Occupational attainment influences survival in autopsy-confirmed frontotemporal degeneration

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ABSTRACT

Objective: To examine the influence of occupational attainment and education on survival in autopsy-confirmed cases of frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD).

Methods: We performed a retrospective chart review of 83 demographically matched, autopsy-confirmed FTLD (n = 34) and AD (n = 49) cases. Each patient's primary occupation was classified and ranked. Level of education was recorded in years. Survival was defined as time from symptom onset until death. Linear regression was used to test for associations among occupational attainment, education, and patient survival.

Results: Median survival was 81 months for FTLD and 95 months for AD. Years of education and occupational attainment were similar for both groups. We found that higher occupational attainment was associated with longer survival in FTLD but not AD.

Conclusions: Our findings suggest that higher occupational attainment is associated with longer survival in autopsy-confirmed FTLD. The identification of protective factors associated with FTLD survival has important implications for estimates of prognosis and longitudinal studies such as treatment trials. *Neurology*® 2015;84:1–6

GLOSSARY

AD = Alzheimer disease; **CR** = cognitive reserve; **FTD** = frontotemporal degeneration; **FTLD** = frontotemporal lobar degeneration.

Cognitive reserve (CR) posits that a person develops cognitive strategies and neural connections over the course of a lifetime through experiences such as education, occupation, and mental engagement.[1] These factors may modulate the effects of neurodegenerative disease because of compensatory cognitive strategies learned as a result of good education or higher professional performance.[2] Furthermore, those with higher levels of CR may have richer neural connectivity that can tolerate a greater burden of disease, suggesting that more pathology is necessary for clinical symptoms to be expressed.[3] One possibility is that onset of clinical symptoms is delayed in individuals with higher reserve, resulting in a shortened survival time.[3,4] Alternately, CR may have a more protective role, lengthening survival during the course of the disease.[5]

Frontotemporal degeneration (FTD) is a common form of young-onset dementia.[6] FTD presents clinically with difficulty regulating social behaviors, executive limitations, and language impairments.[7,8] FTD is typically caused by a spectrum of pathologies known as frontotemporal lobar degeneration (FTLD), most commonly including FTLD-tau and FTLD-TDP.[9] Survival in pathologically confirmed FTLD ranges from 72 months to 126 months from onset to death,[10–13] but little is known about factors that contribute to this large range.

The possible role of CR in FTLD survival has been investigated in a small number of studies, but these are restricted to neuroimaging studies in patients without autopsy confirmation.[14–16] In this study, we examined the effects of education and occupation on survival in autopsy-confirmed FTLD and Alzheimer disease (AD).

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Table 1 Demographic features of the patients

	Frontotemporal degeneration	Alzheimer disease	*p* Value
Sex, M/F	23/11	32/17	0.82
Mean education, y	15.3 (±3.3)	15.5 (±2.5)	0.67
Mean age at onset, y	60.6 (±10.2)	62.5 (±12.0)	0.47
Mean age at death, y	68.1 (±11.2)	71.4 (±11.7)	0.20
Median survival from onset, mo	80.7	95.3	0.25
% frequency of *MAPT* H2 haplotype	47.1	36.7	0.95
% frequency of *APOE* ε4 carrier	20.6	36.7	0.006

METHODS

Patients. A brain bank of more than 600 patients with neurodegenerative diseases at the Center for Neurodegenerative Disease Research at the University of Pennsylvania was examined to identify patients who had FTD, a pathologic diagnosis, and sufficiently detailed clinical and neuropsychological information corresponding to a clinical FTD syndrome during life. Pathologic diagnoses in the FTLD group included conditions such as Pick disease, argyrophilic grain disease, and FTD with TDP inclusions.[17] Patients with a pathologic diagnosis of motor neuron disease, corticobasal degeneration, or progressive supranuclear palsy were excluded because of their known shorter lifespan associated with motor factors.[10,18] Autopsy was performed using standard techniques previously described.[19] All autopsies were performed at the University of Pennsylvania from 1995 through 2012.

Standard protocol approvals, registrations, and patient consents. All subjects completed a written informed consent procedure in accordance with the Declaration of Helsinki and approved by the institutional review board of the University of Pennsylvania.

Table 2 Clinical phenotypes and occupational features of the patients

	Frontotemporal degeneration	Alzheimer disease
Initial clinical phenotype		
bvFTD	22 (64.7)	6 (12.2)
svPPA	4 (11.7)	1 (2.0)
naPPA	1 (2.9)	2 (4.1)
lvPPA	1 (2.9)	13 (26.5)
AD	0	15 (30.6)
CBS	4 (11.8)	9 (18.4)
DLB	2 (5.9)	3 (6.1)
Total	34	49
Occupational level[a]		
3	3 (8.8)	5 (10.2)
4	13 (38.2)	16 (32.7)
5	18 (52.9)	28 (57.1)
Total	34	49

Abbreviations: AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal degeneration; CBS = corticobasal syndrome; DLB = dementia with Lewy bodies; lvPPA = logopenic variant of primary progressive aphasia; naPPA = nonfluent/agrammatic variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia. Data are n (%).

[a] Occupational code 3 = operative and service workers; occupational code 4 = craftsmen and foremen, managers, administrators, clerical, and sales; occupational code 5 = professional and technical workers.

Clinical features. Inclusion criteria included all subjects followed by the University of Pennsylvania Frontotemporal Degeneration Center with FTLD and AD neuropathology. Medical records were reviewed for historical information including clinical phenotype, age at evaluation, age at death, sex, and race. FTLD and AD groups were matched for these characteristics (see table 1). Symptom onset was estimated at first contact based on a family report of the earliest persistently abnormal clinical feature in the domains of language, social function or personality change, memory, and executive and visual–spatial functioning. Survival time was computed from the time of symptom onset until the time of death. The subject's primary occupation was classified (see table 2) and ranked based on US census categories with a score ranging from 1 to 5: 1 = no occupation; 2 = unskilled laborers; 3 = operative and service workers; 4 = craftsmen and foremen, managers, administrators, clerical, and sales; and 5 = professional and technical workers. FTLD and AD groups were matched across occupational categories ($\chi^2 = 0.283$, $p = 0.868$). Subjects who were missing occupational status (n = 3), or unskilled laborer (n = 1) were omitted because they had no values to contribute to the statistical models described below. Those classified as no occupation (n = 12) were also omitted because of their heterogeneity (i.e., this group consisted of unemployed subjects and homemakers). This yielded a final list of autopsy-confirmed cases of FTLD (n = 34). Our group of autopsy-confirmed patients with AD (n = 49) had similar demographic and clinical information. Level of education was recorded in years. Tau haplotype (*MAPT*) and *APOE* ε4 genotype were also available for analyses. In each subject, genetic characteristics were coded using a dominant model: *APOE* ε4 carrier vs not; *MAPT* H2 carrier vs not.

Statistical analysis. Descriptive statistics were calculated for demographic and clinical variables. Between-group differences in baseline demographic and clinical variables were assessed using *t* tests, χ^2 tests, or Wilcoxon-Mann-Whitney tests, as appropriate. Our main outcome was disease duration (onset to death), and all subjects had this information. Because all subjects had the outcome of death, there were no censored observations in this study, so linear regressions were used to assess associations between predictors and survival time rather than Cox regression models. A Shapiro-Wilk test for normality revealed that the outcome of survival was not normally distributed in FTLD ($W = 0.928$, $p = 0.03$). After using a log transformation of survival time, Shapiro-Wilk test indicated normality in both groups (FTLD: $W = 0.949$, $p = 0.11$; AD: $W = 0.979$, $p = 0.51$); therefore, survival time was log-transformed for the linear regressions. For each of the AD and FTLD groups, we first conducted univariate analyses (unadjusted models) for each predictive factor, and then adjusted analyses of survival by including the following independent variables: age at symptom onset, education, occupational attainment, and genetic information. Statistical analyses were performed using Stata statistical software, release 13 (StataCorp, College Station, TX). All statistical tests were 2-sided. Statistical significance was set at the 0.05 level.

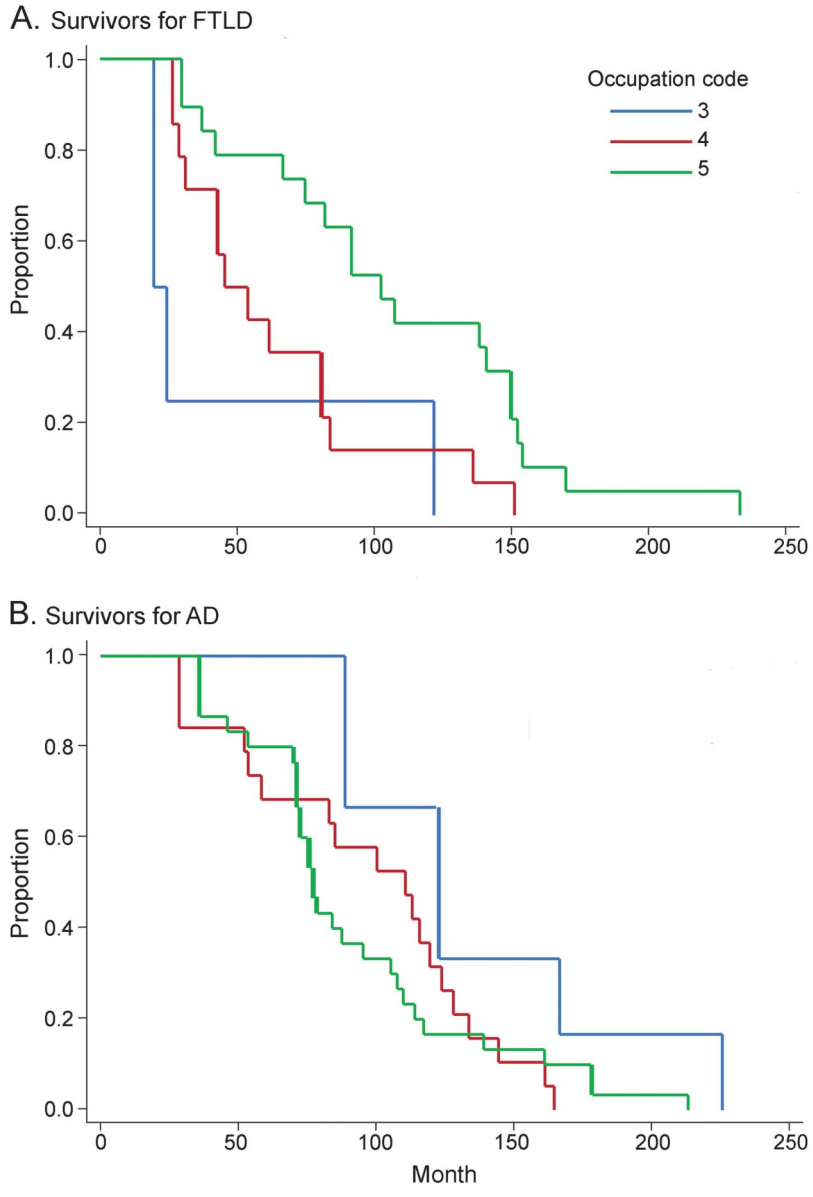
RESULTS

Median survival from symptom onset for the entire cohort was 87.6 months. The AD group had a median survival of 95.3 months and the FTLD group had a median survival of 80.7 months. In the univariate regression analyses, being male was associated with longer survival in FTLD (95% confidence interval = 0.090, 1.020; $t = 2.43$; $df = 33$, $p = 0.021$), but

not in AD. Older age at onset was associated with shorter survival in AD (95% confidence interval = −0.023, −0.001; $t = 2.23$; $df = 47$, $p = 0.030$), but not FTLD.

In the adjusted models, higher occupational attainment was associated with longer survival in FTLD ($F = 6.31$; $df = 2,27$; $p = 0.006$), but not in AD (see figure). Pairwise comparisons of occupational levels in FTLD also demonstrated longer survival times with higher occupational levels (4 vs 3: $t = 2.17$, $p = 0.039$; 5 vs 3: $t = 3.43$, $p = 0.002$; 5 vs 4: $t = 2.08$, $p = 0.047$). Since occupational level 3 consisted of few patients, we performed an exploratory post hoc analysis combining those with occupational levels 3 and 4 in a single group (5 vs groups 3 and 4). We continued to observe that survival is modulated by occupation ($t = 2.64$; $p = 0.013$). Years of education were not associated with survival time for either group. In an exploratory analysis constrained to only sporadic cases of FTLD, we also observed that survival is modulated by occupational status ($t = 2.46$; $p = 0.025$). Genetic characteristics of *MAPT* and *APOE* ε4 status were not associated with the survival time for either group.

Figure Proportion of survivors for FTLD (A) and AD (B) by occupation[1]



Occupational code 3 (blue) = operative and service workers; occupational code 4 (red) = craftsmen and foremen, managers, administrators, clerical, and sales; occupational code 5 (green) = professional and technical workers. AD = Alzheimer disease; FTLD = frontotemporal lobar degeneration.

DISCUSSION This study investigated the effect of occupational attainment and education on survival in autopsy-confirmed FTLD and AD. We found that higher occupational attainment was associated with longer survival in FTLD, but not in AD. Years of education did not have an effect on survival in either group. These results provide support for the protective effects of occupation in FTLD, a common cause of young-onset dementia.

While previous work used imaging as a surrogate for survival, the present study uniquely examined the influence of occupational attainment on true survival in persons with autopsy-confirmed FTLD and AD. Imaging studies in FTLD have been interpreted to suggest that occupational level is associated with pathologic burden.[16,20] One study thus reported that higher occupational attainment is associated with lower regional cerebral blood flow in medial frontal cortex and left dorsolateral frontal cortex, brain areas known to be affected in FTLD.[16] This observation was interpreted to suggest that persons with higher occupational attainment have greater reserve capacity, as reduced cerebral perfusion reflecting increased pathologic load must be present for clinical symptoms to manifest. A second study reported a similar effect, claiming that higher levels of occupational skill were associated with more advanced disease in specific frontal brain regions.[20] For example, subjects whose occupation required greater verbal skills had reduced regional glucose utilization in the left inferior frontal gyrus, and those whose jobs were more physically demanding showed reduced metabolic rate of glucose utilization in the supplementary motor area. To the extent that actual FTLD pathology determines survival, not merely the FTD phenotype, these reports should be interpreted cautiously because of considerable uncertainty estimating pathology based only on clinical diagnosis.[19]

Occupation has been shown to modulate survival in healthy aging and AD. Several epidemiologic studies in healthy aging have examined the protective influence of high occupation status on cognitive performance in late life and survival.[21–23] Other work has shown that individuals with higher occupational levels have a lower incidence of various types of dementia,

including vascular dementia and probable AD, providing additional evidence for occupation as a protective factor.[24,25] We may not have demonstrated a relationship between survival and occupation as well as other factors such as *APOE* ε4 in AD in the present study because of differences in participant characteristics. We did not find an association between *APOE* ε4 status and mortality in AD. Some studies report a positive association between *APOE* ε4 status and increased mortality risk, especially in those who are older.[26,27] Our AD sample was comprised of mostly young-onset AD (median age of 62.5 years) and this may explain why *APOE* ε4 status did not have an effect on survival in our sample. Our AD sample included many presenting with atypical AD such as logopenic variant primary progressive aphasia, and additional work is needed to determine whether the phenotypic characteristics of young-onset AD contribute to survival in these patients. Another important difference is that onset was defined in some studies as initial clinical evaluation,[4] and we chose to examine time from symptom onset because there is often a significant delay in making the clinical diagnosis of FTD and atypical presentations of AD.[28] Another issue is the way in which occupation was ranked. While some chose to dichotomize occupation (high vs low),[4] we chose to look at the difference between levels of occupation and we found a protective effect at every level.

The role of education on survival in FTLD has not been investigated previously. We failed to find a relationship between survival and education as a surrogate marker for reserve in FTLD. This is consistent with much work examining education as a proxy measure for reserve in AD. Although education may predict cognitive performance during life,[29] 2 meta-analyses failed to demonstrate a relationship between education and survival in probable AD.[30,31] Perhaps the mental stimulation associated with lifelong, work-related activities influences reserve differently than early-life education. Education may be a confounded measure of CR because those with higher education also tend to seek greater physical and mental stimulation throughout life, and this may selectively affect cognitive decline and disease progression.[30] Another potential reason for the failure of these studies to observe a protective effect of education may be related in part to the substantial variability in the quality of educational attainment in the United States.[32] The rate of cognitive decline and risk of death in probable AD is most apparent in those with lower levels of education, suggesting that survival may be most malleable in those with the least reserve capacity.[33] Our cohort was highly educated and it would be valuable to replicate our analysis in those with lower educational levels.

Previous studies suggest that genetic factors may be related to mortality risk in FTD[34] and thus survival could be confounded by the presence of genetic mutations. An exploratory analysis including only sporadic cases also observed that survival is modulated by occupational status. This suggests that genetic status does not confound our observations. Nevertheless, other work suggests that genetic factors may affect clinical FTD, such as the recent finding that methylation of *C9orf72* is protective in repeat expansion carriers.[35] Future work should evaluate how genetic factors like *MAPT* haplotype, *APOE* status, and single nucleotide polymorphisms such as that in the region coding for *MOBP*[36] interact with CR to influence survival.

Some investigators postulate that those with higher reserve begin to develop pathologic changes many years before the disease is expressed clinically.[37] From this perspective, the burden of brain pathology is likely to be greater in patients with greater reserve before clinical symptoms emerge. Thus, symptom onset may be delayed.[38] Since clinical symptoms would appear relatively late in the disease trajectory, there may be the appearance of shortening survival as pathologic changes progress relentlessly. The assumption here is that biological factors determining overall disease survival are not affected by CR. Inspection of the figure shows a trend in this direction in AD, with higher occupational levels associated with shorter survival. An alternate possibility is that individuals are able to achieve higher occupational attainment and more years of education because of a strong genetic background. For instance, there may be potential genetic background factors that contribute to the protective properties of occupational attainment. Studies have suggested that genetic factors modulate intelligence,[39] enabling an individual to achieve a high occupational status. These individuals may have neuronal richness and greater brain connectivity, allowing the brain to sustain greater disease burden before succumbing. From this perspective, reserve may be associated with relatively late clinical manifestations of disease, and may also be associated with a true prolongation of survival. This is consistent with our finding in the FTLD cohort. Yet another possibility is that early frontal lobe disease in FTLD may limit compensatory resources and thus make patients with FTD more vulnerable to early disease. This may be most evident in those with higher occupational attainment who are more dependent on executive resources associated with the frontal lobe. Additional work is needed to help determine the biological mechanism underlying the changes in survival that are associated with occupation and education as proxies of CR, and investigate the basis for potentially different mechanisms modulating survival in FTLD and AD.

Several caveats should be kept in mind when interpreting our findings. We investigated a well-characterized autopsy cohort with a definitive diagnosis

and known survival, but our sample was relatively small. While we examined education and occupation, the most common proxies for CR, future investigations should also examine the protective effects of leisure activities.[40] The rudimentary categorization of occupational categories limited our sensitivity to this measure of CR. For example, we did not include homemakers in our analysis, because this occupation did not fit into the prescribed classifications. Since patients in our study had higher levels of education and occupation, generalization of our findings is restricted. For example, occupational level 3 consisted of few patients. An exploratory analysis combining those with occupational levels 3 and 4 into a single group nevertheless continued to reveal that survival is modulated by occupation. It will be important for future studies to recruit patients with lower occupational attainment. Lastly, occupational attainment is often related to socioeconomic status, and other associated factors such as income level and diet may be contributing to survival.[32]

With these caveats in mind, our study builds on the small body of literature assessing factors that modulate survival in FTLD. Our findings suggest that occupational level provides a protective effect, lengthening survival time in autopsy-confirmed FTLD. This is consistent with a biologically based model of reserve in which neuronal integrity and brain connectivity may be relatively robust to young-onset FTLD spectrum diseases and allow longer survival in the face of these neurodegenerative conditions. The association found between occupation and survival stimulates questions about occupation-related effects on neuroprotection, and suggests the importance of incorporating this factor in treatment trials and prognostic considerations in persons with FTD.

AUTHOR CONTRIBUTIONS

Lauren Massimo was responsible for drafting the manuscript, study concept and design, analysis and interpretation of data, acquisition of data, statistical analysis, and obtaining funding. Dr. Massimo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Jarcy Zee was responsible for analysis of data. Sharon Xie was responsible for analysis of data. Corey McMillan was responsible for revising the manuscript and interpretation of data. Katya Rascovsky was responsible for study design and interpretation of data. David Irwin was responsible for interpretation of data. Ann Kolanowski was responsible for study design and interpretation of data. Murray Grossman was responsible for revising the manuscript, study design, interpretation of data, study supervision, and obtaining funding.

STUDY FUNDING

This work was supported in part by US Public Health Service (F32NR014777, AG017586, AG015116, AG010124, AG043503, NS053488, and NS044266) and the Wyncote Foundation.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received November 12, 2014. Accepted in final form February 11, 2015.

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