Frontotemporal Lobar Degeneration Without Lobar Atrophy

Keith A. Josephs, MST, MD; Jennifer L. Whitwell, PhD; Clifford R. Jack, MD; Joseph E. Parisi, MD; Dennis W. Dickson, MD

Background: Frontotemporal lobar degeneration with ubiquitin-only–immunoreactive neuronal inclusions (FTLD-U) is the most common form of frontotemporal dementia. Neuronal loss and gliosis in cornu ammonis 1 and the subiculum of the hippocampus are features of hippocampal sclerosis (HpScl), which occurs in many cases of FTLD-U.

Objective: To determine if there were any clinical or magnetic resonance imaging correlates of HpScl in FTLD-U.

Design: We reviewed demographics and clinical features of 24 cases of FTLD-U and subjectively assessed the severity of neuronal loss and frequency of ubiquitin-positive neuronal lesions in the frontal and temporal cortices and the dentate gyrus of the hippocampus.

Setting: Mayo Clinic, Rochester, Minn.

Patients: Twenty-six cases were identified from the medical records linkage system query that met clinical criteria and had autopsy material available for additional studies. Two cases were excluded from further analysis after pathologic studies revealed coexisting Alzheimer disease, leaving 24 cases included in the study. Cases were subdivided based on the presence or absence of HpScl.

Main Outcome Measures: Patterns of gray matter atrophy were assessed in cases of FTLD-U with and without HpScl using voxel-based morphometry.

Results: Six of the 24 cases of FTLD-U did not have HpScl. No differences were found in demographic or clinical features, including disease duration, between cases with and without HpScl; however, voxel-based morphometry analysis revealed minimal cortical atrophy in cases without HpScl, which was significantly different from the pattern of moderate to severe frontal and temporal lobe atrophy in FTLD-U with HpScl. This finding was in keeping with histopathologic observations.

Conclusions: Despite similar clinical features, cases of FTLD-U with HpScl differ from those without HpScl with respect to pathologic findings and structural imaging. Specifically, FTLD-U without HpScl showed on average minimal or no cortical atrophy, even at end-stage disease. Consequently, FTLD-U without HpScl does not conform to the proposed FTLD staging scheme, is underrecognized, and may have different genetic and environmental underpinnings.

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Several distinct clinical syndromes characterized by progressive neurologic deterioration with prominent behavioral and language impairment are subsumed under the term frontotemporal dementia (FTD).1 The cardinal feature of FTD is atrophy of the frontal and temporal lobes, first described more than a century ago by Pick.2 Magnetic resonance imaging (MRI) studies of the head show frontal and temporal lobe atrophy,3,4 and at autopsy, the frontal and temporal lobes are atrophic and show neuronal loss and gliosis on histologic analysis. The term frontotemporal lobar degeneration (FTLD) has been used to describe the entire group of neurodegenerative disorders.2 The most common histopathologic finding in FTLD is the presence of neuronal cytoplasmic and occasionally intranuclear inclusions, as well as dystrophic neurites, that are immunoreactive for ubiquitin but negative for tau and α-synuclein.6,7 Cases with this histopathologic finding are referred to as FTLD-U.6,8 Cases with similar pathologic findings but also evidence of upper or lower motor neuron degeneration (MND) are referred to as FTLD-MND.6,8,9 A common finding in many cases of FTLD-U is neuronal loss and gliosis in vulnerable regions of the hippocampus, including cornu ammonis (CA) 1 and the subiculum, with relative sparing of the resistant sectors CA4, CA3, and CA2.10-12 This pattern of neuronal loss is known as hippocampal sclerosis (HpScl).13,14 In many but not all cases of FTLD-U with HpScl, neuronal loss and gliosis extend to other medial temporal lobe structures, such as the amygdala. However, not all cases of FTLD-U have HpScl, and to our knowledge no reports...
have explored clinical and imaging differences between cases with and without HpScl in FTLD-U. Our study addressed this issue by comparing cases of FTLD-U with and without HpScl with respect to clinical features and MRI and histopathologic findings.

METHODS

The medical records linkage system of the Mayo Clinic in Rochester was queried for autopsy-confirmed cases of FTLD. These archived cases were reanalyzed clinically and pathologically using the most recent immunohistochemical techniques. A final pathologic diagnosis was made according to the proposed criteria for FTLD. A total of 26 cases of FTLD-U were available for this study.

CLINICAL ASCERTAINMENT

A behavioral neurologist with expertise in FTD (K.A.J.) reviewed the medical records of all 26 cases to abstract demographic and clinical information. On the basis of all available clinical information, FTD was subclassified using current criteria. The age at onset was defined as the age of the patient at the time of the first symptom onset as reported in the medical records. The illness duration was defined as the difference between the age at death and the age at symptom onset. Records were reviewed for cardiovascular risk factors, including hypertension, coronary artery disease, a history of smoking, and other features that have been included in other studies of HpScl.

PATHOLOGIC ANALYSIS

The pathologic criteria for FTLD-U have been previously described in detail. Briefly, FTLD-U was diagnosed if there was a history of FTD and histologic findings of ubiquitin-positive but tau-negative and α-synuclein-negative neuronal inclusions in the frontal or temporal cortices or in the dentate gyrus of the hippocampus. All cases were carefully screened for the presence of histologic evidence of MND, so-called FTLD-MND, in the motor cortex, descending corticospinal tract, brainstem motor neurons, and spinal cord motor neurons if spinal cord was available, as previously described in detail. Any case with evidence of MND was not included.

The presence of HpScl was assessed in all cases by one neuropathologist (D.W.D.) in coronal sections of the hippocampus using a 4-point grading scale as follows: 0, no overt neuronal loss or gliosis; 1, mild neuronal loss, usually associated with microvacuolation in superficial cortical layers; 2, moderate neuronal loss and gliosis that affects all cortical layers and associated with thinning of the cortical ribbon; and 3, end-stage neuronal loss and gliosis with severe thinning of the cortical ribbon producing so-called status spongiosis. Sections are from the frontal neocortex (hematoxylin-eosin, original magnification ×10).

Figure 1. The 4-point grading scale used for the assessment of neuronal loss. The scores are as follows: 0, no overt neuronal loss or gliosis (A); 1, mild neuronal loss, usually associated with microvacuolation in superficial cortical layers (B); 2, moderate neuronal loss and gliosis that affects all cortical layers and associated with thinning of the cortical ribbon (C); and 3, end-stage neuronal loss and gliosis with severe thinning of the cortical ribbon producing so-called status spongiosis (D). Sections are from the frontal neocortex (hematoxylin-eosin, original magnification ×10).

The severity of ubiquitin abnormalities was assessed in tissue sections immunostained with ubiquitin (clone Ubi-1 [MAB1510], 1:250; Chemicon, Temecula, Calif) as follows: 0 indicates no inclusions or neurites; 1, sparse inclusions or neurites; 2, a moderate number of inclusions and neurites; and 3, frequent inclusions and neurites.

IMAGE ANALYSIS

Seventeen cases of FTLD-U had at least 1 volumetric MRI study. These patients were matched for age and sex to a group of 17 controls. Volumetric MRI studies were obtained using a protocol described previously. Patterns of gray matter (GM) atrophy were analyzed using an optimized method of voxel-based morphometry (VBM) in the SPM2 software package (http://www.fil.ion.ucl.ac.uk/spm). Customized templates and prior probability maps were generated from all study participants. To create the customized template and prior probability maps, all study images (n=34) were first normalized to the Montreal Neurological Institute (MNI) template using a 12-df affine registration and segmented into GM, white matter, and cerebrospinal fluid using the MNI prior probability maps. The segmented GM images were then normalized using a nonlinear registration to the MNI GM prior probability.
map, the registration parameters were applied to the original whole head, and the images were segmented using the MNI prior probability maps. Average images were created of the whole head, GM, white matter, and cerebrospinal fluid and spatially smoothed using an 8-mm full width at half maximum smoothing kernel. All study images were then normaliz ed to the customized whole-brain template using a 12-df affine registration. Images were segmented using the customized prior probability maps, and the GM images were normalized to the custom GM prior probability maps using a nonlinear normalization. The normalization parameters were then applied to the original whole head, and the images were segmented once again using the customized prior probability maps. All images were modulated and smoothed with an 8-mm full width at half maximum smoothing kernel. A reinitialization routine was also implemented. This approach uses the parameters from the initial normalization to the MNI template (performed to generate the customized template) to initialize the normalization to the custom template. The smoothed modulated GM images were compared between the FTLD-U with HpScl group and the FTLD-U without HpScl group and controls, using a 2-sided t test at an uncorrected threshold of P <.001.

STATISTICAL ANALYSIS

Statistical analysis was conducted using JMP software, version 6.0 (SAS Institute, Cary, NC) with statistical significance set at P <.05. The Wilcoxon rank sum test was used to compare

<table>
<thead>
<tr>
<th>Feature</th>
<th>HpScl</th>
<th>No HpScl</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M:F</td>
<td>9:9</td>
<td>5:1</td>
<td>14:10</td>
</tr>
<tr>
<td>Age at death, median (range), y</td>
<td>70 (52-93)</td>
<td>57.5 (56-74)</td>
<td>66 (52-93)</td>
</tr>
<tr>
<td>Disease duration, median (range), y</td>
<td>8 (2-13)</td>
<td>9 (3-13)</td>
<td>8 (2-13)</td>
</tr>
<tr>
<td>Immediate family history</td>
<td>10</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Education, median (range), y</td>
<td>16 (8-20)</td>
<td>16 (14-17)</td>
<td>16 (8-20)</td>
</tr>
<tr>
<td>STMS score, median (range)</td>
<td>32 (17-36)</td>
<td>26 (20-36)</td>
<td>31 (17-36)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: FTLD-U, frontotemporal lobar degeneration with ubiquitin-only–immunoreactive neuronal inclusions; HpScl, hippocampal sclerosis; STMS, Short Test of Mental Status.

*: Data are presented as number of patients unless otherwise indicated.

Table 2. Clinical Features of Patients With FTLD-U Without HpScl

<table>
<thead>
<tr>
<th>Case No./Sex</th>
<th>Disease Duration, y</th>
<th>Age at Death, y</th>
<th>Presenting Symptoms</th>
<th>Prominent Symptoms During Disease Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>12</td>
<td>74</td>
<td>Socially withdrawn</td>
<td>Irritable, limited insight, lack of initiative, neglect of personal hygiene, poor judgment, comprehension problems</td>
</tr>
<tr>
<td>2/M</td>
<td>4</td>
<td>56</td>
<td>Inattentiveness, personality change</td>
<td>Memory loss, lack of interest, neglect of personal hygiene, inappropriate behaviors</td>
</tr>
<tr>
<td>3/M</td>
<td>13</td>
<td>58</td>
<td>Personality change, loss of insight</td>
<td>Socially withdrawn, lack of initiative, altered eating habits, obsessed with cleaning plates</td>
</tr>
<tr>
<td>4/M</td>
<td>3</td>
<td>57</td>
<td>Word-finding difficulties</td>
<td>Reading and writing difficulties, loss of word meaning, poor comprehension</td>
</tr>
<tr>
<td>5/F</td>
<td>11</td>
<td>56</td>
<td>Inattentiveness, trouble with organization</td>
<td>Socially withdrawn, weight gain, poor judgment, disinhibited</td>
</tr>
<tr>
<td>6/M</td>
<td>7</td>
<td>59</td>
<td>Personality change, odd behaviors, compulsions</td>
<td>Obsessed with certain foods, lack of insight, decreased concentration</td>
</tr>
</tbody>
</table>

Abbreviations: FTLD-U, frontotemporal lobar degeneration with ubiquitin-only–immunoreactive neuronal inclusions; HpScl, hippocampal sclerosis.

RESULTS

CLINICAL FINDINGS

A total of 26 cases were identified from the medical records linkage system query that met clinical criteria and had autopsy material available for additional studies. Two cases were excluded from further analysis after pathologic studies revealed coexisting Alzheimer disease; neither of these excluded cases had had volumetric MRI studies. The demographic and clinical features of the 24 patients are summarized in Table 1. All cases had typical features of FTD and met research diagnostic clinical criteria for FTD.2 Twenty cases were classified as the behavioral variant of FTD and 4 cases as primary progressive aphasia, using published criteria.1 More than half of the patients had a family history in a first-degree relative of motor neuron disease or dementia, with 1 patient with autopsy-confirmed progressive supranuclear palsy in a first-degree relative. Ten patients had a history of smoking, 7 had hypertension, 2 had chronic obstructive pulmonary disease, and 1 each had peripheral vascular disease, obstructive sleep apnea, and seizures.

PATHOLOGIC ANALYSIS

Of the 24 patients, 6 had no evidence of HpScl (Table 2 and Table 3). Five of the 6 cases were classified as the behavioral variant of FTD and the other as primary progressive aphasia (Table 2).2 No significant difference was found between patients with and without HpScl with respect to sex, age at death, disease duration, family history of neurodegenerative disease, history of smoking, coronary artery disease, hypertension, or obstructive sleep apnea. There was, however, a trend for patients with HpScl to be older (70 years vs 57 years) (P = .05) and to have a
history of hypertension ($P= .07$). Surprisingly, in 2 of the 6 patients without HpScl, frontal and temporal lobe atrophy was absent on review of histologic sections. In none of the other 4 patients without HpScl was there ever more than, on average, mild atrophy that affected the combined frontal and temporal cortices. Overall, the patients without HpScl had significantly less temporal lobe atrophy compared with the patients with HpScl (median histologic atrophy score, 0.5 vs 3.0; $P= .003$), with a similar trend noted for the frontal lobe atrophy (0.5 vs 2.0; $P= .07$). In contrast, in the patients with HpScl, 61% had moderate to severe atrophy that affected the frontal or temporal lobes; 17% had severe atrophy that affected both regions. With the exception of 2 patients with HpScl, the temporal lobe was equal or more severely affected than the frontal lobe ($P= .008$). In the patients without HpScl, no correlation was found between the degree of cortical atrophy and disease duration. However, disease duration correlated with temporal lobe atrophy in patients with HpScl ($r= .80; P< .001$).

No correlation was found between the degree of cortical atrophy and the number of cortical ubiquitin-positive inclusions ($r= .26$). Similar to patients with HpScl, in patients without HpScl, there were moderate to frequent neuronal inclusions in the dentate gyrus as well as in the frontal and temporal neocortex, even in the 2 patients without frontal or temporal lobe atrophy. Of the 18 patients with HpScl, 11 had neuronal loss and gliosis that affected both the CA1 and the subiculum, whereas HpScl limited to the subiculum was found in 7 patients.

**IMAGE ANALYSIS**

Twelve patients with HpScl and 5 patients without HpScl received volumetric MRI. No significant difference was found between the patients with and without HpScl with respect to age at time of MRI, time between symptom onset and MRI, and time between MRI and death (Table 4).

The FTLD-U cases without HpScl showed little GM atrophy compared with controls. Small regions of loss were scattered in the frontal and temporal lobes (uncorrected for multiple comparisons; $P< .001$) (Figure 2A), but none of these regions survived correction for multiple comparisons at $P< .05$. In contrast, the cases with HpScl showed a pattern of GM atrophy that affected predominantly the temporal lobes (but also involved the frontal lobes) compared with controls (Figure 2B). Atrophy in the temporal lobe was noticeably asymmetric, with greater involvement on the left side. Regions of loss that survived the correction for multiple comparisons were found in the temporal lobe ($P< .05$). A direct comparison between the 2 groups showed greater atrophy bilaterally in the hippocampus, orbitofrontal cortex, and patchy regions in the frontal lobes in the FTLD-U with HpScl group (uncorrected; $P< .01$) (Figure 2C).

**COMMENT**

In this study we demonstrated that most patients (approximately 75%) with FTLD-U have HpScl, and these patients showed a typical pattern of frontal and temporal lobe atrophy. In contrast, patients without HpScl generally had minimal or no frontotemporal lobar atrophy.

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**Table 3. Summary of Neuropathologic Features of Patients With FTLD-U With and Without HpScl**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>FTLD-U Without HpScl</th>
<th>FTLD-U With HpScl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cortex Degeneration or Atrophy</td>
<td>Ubiquitin-Positive Inclusions</td>
</tr>
<tr>
<td></td>
<td>Frontal</td>
<td>Temporal</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4. Demographic Features of the Patients Who Had FTLD-U With and Without HpScl According to Volumetric MRI**

<table>
<thead>
<tr>
<th>Feature</th>
<th>HpScl (n = 12)</th>
<th>No HpScl (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M:F</td>
<td>5:7</td>
<td>4:1</td>
</tr>
<tr>
<td>Age at scan, median (range), y</td>
<td>64 (51-80)</td>
<td>55 (50-70)</td>
</tr>
<tr>
<td>Time from onset to MRI, median (range), y</td>
<td>2 (1-6)</td>
<td>5 (1-6)</td>
</tr>
<tr>
<td>Time from MRI to death, median (range), y</td>
<td>4 (1-6)</td>
<td>4 (2-8)</td>
</tr>
</tbody>
</table>

**Abbreviations:** FTLD-U, frontotemporal lobar degeneration with ubiquitin-only–immunoreactive neuronal inclusions; HpScl, hippocampal sclerosis; MRI, magnetic resonance imaging.
Figure 2. Regions of significant loss in the study participants with frontotemporal lobar degeneration with ubiquitin-immunoreactive neuronal inclusions. Sections from patients without hippocampal sclerosis (HpScl) (A) and those from patients with HpScl (B) are compared with controls, overlaid on a 3-dimensional rendering of a healthy control (uncorrected for multiple comparisons; $P < .001$). A representative coronal section (C) illustrates greater hippocampal atrophy in the patients with HpScl compared with those without HpScl (uncorrected; $P < .01$).
To our knowledge, this is the first report of VBM combined with histopathologic correlates of FTLD-U in which a subgroup of patients have been identified who exhibit little or no cortical atrophy, even at autopsy. Interestingly, although these cases showed minimal atrophy, they often had moderate to frequent ubiquitin-immunoreactive inclusions in the cortex and dentate gyrus, suggesting that the presence of ubiquitin-immunoreactive inclusions in FTLD-U is not a secondary process or dependent on neuronal loss and atrophy.

The finding of minimal atrophy in FTLD-U without HpScl was demonstrated by VBM analysis of whole-brain MRI studies and histopathologic evaluation of histologic tissue sections from the frontal and temporal lobes. The VBM analysis was conducted approximately 5 years after symptom onset, whereas histopathologic analysis was conducted on autopsy material collected approximately 9 years after symptom onset. Two patients had no histopathologic evidence of atrophy, one of whom survived for 11 years after symptom onset. No difference was found in disease duration between cases of FTLD-U with and without HpScl, suggesting that the absence of HpScl is not related to disease duration. It is also unlikely that any of the cases without HpScl had FTLD-MND abnormalities because this was specifically screened for, plus the disease durations were much longer than are typically reported in FTLD-MND. Therefore, FTLD-U without HpScl does not conform to the proposed pathologic staging scheme for FTLD, which indicates that progressive atrophy is associated with disease duration.

There are a few possible explanations for our findings. One explanation could be that the absence of significant atrophy on VBM in FTLD-U without HpScl is an artifact and due to small numbers in that group. This is unlikely given that previous studies have also reported significant patterns of loss in small numbers of patients. In addition, we reviewed the pattern of atrophy in 5 randomly selected cases with HpScl and found strong patterns of temporal and frontal lobe involvement. Another explanation could be that HpScl and atrophy are related to aging. This is also unlikely because many of our patients with HpScl and lobar atrophy were younger than those without HpScl, and conversely many patients without HpScl or lobar atrophy were older than those with HpScl. The most likely explanation is that FTLD-U represents a spectrum of disease processes with different genetic and environmental underpinnings. Cases with little lobar atrophy are not widely recognized but have been alluded to in prior studies. Interestingly, this study also showed that the density and distribution of cortical neuronal ubiquitin-immunoreactive inclusions did not correlate with the amount of atrophy in FTLD-U. Patients without HpScl, and hence minimal atrophy, had a moderate to frequent inclusion density in the cortex and dentate gyrus. This finding suggests that the presence of ubiquitin-positive neuronal inclusions is not closely linked to neuronal loss. It has been suggested that ubiquitin-positive neuronal inclusions may not play a critical role in the neurodegenerative process in FTLD-U. However, in the absence of neuronal loss, ubiquitin-positive neuronal inclusions may be playing a role in the manifestation of clinical features of FTD.

The strengths of our study are the availability of detailed histopathologic analysis on all our case patients and the use of the unbiased and automated technique of VBM. Limitations include the relatively small number of cases without HpScl and a possible bias as to which patients underwent autopsy at our institution.

In summary, the present report demonstrates an association between HpScl and frontal and temporal lobe atrophy in FTLD-U. Patients without HpScl showed, on average, minimal or no cerebral atrophy and did not conform to the pathologic staging scheme proposed for FTLD-U. These results argue that FTLD-U represents a critical role in the neurodegenerative process in FTD-U. Patients without HpScl, and hence minimal atrophy, had a moderate to frequent inclusion density in the cortex and dentate gyrus. This finding suggests that the presence of ubiquitin-positive neuronal inclusions is not closely linked to neuronal loss. It has been suggested that ubiquitin-positive neuronal inclusions may not play a critical role in the neurodegenerative process in FTLD-U. However, in the absence of neuronal loss, ubiquitin-positive neuronal inclusions may be playing a role in the manifestation of clinical features of FTD.

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spectrum of disease processes. Further studies are needed to determine if this subset of FTLD-U has a unique genetic underpinning.

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REFERENCES


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