Sporadic and Familial Dementia With Ubiquitin-Positive Tau-Negative Inclusions

Clinical Features of One Histopathological Abnormality Underlying Frontotemporal Lobar Degeneration

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Background: Frontotemporal lobar degeneration comprises a group of diseases with clinical presentations and underlying histopathologies that overlap. Familial disease occurs in up to 50% of frontotemporal lobar degeneration cases. One of several underlying histopathological abnormalities is ubiquitin-positive tau-negative inclusions, similar to those in motor neuron disease.

Objective: To compare clinical features of familial and sporadic cases in this pathological subgroup.

Design and Patients: Case note review of dementia patients with ubiquitin-positive tau-negative inclusion pathological abnormalities proven by autopsy.

Setting: United Kingdom tertiary referral center.

Main Outcome Measures: Analysis of clinical features.

Results: Eleven familial cases (autosomal dominant) and 18 sporadic cases were identified. Most familial case patients presented with behavioral disturbances similar to those seen in sporadic behavioral cases. Semantic dementia was only seen in sporadic cases. Atypical features occurred in a minority. Sporadic and familial behavioral cases showed no differences in age at onset or disease duration. Neuropsychological test results revealed frontal or temporal deficits in most, but unexpected early parietal deficits in 1.

Conclusions: Behavioral features in familial and sporadic cases were similar, but semantic dementia only occurred in sporadic cases. Diagnostic confusion with Alzheimer disease and corticobasal degeneration occurred in some cases.

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The pathology underlying frontotemporal lobar degeneration (FTLD) has been defined more clearly in recent years. Clinical and pathological features overlap, such that apparently similar clinical presentations can be due to different histopathological abnormalities. Frontotemporal lobar degeneration also occurs in both familial and sporadic forms, with 10% to 50% of cases being familial. It is not clear whether sporadic disease and familial disease differ in clinical phenotype. Mutations in the tau gene occur in only half of familial cases. At least 3 different gene loci have been proposed for familial FTLD occurring without tau deposition or tau mutations. An understanding of the similarities or otherwise of familial and sporadic disease will become increasingly important when these genes are identified.

Neary et al defined 3 clinical presentations of FTLD: frontotemporal dementia (FTD), progressive nonfluent aphasia, and semantic dementia (SD). Pathological entities include glial and neuronal tau deposition, Pick disease, corticobasal degeneration, neurofilament inclusion body disease, frontotemporal dementia and parkinsonism linked to chromosome 17, nonspecific histological features, and tau- and α-synuclein–negative ubiquitin-positive inclusions. The latter 3 usually account for familial FTLD. The ubiquitin-positive tau- and α-synuclein–negative inclusions seen in some cases are similar to those observed...
in motor neuron disease (MND), although in patients with dementia these may occur in extramotor cortices and dentate fascia without anterior horn cell disease. Various terms are used for this occurrence. We favor the term dementia with ubiquitin-positive tau- and α-synuclein-negative inclusions (DUI), which avoids implications about clinical presentation or a link to MND. Cortical and/or dentate ubiquitin inclusions may also be seen in patients with MND without dementia.

Clinical features of MND may be associated with FTLD, usually with behavioral disturbance before features of MND appear. However, diagnosis of FTLD may follow that of MND, and features of MND may occur in patients with FTLD.

Several pedigrees with this pathological abnormality have been reported, but this is the first large series of cases comparing familial and sporadic disease.

**METHODS**

Cases were identified from the postmortem series of the Dementia Research Centre, Institute of Neurology, London, England. Patients presented with cognitive impairment and met standard criteria for dementia. A secondary diagnosis of MND was allowed only if the initial presentation was with cognitive impairment (2 cases).

Neuropathological examination included hematoxylin-eosin and silver stains and immunohistochemical analysis with antibodies for tau protein (AT8), ubiquitin, α-synuclein, Aβ, prion protein (12F10), glial fibrillary acidic protein, and neurofilament proteins (RT97 and BF10).

Pathological criteria for diagnosis of DUI were based on accepted consensus, ie, intraneuronal inclusions, commonly in layer 2 of the frontal, temporal, and parietal cortex and in granule cells of the dentate gyrus of the hippocampus, stained by ubiquitin but not by tau or α-synuclein (Figure).

Clinical features were extracted from hospital records and cases were divided into familial and sporadic groups. Familial cases met criteria for autosomal dominant inheritance as defined by Cruts et al, whereby a minimum of 3 affected members in 2 generations are required. For familial cases, mutations in exons 9 to 13 of the tau gene had been excluded in either the patient or an affected first-degree relative. Cases were further grouped according to predominant clinical features. In our analysis, t tests compared age at onset and disease duration. The Fisher exact test was used to compare the proportions of familial and sporadic cases in each clinical group.

Twenty-nine cases were identified from a postmortem series of 234 patients with dementia. Six of these cases had been the subjects of previous reports, including 1 report in which recent review of the pathological features led to reclassification as DUI. Twenty-four cases were assessed clinically at this center. Five cases were referred to the brain bank for research purposes only, and clinical information was obtained from notes available at the time of donation.

Eleven cases from 8 families were familial. Six familial and 12 sporadic cases were men. Mean ages at onset were 56.3 years for sporadic cases and 54.3 years for familial cases (P = .44). Mean durations of disease were 9.3 years (sporadic) and 6.6 years (familial) (P = .05). However, durations were very similar in the 2 groups if cases in which the clinical phenotype was itself associated with very long (semantic) or very short (MND) disease duration were excluded: 8.0 years (n=9; sporadic) and 6.6 years (n=11; familial), at P = .46. Age at onset and disease duration for each of the 6 clinical groups defined below are given in Table 1.

Contemporary clinical diagnoses were of FTD (10 cases), MND (2 cases), SD (7 cases), progressive aphasia (1 case), Alzheimer disease (AD; 5 cases), corticobasal degeneration (1 case), unclassified dementia (2 cases), and unknown (1 case). Without reference to the original clinical diagnoses, cases were divided into 6 groups according to the predominant clinical features: behavioral (13 cases, 5 familial), semantic (7 cases, none familial), mixed amnesic and behavioral (5 cases, 3 familial), mixed language and behavioral (2 cases, 1 familial), parietal (1 case, familial), and features of corticobasal degeneration (1 case, familial). Behavioral features are summarized in Table 2. The Fisher exact test demonstrated that the proportions of familial and sporadic cases were significantly different in the various clinical groups (P = .04). Further comparison of semantic and nonsematic presentations showed that semantic cases were significantly more likely to be sporadic (P = .03).

All cases were assessed before the NINETY criteria were published. Therefore, we applied these criteria (subtypes FTD, SD, and progressive nonfluent aphasia) retrospectively. All semantic cases and 10 of 13 behavioral cases fulfilled the criteria. For 2 behavioral cases there was insufficient information available, and 1 patient had blackouts of uncertain cause at onset but otherwise had a typical FTD presentation. None of the mixed amnesic/behavioral cases met FTD criteria, and there was insufficient information available in the remaining cases.

**BEHAVIORAL CASES**

Disinhibition and apathy occurred with similar frequency in familial and sporadic cases. Two patients (sporadic cases) later developed features of MND. Initial neu-
Neurological examination results revealed a range of only minor nonspecific abnormalities outside cognition in 8 patients (of which 5 cases were familial).

Neuropsychological testing results (available for 11 cases) demonstrated executive dysfunction in all cases. Ten of 11 cases also had weak or impaired memory on formal testing.

Language difficulties (predominantly in naming) were noted in 9 of 10 assessed patients, and perceptual difficulties were observed in 2 of 10 patients, both assessed when they were moderately affected.

**SEMANTIC CASES**

Neurological examination abnormalities were confined to cognition. Neuropsychological testing results demonstrated profound naming difficulties, fluent dysphasia, and associative agnosia. Episodic memory was impaired in only 3 patients and was less affected than semantic memory. Executive and perceptual deficits were absent. Two cases had early minor behavioral changes.

**MIXED AMNESIC AND BEHAVIORAL CASES**

Early memory problems were as prominent in the history as behavioral disturbance, causing diagnostic difficulty. Four patients were clinically diagnosed with AD. Four patients had neuropsychological testing, showing impairment of memory (all 4 patients) and impairment of executive function (3 of 3 patients assessed), but preservation of perceptual skills (4 patients). Behavioral changes included apathy, irritability, and agitation.

**OTHER PRESENTATIONS**

One patient had early parietal deficits revealed by neuropsychological testing, along with behavioral features. In 2 cases, language disturbance and behavioral change were of similar dominance in the history, but information was limited. One patient with features of corticobasal degeneration has been previously described.18

**ATYPICAL FEATURES**

Atypical features included visual hallucinations (1 case), nonepileptiform blackouts (2 cases), emotional lability (4 cases), early paranoia (2 cases), and tinnitus (2 cases). Three behavioral patients also had a degree of speech and language disturbance. Four patients showed neuropsychological evidence of parietal dysfunction, including dyscalculia, dysgraphia, and visuospatial and visuoperceptual impairments, in addition to other deficits.

**IMAGING AND ELECTROENCEPHALOGRAPHIC FINDINGS**

Electroencephalograms were available for 19 cases. Results of 13 patients (4 familial) were normal, 4 patients (none familial) showed minor disturbance of background rhythm, and 2 patients (both familial) were of

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**Table 1. Age at Onset and Disease Duration**

<table>
<thead>
<tr>
<th>Clinical Group</th>
<th>Total No. of Cases</th>
<th>No. of Familial Cases</th>
<th>Age at Onset, Mean (SD), y</th>
<th>Age at Death, Mean (SD), y</th>
<th>Disease Duration, Mean (SD), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>13</td>
<td>5</td>
<td>56.6 (6.7)</td>
<td>62.0 (7.4)</td>
<td>5.4 (2.7)</td>
</tr>
<tr>
<td>Semantic</td>
<td>7</td>
<td>0</td>
<td>56.9 (7.1)</td>
<td>70.0 (5.1)</td>
<td>13.1 (2.7)</td>
</tr>
<tr>
<td>Mixed amnesic/behavioral</td>
<td>5</td>
<td>3</td>
<td>54.2 (4.9)</td>
<td>62.7 (6.3)</td>
<td>8.5 (1.5)</td>
</tr>
<tr>
<td>Mixed language/behavioral</td>
<td>2</td>
<td>1</td>
<td>48.0</td>
<td>57.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Parietal</td>
<td>1</td>
<td>1</td>
<td>45</td>
<td>62.3</td>
<td>17.3</td>
</tr>
<tr>
<td>CBD</td>
<td>1</td>
<td>1</td>
<td>64</td>
<td>67.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

**Table 2. Behavioral Features Noted at or Shortly After Presentation**

<table>
<thead>
<tr>
<th>Clinical Group</th>
<th>Any Early Behavioral Change</th>
<th>Disinhibition</th>
<th>Apathy</th>
<th>Excess Sleep</th>
<th>Paranoia</th>
<th>Self-neglect</th>
<th>Rigid/Obsessive/Compulsive Behavior</th>
<th>Emotional Lability</th>
<th>Excessive Alcohol Intake</th>
<th>Excessive Eating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic (n = 18)</td>
<td>13</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Familial (n = 11)</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>By major feature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral</td>
<td>13</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Semantic</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amnesic/behavioral</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Corticobasal degeneration features</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Language/behavioral</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parietal</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>

Abbreviation: CBD, corticobasal degeneration.
low amplitude. Twenty-three patients (9 familial) had brain imaging performed: 10 patients had computed tomography and 13 patients had magnetic resonance imaging. Atrophy was noted in 22 patients, although focal atrophy was specifically reported in only 10 patients (2 of which were familial). Asymmetry was noted in 10 patients (4 familial and 6 sporadic).

A range of clinical phenotypes was seen in both familial and sporadic cases of DUI. These phenotypes broadly fell within the clinical spectrum of FTLD, although a degree of overlap between syndromes occurred with 6 cases showing mixed features and not meeting the Neary criteria for FTLD. The definition of familial cases by family history (minimum of 3 affected members in 2 generations) is necessary, as the causative gene(s) for this pathological abnormality are yet to be identified. The lack of tau mutations in familial cases is therefore as expected.

Familial and sporadic cases with a behavioral presentation showed no apparent differences in clinical features; positive features, such as disinhibition, and negative features, such as apathy, occurred in both groups. The similar ages at onset and disease durations also suggest no significant difference between familial and sporadic disease when it manifests with early behavioral change.

Statistical analysis supported the finding of a greater proportion of sporadic cases with a semantic presentation, and indeed we are not aware of any reports of familial FTLD with an SD phenotype. If confirmed, this may reflect a genetic influence on the distribution of pathological change. While an SD diagnosis may occasionally be overlooked, that is unlikely here as this center had a particular interest in this entity even before the publication of the Neary criteria.

Cases with a mixed amnesic/behavioral picture present diagnostic difficulty owing to phenotypic overlap with AD. Frontal features may occur in pathologically confirmed AD, but some cases of apparent AD with frontal features may have DUI.

Poor memory test scores can be difficult to interpret in patients with clinical presentations suggestive of FTLD, and the scores should not be overinterpreted. Neary et al highlight that while FTD patients are not clinically amnesic, they may perform inefficiently on formal memory tests.

The finding of parietal dysfunction in 4 cases (early in 1 case) suggests that DUI may sometimes present with features other than those of the 3 recognized presentations of FTLD. The distribution of the pathological change in 8 of the 11 familial cases has been previously reported. Significant reductions in parietal (as well as frontotemporal) cortical width and neuronal density in these cases were found when compared with normal controls. If further studies confirm that early parietal dysfunction may occur with this pathological abnormality, there would be significant implications for accurate clinical diagnosis.

Only 2 patients went on to develop features of MND. Those with predominantly motor features of MND would probably not have been referred to a cognitive disorders clinic. Current evidence favors a clinicopathological continuum relating MND and DUI. None of our patients had a family history of MND, although pedigrees have been reported with some individuals affected by FTD and others by MND.

The electroencephalograms from patients with FTLD are expected to be normal, although this was so in only two thirds of cases for which electroencephalograms were available. Abnormalities were nonspecific. Focal atrophy and asymmetry were noted on brain imaging in about half of the cases, which included both familial and sporadic cases. A relatively low number of patients underwent magnetic resonance imaging examination (13 of 23 patients), possibly explaining why focal atrophy was not noted in the remainder.

Familial patients presented with behavioral disturbances, with additional amnesic features in a minority, while semantic dementia was only found in sporadic cases. Within the behavioral group, clinical features were indistinguishable in sporadic and familial cases. A range of phenotypes was found in both familial and sporadic cases, some with features atypical for FTD, emphasizing the importance of pathological confirmation of diagnosis.

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REFERENCES


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**Trial Registration Required**

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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.