoolwork deteriorated. Four months later his gait became spastic, and this progressed to an inability to walk. He was hospitalised at 7 years. Dark skin was noted, but otherwise not discussed. He had a spastic paraparesis, severe apathy alternating with irritability, did not speak, and was incontinent. He died 8 months later. An older brother had died of a similar illness at 8.5 years. The postmortem brain was studied by Schilder in 1913 who confirmed epidermal pigmentation and diffuse demyelination of the brain.”5

Siemerling (1857–1931) and Creutzfeldt (1885–1964) in 1925 reported a similar case and deserve credit for proving adrenal involvement,6 and thereby founding adrenoleukodystrophy, the term first introduced in 1970.6

Hoefnagel et al summarised the literature and described an afflicted family.7 It included a boy aged 7 years at death with no melanodermia but with diffuse demyelination, absence of pituitary basophils, interstitial cell testicular tumour and adrenal atrophy. Similar abnormalities of the pituitary and adrenal were present in his brother, although neither had clinical hypoadrenocorticism. In contradiction to Poser and van Bogaert in 1956, they believed

“the coexistence of these lesions is not merely coincidental,” but the nature of “the interrelation of these lesions remains entirely conjectural.”7

In 1963, Guido Fanconi (1892–1979) and colleagues8 explained the full clinical picture suggesting an X linked hereditary disorder. Mosser et al subsequently proved this by positional cloning, located at the ABCD1 gene (chromosomal Xq28 locus).9 The defect is in a protein, ABCD1, that has a role in peroxisomal fatty acids.

The full clinical picture of adrenoleukodystrophy protein causes accumulation of very long chain fatty acids.

There are three resulting phenotypes: (1) a childhood cerebral form; (2) an adult adrenomyeloneuropathy and (3) a form with later childhood onset, symptoms of Addison disease but no clinically evident cerebral disorder. The plasma concentration of very long chain fatty acids is elevated in more than 99% of males with X linked adrenoleukodystrophy of all ages, irrespective of symptoms, and is valuable in establishing carrier status and prenatal diagnosis.

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