Clinically Undetected Motor Neuron Disease in Pathologically Proven Frontotemporal Lobar Degeneration With Motor Neuron Disease

Keith A. Josephs, MST, MD; Joseph E. Parisi, MD; David S. Knopman, MD; Bradley F. Boeve, MD; Ronald C. Petersen, MD, PhD; Dennis W. Dickson, MD

Background: Frontotemporal lobar degeneration with motor neuron disease (FTLD-MND) is a pathological entity characterized by motor neuron degeneration and frontotemporal lobar degeneration. The ability to detect the clinical signs of dementia and motor neuron disease in pathologically confirmed FTLD-MND has not been assessed.

Objectives: To determine if all cases of pathologically confirmed FTLD-MND have clinical evidence of frontotemporal dementia and motor neuron disease, and to determine the possible reasons for misdiagnosis.

Method: Review of historical records and semiquantitative analysis of the motor and extramotor pathological findings of all cases of pathologically confirmed FTLD-MND.

Results: From a total of 17 cases of pathologically confirmed FTLD-MND, all had clinical evidence of frontotemporal dementia, while only 10 (59%) had clinical evidence of motor neuron disease. Semiquantitative analysis of motor and extramotor pathological findings revealed a spectrum of pathological changes underlying FTLD-MND. Hippocampal sclerosis, predominantly of the subiculum, was a significantly more frequent occurrence in the cases without clinical evidence of motor neuron disease (P<.01). In addition, neuronal loss, gliosis, and corticospinal tract degeneration were less severe in the other 3 cases without clinical evidence of motor neuron disease.

Conclusions: Clinical diagnostic sensitivity for the elements of FTLD-MND is modest and may be affected by the fact that FTLD-MND represents a spectrum of pathological findings, rather than a single homogeneous entity. Detection of signs of clinical motor neuron disease is also difficult when motor neuron degeneration is mild and in patients with hippocampal sclerosis.

Arch Neurol. 2006;63:506-512

For editorial comment see page 489

As with the clinical syndrome of FTD-MND, pathologic studies have independently identified cases with frontotemporal lobar degeneration and features of typical motor neuron degeneration (FTLD-MND). Therefore, FTLD-MND currently represents a distinct pathological entity.

During the last decade, we and others have observed cases that at autopsy have had histologic evidence of mixed features of FTLD and MND. Furthermore, clinical studies have revealed an increased frequency of MND in cases of FTD, and an increased frequency of FTD in cases of MND. Unfortunately, studies correlating the clinical signs of FTD-MND with the pathologic diagnosis of FTLD-MND are limited. We therefore set out to assess the association of clinical features of FTD-MND and pathologically confirmed FTLD-MND.

METHODS

CASE ASCERTAINMENT

The Mayo Clinic (Rochester, Minn) pathologic database was searched to identify all cases that were autopsied with a pathological diagnosis of Pick disease, FTLD-MND, or demen-
PATHOLOGICAL ANALYSIS

In all cases identified from the previously described electronic search, slides of frontal, temporal, and parietal neocortex, hippocampus, basal ganglia, thalamus, midbrain,pons, medulla, and cerebellum were reviewed. In all cases, sections were studied with hematoxylin-eosin (HE) and modified Bielschowsky staining, as well as other stains needed for routine evaluation, including immunohistochemistry for markers of glial pathology. Those stains include glial fibrillary acidic protein stain, astrocyte antigens such as glial fibrillary acidic protein and macrophages were also available. Neuronal loss and gliosis were assessed semiquantitatively in the hypothalamic and the anterior horn cells of the spinal cord with a + point scale (0 = none; 1 = focal neuronal loss and focal microgliosis; 2 = extensive neuronal loss with microgliosis and empty cell bodies containing macrophages; 3 = almost complete loss of motor neurons with atrophy and astrocytic fibrillar gliosis). The presence of Bunina bodies was assessed on HE staining in motor neurons of the hypoglossal nucleus and anterior horn cells. Lewy body-like hyaline inclusions were assessed on HE staining and ubiquitin immunostains. Neuronal inclusions were assessed on ubiquitin immunostains. The corticospinal tract was assessed for Wallerian degeneration using HE (presence of atrophy with vacuolation and lipid-laden macrophages), myelin staining ( pallor on Luxol fast blue), or macrophage stains (increased ameboid microglia) paying special attention to the pyramids in the medulla and the lateral funiculi in the spinal cord. The severity of corticospinal tract degeneration was assessed semiquantitatively on a + -point scale (0 = none; 1 = very mild vacuolation and sparse macrophages; 2 = vacuolation with many lipid-laden macrophages; 3 = many lipid-laden macrophages with myelin loss; 4 = myelin-laden fiber loss, tract atrophy and astrocytic gliosis). Extramotor inclusions were assessed semiquantitatively with ubiquitin immunostains with a + -point grading scale (0 = none; 0-1 = isolated; 1 = sparse; 2 = moderate; 3 = frequent number). Histopathologic analysis was conducted by neuropathologists with expertise in degenerative neuropathology (J.E.P. and D.W.D.). Semiquantitative analysis was conducted by a neuropathologist (D.W.D.).

Frontotemporal lobar degeneration with motor neuron disease (Figure 1) was diagnosed if there was evidence of brainstem or spinal cord anterior horn cell degeneration or degeneration of the corticospinal tract, or both, in addition to histologic evidence of frontotemporal lobar degeneration. Histologic evidence of motor neuron degeneration included loss of large anterior horn cells in the spinal cord or hypoglossal motor neurons plus (1) shrunken residual motor neurons, (2) evidence of neuronophagia, (3) Bunina bodies, or (4) ubiquitin-immunoreactive intraneuronal inclusions, including Lewy body-like hyaline inclusions, skeinlike inclusions, or pleomorphic cytoplasmic inclusions, which were grouped with skeinlike inclusions for the purpose of analysis. Evidence of frontotemporal lobar degeneration included the presence of superficial spongiosus, neuronal loss, and astrogliosis affecting predominantly layer II of the cortex, with or without the presence of ubiquitin- immunoreactive neuronal cytoplasmic inclusions. Neuronal intranuclear inclusions were not detected.

STATISTICAL ANALYSIS

Statistical analyses were performed with SigmaStat software (Systat Software Inc., Point Richmond, Calif). Univariate correlations for analysis of clinical and pathologic factors used Spearman rank order correlation analysis. A P value of less than .05 was considered significant.

RESULTS

We identified 18 cases that fulfilled pathological criteria for FTLD-MND, including presence of ubiquitin-immunoreactive neuronal inclusions in motor or extramotor neuronal populations or both in all cases. The ubiquitin-positive inclusions were negative for tau, α-synuclein, and neurofilament.

One case was removed from further analysis because of a clinical diagnosis of multiple sclerosis 20 years prior to death. The demographics of the other 17 cases are presented in Table 1. Of these, 13 (76%) were male. The mean age at onset and disease duration were 52 years and 2.3 years, respectively.

CLINICAL FEATURES

All patients had clinical features suggestive of frontotemporal dysfunction; however, only 10 cases carried a diagnosis of FTD-MND or a comparable diagnostic term (such as amyotrophic lateral sclerosis–dementia or dementia with MND) prior to death. Of the other 7 cases, 4 were diagnosed as FTD, 2 with a rapidly progressive dementing illness, and 1 as FTD vs Alzheimer disease. All 10 cases with a clinical diagnosis of FTD-MND had evidence of motor neuron disease on clinical examination, while the other 7 did not.

Two cases were initially diagnosed as FTD only (data not shown); however, they later developed signs of MND and were subsequently diagnosed as FTD-MND. One of these 2 cases (case 13) developed signs of MND approximately 45 months after the onset of symptoms of FTD. In addition to the features in keeping with a diagnosis of FTD, 5 cases (cases 2, 3, 15, 16, and 17) also had symptoms of forgetfulness at initial examination. Memory impairment was not severe or more prominent than the other presenting features in any of these 5 cases.

PATHOLOGIC FINDINGS

Pathologic findings are presented in Table 2 and shown in Figure 1 and Figure 2. All cases met pathologic criteria for FTLD-MND. The hypoglossal nucleus was...
available for review in 16 cases. In 14 cases, the cervical spinal cord, but more often multiple levels of spinal cord, were available for study. Bunina bodies were found in 14 cases and skeinlike inclusions, pleomorphic inclusions, or Lewy body–like hyaline inclusions in motor neurons were found in 11 cases. Extramotor ubiquitin-positive neuronal inclusions were present in all cases, in the dentate fascia, neocortex, or both regions. Four cases had evidence of hippocampal sclerosis predominantly affecting the subiculum. Additional pathologic findings were present in a number of cases including 2 cases with skeletal muscle from the general autopsy; both had evidence of group atrophy with small acutely angulated fibers consistent with neurogenic atrophy.

SEMIQUANTITATIVE RESULTS

Semiquantitative results are presented in Table 2. Neuronal loss and gliosis of the hypoglossal nucleus and spinal anterior horn cells were variable and ranged from...
### Table 2. Semiquantitative Data of Motor and Extramotor Neuron Pathologic Findings in FTLD-MND

<table>
<thead>
<tr>
<th>Case, No.</th>
<th>Neuronal Loss and Gliosis†</th>
<th>Motor Inclusions (Ubiquitin)</th>
<th>Extramotor Inclusions (Ubiquitin)§</th>
<th>Corticospinal Degeneration‡</th>
<th>CA1, SUB</th>
<th>Alzheimer disease</th>
<th>Muscle neurogenic atrophy; none</th>
<th>Mild CAA and senile changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-1 +</td>
<td>1 +</td>
<td>No</td>
<td>No</td>
<td>4 +</td>
<td>3 +</td>
<td>1 +</td>
<td>SUB</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>3 +</td>
<td>3 +</td>
<td>1 +</td>
<td>0-1 +</td>
</tr>
<tr>
<td>3</td>
<td>2 + (BB)</td>
<td>1 + (BB)</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>3 +</td>
<td>3 +</td>
<td>3 +</td>
</tr>
<tr>
<td>4</td>
<td>1 + (BB)</td>
<td>NA</td>
<td>Yes</td>
<td>NA</td>
<td>2 +</td>
<td>1 +</td>
<td>0-1 +</td>
<td>0-1 +</td>
</tr>
<tr>
<td>5</td>
<td>1 + (BB; LBHI)</td>
<td>1 + (BB; LBHI)</td>
<td>Yes</td>
<td>No</td>
<td>1 +</td>
<td>1 +</td>
<td>0-1 +</td>
<td>0-1 +</td>
</tr>
<tr>
<td>6</td>
<td>1 + (BB)</td>
<td>2 + (BB)</td>
<td>No</td>
<td>Yes</td>
<td>1 +</td>
<td>1 +</td>
<td>0-1 +</td>
<td>0-1 +</td>
</tr>
<tr>
<td>7</td>
<td>1 + (BB)</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>0</td>
<td>1 +</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>2 + (BB; LBHI)</td>
<td>2 + (BB)</td>
<td>Yes</td>
<td>Yes</td>
<td>4 +</td>
<td>2 +</td>
<td>1 +</td>
<td>1 +</td>
</tr>
<tr>
<td>9</td>
<td>1 + (BB; LBHI)</td>
<td>1 + (BB)</td>
<td>Yes</td>
<td>Yes</td>
<td>4 +</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
</tr>
<tr>
<td>10</td>
<td>2 + (BB)</td>
<td>2 + (BB; LBHI)</td>
<td>NA</td>
<td>No</td>
<td>3 +</td>
<td>2 +</td>
<td>0-1 +</td>
<td>0-1 +</td>
</tr>
<tr>
<td>11</td>
<td>3 + (BB; LBHI)</td>
<td>2 + (BB; LBHI)</td>
<td>Yes</td>
<td>No</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
<td>0-1 +</td>
</tr>
<tr>
<td>12</td>
<td>2 + (BB)</td>
<td>2 + (BB; LBHI)</td>
<td>No</td>
<td>Yes</td>
<td>1 +</td>
<td>2 +</td>
<td>1</td>
<td>0-1 +</td>
</tr>
<tr>
<td>13</td>
<td>2 + (BB)</td>
<td>1 + (BB; LBHI)</td>
<td>Yes</td>
<td>No</td>
<td>1 +</td>
<td>1 +</td>
<td>0-1 +</td>
<td>0-1 +</td>
</tr>
<tr>
<td>14</td>
<td>1 + (BB; LBHI)</td>
<td>3 + (BB)</td>
<td>No</td>
<td>Yes</td>
<td>0</td>
<td>2 +</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1 + (LBHI)</td>
<td>2 + (LBHI)</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>2 +</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>1 + (BB)</td>
<td>1 + (BB)</td>
<td>No</td>
<td>No</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
</tr>
<tr>
<td>17</td>
<td>NA</td>
<td>1 + (BB)</td>
<td>NA</td>
<td>No</td>
<td>4 +</td>
<td>0-1 +</td>
<td>0-1 +</td>
<td>0-1 +</td>
</tr>
</tbody>
</table>

Abbreviations: BB, Bunina bodies; CA1, cornu ammonis 1; CAA, cerebral amyloid angiopathy; CST, corticospinal tract; FTLD-MND, frontotemporal lobar degeneration with motor neuron disease; LBHI, Lewy body–like hyaline inclusions; NA, not able to evaluate; SUB, subiculum.

*Group 1 (cases 1-7); group 2 (cases 8-17).
†For neuronal loss and gliosis, 0 = none; 1 = focal neuronal loss and focal microgliosis; 2 = extensive neuronal loss with microgliosis and empty cell beds containing macrophages; 3 = almost complete loss of motor neurons with atrophy and astrocytic fibrillary gliosis.
‡For severity of corticospinal tract degeneration, 0 = none; 1 = mild vacuolation and sparse macrophages; 2 = vacuolation with many lipid-laden macrophages; 3 = many lipid-laden macrophages with myelin loss; 4 = myelinated fiber loss, tract atrophy, and astrocytic gliosis.
§For extramotor inclusions, 0 = none; 0-1 + = isolated; 1 = sparse; 2 = moderate; 3 = frequent number.
‖Difficult to exclude Alzheimer disease neurites and inclusions.

Figure 2. A range of ubiquitin-positive inclusions in the dentate fascia including granular inclusions that are polarized or circumferential (A-C), as well as crescent-shaped inclusions (arrows), and round Pick body–like inclusions (arrowheads) (D-F). It should be emphasized that Pick body–like inclusions are the minority in frontotemporal lobar degeneration with motor neuron disease and granular-type inclusions are the most common (for all figures, hematoxylin-eosin stain was used unless otherwise noted, original magnification ×400).
absent to severe, and the severity of motor neuron pathologic features tended to correlate with clinical evidence of motor neuron disease \( (r=0.63, P<.05 \) for hypoglossal nucleus; \( r=0.57, P=.10 \) for anterior horn cells). Similarly, corticospinal tract degeneration ranged from absent to severe. Severity of corticospinal tract degeneration did not correlate with clinical signs of motor neuron disease or with severity of neuronal loss and gliosis in the hypoglossal nucleus and spinal anterior horn cells. There was a weak correlation between severity of corticospinal tract degeneration and cases with cortical ubiquitin-positive inclusions \( (r=0.50, P<.05) \). Extramotor ubiquitin-positive inclusions were absent to sparse in all cortical regions (except case 3 for which it was difficult to exclude Alzheimer disease neurites and inclusions), and absent to moderate in the dentate fascia of the hippocampus in almost all cases. In only 3 cases with hippocampal sclerosis were there frequent inclusions in the dentate fascia.

**CLINICOPATHOLOGIC CORRELATION**

We divided the cases into the following 2 groups: group 1 consisted of those cases that were not clinically diagnosed as FTD-MND (cases 1-7) and group 2 consisted of those that were clinically diagnosed as FTD-MND (cases 8-17). Four of the 7 cases from group 1, but none of the 10 cases from group 2, were found to have hippocampal sclerosis (3 of which also had frequent inclusions in the dentate fascia). In addition, the other 3 cases from group 1 (those without hippocampal sclerosis) were found to have minimal neuronal loss in hypoglossal nucleus and anterior horn cells as well as absent to minimal corticospinal tract degeneration. In contrast, the cases from group 2 had moderate to severe neuronal loss in the hypoglossal nucleus and anterior horn cells, moderate to severe corticospinal tract degeneration, or a mixture of both. Only case 16 from group 2 had minimal hypoglossal and anterior horn cell pathologic features. Spearman rank order correlation confirmed our observations and demonstrated that cases from group 1 were significantly more likely to have hippocampal sclerosis \( (r=0.70, P<.01) \). Patients from group 1 also tended to be female \( (r=0.44, P=.08) \) and hippocampal sclerosis was significantly correlated with female sex \( (r=0.67, P<.01) \).

This study demonstrates many important features regarding the co-occurrence of frontotemporal lobar degeneration and motor neuron disease.

As expected, all 17 cases had neuronal loss and gliosis affecting the frontal and temporal cortices in keeping with a diagnosis of frontotemporal lobar degeneration. In addition, all cases had pathologic evidence of one form of motor neuron degeneration. Therefore, they were appropriately categorized as FTLD-MND. Furthermore, all 17 cases met pathologic criteria for FTLD-MND.

The pathologic features of FTLD-MND were variable. Most cases had a mixture of lower motor neuron degeneration and corticospinal tract degeneration, similar to amyotrophic lateral sclerosis, and the majority had Bunina bodies, which are a histologic hallmark of amyotrophic lateral sclerosis. The severity of motor neuron degeneration was variable and ranged from absent to severe. We found that some cases had a predominance of corticospinal tract degeneration (cases 1, 2, 4, 8, 9, 10, and 17), while others had no corticospinal tract degeneration (cases 3, 7, 14, and 15). Extramotor ubiquitin-positive pathologic findings were minimal overall and mostly granular in all cases. Despite these differences, at the present time there is no way to distinguish between cases on the basis of extramotor ubiquitin-positive pathologic features or on the basis of predominant involvement of upper or lower motor neurons. A larger sample size would be needed to address possible clinically useful subtypes.

Four of the 7 cases without clinical evidence of motor neuron disease had hippocampal sclerosis, predominantly of the subicular region. Hippocampal sclerosis is a common feature of frontotemporal lobar degeneration with ubiquitin-only immunoreactive changes. In addition, 3 of these 4 cases had frequent ubiquitin-positive inclusions in the dentate fascia of the hippocampus, which is another common feature of frontotemporal lobar degeneration with ubiquitin-only immunoreactive changes. We therefore argue that FTLD-MND should be thought of as a spectrum of diseases and include FTLD-MND with hippocampal sclerosis and FTLD-MND without hippocampal sclerosis. Frontotemporal lobar degeneration with motor neuron disease with hippocampal sclerosis seemed strikingly similar to other frontotemporal lobar degenerations with some evidence of MND, while FTLD-MND without hippocampal sclerosis seemed strikingly similar to amyotrophic lateral sclerosis with some evidence of FTLD.

Fibers from the subiculum serve as the major output center for the hippocampus. Therefore, the cases with hippocampal sclerosis predominantly affecting the subiculum were likely to be more amnestic and impaired, which may explain why features of motor neuron disease were not clinically detected in these 4 cases with moderate motor neuron degeneration. Two of these 4 cases were so impaired that a mental status examination was not possible, the third was severely demented with a score of 13 out of 38 on the Short Test of Mental Status, and the fourth was moderately to severely demented with a score of 21 out of 38.

Three of the 7 cases with clinically undetected motor neuron disease, however, did not have hippocampal sclerosis. Semiquantitative analysis in these cases revealed very mild motor neuron pathological features. Therefore, another reason for inability to clinically detect motor neuron disease without the aid of detailed and specialized electrophysiologic studies or muscle biopsy may be very mild subclinal motor neuron degeneration. Routine electromyography had been completed in 2 of the 7 cases without clinical detection of motor neuron disease; in 1 case (case 7), electromyographic recordings had been taken 6 months prior to death and revealed normal findings.

All 17 cases had clinical evidence of frontotemporal impairment and met research criteria for a diagnosis of...
FTD. Five of the cases also had symptoms of mild forgetfulness in addition to the more prominent behavioral features. This is not surprising because memory loss is not an uncommon symptom or sign in FTD.

We also show in this study that when FTD and MND co-occur, signs of MND may not always be present early. In 2 cases, only features of dementia were noted early in the disease course and both initially carried a diagnosis of FTD. Both cases later developed signs of MND. Surprisingly, in 1 of the 2 cases (case 16), there was no evidence of MND until almost 4 years into the disease course. Prior studies had suggested that MND typically postdates the onset of dementia by 6 to 26 months. This study extends this interval to approximately 45 months.

We did not find any cases of spinal cord anterior horn cell degeneration without hypoglossal nucleus involvement and we do not know if such cases exist. Therefore, spinal cord harvesting and analysis are of the utmost importance for future clinicopathologic studies in cases with combined dementia and motor neuron disease.

Accepted for Publication: August 31, 2005.

Correspondence: Keith A. Josephs, MST, MD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (josephs.keith@mayo.edu).

Author Contributions: Study concept and design: Josephs, Parisi, Knopman, Boeve, and Petersen. Acquisition of data: Josephs, Parisi, Knopman, Boeve, and Dickson. Analysis and interpretation of data: Josephs, Parisi, Boeve, Petersen, and Dickson. Drafting of the manuscript: Josephs, Parisi, and Petersen. Critical revision of the manuscript for important intellectual content: Josephs, Parisi, Boeve, and Dickson. Obtained funding: Petersen. Administrative, technical, and material support: Josephs, Parisi, Boeve, and Dickson. Study supervision: Parisi and Knopman.

Funding/Support: This study was supported by grants P50-AG16574 and U01-AG06786 from the National Institute on Aging, Bethesda, Md, and by the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer’s Disease Research Programs of the Mayo Foundation.

Acknowledgment: Phospho-tau was a gift from Peter Davies, PhD, Albert Einstein College of Medicine, Bronx, NY.

REFERENCES