Clinical Features of Pathologic Subtypes of Behavioral-Variant Frontotemporal Dementia

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Objective: To identify clinical features in behavioral-variant frontotemporal dementia that may help predict tau-positive pathology.

Methods: Clinical and historical features of patients with pathologically confirmed tau-positive and tau-negative frontotemporal lobar degeneration from 1970 to 2006 were retrospectively reviewed in a blinded fashion. The initial clinical features of those patients who eventually met consensus criteria for frontotemporal dementia were examined using univariate and cluster analyses to explore characteristics that may be associated with tau pathology.

Results: Fifty-six patients (24 tau-positive cases) were included in the analysis. There was no difference in demographics between the tau-positive and tau-negative cases. Univariate analysis showed that poor planning and/or judgment was more commonly associated with tau-positive pathology (P = .03). Cluster analysis using behavioral characteristics identified 2 groups of patients: cluster 1 contained mainly tau-positive cases (57%) and cluster 2 was mostly tau-negative cases (71%). Poor planning and/or judgment was a common presenting sign in the first group (P < .001), while the second group was more likely to present with impaired regulation of personal conduct (P < .001) and a decline in personal hygiene (P = .005).

Conclusions: Poor planning and/or judgment was associated with behavioral-variant frontotemporal dementia patients who had tau-positive pathology. The constellation of impaired personal conduct and a paucity of dysexecutive symptoms identified tau-negative patients.

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The Mayo Clinic’s (Rochester, Minnesota) autopsy database was searched to identify all cases that had a pathologic diagnosis of FTLD-U, FTLD-MND, Pick disease, FTDP-17, multiple system tauopathy, corticobasal degeneration, or progressive supranuclear palsy between January 1, 1970, and December 31, 2006. Neuropathologists (J.E.P. and D.W.D.) who were experienced in degenerative neuropathology pathologically reexamined all cases with modern techniques, as described elsewhere. Briefly, slides of the frontal, temporal, and parietal neocortex; hippocampus; basal ganglia; thalamus; midbrain;pons; medulla; and cerebellum were reviewed. In all cases, sections were studied using hematoxylin-eosin 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 acid protein for astrocytes and either CD68 or HLA-DR antigens for microglia. Neuronal pathology was studied with antibodies to neurofilament protein, ubiquitin, α-synuclein, and phosphory-tau. Cases originally designated as dementia lacking distinct histopathology were previously reexamined and reclassified according to current histopathologic techniques.

Pick disease was diagnosed if round silver and tau-positive neuronal inclusion bodies were found in the frontotemporal cortex and other subcortical nuclei, multiple system tauopathy was diagnosed by widespread tau-positive globular, neuronal, and glial inclusions and a negative microtubule-associated protein tau screening; and FTDP-17 was diagnosed if there was a mutation found in microtubule-associated protein tau sequencing. Corticobasal degeneration was diagnosed if neurofilament-positive balloononed neurons and tau-positive coiled bodies, threads, and astrocytic plaques affecting cardinal nuclei were found. Progressive supranuclear palsy was diagnosed if tau-positive globose neurofibrillar tangles, coiled bodies, threads, and tulfed astrocytes affecting cardinal nuclei were found. Diagnosis of FTLD-U was made if there was frontal and/or temporal lobe neurodegenerative changes plus ubiquitin-positive, tau-, alpha-synuclein–, and neurofilament-negative abnormal neurites or neuronal inclusions in the frontotemporal cortex, or a dentate granule cell layer of the hippocampus and an absence of histologic evidence of MND. A diagnosis of FTLD-MND was made if there was FTLD and MND or degeneration of the corticospinal tract. Bunina bodies were sought in all cases and determined as helpful in making a diagnosis of FTLD-MND; but alone, they were not sufficient to make this diagnosis.

Once the cases were identified through searching the existing database, patients with clinical presentation of language-variant FTD were excluded. K.A.J. previously reviewed all records throughout the disease course to ensure that the patient met or eventually met consensus criteria for bvFTD, even though at the time of initial clinical evaluation (1970-2006), the diagnosis recorded may not have been FTD. K.A.J. then removed the final pathologic diagnosis from patient records. Cases were included in this study if a behavioral neurologist evaluated patients who had sufficiently detailed history and there was no coexisting pathology that could account for some of the clinical symptoms. W.T.H. then retrospectively reviewed his own clinical notes and medical records to determine the presence of key features of FTD, such as or their presence was not mentioned. Because a behavioral neurologist with expertise in FTD examined all patients, the inclusion of symptoms in this study required the symptom to be of at least a mild to moderate severity. We paid special attention to clinical characteristics outlined in the consensus diagnostic criteria of bvFTD, including core features, supportive features, and exclusion criteria. These include personality and behavior change, decline in social interpersonal conduct, impaired regulation of personal conduct, emotional blunting, and poor planning and/or judgment (including poor organization and poor problem solving in daily activities or at work); loss of insight, decline in personal hygiene and grooming, hyperorality, dietary change, perseverative and/or repetitive behavior, loss of empathy, speech and language dysfunction, and incontinence; motor symptoms including parkinsonism, spasticity, or myoclonus; and delusions and/or paranoia, forgetfulness and/or amnesia, topographical disorientation, and deficits in facial recognition. Some of these patients may have had minor symptoms related to previous psychiatric or other comorbid illnesses; thus, consideration was given to dominant symptoms. An additional feature of hypersomnolence was included, as a number of patients’ family members shared a complaint that the patients slept all day. Features of mental rigidity and inflexibility, distractibility and impersistence, utilization behavior, and logoclonic speech were not found in the patients’ records and were therefore not included in the statistical analysis. Primitive reflexes were also excluded as they were inconsistently documented. Additional information that was abstracted included patients’ age at onset, age at initial evaluation, duration of disease (time from symptomatic onset to death), sex, family history of dementia (including FTD and other nonstroke-related cognitive impairment) and/or MND, and any abnormality on cerebral spinal fluid examination.

PGRN mutation status was available for 17 patients with a pathologic diagnosis of FTLD-U, as described elsewhere. Statistical analyses were performed using JMP computer software, version 6.0.0 (SAS Institute Inc, Cary, North Carolina), with statistical significance set at P < .05. For univariate analysis, χ² or Fisher exact tests were used for dichotomous variables and the t test was used for continuous variables. For cluster analysis, only behavioral features (excluding pathologic diagnosis, age, sex, and family history) that were present in more than 20% of all patients were included. Behavioral characteristics found to distinguish features between newly generated clusters were then added to the list of behavioral features if they were initially excluded. Using this method, a hierarchical cluster analysis of the cases was performed using only the behavioral variables of interest (personality and behavioral change, decline in social interpersonal conduct, impaired regulation of personal conduct, perseverative and/or repetitive behavior, poor planning and/or judgment, decline in personal hygiene, delusions and/or paranoia, hyperosomnolence, and motor symptoms including parkinsonism). A clustering procedure from SAS, version 8.0 (SAS Institute Inc), which identified hierarchical clusters of observations from the data set of small sample sizes, was used for the analysis. The Ward minimum-variance method, in which the distance between 2 clusters was the analysis of variance sum of squares between the 2 clusters added across all the variables, was used. At each generation, the within-cluster sum of squares was minimized across all partitions obtainable by merging 2 clusters from the previous generation. The sums of squares were then divided by the total sum of squares to give proportions of variance (squared semipartial correlations) for ease of interpretation. Pseudo F statistic and pseudo t statistic were primarily used to judge the number of clusters appropriate for this data set. Squared multiple correlation, which was the proportion of variance accounted for by the clusters, was also estimated.
A total of 66 cases of tau-positive and tau-negative neurodegenerative diseases were identified from the Mayo Clinic’s autopsy database. Ten cases were excluded owing to insufficient history (4 FTLD-U, 2 FTLD-MND, and 2 Pick disease cases), lack of evaluation by a behavioral neurologist (1 Pick disease case), and concurrent demyelinating pathology (1 FTLD-U case). Thus, 32 tau-negative cases (26 FTLD-U and 6 FTLD-MND cases) and 24 tau-positive cases (10 Pick disease, 4 FTD-PD-17, 1 multiple system atrophy, 5 corticobasal degeneration, and 4 progressive supranuclear palsy cases) were included in this study. Five of the tau-negative cases had PGRN mutations (all FTLD-U). The median time from symptomatic onset to clinical evaluation was 3 years for tau-positive cases and 2 years for tau-negative cases. There was no statistically significant difference in sex, age at onset, age at evaluation, or age at death. Patients with tau-positive pathology tended to have longer disease duration than patients with tau-negative pathology (P = .07). Among disease subtypes, patients with FTLD-MND had the shortest disease duration (median survival, 3 years vs 8 years for FTLD-U and 8 years for tau-positive FTLD cases; P < .001), which reflected the previously observed trend.10

Univariate analysis revealed poor planning and/or judgment to be more common among cases with tau-positive pathology (P = .03) (Table 1) and family history to be more common among tau-negative cases. In addition, cases with tau-negative pathology were more likely to have delusions and/or paranoia or an initial clinical diagnosis of FTD. Among cases not given an initial diagnosis of FTD, 1 tau-positive case and 1 tau-negative case were diagnosed as corticobasal degeneration syndrome; 1 tau-positive case was diagnosed as parkinsonism-plus syndrome; and 1 tau-negative case was diagnosed as clinically possible Alzheimer disease with parkinsonism. Other cases were either diagnosed as clinically possible Alzheimer disease (2 tau-positive and 3 tau-negative cases), mild cognitive impairment (1 tau-positive case), or dementia (4 tau-positive cases).

Cluster analysis using 9 behavioral variables (personality and behavioral change, decline in social interpersonal conduct, impaired regulation of personal conduct, preservative and/or repetitive behavior, poor planning and/or judgment, decline in personal hygiene, delusion and/or paranoia, hypersonomlence, and motor symptoms including parkinsonism) generated 2 clusters of patients (Figure). Compared with a smaller or larger number of clusters, having 2 clusters via the Ward minimum-variance method gave a relatively large pseudo $F$ statistic of 11.6, indicating that an appropriate number of clusters was generated. This was confirmed by the pseudo $t^2$ statistic of 8.4, which was markedly larger than values generated from fewer or more clusters. The dendrogram generated from this clustering (Figure) showed the proportion of variance accounted by the clustering to be about 18%. With the clinical information available, this was the most preferred clustering strategy. Patients in cluster 1 and cluster 2 were distinct clinically and pathologically (Table 2). Clinically, patients in cluster 1 were more likely to have poor planning and/or judgment (P < .001), and patients in cluster 2 were more likely to have impaired regulation of personal conduct (P < .001) and decline in personal hygiene (P < .005). Pathologically, tau-positive cases were more common in cluster 1, which contained the majority of Pick disease (8 of 10) and corticobasal degeneration (4 of 5) cases, but this only approached statistical significance (P = .052). On the other hand, 20 of 28 patients (71%) in cluster 2 were tau negative. A search of the original group of 56 patients with results from the cluster analysis showed that constellation of impaired regulation of conduct and absence of prominent planning and/or judgment difficulties identified a group of 22 patients, 77% of which were tau-negative, which represented 62% of all tau-negative cases in this study.

As a secondary observation, we noted that 4 of the 12 tau-negative cases in cluster 1 had PGRN mutations, while

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**Table 1. Clinical Characteristics of Patients With Tau-Positive and Tau-Negative Cases of FTLD**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tau-Positive FTLD</th>
<th>Tau-Negative FTLD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>10 (42)</td>
<td>14 (44)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Median age at symptom onset (range), y</td>
<td>58 (40–78)</td>
<td>56.5 (45–85)</td>
<td>.87</td>
</tr>
<tr>
<td>Median age at evaluation (range), y</td>
<td>61.5 (41–79)</td>
<td>58.5 (47–87)</td>
<td>.98</td>
</tr>
<tr>
<td>Median age at death (range), y</td>
<td>66 (47–89)</td>
<td>63 (49–94)</td>
<td>.7</td>
</tr>
<tr>
<td>Mean duration of disease (median, range), y</td>
<td>8.29 (8, 3–15)</td>
<td>6.63 (8, 1–12)</td>
<td>.07</td>
</tr>
<tr>
<td>Patients with family history of disease</td>
<td>9 (38)</td>
<td>18 (56)</td>
<td>.18</td>
</tr>
<tr>
<td>Personality and behavior change</td>
<td>20 (83)</td>
<td>31 (97)</td>
<td>.15</td>
</tr>
<tr>
<td>Impaired regulation of personal conduct</td>
<td>18 (75)</td>
<td>28 (88)</td>
<td>.3</td>
</tr>
<tr>
<td>Emotional blunting</td>
<td>1 (4)</td>
<td>3 (9)</td>
<td>.63</td>
</tr>
<tr>
<td>Poor planning/judgment</td>
<td>17 (71)</td>
<td>13 (41)</td>
<td>.03</td>
</tr>
<tr>
<td>Loss of insight</td>
<td>5 (21)</td>
<td>8 (25)</td>
<td>.76</td>
</tr>
<tr>
<td>Decline in personal hygiene</td>
<td>5 (21)</td>
<td>6 (19)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Hyperorality and dietary</td>
<td>4 (17)</td>
<td>8 (25)</td>
<td>.53</td>
</tr>
<tr>
<td>Impaired regulation of personal conduct</td>
<td>5 (21)</td>
<td>9 (28)</td>
<td>.76</td>
</tr>
<tr>
<td>Loss of empathy</td>
<td>3 (13)</td>
<td>2 (6)</td>
<td>.64</td>
</tr>
<tr>
<td>Incontinence</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Delusion/paranoia</td>
<td>1 (4)</td>
<td>8 (25)</td>
<td>.06</td>
</tr>
<tr>
<td>Hypersonomlence</td>
<td>4 (17)</td>
<td>8 (25)</td>
<td>.53</td>
</tr>
<tr>
<td>Disorders of language</td>
<td>8 (33)</td>
<td>13 (41)</td>
<td>.78</td>
</tr>
<tr>
<td>Motor symptoms</td>
<td>9 (38)</td>
<td>9 (28)</td>
<td>.57</td>
</tr>
<tr>
<td>Forgetfulness/loss of memory</td>
<td>13 (54)</td>
<td>21 (67)</td>
<td>.42</td>
</tr>
<tr>
<td>Topographical disorientation</td>
<td>8 (33)</td>
<td>9 (28)</td>
<td>.77</td>
</tr>
<tr>
<td>Deficits in facial recognition</td>
<td>3 (13)</td>
<td>6 (19)</td>
<td>.72</td>
</tr>
<tr>
<td>Elevated CSF protein level</td>
<td>3a</td>
<td>8c</td>
<td>NS</td>
</tr>
<tr>
<td>Initial clinical diagnosis of FTD</td>
<td>15 (63)</td>
<td>27 (84)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; NS, not significant.

aValues are number of patients (percentage) unless otherwise indicated. Univariate analysis was performed for categorical variables and the $t$ test was performed for continuous variables.

b $n=17$.

c $n=14$. 

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and nonfluent variants with high pathologic concor-
dance.16 Knibb et al16 demonstrated that 53% of the flu-
ent group had ubiquitin-associated pathologic changes and that 43% of the nonfluent language group had non–
Alzheimer disease tauopathies. Using a similar tech-
nique, behavioral stratification of bvFTD cases in our se-
ries created 2 behaviorally distinct groups. Patients with
tau-positive pathology, who were characterized behav-
orially by the occurrence of early dysexecutive symp-
toms of poor planning and/or judgment, were more likely
to be found in cluster 1. This corresponds with previous ob-
servations that tau-positive cases of FTLD have rela-
tively more severe atrophy in the bilateral prefrontal re-
gions.17 However, cluster analysis did not significantly
improve the predictive value for tau pathology. Interes-
tingly, a significant percentage of tau-negative cases in
cluster 1 were FTLD-U cases with PGRN mutations, raising
the possibility that tau-positive cases (the largest sub-
group being Pick disease) and FTLD-U with PGRN mu-
tations share a common clinical phenotype. One expla-
nation may be a shared pattern of lobar degeneration in
tau-positive cases and FTLD-U with PGRN mutations. In
2 separate series, patients with Pick disease mutations
were shown to have a greater degree of frontal lobe at-
rophy on radiographic studies when compared with other
FTLD subtypes.18,19 At the same time, cases of FTLD-U
with PGRN mutations also demonstrated more frontal lobe
atrophy than cases of FTLD-U without PGRN muta-
tions on pathologic studies.9 Therefore, in patients who
display behavioral characteristics that are common in clus-
ter 1 or significant frontal lobar atrophy, PGRN mutation
screening will be useful in refining the predictive model of tau positivity. Cases with PGRN mutations may be
suitable for PGRN-specific therapies in the future, and
cases without PGRN mutations will have a high likeli-
hood of being tau positive.

We also noted that previous series reported higher
prevalence of executive dysfunction in clinically diag-

**Table 2. Clinical Characteristics According to Grouping
by Cluster Analysis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cluster 1 Cases, %</th>
<th>Cluster 2 Cases, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive tau pathology</td>
<td>57</td>
<td>29</td>
<td>.06</td>
</tr>
<tr>
<td>Poor planning and/or judgment</td>
<td>82</td>
<td>25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Motor symptoms</td>
<td>42</td>
<td>21</td>
<td>.15</td>
</tr>
<tr>
<td>Delusions/paranoia</td>
<td>7</td>
<td>25</td>
<td>.14</td>
</tr>
<tr>
<td>Decline in personal hygiene</td>
<td>4</td>
<td>36</td>
<td>.005</td>
</tr>
<tr>
<td>Impaired regulation of personal</td>
<td>64</td>
<td>100</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>conduct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personality and behavior change</td>
<td>82</td>
<td>100</td>
<td>.05</td>
</tr>
</tbody>
</table>

a n = 28 (frontotemporal lobar degeneration with ubiquitin-positive and tau- and α-synuclein–negative inclusions [FTLD-U], 9 cases; FTLD with motor neuron degeneration [FTLD-MND], 3 cases; Pick disease, 8 cases; frontotemporal dementia with parkinsonism linked to chromosome 17 [FTDP-17], 2 cases; corticobasal degeneration, 4 cases; progressive supranuclear palsy, 2 cases). Four cases had progranulin gene (PGRN) mutations.

b n = 28 (FTLD-U, 17 cases; FTLD-MND, 3 cases; Pick disease, 2 cases; FTDP-17, 2 cases; corticobasal degeneration, 1 case; progressive supranuclear palsy, 2 cases; multiple system tauopathy, 1 case). One case had a PGRN mutation.

With the development of the consensus diagnostic cri-
tera,1 FTLD can be diagnosed clinically with high speci-
ficity and relatively high sensitivity.13 However, little is
known about the association between clinical features and
FTLD subtypes. In this large group of bvFTD patients
with autopsy-confirmed FTLD, we observed 2 behav-
ioral groups with most cases within each being either tau-
positive (cluster 1) or tau-negative (cluster 2). Thus, spe-
cific behavioral phenotypes are likely associated with
FTLD subtypes, though predicting tauopathy with behav-
ioral phenotype alone lacks high specificity.

Clustering of clinical characteristics was previously
used to divide the language variant of FTD into fluent
and nonfluent variants with high pathologic concor-

**Figure. Clustering of clinical characteristics was previously
divided the language variant of FTD into fluent
and nonfluent variants with high pathologic concor-

only 1 of the 20 tau-negative cases in cluster 2 had a PGRN
mutation. After excluding patients with PGRN muta-
tions, 67% of patients in cluster 1 had a tau-positive neu-
rodegenerative disease.
nosed cases of FTD. One study reported that more than 70% of patients with clinically diagnosed bvFTD showed symptoms of poor planning and lack of judgement. Another showed a high prevalence (87%) of dysexecutive features in cases of familial tau mutation–negative cases of FTD. This may reflect a different proportion of tau-positive cases based on findings from our study, as 2 large clinicopathologic series have previously demonstrated higher proportions of tau-positive cases (+6 of 76 cases3 and 31 of 61 cases4). Similarly, symptoms of FTD may increase in severity over time, and a higher prevalence of symptoms may reflect clinical evaluations later in the disease course. As there was minimal difference in the median time to evaluation from symptom onset between tau-positive and tau-negative cases, the observed tendency of patients with tau-positive disease to have poor planning and/or judgment early in the disease course in our series likely cannot be explained by disease duration alone. However, there remains the possibility that tau-positive and tau-negative cases will have similar rates of planning and/or judgment deficits late in the disease course. With the available pathologic and genetic information in our series, we propose that patterns of early abnormal behaviors associated with tau-positive FTLD may increase the clinical diagnostic accuracy of FTD subtypes in conjunction with other techniques, such as volumetric imaging and PGRN mutational studies.19

This study has a number of limitations. This was a retrospective study and we did not adjust for the multiple comparisons problem owing to the overall sample size, though the very small allowable errors in the univariate comparison following cluster analysis for poor planning and/or judgment and impaired regulation of personal conduct support significant differences between the clusters. The extent of clinical documentation may have varied even among expert behavioral neurologists, which could have been reflected in the underreporting of nonbehavioral symptoms. Importantly, we recognize that absence of documentation likely may not always reflect absence of symptoms, though the recording of symptoms not thought to be common to FTD, such as hypersomnolence, would support the notion that even mild symptoms were indeed documented. At the same time, there was a high degree of concordance in the pattern of clinical features noted with previous reports. Tau-negative FTLD-U cases were more likely to display signs of social or behavioral changes than tau-positive cases including Pick disease in one study, and only half of patients with tau-positive Pick disease had FTD as their first clinical syndrome in another study. However, to definitively confirm the trends observed in this and previous studies, the dominant clinical phenotypes identified here could form the basis for prospective clinicopathologic studies to determine the utility of behavioral phenotypes in predicting tau-positive neurodegenerative diseases, with standardized neuropsychometric batteries to better assess severity of common symptoms and special attention to focus on less common but perhaps characteristic symptoms, such as delusions/paranoia and decline in personal hygiene.

We present a clinicopathologic study of FTLD subtypes and found that poor planning and/or judgment is more prevalent among patients with tau-positive pathology and that impaired regulation of personal conduct and delusion and/or paranoia is more commonly associated with tau-negative cases. In conjunction with imaging and PGRN mutational screening, these findings may help predict FTLD. However, overlap of clinical syndromes and potential conversion between FTD subtypes may complicate the interpretation of early behavioral deficits. Long-term prospective clinicopathologic studies are necessary to determine the predictive values of subcategorizing bvFTD based on specific behavioral features. Biomarkers for tauopathies and ubiquitinopathies are needed to reliably differentiate these cases in the clinical setting.

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Author Contributions: Drs Hu and Josephs had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hu and Josephs. Acquisition of data: Hu, Parisi, Boeve, Petersen, Hutton, Dickson, and Josephs. Analysis and interpretation of data: Hu, Mandrekar, Parisi, Knopman, and Josephs. Drafting of the manuscript: Hu and Josephs. Critical revision of the manuscript for important intellectual content: Hu, Mandrekar, Parisi, Knopman, Boeve, Petersen, Hutton, Dickson, and Josephs. Statistical analysis: Mandrekar and Josephs. Administrative, technical, and material support: Dickson and Josephs. Study supervision: Boeve, Petersen, Hutton, and Josephs.

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REFERENCES


**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.