Different Patterns of Magnetic Resonance Imaging Atrophy for Frontotemporal Lobar Degeneration Syndromes

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Background: Frontotemporal lobar degeneration (FTLD) is an uncommon degenerative dementia that presents with focal cognitive and behavioral deficits.

Objective: To determine the correlation of the different presentations of FTLD with structural neuroimaging findings.

Design and Patients: In a blinded study, we retrospectively evaluated the clinical presentations and magnetic resonance imaging (MRI) patterns of atrophy in 59 patients with FTLD and 26 patients with probable Alzheimer disease at a memory disorders clinic.

Results: Analysis of variance revealed a significant difference in the patterns of atrophy in the FTLD and Alzheimer disease groups. Patients with FTLD presenting with altered personal conduct had significant bifrontal atrophy, whereas patients presenting with semantic dementia had significant left temporal and bifrontal atrophy compared with other groups. Disinhibited behavior and hyperphagia correlated with right frontal atrophy, and fluent, anomic aphasia correlated with left temporal atrophy.

Conclusions: We found that the type of clinical presentation of FTLD correlates with specific areas of atrophy. Our method of analysis may be useful to elicit further anatomic-behavioral relationships in degenerative brain disorders.

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FOCAL CORTICAL DEGENERATION produces a variety of clinical syndromes ranging from progressive perceptual impairments to neuropsychiatric disturbances. Frontotemporal lobar degeneration (FTLD) is a prototypical focal degenerative syndrome affecting the frontal and anterior temporal lobes, and because of the relative focal distribution of pathology, FTLD may be useful to examine anatomic-behavioral relationships. However, FTLD accounts for only about 3% to 10% of cases of dementia and has a prevalence of only about between 1.2 to 28.0 per 1 million population aged 30 to 70 years. Therefore, few large, blinded series have examined the relationship between the distribution of pathology and the clinical syndrome or symptomology. The 3 clinical syndromes of FTLD as defined by the consensus criteria are frontotemporal dementia (FD), progressive nonfluent aphasia (PAN), and semantic dementia (SD). Frontotemporal dementia is a progressive disturbance of personal and social conduct and usually shows bilateral frontal lobe abnormalities on neuroimaging. Progressive nonfluent aphasia constitutes the breakdown of the grammatical and lexical aspects of language, usually with left frontal abnormalities. Progressive left temporal lobe degeneration often results in SD, in which there is dissolution of the semantic aspects of language. Some cases of SD also have a visual agnosia or prosopagnosia that may reflect more right temporal involvement.

Our aim is to examine these anatomic-behavioral relationships in a large, blinded study. During a 10-year period, we obtained a large series of patients with FTLD (hereafter referred to as FTLD patients) by retrospectively evaluating clinical data and developed a method to blindly analyze the clinical symptomology and structural neuroimaging findings. We then examined for relationships between specific clinical syndromes or clinical signs and the pattern of atrophy on structural imaging.

METHODS

All patients had undergone evaluation at the Mayo Clinic, Jacksonville, Fla, from January 1, 1992, through June 30, 2001, and those who...
agreed were enrolled in the dementia patient registry. The registry was reviewed for the following diagnoses: frontotemporal dementia, Pick disease, frontal lobe dementia, SD, chronic progressive aphasia, and primary progressive aphasia. A control group with the diagnosis of probable Alzheimer disease (AD) was also selected. Only patients with available magnetic resonance imaging (MRI) findings were included in the study. Neurology and neuropsychology records at the time of the initial dementia evaluation were obtained, and any references to neuroimaging results or diagnostic impression were deleted. At least 2 of 3 neurologists (R.A.S., Z.A., and N.R.G.-R.) reviewed each patient’s records to obtain a clinical diagnosis of FTLD or non-FTLD. The reviewers were blinded to each other’s diagnosis and the neuroimaging data. If the diagnosis was FTLD, then a secondary diagnosis of FD, PA, or SD was assigned. A few patients presented with an overlap syndrome with prominent changes in personal conduct and language that were labeled as FD plus aphasia (FD+A). The Neary criteria were used as guidelines for these diagnoses. However, because many patients were seen before the publication of the Neary criteria, not all criteria for a specific diagnosis were necessarily documented. In particular, not all patients with SD were documented to have impairment of word meaning. Although we have not found this necessarily to be present early in the illness, it is highly likely that impairment of word meaning would have been present in most cases if they underwent formal evaluation, because it has been present when evaluated in our most recent cases. Non-FTLD patients were also assigned a more specific diagnosis, mostly probable AD, although a few received diagnoses of other dementias (such as AD) as FTLD or AD (n=7) were excluded from subsequent analysis. For a subtype diagnosis of FTLD vs non-FTLD, the clinical reviewers agreed on the initial review in 88 (96%) of 92 cases. For a subtype diagnosis of FTLD, reviewers agreed on 50 (85%) of 59 cases in the initial review. The cases with disagreement were brought to the third reviewer, and a final diagnosis of FTLD was reached in 59 patients and probable AD in 26 patients. The FTLD subtype diagnoses were FD in 18 patients, PA in 11, SD in 24, and FD+A in 6. Sex ratio, average age, duration of illness, and Mini-Mental State Examination scores are presented in Table 1. Patients who were not thought to have FTLD or AD (n=7) were excluded from subsequent analysis. Agreement for clinical symptoms ranged from 76% and temporal inferior. Anatomic landmarks were used to identify these areas. For example, frontal superior was designated as 1 axial imaging section above the most superior level of the frontal horn. Degrees of atrophy were normal (0), mild (1), moderate (2), or severe (3). The primary determinants of the degree of atrophy were the cortical sulcal enlargement in a given area or the size of a specific structure (such as the caudate head or the frontal horn). The average atrophy rating was computed for the right frontal, left frontal, right temporal, and left temporal areas. For example, the atrophy ratings for right frontal superior, right frontal middle, right frontal inferior, right frontal orbital, and right frontal horn were averaged for a total right frontal score. Only T1-weighted or fluid-attenuated inversion recovery images and axial sections were used for the exemplars. Using these exemplars, 2 neuroradiologists (D.F.B. and A.P.) blinded to clinical data reviewed the MRI findings of all patients and assigned atrophy rating scores to the 12 anatomic areas in each cerebral hemisphere.

Subsequent analysis was limited to patients meeting criteria for FTLD or AD. The analysis relating atrophy to diagnostic group and anatomic location used a repeated-measures analysis of variance (ANOVA). Atrophy was the dependent variable. The repeated-measures independent variable was anatomic location, and the second independent variable was the diagnostic group. The ANOVA model included a test for interaction to test the hypothesis that the pattern of atrophy differed among the diagnostic groups. On establishing this hypothesis, subsequent pairwise comparisons were performed using the Fisher least significant difference method.

For each clinical finding, we compared the atrophy among locations between subjects with and without the clinical finding using linear discriminant analysis. We also assessed the sensitivity and specificity of various patterns of atrophy for differentiating FTLD syndromes from each other and from AD.

### RESULTS

For a diagnosis of FTLD vs non-FTLD, the clinical reviewers agreed on the initial review in 88 (96%) of 92 cases. For a subtype diagnosis of FTLD, reviewers agreed on 50 (85%) of 59 cases in the initial review. The cases with disagreement were brought to the third reviewer, and a final diagnosis of FTLD was reached in 59 patients and probable AD in 26 patients. The FTLD subtype diagnoses were FD in 18 patients, PA in 11, SD in 24, and FD+A in 6. Sex ratio, average age, duration of illness, and Mini-Mental State Examination scores are presented in Table 1. Patients who were not thought to have FTLD or AD (n=7) were excluded from subsequent analysis. Agreement for clinical symptoms ranged from 76%

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sex, No. M/F</th>
<th>Mean (SD) Age, y</th>
<th>Mean (SD) Duration, y</th>
<th>Mean (SD) MMSE Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>15/11</td>
<td>74.2 (10.3)</td>
<td>2.7 (1.2)</td>
<td>19.3 (4.8)</td>
</tr>
<tr>
<td>FTLD</td>
<td>30/29</td>
<td>69.6 (8.5)</td>
<td>2.8 (1.0)</td>
<td>22.2 (6.7)</td>
</tr>
<tr>
<td>FD</td>
<td>7/11</td>
<td>66.5 (9.7)</td>
<td>2.5 (2.1)</td>
<td>24.2 (5.5)</td>
</tr>
<tr>
<td>PA</td>
<td>6/5</td>
<td>68.8 (6.1)</td>
<td>2.3 (1.6)</td>
<td>16.5 (9.4)</td>
</tr>
<tr>
<td>SD</td>
<td>14/10</td>
<td>72.4 (8.5)</td>
<td>3.1 (2.2)</td>
<td>22.8 (5.8)</td>
</tr>
<tr>
<td>FD+A</td>
<td>3/3</td>
<td>70.0 (6.1)</td>
<td>3.2 (1.2)</td>
<td>23.0 (4.6)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; FD, frontotemporal dementia; FD+A, FD plus aphasia; FTLD, frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination; PA, progressive nonfluent aphasia; SD, semantic dementia.
for fluent, anomic aphasia (agreement in 65 of 85 patients) to 97% for hyperphagia (in 82 of 85 patients). Again, any disagreement was brought to a consensus diagnosis. For the MRI atrophy measurements, the radiology reviewers agreed within 1 degree of atrophy 95% of the time (in 81 of 85 patients). An example of the exemplars used for the 4 levels of atrophy in the frontal superior area is shown in Figure 1.

The ANOVA findings were significant ($P = .001$) for overall differences in patterns of atrophy among diagnostic groups. Figure 2 shows the pattern of atrophy for the diagnostic groups FD, PA, SD, and AD. Comparisons with the Fisher least significant paired $t$ test that were significant at the .05 level are listed in Table 2. The results show that the significant areas of atrophy are bifrontal in the FD group and left temporal and bifrontal in the SD group.

In FTLD and AD subjects, the discriminant function analysis for the presence of disinhibition correlates positively with right frontal atrophy ($P = .004; r = 0.65$) but negatively with left frontal atrophy ($P = .01; r = -0.57$). Similarly, the presence of hyperphagia correlates positively with right frontal atrophy ($P = .003; r = 0.63$) and negatively with left frontal atrophy ($P = .009; r = -0.53$). The presence of a fluent, anomic aphasia correlates positively with left temporal atrophy ($P = .03; r = 0.31$). No other symptoms or signs have significant correlation with any areas of atrophy. The analysis was also performed using age and duration of illness as covariates, which did not affect the significance of the results. To further elucidate the specific anatomic areas important in these symptoms, the discriminant analysis was rerun for the 6 areas in the right frontal lobe for disinhibition and hyperphagia and the 4 areas in the left temporal lobe for fluent, anomic aphasia. Fluent, anomic aphasia had a trend toward positive correlation with atrophy at the left temporal inferior level ($P = .06; r = 0.19$). There were no significant correlations for disinhibition and hyperphagia, although disinhibition correlated best with atrophy at the right frontal inferior level ($P = .17; r = 0.20$). The patterns of atrophy that differentiated the FTLD syndromes from AD in general had low sensitivity (range, 36%-58%) but high specificity (range, 69%-96%).

**Table 2. MRI Atrophy Differences**

<table>
<thead>
<tr>
<th>Anatomic Area</th>
<th>Significant Differences in Degree of Atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left frontal</td>
<td>FD $&gt;$ AD; SD $&gt;$ AD</td>
</tr>
<tr>
<td>Right frontal</td>
<td>FD $&gt;$ AD, FD $&gt;$ PA, SD $&gt;$ AD</td>
</tr>
<tr>
<td>Left temporal</td>
<td>SD $&gt;$ AD, SD $&gt;$ FD</td>
</tr>
<tr>
<td>Right temporal</td>
<td>None</td>
</tr>
<tr>
<td>Left SF</td>
<td>None</td>
</tr>
<tr>
<td>Right SF</td>
<td>None</td>
</tr>
<tr>
<td>Left CH</td>
<td>None</td>
</tr>
<tr>
<td>Right CH</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CH, caudate head; FD, frontotemporal dementia; MRI, magnetic resonance imaging; PA, progressive nonfluent aphasia; SD, semantic dementia; SF, sylvian fissure.

Traditionally, anatomic-behavioral relationships have relied on lesion analysis studies that have not included patients with degenerative diseases. The most common lesion in these studies is cerebrovascular ischemia, which...
limits the anatomic sites of involvement to vascular distributions. Therefore, confirming these relationships in degenerative brain diseases is important and may allow new insights because of the different anatomic distribution of lesions. For example, the lateralization and localization of function of the frontal lobes has proved difficult because of the diffuse pathology that occurs with lesions that commonly affect the frontal lobes. However, evidence from brain-injured patients suggests that the right frontal lobe is important in the expression and regulation of emotion. Patients with damage to large areas of the right frontal lobe may have difficulty in expressing the emotional aspects of speech (prosody), and right orbitofrontal damage is correlated with mania. However, studies of patients with FTLD have indicated that the right frontal lobe is particularly important in controlling social behaviors. Mychack and colleagues recently reported that 11 of 12 FTLD patients with predominantly right frontal involvement on structural or functional neuroimaging presented with socially undesirable behavior. The correlation of disinhibited behavior with right frontal atrophy in our study confirms this finding in an independent sample using only structural neuroimaging. Another anatomic relationship that has emerged is the importance of the left temporal lobe in emerging is the importance of the left temporal lobe in retrieving semantic memories. Three recent studies using volumetric MRI showed the areas most consistently affected in SD were the left temporal pole and inferior and middle temporal gyri. Although not surprising, our results strengthen this association.

The other important aspect of our study is the presence of focal atrophy to distinguish FTLD syndromes from probable AD. Focal atrophy appears to be specific but not sensitive in differentiating patients presenting with FTLD syndromes from those with AD. A likely reason is that FTLD patients may have very mild degrees of atrophy early in the course of illness. In these cases, functional neuroimaging such as single-photon emission computed tomography or positron emission tomography can be helpful in confirming the focal involvement of the frontal or temporal lobes. The additive value of combining functional with structural neuroimaging may be important in future studies of anatomic-behavioral correlations.

Clinicopathologic studies will also be important to distinguish between various pathological forms of FTLD, including Pick disease and dementia lacking distinctive histology, and AD. Asymmetry on structural neuroimaging has been proposed as a core feature of Pick disease. Also, clinicopathologic studies will be important in confirming the above relationships, because we are assuming that the area of greatest atrophy is the area with greatest pathologic involvement. A recent study of a small group of FTLD patients showed a trend toward an association of synapse loss and lateralizing clinical deficits.

Our study has some methodological limitations. First, the study was retrospective to obtain sufficient numbers of FTLD patients to perform the analysis, limiting the number of symptoms or signs that can be analyzed. Some of the clinical symptoms or signs that would be interesting to study were not documented or tested for in every patient at the time of the initial dementia evaluation. For example, in FTLD patients, evidence suggests that right temporal lobe dysfunction results in prosopagnosia, but most patients did not undergo testing for prosopagnosia at the first evaluation. Some patients have undergone testing for such a deficit at subsequent evaluations. However, the review of the clinical data was limited to the initial dementia evaluation, so that the history and examination would be free of influence from the results of neuroimaging.

Another limitation is variability in neuroimaging data. The standard MRI pulse sequences, section thickness, and angle of acquisition used for routine clinical evaluations changed over time at our institution. Also, some MRIs were obtained at other institutions. Thus, the pulse sequence, section thickness, and angle of acquisition differed from patient to patient. However, because our study was retrospective to obtain sufficient numbers of FTLD patients, we are unable to control for the variability in the MRIs. Despite these limitations, our method of obtaining neuroimaging data may be useful for future studies, because volumetric MRIs are not routinely obtained in clinical practice. If validated with further studies, our exemplars may be useful to the practicing neurologist or neuroradiologist.

We have shown that the pattern of cerebral atrophy differs and correlates with clinical symptomology in FTLD. We believe that this is an important step in further defining the relationships between specific behaviors or cognitive deficits and areas of cortical involvement in relatively focal neurodegenerative diseases such as FTLD. With continued prospective collection of FTLD patients, we can obtain more detailed clinical assessments and increase the number of patients to obtain useful insights into brain-behavior relationships. Such relationships in the past have come mostly from lesion analysis studies that focus primarily on lesions produced by strokes occurring in relatively limited cerebrovascular distributions. Using focal degenerative dementia such as FTLD will be a useful corollary to these lesion analysis studies, because the distribution of lesions is not limited to specific cerebrovascular territories. A wide range of frontal lobe behaviors from disinhibited to dysexecutive to apathetic syndromes and neuropsychological variables can be analyzed using these methods to understand the underlying neural substrate producing such behaviors. Another goal is to ultimately determine the usefulness of the neuroimaging atrophy pattern in predicting the underlying histopathology by following up these patients to autopsy.

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Radford. Drafting of the manuscript: Short and Graff-Radford. Critical revision of the manuscript for important intellectual content: Broderick, Patton, Arvanitakis, and Graff-Radford. Obtained funding: Graff-Radford. Administrative, technical, and material support: Arvanitakis. Study supervision: Graff-Radford.

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REFERENCES


Correction

Errors in Table. In the Original Contribution by McArthur et al titled “Attenuated Central Nervous System Infection in Advanced HIV/AIDS With Combination Antiretroviral Therapy,” published in the November 2004 issue of the ARCHIVES (2004;61:1687-1696), errors occurred on page 1690 in Table 2. In that table, the units for both plasma and cerebrospinal fluid (CSF) levels of monocyte chemotactic protein type 1 (MCP-1) and macrophage colony-stimulating factor (M-CSF) should have been listed as nanograms per milliliter.