Frontotemporal Lobar Degeneration

Demographic Characteristics of 353 Patients

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Background: Until recently, frontotemporal lobar degeneration (FTLD) was considered a rare neurodegenerative disorder that was difficult to diagnose. The publication of consensus criteria for FTLD, however, prompted systematic studies. The criteria categorize FTLD into 3 subgroups: frontotemporal dementia, semantic dementia, and progressive nonfluent aphasia.

Objective: To compare demographic characteristics of patients in the 3 FTLD subgroups.

Design: We compared diagnostic breakdown, age at onset, sex, Mini-Mental State Examination score at first visit, education, and neuropathological diagnoses in a large sample of FTLD patients from 3 different university dementia clinics, including 2 neurologic clinics in the United States and 1 psychiatric clinic in Germany.

Results: The frontotemporal dementia subgroup represented approximately half of all FTLD diagnoses. Patients diagnosed as having frontotemporal dementia (mean age, 57.5 years) and semantic dementia (mean age, 59.3 years) had an earlier age at onset than patients diagnosed as having progressive nonfluent aphasia (mean age, 63.0 years). There were significantly more men diag-

nosed as having frontotemporal dementia (63.5%) and semantic dementia (66.7%) when compared with progressive nonfluent aphasia (39.1%) (P=.005 for frontotemporal dementia vs progressive nonfluent aphasia and P=.002 for semantic dementia vs progressive nonfluent aphasia). Generally, the demographic features and diagnostic categories of the patient populations across the 3 sites were comparable. There were 68 deaths and 37 autopsies. Frontotemporal lobar degeneration with ubiquitin-positive τ-negative inclusions (48.5%), dementia lacking distinctive histopathological features (18.2%), and Pick disease (15.2%) were the most common neuropathological diagnoses.

Conclusions: These findings show that cohorts of patients can be combined using new research criteria for FTLD and demonstrate striking demographic differences among FTLD subgroups. The sex and age-at-onset differences suggest that there may be biological differences among FTLD subgroups. In this sample, FTLD with ubiquitin-positive inclusions accounted for half of all neuropathological diagnoses.

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THERE HAS BEEN EXTENSIVE research about the epidemiological features of Alzheimer disease, which has helped direct therapeutic approaches. Until recently, frontotemporal lobar degeneration (FTLD) was considered to be rare and difficult to diagnose,[1,2] and relatively little is known about the demographic features. Recent studies[3,4] suggest that FTLD is the second most common diagnosis of dementia in individuals younger than 65 years. Many factors have limited research into FTLD. In particular, the size of FTLD cohorts at any one center is modest. In addition, until recently, low diagnostic accuracy for FTLD and related disorders has diminished enthusiasm for epidemiological research about this neurodegenerative disease. Finally, collaborative studies have not been possible because definitions of FTLD have varied between sites, thereby limiting the ability to combine cohorts.

Only a few reports have explored the demographic features of FTLD. It is well accepted that FTLD is a presenile dementia with a strong genetic component,[5-7] but other risk factors for FTLD remain largely unexplored.[8] The recent establishment of consensus criteria for FTLD[9] represents an opportunity to begin large-scale studies

about the demographic features of FTLD. These criteria divide FTLD into 3 major subgroups: frontotemporal dementia (FTD), semantic dementia, and progressive nonfluent aphasia (PNFA). Thus, this article analyzes the demographic features of a large group of patients diagnosed as having FTLD at 3 dementia clinics.

METHODS

We selected consecutive patients who met the criteria of Neary et al[9] for FTLD from 3 university dementia clinics. All patients were assessed between January 1, 1998, and December 31, 2003. Two sites are outpatient neurology clinics (University of California, San Francisco [UCSF] and University of California, Los Angeles [UCLA]), and one is located in an outpatient memory clinic in a department of psychiatry (Technische Universität Munich). All 3 centers are located in metropolitan areas, and all are referral centers for FTLD patients.

The clinical diagnosis at all 3 sites was based on the neurologic and physical examination results, medical history, informant interview, a neuropsychological evaluation, laboratory screening, and brain imaging. The Mini-Mental State Examination (MMSE)[10] is administered at all sites. The neuropsychological tests and brain imaging methods differ between sites. Patients at UCSF are administered a 1-hour neuropsychological battery that measures memory, language, executive function, visuospatial skills, and praxis.[11] All undergo brain magnetic resonance imaging. Patients at UCLA are administered a 1-hour neuropsychological battery, including tests from the Consortium to Establish a Registry for Alzheimer's Disease[12] and the Neurobehavioral Cognitive Status Examination.[13] Magnetic resonance imaging and single-photon emission computed tomographic or positron emission tomographic results are obtained for all patients. Patients in Munich are administered the German Consortium to Establish a Registry for Alzheimer's Disease battery.[14] Additional tests of executive function are obtained in approximately two thirds of the cohort. Patients in the Munich cohort underwent either brain computed tomography or magnetic resonance imaging, and 65 were examined with fluorine 18–labeled deoxyglucose positron emission tomography. Age at onset is queried as part of the clinical interview, and is defined as the age at which the first change in cognition or behavior is noted by the caregiver or the patient. Education is coded as the number of years of formal education. The diagnosis at all sites is determined by consensus, including the neurologist or psychiatrist and neuropsychologist (J.K.J., J.D., M.F.M., T.W.C., H.J.R., H.F., A.K., B.L.M.); disagreements in diagnosis are resolved during discussion.

The criteria of Neary et al[9] for FTD require (1) insidious onset and gradual progression, (2) early decline in social interpersonal conduct, (3) early impairment in regulation of personal conduct, (4) early emotional blunting, and (5) early loss of insight. Patients meet the criteria for semantic dementia if they exhibit (1) insidious onset and gradual progression; (2) a language disorder characterized by empty fluent speech, loss of word meaning, or semantic paraphasias; (3) a perceptual disorder characterized by impaired recognition of familiar faces or object identity; (4) preserved perceptual matching and drawing reproduction; (5) preserved single-word repetition; and (6) preserved ability to read aloud and write to dictation orthographically regular words. Finally, patients meet the criteria for PNFA if they have (1) insidious and gradual progression and (2) nonfluent spontaneous speech with at least one of agrammatism, phonemic paraphasias, or anomia. Patients were diagnosed as having probable or possible amyotrophic lateral sclerosis (ALS) using the El Escorial criteria.[15]

Deaths and neuropathological diagnoses were also compiled. Neuropathological examinations were done by the University of Pennsylvania Center for Neurodegenerative Disease Research for UCSF and the Departments of Neuropathology at UCLA and Munich. Published neuropathological criteria were used for diagnosis. We classified FTLD neuropathological diagnoses according to McKhann and colleagues.[16] We used the term FTLD–motor neuron disease to represent patients with ubiquitin-positive τ-negative inclusions with or without clinically diagnosed ALS.

We assessed differences in continuous variables, such as education and age at disease onset, among diagnostic groups and associations with other variables using analysis of variance methods. We assessed differences in the sex distribution using logistic regression.

RESULTS

From January 1, 1998, to December 31, 2003, 353 patients were diagnosed as having FTLD across all 3 sites, including 132 from UCSF, 130 from UCLA, and 91 from Munich. **Table 1** displays the demographic variables by diagnostic subgroups and site, and combined across sites.

DIAGNOSTIC SUBGROUPS

Overall, FTD was the most common diagnostic subgroup, and accounted for 56.7% of all diagnoses (n=200). Progressive nonfluent aphasia was the second most common diagnostic subgroup (n=87), followed by semantic dementia (n=66). The diagnostic breakdown differed significantly across the 3 sites (χ^2_4=22.11, P<.001). The psychiatry clinic in Munich examined the most FTD patients and the fewest PNFA patients compared with the 2 neurology clinics in California. Of the FTD patients, 9.0% were also diagnosed as having probable or possible ALS, whereas only 3.0% of semantic dementia and 3.4% of PNFA patients had a concomitant ALS diagnosis. The trend for ALS to be more common in FTD patients compared with patients with the other subtypes approached, but did not reach, statistical significance (Fisher exact test, P=.11).

AGE AT ONSET

Age at onset ranged from 35 to 80 years. An additive 2-way analysis of variance yielded significant differences in age at onset between diagnostic subgroups ($F_{2,340}$=10.56, P<.001) and sites ($F_{2,340}$=3.52, P=.03), but no interaction ($F_{4,336}$=1.02, P=.40). Overall, patients with PNFA had a later age at onset than patients with FTD and semantic dementia. Approximately one quarter of the patients diagnosed as having FTD and semantic dementia, and almost half of PNFA patients, had a disease onset after the age of 65 years. Patients with FTD at UCSF had a slightly younger age at onset compared with those at UCLA and Munich.

EDUCATION

Education ranged from 8 to 22 years. Ten subjects were missing education data (FTD group, 7; semantic demen-

Table 1. Demographic Variables by Diagnosis and Site*

Variable	UCSF (n = 132)	UCLA (n = 130)	Munich, Germany (n = 91)	Overall (N = 353)
	FTD			
FTD diagnosis†	50.8	53.8	69.2	56.7
Initial MMSE score	22.4 (7.0)	23.1 (6.9)	22.7 (6.0)	22.7 (6.6)
Age at onset, y	54.9 (8.7)	58.6 (9.9)	59.3 (9.9)	57.5 (9.7)
Onset age >65 y†	13.4	27.1	28.8	23.0
Education, y	15.8 (2.1)	15.6 (2.4)	12.7 (3.2)	14.8 (3.0)
Male sex†	70.1	52.9	68.3	63.5
	SD			
SD diagnosis†	27.3	11.5	16.5	18.7
Initial MMSE score	19.8 (8.5)	23.5 (7.8)	24.1 (3.1)	21.5 (7.8)
Age at onset, y	60.0 (8.6)	57.8 (8.0)	59.3 (7.5)	59.3 (8.2)
Onset age >65 y†	25.7	20.0	15.4	22.2
Education, y	16.1 (3.7)	14.9 (2.3)	13.2 (3.9)	15.2 (3.6)
Male sex†	63.9	60.0	80.0	66.7
	PNFA			
PNFA diagnosis†	22.0	34.6	14.3	24.6
Initial MMSE score	23.3 (7.9)	23.1 (6.3)	18.6 (6.8)	22.5 (7.0)
Age at onset, y	61.0 (10.2)	63.6 (8.9)	65.3 (11.1)	63.0 (9.7)
Onset age >65 y†	44.8	44.4	50.0	45.3
Education, y	15.6 (2.3)	14.3 (2.2)	12.8 (3.3)	14.5 (2.6)
Male sex†	31.0	44.4	38.5	39.1

Abbreviations: FTD, frontotemporal dementia; MMSE, Mini-Mental State Examination; PNFA, progressive nonfluent aphasia; SD, semantic dementia; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco.
*Data are given as mean (SD) unless otherwise indicated.
†Data are given as percentage of each group.

tia group, 1; and PNFA group, 2). An additive 2-way analysis of variance yielded significant differences in education between sites ($F_{2,338}$=33.26, P<.001) but not diagnostic subgroups ($F_{2,338}$=1.81, P=.17). Subjects from Munich had fewer years of education than those from UCSF or UCLA.

SEX

A logistic regression analysis of the proportion of men by site and diagnostic subgroup yielded significant differences in sex by diagnostic subgroup (likelihood ratio χ_2^2=14.32, P<.001) but not site (likelihood ratio χ_2^2=2.49, P=.29). More important, there was no interaction between subgroup and site (likelihood ratio χ_4^2=5.85, P=.21). There were significantly more men diagnosed as having FTD and semantic dementia compared with PNFA (P=.005 for FTD vs PNFA and P=.002 for semantic dementia vs PNFA).

MMSE SCORE AT FIRST VISIT

Twenty-nine subjects were missing an MMSE score (FTD group, 19; semantic dementia group, 5; and PNFA group, 5). An additive 2-way analysis of variance did not suggest differences in MMSE score between sites ($F_{2,319}$=0.85, P=.43) or diagnostic subgroups ($F_{2,319}$=0.53, P=.59).

NEUROPATHOLOGICAL DIAGNOSES

As of July 31, 2004, there were 68 deaths, and 37 had undergone a neuropathological examination (4 are pend-

ing diagnosis). There was a similar proportion of deaths in the 3 cohorts, ranging from 17.7% to 20.9% (Fisher exact test, P=.92). When including all of the deceased patients, the mean age at death was 64.6 years (SD, 11.0 years; range, 41-82 years), and 60.3% of the patients were men. The mean age at onset was 58.3 years (SD, 10.5 years; range, 37-79 years), and 29.2% of the patients had an age at onset of older than 65 years. The mean MMSE score at the first visit was 21.7 (SD, 2.7), and the mean education for the population was 15.3 years (SD, 2.7 years).

Table 2 summarizes the neuropathological diagnostic breakdown and demographic characteristics for the patients with neuropathological examinations (16 at UCSF, 13 at UCLA, 4 at Munich, and 4 pending diagnosis). The most common neuropathological diagnosis was FTLD–motor neuron disease[16] (48.5%), followed by dementia lacking distinctive histological features (18.2%), and Pick disease (15.2%). The remaining pathological diagnoses included progressive supranuclear palsy,[17] progressive supranuclear palsy with definite Alzheimer disease,[18] corticobasal degeneration,[19] and definite Alzheimer disease.

COMMENT

The present study is the first, to our knowledge, to summarize demographic data across 3 sites with many FTLD patients. There were significant differences in diagnostic breakdown, sex, and age at onset across the 3 FTLD subtypes. In contrast, there were no differences in MMSE score at first visit. Education differed only between sites,

Table 2. Demographic Characteristics by Neuropathological Diagnosis

Neuropathological Diagnosis	No. of Subjects	Male-Female Ratio	Age at Onset, y*	Age at Death, y*	Initial MMSE Score*	Those With ALS†	Onset Age >65 y†
FTLD-MND	16	11:5	56.7 (12.2)	62.3 (12.6)	24.0 (5.1)	43.8	25.0
DLDH	6	2:4	59.2 (12.2)	63.8 (11.1)	21.5 (4.4)	0	33.3
PiD	5	3:2	62.2 (9.7)	72.8 (7.2)	19.0 (8.0)	0	40.0
PSP	2	2:0	57.0 (11.3)	66.0 (14.1)	‡	0	0
PSP-AD	2	2:0	75.5 (5.0)	80.0 (2.8)	25.5 (3.5)	0	100
CBD	1	1:0	58.0	61.0	25.0	0	0
AD	1	0:1	54.0	60.0	10.0	0	0
Overall	33	21:12	59.1 (11.2)	65.3 (11.6)	21.5 (7.3)	21.2	30.3

Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; CBD, corticobasal degeneration; DLDH, dementia lacking distinctive histology; FTLD, frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination; MND, motor neuron disease; PiD, Pick disease; PSP, progressive supranuclear palsy.
*Data are given as mean (SD). The SD is not given when it is not applicable.
†Data are given as percentage of subjects.
‡Both subjects had missing initial MMSE scores.

but not diagnostic groups, most likely reflecting referral biases of the clinics. Munich is a public clinic with patients from a wide variety of socioeconomic backgrounds, while UCSF and UCLA are tertiary referral sites that are more likely to see patients with a higher education. More important, the MMSE score at first visit was similar across all sites and diagnostic categories, suggesting that all sites were diagnosing patients in a similar stage of dementia.

Frontotemporal dementia was the most common diagnostic subgroup at all 3 sites, and accounted for approximately half of all FTLD diagnoses. Semantic dementia and PNFA were slightly less common, and accounted for approximately one quarter for each. The site differences in diagnosis likely reflect a referral bias. Patients with behavioral and psychiatric changes are often referred to psychiatric services,[20] whereas patients with language symptoms are more likely to be referred to a neurology clinic. This distribution of diagnostic subgroups has also been noted in smaller cohorts of FTLD patients.[21,22]

The present study also suggests that patients diagnosed as having FTD and semantic dementia have an earlier age at onset than PNFA patients. The age at onset for FTD in the present study is consistent with that in the other smaller studies.[21,23-25] Our data also suggest that the age at onset for PNFA is later than for either FTD or semantic dementia, a finding that has been observed in other smaller studies.[21,22,26] In the present study, almost one quarter of patients with FTD and semantic dementia and almost half of patients with PNFA had an onset of symptoms after the age of 65 years. Although FTD is considered to be a predominantly presenile cause of dementia,[3,9,23] many patients had an onset of symptoms after the age of 65 years, particularly those with PNFA. A recent study[27] found that 3% of a population of 85-year-old patients met the clinical criteria for FTD, suggesting that this disorder also occurs in older patients. The age at onset for FTLD is an important issue to resolve because several studies[3,28] have used an age of 65 or 70 years as the cutoff to estimate the prevalence of FTD. By using these definitions, there is an inherent diag-

nostic bias against the diagnosis of FTLD in the very old. A wide range in the age at onset across all diagnostic groups was also similar to that found in smaller studies.[22,23] However, the diagnoses in only a few patients, particularly in the older age range, have been autopsy confirmed. The pathological diagnosis of FTLD may be more difficult in older individuals because neuritic plaques and neurofibrillary tangles are common. In addition, Alzheimer disease can present with prominent language or executive function disorders and may be confused with FTLD.[29,30]

In terms of sex, there was a predominance of men diagnosed as having FTD and semantic dementia, while women were overrepresented in the PNFA group. A few studies[31,32] document a predominance of men in patients with FTD. However, others report a predominance of women,[6,33] and yet others find an equal sex distribution.[5,8,21,22] Fewer studies have evaluated the sex distribution in those with semantic dementia and PNFA. Snowden and colleagues[21] demonstrated a 2:1 ratio of women to men with semantic dementia, while Hodges and colleagues[22] found a predominance of women in 8 PNFA patients and a predominance of men in 9 patients with semantic dementia. The confusing pattern of sex differences may be due to the small samples previously described. The male predominance for FTD and semantic dementia and the female predominance for PNFA observed in this study may reflect differences in biological vulnerability to the 3 anatomically distinct syndromes. This cortical asymmetry may reflect different vulnerabilities to neurodegeneration between women (left frontal) and men (right frontal and/or bilateral temporal).

In the autopsied patients, FTLD–motor neuron disease accounted for half of the neuropathological diagnoses, followed by dementia lacking distinctive histological features and Pick disease. Other recent reports[34-36] suggest that FTLD with ubiquitin-positive τ-negative inclusions is common, with a frequency ranging from 24% to 62% of FTLD cases. The observation that 19% of the patients died in less than 5 years of surveillance suggests that FTLD has a rapid course. In particular, the FTLD–motor neuron disease popula-

tion had a fulminant course. More research into the mechanisms of neurodegeneration associated with FTLD should offer new insights into the selective vulnerability and different rates of progression for the FTLD subtypes.

Based on the demographic similarities in the cohorts studied herein, it is possible to compare patients across different sites if standard diagnostic criteria are used. The clinical criteria for FTLD represent a first step toward understanding neurodegenerative disorders that affect the frontal and anterior temporal lobes. The results of this study suggest that there may be significant biological differences among diagnostic subgroups. Whether FTD and semantic dementia, with a younger age of onset and a male predominance, represent a distinctive disorder or different manifestations of the same illness needs further study. Combining large cohorts from across the world represents a viable strategy for exploring the epidemiological and biological features.

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