ORIGINAL CONTRIBUTION

Clinical and Psychometric Distinction of Frontotemporal and Alzheimer Dementias

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Background: A proportion of patients who meet the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations criteria for Alzheimer disease (AD) have frontotemporal lobar degeneration (FTLD) confirmed at autopsy, with or without concomitant AD. Thus, the clinical phenotypes of the 2 disorders may overlap.

Objective: To identify clinical and psychometric indicators that distinguish AD from FTLD at initial presentation.

Design: Longitudinal study of memory and aging.

Setting: Alzheimer's Disease Research Center, Washington University School of Medicine.

Participants: Forty-eight clinically well-characterized cases of autopsy-confirmed FTLD (27 with psychometric testing results) were compared with 27 autopsy-confirmed AD cases.

Results: Behavioral abnormalities, particularly impulsivity ($P<.001$), disinhibition ($P<.001$), social withdrawal ($P=.01$), and progressive nonfluent aphasia, distinguished individuals with FTLD from those with AD. The individuals with FTLD performed better than those with AD on a visual test of episodic memory ($P=.01$), but worse on word fluency ($P=.02$) (performance correlated with aphasic features). Other cognitive and clinical features, including executive dysfunction and memory impairment, were comparable between the FTLD and AD groups. Concomitant histopathological AD was present in 11 of the 48 individuals with FTLD.

Conclusions: Clinical and cognitive features of FTLD may overlap with AD, although behavioral and language difficulties distinguish those with FTLD. Memory loss in those with FTLD may in part reflect word-finding difficulties stemming from language dysfunction. Compounding the overlap of FTLD and AD clinical phenotypes is the presence of histopathological AD in almost one fourth of individuals with FTLD.

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FRONTOTEMPORAL LOBAR DEgeneration (FTLD) represents a group of disorders that is considered to be clinically and pathologically distinct from Alzheimer disease (AD),[1] although FTLD may be mistaken for AD in the early clinical stages.[2,3] Based on clinicopathological consensus criteria,[4] the FTLDs are classified into 3 groups. One group is represented by the tauopathies, characterized by inclusions containing aggregates of the microtubule-associated protein τ: Pick disease, corticobasal degeneration, progressive supranuclear palsy, tangle-only dementia, argyrophilic grain disease, and familial cases with τ mutations, also called frontotemporal dementia with parkinsonism linked to chromosome 17. Another group, which represents most cases of FTLD, is characterized by ubiquitin-positive τ-negative inclusions, FTLD with motor neuron disease–type inclusions, or inclusion body myositis with Paget disease and frontotemporal dementia. The final group represents cases with no detectable inclusions, generically called FTLD or dementia lacking distinctive histopathological features.

The FTLDs clinically present as either behavioral or aphasic syndromic variants,[5] reflecting the topography of the underlying synaptic and neuronal loss. Behavioral or frontal variant FTLD is associated with disinhibition, impulsivity, apathy, and loss of insight that disturbs social comportment and typically is accompanied by marked frontal lobe atrophy. The aphasic variant is further divided into 2 subtypes: the nonfluent form (primary progressive aphasia), with hesitant diminished speech output that eventually culminates in muteness and for which left frontotemporal lobe involve-

Table 1. Demographic Characteristics of the Study Groups

Characteristic	FTLD Only Group (n = 37)	FTLD Plus AD Group (n = 11)	t_{46} Value	*P* Value
Age at onset, y				
Mean ± SD	58.9 ± 9.9	63.5 ± 5.8	1.07	.15
Range	33-77	55-74		
Female/male, No.	14/23	5/6	NA	.73
Age at death, y				
Mean ± SD	69.4 ± 11.6	74.7 ± 6.6	1.46	.15
Range	35-99	66-84		
Duration of illness, y				
Mean ± SD	9.6 ± 3.9	11.2 ± 5.4	1.09	.28
Range	2-19	6-22		
APOE status, No.				
ε2/3	3	1	NA	*
ε3/3	24	3	NA	*
ε3/4	2	2	NA	*

Abbreviations: AD, Alzheimer disease; *APOE*, apolipoprotein E; FTLD, frontotemporal lobar degeneration; NA, data not applicable.
* Not calculated because of the small sample. Genotype was not available for 8 individuals in the FTLD Only and 5 in the FTLD Plus AD groups.

ment is characteristic; and the fluent form (semantic dementia), with severe naming and word comprehension and visual recognition deficit (agnosia) for faces and objects that involves bilateral anterior temporal lobes.

Although certain clinical features of FTLD seem to be distinct from dementia of the Alzheimer type,[6-9] some studies[2,3] show clinical overlap. In a study[2] of 21 patients with Pick disease, 85% were misdiagnosed during life as having AD. Nevertheless, autopsy-proved FTLD cases alone or in combination with AD can meet the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations[10] clinical criteria for AD during life,[11] suggesting that the clinical distinction between the 2 phenotypes remains poor. Thus, this study aimed to examine the role of AD pathological features in FTLD by distinguishing between these 2 broad phenotypes using well-characterized and neuropathologically confirmed cases of FTLD and AD.

METHODS

SAMPLE

We reviewed 48 cases of FTLD meeting the neuropathological criteria for FTLD,[4] 5.1% of 935 cases undergoing autopsy between January 1, 1988, and December 31, 2004, at the Alzheimer's Disease Research Center, Washington University School of Medicine. All but 1 of the cases had been enrolled in the research studies of the Alzheimer's Disease Research Center[12]; the exception was a case obtained from an affiliated clinical practice. Herein, we present data from the initial assessment of each individual. There was no specific recruitment of individuals with FTLD, who may have presented for assessment if there had been consideration of AD. Because the Alzheimer's Disease Research Center's research goals focused on AD, psychometric data for individuals clinically diagnosed as having FTLD were not always obtained if resources did not permit. Informed consent was obtained from all participants in accordance with the policies and procedures of the Washington University School of Medicine Human Studies Committee.

CLINICAL PROFILE

Experienced clinicians (including J.C.M.) diagnosed dementia and staged its severity based on semistructured interviews with the participant and a knowledgeable collateral source; a neurological examination of the participant also was performed. The clinical diagnosis was based solely on clinical methods (without reference to psychometric performance results). Dementia was evaluated according to the Clinical Dementia Rating Scale.[13] Alzheimer disease was diagnosed in accordance with standard criteria,[12] and frontotemporal dementia (now often termed *FTLD*) was diagnosed in accordance with the criteria of Neary et al.[5] Depressive features were assessed in accordance with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,[14] criteria.

NEUROPATHOLOGICAL ASSESSMENT

Brain tissue was obtained with the consent of the next of kin and with the approval of the Washington University School of Medicine Human Studies Committee. Autopsies and neuropathological procedures were performed according to established protocols.[12] Abnormal protein aggregates were detected using ubiquitin, τ, α-synuclein, β-amyloid, α-internexin, and valosin-containing protein immunohistochemistry on representative sections. Cases were diagnosed according to established and other neuropathological criteria.[4,15-17] The neuropathological assessment of AD was based on the criteria of Khachaturian,[18] the Consortium to Establish a Registry for Alzheimer's Disease,[19] or the National Institute on Aging and Reagan Institute criteria.[20] Alzheimer disease–type changes were defined by a Braak neurofibrillary tangle stage of IV or greater and β-amyloid stage B or C,[15] even in the presence of other pathological features.

The demographic characteristics of these 48 individuals are shown in **Table 1**. Psychometric testing results were obtained in 30 of the individuals with FTLD; 3 of these individuals also had AD and were excluded from analyses because this cell was too small. Thus, psychometric data from 27 individuals with FTLD and without concomitant AD were available for analysis and were compared with psychometric data from 27 individuals (12 women) with autopsy-confirmed AD and with similar age at death, education, and dementia severity. The in-

dividuals with AD fulfilled validated clinical criteria for AD[12] and its equivalent, probable AD.[10] The mean±SD age at death of the 27 individuals with AD was 69.7±7.2 years (range, 55-88 years); the mean±SD age of the 27 participants with FTLD (9 women) was 65.8±10.1 years (range, 44-77 years) (t_{52}=1.60, P=.12). Both groups had approximately 14 years of education. The dementia severity of the 2 groups at enrollment was comparable (Kolmogrov-Smirnoff z=0.30).

PSYCHOMETRIC ASSESSMENT

A battery of standard psychometric tests[21] was applied (**Table 2**). Episodic memory is assessed with the logical memory and associate learning subtests from the Wechsler Memory Scale[22] and with the Visual Retention Test.[23] Semantic memory is assessed with the information subtest of the Wechsler Adult Intelligence Scale[24] and the Boston Naming Test.[25] Attention and executive functions are assessed with the digit span measures from the Wechsler Memory Scale, a word fluency test,[26] and the Wechsler Memory Scale mental control subtest. Finally, speeded visuospatial measures include the Wechsler Adult Intelligence Scale block design and digit symbol and Trail-Making Test A.[27]

APOE GENOTYPING

Genomic DNA was extracted from fresh-frozen brain or antemortem blood samples, as described elsewhere.[12] For 9 individuals, however, there was insufficient biological material available and, in 4, DNA fragment extraction from the paraffin-embedded brain sections[28] did not allow for reliable *APOE* (apolipoprotein E) genotyping.

IMAGING

Of the 48 individuals, 46 (96%) underwent brain imaging early in the course of the disease; computed tomography was performed in 25 individuals and magnetic resonance imaging in 21. The neuroimages were obtained on different scanners for clinical, not research, purposes; hence, the findings are not suitable for analysis and only general observations are appropriate.

DATA ANALYSIS

Comparisons of 2 groups were conducted with t tests for quantitative measures (eg, age and psychometric measures) and the Fisher exact test (2-tailed) for frequency data (eg, sex) using a commercially available software program (SPSS, version 11.0; SPSS Inc, Chicago, Ill). Comparisons of frequency data for the 2 FTLD groups and the AD group were made using the χ^2 test of association. Although multiple statistical tests were conducted, α was set at .05 because of the relatively small sample sizes and limited statistical power.

RESULTS

DEMOGRAPHICS AND CLINICAL FEATURES

There was a trend for estimated age at symptom onset to be lower in the FTLD group compared with the FTLD plus AD group, but this failed to reach statistical significance (Table 1). Also, the 2 groups did not differ in age at death or duration of illness.

Individuals with FTLD (without or with AD) differed from those with AD on impulsivity, disinhibition, and hyperorality, with the FTLD group showing the most deficits (**Table 3**). The reverse was true of social withdrawal, which was more common in the AD than in the 2 FTLD groups. In both FTLD groups, memory impairment was present, as indicated by the collateral source or the participant. This deficit, however, was universal in those with AD. Many individuals with FTLD (without or with AD) reported language-related symptoms (dysfluency, agrammatism, and speech hesitancy or effortful speech), which were rare in those with AD. Word-finding difficulty was more common in both FTLD groups than in the AD group; the difference approached significance. Except for hallucinations, no significant group differences (P>.05) were found for the remaining clinical features.

Table 2. Comparison of Psychometric Performance of the FTLD and AD Groups at First Assessment

Measure	FTLD Group (n = 27)*	AD Group (n = 27)*	t_{52} Value†
Logical memory	3.79 ± 2.55	2.74 ± 2.33	1.57
Associate learning	6.13 ± 3.72	7.20 ± 3.58	1.03
Visual Retention Test	3.85 ± 1.96	2.42 ± 1.81	2.65‡
Information	9.85 ± 6.60	13.44 ± 6.54	1.91
Boston Naming Test	30.38 ± 20.61	38.85 ± 15.71	1.63
Digit span forward	5.34 ± 1.60	6.07 ± 1.38	1.72
Digit span backward	3.09 ± 1.72	3.48 ± 1.28	0.91
Word fluency for S and P	12.61 ± 7.91	19.41 ± 10.39	2.53‡
Mental control	4.86 ± 2.88	4.67 ± 3.22	0.22
Block design	17.41 ± 13.82	13.44 ± 11.69	1.09
Digit symbol	28.00 ± 13.58	17.78 ± 14.64	2.66‡
Trail-Making Test A	81.33 ± 46.74	104.89 ± 52.69	1.74

Abbreviations: See Table 1.
*Data are given as mean±SD. Higher scores indicate good performance for all measures, except the Trail-Making Test A (for which the score is measured in seconds).
†The degrees of freedom were slightly less for some measures because of missing data.
‡P<.05.

PSYCHOMETRICS

The FTLD and AD groups differed significantly at enrollment on 3 of the 12 measures in the psychometric battery (Table 2). Compared with the AD group, the FTLD group performed significantly worse on word fluency, which assesses executive function. The difference between the 2 groups approached significance (P<.06) on a test of semantic memory (information subtest of the Wechsler Adult Intelligence Scale); the FTLD group again performed worse than the AD group. The FTLD group performed significantly better than the AD group on 2 tests, both of which were visuospatial: digit symbol, which is speeded; and the Visual Retention Test, which measures episodic memory.

NEUROPATHOLOGICAL FEATURES AND *APOE* GENOTYPING

Of 48 cases of FTLD, 17 were tauopathies: corticobasal degeneration (n=9), frontotemporal dementia with parkinsonism linked to chromosome 17 (n=3, 2 of which had τ R406W mutations and 1 in which no mutation had

Table 3. Clinical Features of Study Individuals*

Clinical Feature	FTLD Only Group (n = 37)	FTLD Plus AD Group (n = 11)	AD Only Group (n = 27)	χ^2_2 Value	*P* Value
Memory-loss	28 (76)	7 (64)	27 (100)	9.70	.01
Frontal variant FTLD					
Disinhibition	17 (46)	6 (55)	1 (4)	15.81	<.001
Impulsivity	16 (43)	9 (82)	3 (11)	17.79	<.001
Executive dysfunction	18 (49)	8 (73)	13 (48)	2.22	.33
Social withdrawal	8 (22)	1 (9)	14 (52)	9.53	.01
Hyperorality	3 (8)	3 (27)	0	7.90	.02
Apathy	10 (27)	1 (9)	8 (30)	1.85	.40
Loss of insight	8 (22)	1 (9)	2 (7)	2.84	.24
Progressive nonfluent aphasia					
Dysfluency	16 (43)	7 (64)	4 (15)	9.74	.01
Agrammatism	13 (35)	7 (64)	3 (11)	10.83	.004
Speech hesitancy or effortful speech	15 (41)	8 (73)	7 (26)	7.14	.03
Word-finding difficulty	20 (54)	8 (73)	9 (33)	5.50	.06
Semantic dementia					
Prosopagnosia	2 (5)	0	2 (7)	0.85	.65
Semantic dysnomia	8 (22)	2 (18)	1 (4)	4.13	.13
Motor difficulties					
Dyspraxia	8 (22)	4 (36)	2 (7)	4.74	.09
Pyramidal signs	3 (8)	1 (9)	0	2.39	.30
Primitive reflexes	3 (8)	2 (18)	0	4.40	.11
Extrapyramidal signs	4 (11)	3 (27)	4 (15)	1.84	.40
Incontinence	1 (3)	1 (9)	2 (7)	1.04	.59
Psychiatric signs					
Depression	6 (16)	2 (18)	6 (22)	0.37	.83
Delusions	3 (8)	1 (9)	1 (4)	0.61	.74
Hallucinations	0	0	4 (15)	7.51	.02

Abbreviations: See Table 1.
*Data are given as number (percentage) of each group unless otherwise indicated, and are based on the criteria of Neary et al.[5]

been identified), Pick disease (n=2), progressive supranuclear palsy (n=1), argyrophilic grain disease (n=1), and tangle-only dementia (n=1). Most cases (n=27), however, had ubiquitin-positive, τ-negative, cytoplasmic inclusions (FTLD with motor neuron disease–type inclusions); there was also 1 case of inclusion body myositis with Paget disease and frontotemporal dementia and 3 cases of dementia lacking distinctive histopathological features. In 11 cases, there were additional AD pathological features.

The *APOE* genotypes were obtained in 29 individuals in the FTLD group and in 6 individuals in the FTLD with AD group, of 48 total individuals (Table 1). From 6 of 11 individuals with additional AD pathological features, 2 bore at least 1 copy of the *APOE* ε4 allele.

COMMENT

We identified clinical and psychometric differences between neuropathologically confirmed FTLD (without or with AD pathological features) and AD. Behavioral features, including impulsivity, disinhibition, hyperorality, and social withdrawal, significantly differed in the FTLD groups vs the AD group, as reported previously.[6,8,9] However, Varma and colleagues[11] failed to differentiate FTLD from AD using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations[10] clinical criteria, showing a lack of specificity in commonly used criteria for both diseases. Language features differed significantly in the FTLD group (with or without AD) vs the AD group, as suggested by Hodges et al.[29] However, the FTLD with AD group showed more deficit, suggesting a synergistic interaction between the 2 phenotypes. Amnesia as an initial symptom, despite being characteristic of individuals with AD, was present in high percentage in both FTLD groups, as reported in other clinicopathological studies.[6,29] Episodic memory impairment in FTLD may also derive from alterations in attention and working memory. Also, deficits in verbal processing abilities and word retrieval may contribute to the decreased memory performance and to the impression of the caregiver that memory is impaired.

The most distinctive feature of FTLD, on psychometric tests, was significant impairment of frontal lobe functioning, as reported by Rascovsky et al.[7] One of the limitations of the present study is that nonverbal tests of executive function were not included. Given the better performance by the FTLD group on the nonverbal episodic memory test, it is possible that the memory impairment in FTLD may represent primarily a word-finding difficulty, which would influence performance on verbal memory tests, rather than an episodic memory deficit, as in AD.

As in other series, we found a spectrum of neuropathological entities causing FTLD.[4] The relatively large

proportion of cases of FTLD with motor neuron disease–type inclusions in this series (27 [56%]) is explained by the long-established interest in hereditary disinhibition dysphasic dementia (n=11). About one quarter of FTLD cases (11 [23%]) had mild to moderate numbers of β-amyloid plaques in the brain, and 2 participants, both heterozygous for the *APOE* ε4 allele, showed more extensive neuritic plaques and neurofibrillary tangles, similar to observations in familial FTLD with τ mutations.[30] The *APOE* ε4 allele was increased in the FTLD with AD group, suggesting an association between the *APOE* ε4 allele and AD.[31] In the present study, about one quarter of individuals with FTLD (13 [27%]) had an onset of symptoms after the age of 65 years, particularly those with additional AD pathological features, suggesting that FTLD also occurs in older patients.[32] The demographic data available were consistent with those in a previous study.[33]

Our study has some methodological limitations. First, it was a retrospective study, and in some cases, specific features that would have been important to confirm the diagnosis of semantic dementia were rarely mentioned. Furthermore, the current series of FTLD cases is being mostly examined at the Alzheimer's Disease Research Center, which may bias the clinical diagnoses.

In summary, the clinical phenotype of FTLD overlapped with that of AD in several domains, including memory and executive dysfunction, but was distinct in terms of behavioral problems and language difficulties. Memory loss in FTLD may reflect word-finding difficulties stemming from language dysfunction. Clinical heterogeneity may reflect the neuropathological heterogeneity. Compounding the overlap of FTLD and AD clinical phenotypes is the presence of coexisting AD pathological features in one quarter of FTLD cases.

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Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Neurology* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of *Archives of Dermatology* (2005;141:76-77). Also see the Instructions to Authors on our Web site: www.archneurol.com.