CME

Rate of progression differs in frontotemporal dementia and Alzheimer disease

K. Rascovsky, MA; D.P. Salmon, PhD; A.M. Lipton, MD, PhD; J.B. Leverenz, MD; C. DeCarli, MD; W.J. Jagust, MD; C.M. Clark, MD; M.F. Mendez, MD, PhD; D.F. Tang-Wai, MD; N.R. Graff-Radford, MD; and D. Galasko, MD

Abstract—*Objective:* To compare survival and rates of cognitive and functional decline in patients with autopsy-confirmed frontotemporal dementia (FTD) and Alzheimer disease (AD) in a large multicenter study. *Background:* Despite advances in the clinical characterization of FTD, little is known about its rate of progression. Characterizing survival and rate of decline in FTD is important because it can provide prognostic guidelines and benchmarks to use in the evaluation of disease-modifying drugs. *Methods:* Seventy patients with FTD and 70 patients with AD who were followed by seven Alzheimer disease research centers until confirmation of diagnosis at autopsy were matched for overall age, education, and Mini-Mental State Examination (MMSE) score at initial evaluation. Survival and rates of cognitive and functional decline were compared. *Results:* Patients with FTD had significantly shorter survival from initial evaluation to death than patients with AD (FTD = 4.2 years, AD = 6.0 years; log-rank test = 5.17, $p < 0.05$), and they declined significantly faster over one year on the MMSE (mean annual rate of change: −6.7 points for FTD vs −2.3 points for AD). A significantly greater proportion of patients with FTD were impaired in basic activities of daily living (ADLs) at initial evaluation, and lost the capacity for independent or minimally-assisted ADLs over the subsequent year. *Conclusions:* The results are consistent with shorter survival and faster rates of cognitive and functional decline in patients with frontotemporal dementia (FTD) compared to those with Alzheimer disease (AD). This suggests that FTD follows a more malignant disease course than AD once dementia is clinically recognized.

NEUROLOGY 2005;65:397–403

Frontotemporal dementia (FTD) is the overarching label used to describe a spectrum of neurodegenerative disorders characterized by a progressive dementia syndrome arising from relatively circumscribed frontal and temporal lobar atrophy.[1] It is estimated that approximately 3 to 20% of all cases of dementia may be FTD[2-7] and the disorder is particularly prevalent when the age at onset of dementia is younger than 65.[2,4] FTD is pathologically heterogeneous and includes tau-positive pathology with or without Pick bodies (i.e., Pick disease), tau-negative, ubiquitin-positive inclusions associated with motor neuron disease (FTD–MND), or may lack distinctive histopathology (i.e., dementia lacking distinctive histopathology [DLDH]).[8] Recent consensus criteria have identified three distinct clinical syndromes associated with FTD: the classic frontal-variant dementia, progressive nonfluent aphasia, and semantic dementia.[9] Depending on the initial topography of pathology, patients with FTD present with one of these clinical syndromes, but they may eventually develop features of the other syndromes as the disease progresses. FTD shares many clinical features with the more common Alzheimer disease (AD), but recent studies indicate that these disorders can often be differentiated based on specific behavioral[10-18] and cognitive[19-25] characteristics.

An aspect of FTD and AD that has not been carefully compared is survival and the nature and rate of clinical decline. Although extensive research has been conducted on the natural history of AD,[26-28] much less is known about survival and clinical deterioration in FTD. Characterizing survival and rates of functional and cognitive decline in FTD is important for a variety of reasons: 1) distinct patterns of decline over time may aid in differential diagnosis, 2) information about survival and rate of decline provides prognostic guidelines for patients and their

From the University of California, San Diego (Drs. Rascovsky, Salmon, and Galasko); The University of Texas Southwestern Medical Center (Dr. Lipton), Dallas; University of Washington (Dr. Leverenz), Seattle; University of California, Davis (Dr. DeCarli); University of California, Berkeley (Dr. Jagust); University of Pennsylvania (Dr. Clark), Philadelphia; University of California, Los Angeles (Dr. Mendez); Mayo Clinic (Drs. Tang-Wai and Graff-Radford), Jacksonville, FL.

This study was supported with funding from the National Alzheimer's Coordinating Center and NIA grants P30 AG10129, P30 AG-12300, P50 AG16574, P50 AG10124, P50 AG05131 and P50 AG05136.

Disclosure: The authors report no conflicts of interest.

Received November 3, 2004.Accepted in final form April 18, 2005.

Address correspondence and reprint requests to Dr. David Salmon, Alzheimer's Disease Research Center, University of California, San Diego, Mail Code 0948, 9500 Gilman Drive, La Jolla, CA 92093-0948; e-mail: dsalmon@ucsd.edu

families, and 3) knowledge of the typical rate of decline in FTD is crucial for the evaluation of disease-modifying drugs.

Two of the largest studies to explore survival in FTD[29,30] revealed a particularly malignant course. A median interval of 6 years from estimated onset of symptoms to death was observed in a sample of patients with autopsy-confirmed FTD.[30] A similar median survival of 8 years was found in a mixed clinically-diagnosed and autopsy-confirmed FTD series.[29] These values fall within the range of years of survival usually reported for patients with AD,[27,28] but neither study directly compared survival in the two disorders. A study that directly compared FTD and AD[31] found similar duration of survival in the two groups after age at first visit, level of education, and sex had been statistically controlled. However, this finding remains open to question because the patient groups were largely not autopsy-confirmed, they differed substantially in estimated age at onset of symptoms, and they were not matched for dementia severity at baseline. Previous studies have shown that these latter two variables can have an important influence on duration of survival in patients with AD[27,28] and it is possible that they also influence survival in patients with FTD.

Two recent studies directly compared rates of cognitive and behavioral decline in FTD and AD.[31,32] The first of these studies modeled rates of cognitive and functional decline in the two groups using cross-sectional and longitudinal data from a mixed sample of clinically-diagnosed (Pick disease) and autopsy-confirmed FTD cases.[32] Patients with clinical Pick disease declined significantly faster than those with AD on measures of global dementia severity, language, and a scale measuring activities of daily living. The clinical diagnosis of Pick disease was made in individuals with progressive dementia, prominent language impairments, and subtle personality changes, so this sample may not be representative of the full FTD spectrum of disorders. Furthermore, rate of decline was modeled against duration of illness by caregiver report, an interval that can be difficult to establish reliably. In contrast to these results, the second study found that cognitive abilities measured by the Mini-Mental State Examination (MMSE) declined more slowly in patients with FTD than in those with AD.[31] It should be noted, however, that the patient groups were not matched for age or MMSE scores at the initial assessment, so the observed difference in rate of decline could simply reflect these factors and not fundamental differences between the two disorders.

Given the paucity of knowledge and inconsistent findings regarding potential differences in the natural history of FTD and AD, we directly compared survival and rates of cognitive and functional decline exhibited by patients with autopsy-confirmed FTD or AD who were followed at a group of dementia research centers. Specifically we set out to 1) compare survival in patients with autopsy-confirmed FTD and AD who were matched on age and dementia severity at baseline, 2) compare the severity of functional impairment in these matched patient groups, and 3) compare the rates of cognitive and functional decline in FTD and AD over a 12-month period.

Methods. In 2002 we developed a multi-center registry of autopsy-confirmed FTD cases through the auspices of the National Alzheimer's Coordinating Center (NACC). The following analyses are based on clinical data collected prospectively at seven NACC-participating National Institutes of Aging (NIA)–funded AD Centers from around the United States (University of California, San Diego; University of Texas Southwestern Medical Center, Dallas; University of Washington, Seattle; University of California, Davis; University of Pennsylvania, Philadelphia; University of California, Los Angeles; Mayo Clinic, Jacksonville). The ADRCs are specialty centers dedicated to research on the course, clinical presentation, diagnosis, and treatment of dementia. Because cognitive symptoms are usually the chief problem prompting referral to the centers, patients included in this study may differ from samples collected elsewhere (e.g., community-based samples and sites that include referrals for psychiatric or behavioral problems). Although diagnostic expertise at the Centers leads to referral of unusual or diagnostically difficult patients, it is possible that patients with FTD with slowly progressive behavioral and personality changes may have been excluded from this study.

Subjects. The FTD patients included in this study demonstrated progressive dementia and received a primary neuropathological diagnosis of FTD at autopsy. Patients were recruited between 1980 and 2001, and came to autopsy by fall 2003. As inclusion criteria, patients were required to have dementia at their initial ADRC evaluation, with MMSE[33] scores greater than 14/30. Data were compiled for 70 patients with FTD (The University of Texas Southwestern Medical Center = 16; University of California, San Diego = 15; University of Washington = 10; University of California, Davis = 10; University of Pennsylvania = 9; University of California, Los Angeles = 8; Mayo Clinic, Jacksonville = 2). Final clinical diagnoses for the autopsy-confirmed FTD patients were as follows: FTD = 34, primary progressive aphasia = 2, corticobasal degeneration = 1, probable or possible AD = 25, dementia with Lewy bodies = 1, other = 7. It is not clear whether the high rate of AD diagnoses in our FTD sample was due to unusual clinical presentations (i.e., prominent memory deficits), or reflects a lack of access or familiarity with diagnostic criteria for FTD (most of these patients were diagnosed before consensus diagnostic criteria were established). Of the 70 autopsy-confirmed FTD cases, 48 formed a longitudinally-studied subset with clinical data from their initial ADRC evaluation (evaluation 1) and an annual follow-up evaluation (evaluation 2). The annual interval between the first and second evaluations was defined as more than 6 months and less than 18 months, with an average of 12 months (table 1). The remaining 22 cases were either lost to clinical follow-up or had follow-up evaluations that exceeded the specified time interval.

The matched patients with AD were selected from a larger series of patients with autopsy-confirmed AD, who had completed baseline evaluations at these same centers, with the restriction that one patient with AD was matched to each FTD patient for age, years of education, and baseline MMSE score. Patients with AD matched to the FTD patients that formed the longitudinally-studied subset also had to have at least a baseline and an annual follow-up evaluation within a 6 to 18 month period.

Mean age, years of education, MMSE scores, and years from estimated onset to evaluation 1 are presented in table 1. As expected from the matching procedure, patient groups did not differ significantly in age [FTD = 65.0 years; AD = 67.0 years; t (138) = 1.40; $p > 0.05$], education [FTD = 14.2 years; AD = 14.1 years; t (137) < 1], or MMSE scores at evaluation 1 [FTD = 23.2, AD = 22.6; t (138) < 1]. Interestingly, 38 of 70 patients with FTD presented to the ADRCs after the age of 65 and 26 of 70 patients with FTD were reported to have symptom onset after the age of 65, arguing against the prevalent view of FTD as an exclusively presenile dementia. Although not part of the matching procedure, patients with FTD and AD also had comparable intervals from estimated onset of symptoms to initial evaluation [FTD = 3.96

Table 1 *Means, SDs, and ranges for age (in years), years of education, and Mini-Mental State Examination scores of patients with frontotemporal dementia or Alzheimer disease*

	Baseline			Longitudinal subset		
	FTD, n = 70	AD, n = 70	*p*	FTD, n = 48	AD, n = 54	*p*
Age at evaluation 1 (SD), y	65.0 (9.4)	67.0 (8.1)	0.16	65.5 (9.3)	66.0 (7.9)	0.41
Range	44–88	53–85		49–88	53–81	
Education (SD), y	14.2 (3.1)	14.1 (2.8)	0.88	14.1 (3.0)	14.3 (3.0)	0.98
Range	3–22	8–20		3–22	8–20	
MMSE score (SD)	23.2 (3.8)	22.6 (3.8)	0.41	22.8 (4.1)	23.0 (3.9)	0.86
Range	15–30	14–30		15–30	15–30	
Years from estimated onset to evaluation 1 (SD)	4.0 (2.8)	3.7 (2.6)	0.62	1.0 (0.23)	1.05 (0.20)	0.20
Range	0–16	0–13		0.5–1.5	0.5–1.5	

Data for all patients who received a baseline evaluation are shown on the left and data for a subset of patients followed longitudinally for 1 year are shown on the right.

FTD = frontotemporal dementia; AD = Alzheimer disease; eval = evaluation; MMSE = Mini-Mental State Examination.

years, AD = 3.73 years; t (138) < 1], consistent with a similar disease stage in both groups.

Patient groups did not differ significantly in sex distribution (FTD: males = 39, females = 31; AD: males = 33, females = 37; $\chi^2 = 1.03$, $p > 0.05$), or family history of a similar dementing illness (FTD: positive family history = 31, negative family history = 38; AD: positive family history = 25, negative family history = 44; $\chi^2 = 1.08$, $p > 0.05$).

Basic demographic characteristics of patients followed over a one year period are shown in table 1. Within this longitudinally-followed subset, patient groups were comparable in terms of age [FTD = 65.5 years; AD = 66.0 years; t (100) < 1], education [FTD = 14.1 years; AD = 14.3 years; t (100) < 1], and MMSE scores at evaluation 1 [FTD = 22.8, AD = 23.0; t (100) < 1]. The interval between initial evaluation and follow-up was just over 1 year for both FTD and AD groups [FTD = 1.00 years, AD = 1.05 years; t (100) = 1.13; $p > 0.05$].

Neuropathologic diagnosis. Autopsy was performed according to established protocols at each ADRC. Brains were examined by an experienced neuropathologist at each site in order to make a clinicopathologic diagnosis. The classification of FTD pathology was made according to McKhann et al.[8] guidelines. Pick disease was defined by the presence of Pick bodies in the hippocampal granule cell layer and/or pyramidal cell layer of the frontal and temporal cortices. Pick bodies were identified by their characteristic morphology on hematoxylin and eosin sections, and additional staining according to the protocol of each site. Cases with tau-negative, ubiquitin-positive inclusions in brainstem motor nuclei and/or hippocampus (typical of MND), were classified as FTD with MND-type inclusions. Finally, cases with nonspecific atrophy and spongy vacuolization in frontal and/or temporal areas in the absence of silver-, tau-, or ubiquitin-positive intraneuronal inclusions were defined as DLDH. All FTD brains lacked significant AD pathology. For the purposes of data analyses, tau-predominant FTD pathology was used as a single category, and was not split according to the type of microtubule binding repeats. Among FTD subjects, 19 of 67 cases presented with tau-postive inclusions (three cases were not specifically stained for tau). Out of 56 cases with reported ubiquitin staining, 24 presented with ubiquitin-positive inclusions. The clinicopathologic diagnosis of AD was made according to both NIA[34] and Consortium to Establish a Registry for AD (CERAD) criteria.[35]

Procedure. Data collected for each patient at each site included estimated age at onset (based on interview with a knowledgeable informant), baseline (i.e., evaluation 1) MMSE score, and the informant's rating of functional capacity to perform basic ADLs at baseline. Basic ADL ratings were obtained for bathing, dressing, grooming (defined as combing hair, washing face, putting on make-up), and toileting using the following scale: 0 = no problems, independent; 1 = needs reminders or some help; 2 = needs extensive help or is unable to perform the function. For comparison of basic ADL capacity at baseline, FTD and AD patients were defined as impaired if they were rated as 1 or 2 at the initial evaluation.

Date of death and date of the baseline evaluation for each patient was reported by each site. Survival was measured in two ways: 1) the number of years from evaluation 1 to death and 2) the number of years from estimated disease onset to death.

A subset of FTD patients and matched AD patients had a systematic reevaluation after an interval of approximately one year. Follow-up MMSE scores from evaluation 2 were available for this subgroup, which allowed us to calculate the annual rate of change (ARC) in MMSE score for each patient using the following formula:

ARC = [MMSE at evaluation 2 − MMSE at evaluation 1]/time between evaluations (years).

Decline in functional abilities was calculated by determining whether or not a basic ADL that was intact or minimally impaired (i.e., rated 0 or 1) at evaluation 1 was lost (i.e., completely impaired or needed extensive help and rated 2) by evaluation 2.

Data analysis. Survival in the FTD and AD groups was analyzed using Kaplan–Meier Survival Analysis and log rank tests. Group comparisons of basic ADL's were made with χ^2 tests or with Student t tests. Rate of decline on the MMSE was analyzed using repeated measures analysis of variance (RM ANOVA). All statistical analyses were performed using SPSS version 11 (SPSS, Chicago, IL).

Results. Despite comparable baseline MMSE scores and similar intervals between the estimated onset of disease and the baseline evaluation, patients with FTD had significantly shorter survival from the initial evaluation to death than patients with AD (log-rank test = 5.17, $p < 0.05$; [figure, upper panel]). Patients with FTD survived a median of 4.2 years (95% CI = 3.4 to 5.1 year) compared to a median of 6.0 years (95% CI = 5.2 to 6.7 years) for patients with AD. Patients with FTD also had shorter survival from estimated disease onset to death than patients with AD, although this difference was not significant (log-rank test = 1.95, $p = 0.16$; [see figure, lower panel]). Patients with FTD survived a median of 8.0 years (95% CI = 6.9 to 9.1 year) from estimated disease onset, whereas patients with AD survived a median of 9.0 years (95% CI = 8.2 to 9.8 years). Within the FTD group, survival from baseline evaluation to death did not differ by sex (log-rank test = 0.97, $p > 0.05$) or by presence of family

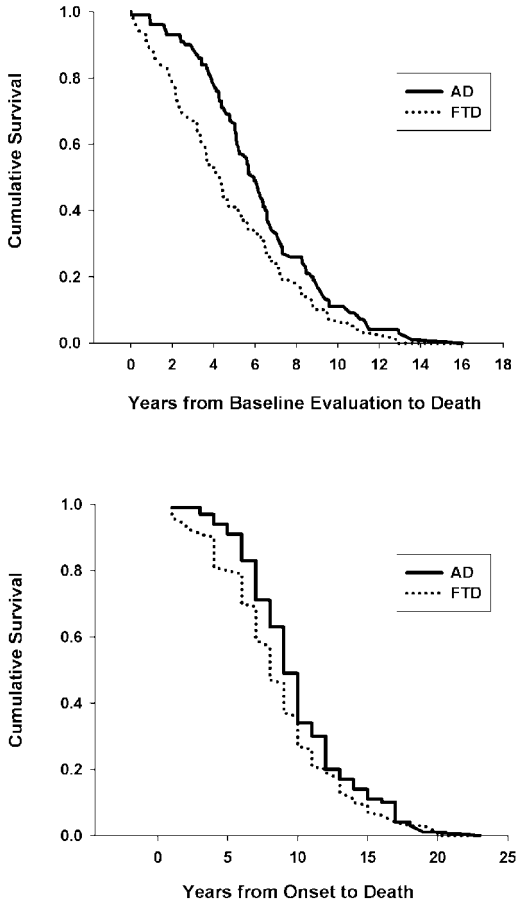

Figure. Kaplan–Meier survival curves for frontotemporal dementia (FTD) (broken lines) or Alzheimer disease (AD) (straight lines). Upper panel shows significantly shorter survival from baseline evaluation to death in FTD than AD. Lower panel shows shorter survival from estimated symptom onset to death in FTD than AD (not significant).

history of a similar dementing illness (log-rank test = 0.28, $p > 0.05$).

The percentage of patients with FTD and AD who were impaired (i.e., rated as 1 or 2) on each basic ADL at the baseline evaluation is shown in table 2 (Complete impairment at initial evaluation (i.e., rated as 2) was seen in 8% of patients with FTD and 0% of patients with AD for bathing; 5% of patients with FTD and 3% of patients with AD for dressing; 3% of patients with FTD and 0% of patients with AD for grooming and 12% of patients with FTD and 3% of patients with AD for toileting). It should be noted that the sample sizes for each ADL differ because of differences in the data collected at each site. Although the patient groups had comparable baseline MMSE scores and similar intervals between estimated onset of disease and the baseline evaluation, a significantly greater proportion of FTD patients than patients with AD were impaired in bathing ($\chi^2 = 8.68$, $p < 0.01$), dressing ($\chi^2 = 5.39$, $p < 0.05$), grooming ($\chi^2 = 8.34$, $p < 0.01$), and toileting ($\chi^2 = 10.73$, $p < 0.01$).

Table 2 *Percentage of patients with frontotemporal dementia or Alzheimer disease impaired on each basic activity of daily living at the baseline evaluation*

	FTD	AD	*p*
Bathing, n (%)	16/37 (43.2)	4/34 (11.8)	0.003
Dressing, n (%)	23/60 (38.3)	11/58 (19.0)	0.020
Grooming, n (%)	19/35 (54.3)	7/34 (20.6)	0.004
Toileting, n (%)	23/60 (38.3)	7/58 (12.1)	0.001

FTD = frontotemporal dementia; AD = Alzheimer disease.

Table 3 *Percentage of patients with frontotemporal dementia or Alzheimer disease who lost each activity of daily living during a 1-year period after the baseline evaluation*

	FTD	AD	*p*
Bathing, n (%)	11/24 (45.8)	1/21 (4.8)	0.002
Dressing, n (%)	18/41 (43.9)	1/37 (2.7)	<0.001
Grooming, n (%)	14/24 (58.3)	0/21 (0.0)	<0.001
Toileting, n (%)	11/37 (29.7%)	1/37 (2.7)	0.002

FTD = frontotemporal dementia; AD = Alzheimer disease.

Repeated measures ANOVA revealed a significant group by evaluation interaction [$F(1,96) = 12.29$, $p < 0.01$] reflecting significantly faster decline in MMSE scores for the FTD patients than for the AD patients. Indeed, patients with FTD had an average ARC of −6.7 points on the MMSE, more than double the average −2.3 point ARC of patients with AD. Within the FTD group, the ARC in MMSE scores did not differ significantly by sex [$t(42) < 1$] or by presence of family history of a similar dementing illness [$t(42) < 1$, $p > 0.05$].

In addition to faster decline on the MMSE, patients with FTD exhibited faster decline than AD patients in basic activities of daily living (table 3). A significantly higher percentage of patients with FTD lost the capacity for independent or minimally-assisted bathing ($\chi^2 = 9.66$, $p < 0.01$), dressing ($\chi^2 = 17.91$, $p < 0.01$), grooming ($\chi^2 = 17.78$, $p < 0.01$), or toileting ($\chi^2 = 9.95$, $p < 0.01$) over the 1 year period following the baseline evaluation. Indeed, from one-fourth to more than one-half of the patients with FTD lost the facility for these basic ADL's, whereas at most one AD patient lost these basic functional abilities by year 2. It should be noted that this analysis only pertains to those patients with FTD and AD who maintained some capacity (i.e., were rated as 0 or 1) for the basic ADL's at the baseline evaluation, and does not include those who were initially completely impaired (i.e., rated as 2 at baseline).

To determine whether the functional loss of patients with FTD mirrored their cognitive loss, the mean ARC in MMSE scores were compared for those patients with FTD who lost or retained each basic ADL over the 1-year period after the baseline evaluation (table 4). A significantly greater decline in MMSE score was evident in patients with FTD who lost bathing [$t(21) = 3.16$; $p < 0.01$], dressing [$t(36) = 3.38$; $p < 0.01$], and grooming [$t(20) = 2.25$; $p < 0.05$] than in those who did not completely lose these abilities. The FTD patients who lost toileting abilities had a greater annual decline on the MMSE than those who did not, but this difference only approached significance [$t(32) = 1.82$; $p = 0.078$].

In order to explore differences in survival and rate of cognitive decline by pathologic subgroup, FTD cases were

Table 4 Means and SDs for the annual rate of change in Mini-Mental State Examination score for patients with frontotemporal dementia who lost or retained each activity of daily living during a 1-year period after the baseline evaluation

	Lost ADL	Retained ADL	*p*
Bathing, means (SD), n	−12.55 (7.6), 10/23	−3.69 (5.9), 13/23	0.005
Dressing, means (SD), n	−11.51 (6.6), 15/38	−4.67 (5.7), 23/38	0.002
Grooming, means (SD), n	−10.63 (8.0), 10/22	−3.53 (6.4), 12/22	0.036
Toileting, means (SD), n	−10.90 (8.7), 9/34	−5.8 (6.6), 25/34	0.078

ADL = activity of daily living.

classified according to the presence or absence of tau-positive or ubiquitin-positive inclusions. Tau-positive FTD cases survived a median of 5.7 years (95% CI = 3.2 to 8.1 year) from initial evaluation to death compared to a median of 3.7 years (95% CI = 2.7 to 4.6 years) for tau-negative patients. Although tau-positive cases showed a trend toward longer survival, this difference did not reach significance (log-rank test = 2.05, $p = 0.152$). Annual rates of change in MMSE scores did not differ significantly by the presence or absence of tau-positive pathology [tau-positive ARC = 5.6 points, tau-negative ARC = 7.1 points; $t\ (43) < 1$]. Conversely, ubiquitin-positive cases showed a trend toward shorter survival from initial evaluation to death (3.6 years; 95% CI = 3.0 to 4.2 years) compared to ubiquitin-negative cases (4.7 years; 95% CI = 3.4 to 5.9 years), but this difference was not significant (log-rank test = 0.57, $p = 0.45$). Annual rates of change in MMSE scores did not differ significantly by the presence or absence of ubiquitin-positive pathology [ubiquitin-positive ARC = 7.9 points, ubiquitin-negative ARC = 5.9 points; $t\ (36) = 1.05$; $p > 0.05$].

Discussion. The results of this study are consistent with shorter survival and a more rapid cognitive and functional decline in patients with FTD than patients with AD. Although the patients with FTD and AD were of similar age and stage of dementia as measured by MMSE scores or time since estimated onset of symptoms, median survival among patients with FTD from time of initial evaluation was 4.2 years, compared to 6.0 years for AD. Survival from estimated disease onset to death also tended to be shorter in patients with FTD (a median of 8.0 years) than in those with AD (a median of 9.0 years), although estimates of disease onset based upon informant report may be unreliable and difficult to compare across disorders with different presenting symptoms. The total duration of survival for the FTD patients in the present study is similar to the 6 to 8 years previously reported.[29,30] The 9.0 years of survival for patients with AD is also within the range of previously reported survival for these patients, although it is considerably longer than the duration of survival observed in a population-based prevalent sample[26] that had a much higher average age than the present series (AD = 83.8 years vs FTD = 68.0 years). Not surprisingly, median survival after diagnosis of AD is critically age-dependent, with younger patients surviving longer; one study reported median survival of 8 years at age 65 and approximately 3 years at age 95.[27]

Despite comparable MMSE scores and estimated time since first symptoms at baseline, patients with FTD were more impaired than those with AD on basic ADL's such as bathing, dressing, grooming and toileting. This finding is consistent with previous reports,[32] and suggests that FTD has a more malignant course than AD in terms of its impact on the ability to function independently. The more rapid deterioration of basic functional abilities in patients with FTD than in those with AD was confirmed by the longitudinal analysis which showed that one-fourth to more than one-half of FTD patients who could perform ADLs independently or with minimal assistance at an initial evaluation lost that ability within 1 year. Virtually all patients with AD in contrast, retained these basic functional abilities over the same time period. The particularly rapid rate of functional decline in patients with FTD might be mediated by both cognitive and behavioral deficits arising from frontal lobe damage. Patients with FTD often present with prominent behavioral problems such as apathy, disinhibition, poor planning, and an inability to appreciate the consequences of their behavior,[10-12,14,16,17,36] and these deficits might contribute to their early neglect of hygiene and to their particularly severe functional decline. It is likely that functional decline is also related to cognitive impairment, as those patients with FTD who lost their basic ADLs showed significantly greater decline on the MMSE than those who did not. More detailed longitudinal studies are needed to identify the relative contributions of cognitive and behavioral deficits to functional decline in patients with FTD, including their impact on more complex instrumental ADLs. Unfortunately, information regarding instrumental ADLs was unavailable for the present analysis because widely differing scales were administered across sites. However, such studies will be particularly important since functional disability may be one of the most problematic aspects of FTD, leading to an early need for increased home care or institutionalization.

In addition to shorter survival, patients with FTD exhibited faster cognitive decline than patients with AD over 1 year. This difference occurred despite

equivalent baseline MMSE scores and estimated time since onset of symptoms for the two groups, indicating similar levels of dementia severity for both groups. The 2.3 point annual decline on the MMSE for the patients with AD is consistent with previous reports (for review, see Aguero-Torres[37]), but was significantly lower than the 6.7 point decline exhibited by patients with FTD. Although the brevity of the MMSE does not allow an examination of the specific cognitive abilities that may be particularly vulnerable to FTD, the test is heavily language dependent and could be especially susceptible to decline in those FTD patients who have semantic dementia or primary progressive aphasia. It should also be noted that the MMSE may not be ideal for tracking cognitive decline because it is susceptible to floor and ceiling effects.[38] Future studies comparing the rate and nature of cognitive decline in FTD and AD patients using neuropsychological instruments that thoroughly assess a wider range of cognitive functions are warranted.

There are a number of caveats to consider when interpreting the present results. First, it is possible that the clinical and pathologic heterogeneity within the spectrum of FTD disorders[8,9] gives rise to distinct rates of disease progression that differs by clinical or pathologic subtype. Although the present study was relatively underpowered to perform subgroup analyses, our findings revealed a trend toward shorter survival and faster rates of cognitive decline in FTD cases with tau-negative and ubiquitin-positive inclusions. These preliminary findings are consistent with a previous study that found shorter survival in patients with FTD and MND, as well as longer survival in patients with tau-positive pathology.[30] Similarly, distinct rates of cognitive and functional deterioration might occur in the various clinical subtypes of FTD, but we are unable to address this possibility due to insufficient retrospective clinical data to allow differential diagnoses within the FTD sample.

Second, the present results may under-estimate survival and over-estimate rates of cognitive and functional decline because this is an autopsy-based sample that may be biased toward individuals who progress rapidly and die. Patients with slower progression and longer survival may be less likely to come to autopsy. While we cannot rule out this possibility, its likelihood is small because the brain donor programs at the participating sites have been operating much longer than the expected duration of the diseases of interest and make strong effort to enroll all potential patients. If a survival bias exists in the sample, it should have an equivalent impact on patients with FTD or AD. Thus, the disparate durations of survival and rates of progression observed for the two disorders should not be a result of this factor.

Finally, the matching procedures used in the present study may not have adequately equated the groups in terms of initial severity of impairment or estimated time of onset of symptoms. It is possible that the patients with FTD were actually farther along in disease course than those with AD at the time of the initial evaluation, given the observed differences in functional impairment at baseline. Although the groups were matched on MMSE scores, the MMSE may not be sensitive to the earliest neurocognitive changes that occur in FTD. We had access to limited standardized clinical data across the centers, and chose ratings for dementia severity and ADL that are widely used in research and practice. The development of a clinical staging system using the most appropriate rating scales for FTD would assist future studies. Because the patients with FTD were recruited before clinical criteria for the disorder were well established and specific behavioral questionnaires were not available, it is possible that informants underestimated time of onset of the disorder given the unusual and insidious nature of the symptoms. It is also possible that the FTD sample is not highly representative of the entire population. Cases were obtained from ADRCs that usually receive referrals because of suspected cognitive impairment rather than behavioral dysfunction that may characterize early FTD. Furthermore, the patients with FTD and AD were matched for age which may have resulted in a somewhat older than usual sample of patients with FTD and younger than usual sample of patients with AD. However, because age strongly influences rates of cognitive decline, and is associated with changes in mobility and physical health, we did not want to allow a wide mismatch between the AD and FTD groups. Despite the potential biases the matching procedures may have introduced, they allowed cognitive and functional decline to be measured over a defined period of time from a reliably known starting point, and they controlled for any differential effect of the well-known impact of age on survival.

Our findings suggest that brief clinical ratings of cognitive and functional abilities can serve as measures of clinical progression in FTD. More precise and detailed instruments will help to characterize the relationship between cognition, behavior and function in FTD, and will help to determine the extent to which factors such as clinical and pathologic subtypes of FTD and genetic or biologic factors influence rates of progression.

References

1. Kertesz A, Muñoz DG, Hillis A. Preferred terminology. Ann Neurol 2003;54(supp 5):S3–S6.
2. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. Neurology 2002;58:1615–1621.
3. Neary D. Overview of frontotemporal dementias and the consensus applied. Dementia Geriatr Cogn Disord 1999;10(suppl):6–9.
4. Rosso S. *Frontotemporal dementia in the Netherlands: patient characteristics and prevalence estimates from a population-based study. In Rosso, S. (ed.), Frontotemporal dementia in the Netherlands. Rotterdam: Optima Grafische Communicatie, 2003;29–40.*
5. Knopman DS, Mastri AR, Frey W, Sung JH, Rustan T. Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. Neurology 1990;40:251–256.
6. Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer's disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord 2002;16:203–212.

7. Gislason TB, Sjorgren M, Larsson L, Skoog I. The prevalence of frontal variant frontotemporal dementia and the frontal lobe syndrome in a population based sample of 85 year olds. J Neurol Neurosurg Psychiatry 2003;74:867–871.
8. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia. Report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001;58:1803–1809.
9. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51: 1546–1554.
10. Levy ML, Miller BL, Cummings JL, Fairbanks LA, Craig A. Alzheimer disease and frontotemporal dementias: behavioral distinctions. Arch Neurol 1996;53:687–690.
11. Bozeat S, Gregory CA, Lambon-Ralph MA, Hodges JR. Which neuropsychiatric and behavioral features distinguish frontal and temporal variants of frontotemporal dementia and Alzheimer's disease? J Neurol Neurosurg Psychiatry 2000;69:178–186.
12. Lebert F, Pasquier F, Souliez L, Petit H. Frontotemporal Behavioral Scale. Alzheimer Dis Assoc Disord 1998;12:335–339.
13. Miller BL, Ikonte C, Ponton M, et al. A study of the Lund-Manchester research criteria for frontotemporal dementia: clinical and single-photon emission CT correlations. Neurology 1997;48:937–942.
14. Barber R, Snowden JS, Craufurd D. Frontotemporal dementia and Alzheimer's disease: retrospective differentiation using information from informants. J Neurol Neurosurg Psychiatry 1995;59:61–70.
15. Swartz JR, Miller BL, Lesser IM, et al. Behavioral phenomenology in Alzheimer's disease, frontotemporal dementia and late-life depression: a retrospective analysis. J Geriatr Psychiatry Neurol 1997;10:67–74.
16. Mendez MF, Perryman KM, Miller BL, Cummings JL. Behavioral differences between frontotemporal dementia and Alzheimer's disease: a comparison on the BEHAVE-AD rating scale. Int Psychogeriatrics 1998;10:155–162.
17. Kertesz A, Nadkarni N, Davidson W, Thomas AW. The frontal behavioral inventory in the differential diagnosis of frontotemporal dementia. J Int Neuropsychol Soc 2000;6:460–468.
18. Kertesz A, Davidson W, McCabe P, Munoz D. Behavioral quantitation is more sensitive than cognitive testing in frontotemporal dementia. Alzheimer Dis Assoc Disord 2003;17:223–229.
19. Pachana NA, Boone KB, Miller BL, Cummings JL, Berman N. Comparison of neuropsychological functioning in Alzheimer's disease and frontotemporal dementia. J Int Neuropsychol Soc 1996;2:505–510.
20. Lindau M, Almkvist O, Johansson SE, Wahlund LO. Cognitive and behavioral differentiation of frontal lobe degeneration of the non-Alzheimer's type and Alzheimer's Disease. Dementia Geriatr Cogn Disord 1998;9:205–213.
21. Elfgren C, Brun A, Gustafson L, et al. Neuropsychological tests as discriminators between dementia of Alzheimer's type and frontotemporal dementia. Int J Ger Psychiatr 1994;9:635–642.
22. Gregory CA, Orrell M, Sahkian B, Hodges J. Can frontotemporal dementia and Alzheimer's disease be differentiated using a brief battery of tests? Int. J Ger Psychiatr 1997;12:357–383.
23. Rascovsky K, Salmon DP, Ho GJ, et al. Cognitive profiles in autopsy-confirmed frontotemporal dementia and AD. Neurology 2002;58:1801–1808.
24. Perry RJ, Hodges JR. Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's Disease. Neurology 2000;54: 2277–2284.
25. Kramer JH, Jurik J, Sha SJ, et al. Distinctive neuropsychological patterns of frontotemporal dementia, semantic dementia, and Alzheimer's Disease. Cog Behav Neurol 2003;16:211–218.
26. Wolfson C, Wolfson DB, Assgharian M, et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med 2001; 344:1111–6.
27. Brookmeyer R, Corrada MM, Curriero FC, Kawas C. Survival following a diagnosis of Alzheimer's Disease. Arch Neurol 2002;59:1764–1767.
28. Larson EB, Shadlen MF, Wang L, et al. Survival after initial diagnosis of Alzheimer's Disease. Ann Intern Med 2004;140:501–509.
29. Grasbeck A, Englund E, Horstmann V, Passant U, Gustafson L. Predictors of mortality in frontotemporal dementia: a retrospective study of the prognostic influence of pre-diagnostic features. Int J Ger Psychiatr 2003;18:594–601.
30. Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia. Neurology 2003;61:349–354.
31. Pasquier F, Richard F, Lebert F. Natural history of frontotemporal dementia: comparison with Alzheimer's disease. Dementia Geriatr Cogn Disord 2004;17:253–257.
32. Binetti G, Locascio JJ, Corkin S, Vonsattel JP, Growdon JH. Differences between Pick disease and Alzheimer disease in the clinical appearance and rate of cognitive decline. Arch Neurol 2000;57:225–232.
33. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the mental state of patients for a clinician. J Psychiatr Res 1975;12:189–198.
34. Khachaturian ZS. Diagnosis of Alzheimer's disease. Arch Neurol 1985; 42:1097–1105.
35. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479–486.
36. Rosen HJ, Narvaez JM, Hallam B, Kramer JH, Wyss-Coray C, Gearhart R, Johnson JK, Miller BL. Neuropsychological and functional measures of severity in Alzheimer's Disease, Frontotemporal Dementia, and Semantic Dementia. Alzheimer Dis Assoc Disord 2004;18:202–207.
37. Aguero-Torres H, Fratiglioni L, Winblad B. Natural history of Alzheimer's disease and other dementias: review of the literature in light of the findings from the Kungsholmen Project. Int J Ger Psychiatr 1998; 13:755–766.
38. Galasko DR, Gould RL, Abramson IS, Salmon DP. Measuring cognitive change in a cohort of patients with Alzheimer's disease. Statist Med 2000;19:1421–1432.

RESIDENT AND FELLOW PAGE

Call for teaching videos

The *Neurology* Resident page is featured online at www.neurology.org. The Editorial Team of this section is seeking teaching videos that will illustrate classic or uncommon findings on movement disorders. Such videos will aid in the recognition of such disorders. Instructions for formatting videos can be found in the Information for Authors at www.neurology.org. Please contact the Editor, Karen Johnston (kj4v@virginia.edu), for more information or submit teaching videos online at http://submit.neurology.org.