Progression in Frontotemporal Dementia

Identifying a Benign Behavioral Variant by Magnetic Resonance Imaging

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Objective: To assess the clinical course and prognosis in patients with behavioral-variant frontotemporal dementia (FTD) lacking evidence of brain atrophy on magnetic resonance imaging (MRI).

Design: Patients were enrolled into this prospective cohort study over a period of 15 years; cognitive status, duration of symptoms, and behavioral indexes were recorded. Brain MRIs were rated using a standardized scale.

Setting: Regional early-onset dementia clinic.

Participants: Thirty-one participants diagnosed clinically with behavioral-variant FTD.

Intervention: Rating of MRIs.

Main Outcome Measures: Death or institutionalization after a minimum of 3 years' follow-up indicated poor prognosis, while the ability to live independently was regarded as a good prognosis for the purpose of survival (Kaplan-Meier) and discriminant function analysis.

Results: Patients with normal or borderline MRI findings (n=15) showed significantly longer survival to institutionalization or death than those (n=16) with definite frontotemporal atrophy (mean±SE, 9.3±1.7 years vs 3.0±0.7 years; P<.01). Using groups defined by 3-year outcome (good or bad prognosis), cerebral atrophy predicted poor outcome while age, symptom duration, cognitive performance, behavioral impairment, and overall disability at baseline did not.

Conclusions: Patients with FTD with normal MRI results follow a more benign course than cases with atrophy at presentation. The substrate of the behavioral symptoms in such cases may differ from the neurodegenerative pathological features typically associated with FTD.

Arch Neurol. 2006;63:1627-1631

Following a diagnosis of dementia, questions regarding prognosis inevitably arise. In the case of frontotemporal dementia (FTD), the second most prevalent early-onset dementia, the outlook is particularly poor, with recent reports indicating a median survival of just 3 years following clinical presentation. Several clinical variants of FTD are described. The behavioral variant (bvFTD), characterized by progressive changes in personality including disinhibition, apathy, loss of empathy, altered eating patterns, and stereotyped behavior, is most common. Two aphasic variants are also recognized: progressive nonfluent aphasia and semantic dementia. Post-mortem findings in FTD consistently include frontotemporal atrophy with severe neuronal loss, although the accompanying inclusion pathological features are heterogeneous. In vivo volumetric studies demonstrate that local brain atrophy can be severe, even at the time of diagnosis, and that this feature may help to distinguish between FTD and other dementing conditions. Furthermore, the pattern of atrophy in FTD varies according to clinical features. Cases with bvFTD tend to show frontal or right temporal lobar atrophy. Current consensus criteria, however, do not mandate abnormal imaging findings; such changes are merely supportive of the diagnosis. Thus, a number of patients formally diagnosed with FTD have normal structural imaging findings.

Our clinical experience suggests the existence of a subgroup of patients with bvFTD with a substantially better prognosis than the literature implies. Since the identification of such patients might have profound consequences for patients and their families, we were interested in exploring whether specific imaging or demographic features could predict prognosis and to what extent our clinical observations could be formally substantiated. We...
hypothesized that patients fulfilling clinical criteria for bvFTD but lacking evidence of frontotemporal atrophy on magnetic resonance imaging (MRI) would have prolonged survival.

METHODS

Patients were assessed in the Early Onset Dementia Clinic at Addenbrooke’s Hospital, Cambridge, England. The study included all cases fulfilling consensus criteria for FTD with predominant behavioral symptoms (bvFTD) who had undergone MRI and then been followed up for a minimum of 3 years or died within that time (n=31). This period was based on published estimates of median survival of 3 years. It is important to emphasize that (1) clinical, and not imaging, characteristics formed the basis of inclusion into the study, and (2) all patients presented with a history of gradual onset and progression of their clinical features.

Demographic data were available in all patients; these included sex, age at MRI, and symptom duration to MRI. Measures of overall disability (Clinical Dementia Rating [CDR]) and cognition (Addenbrooke’s Cognitive Examination [ACE]) were also available and had been measured within 6 months of acquiring MRI. Information on behavioral changes was available from either the Cambridge Behavioral Inventory or the Neuropsychiatric Inventory. Data were extracted to give a dichotomized score for 13 behavioral domains (summated such that a score of 13 indicates abnormality in every domain): delusions, hallucinations, depressed mood, anxiety, irritability, elevated mood, agitation, apathy, sleep, disinhibition, motor stereotypies, dietary changes, and ritualized behavior. End points to follow-up were (1) date of death or (2) date of entering institutional care.

Two raters, blind to individual clinical details, rated T1 coronal MRIs in accordance with a standardized schema. The schema was developed for assessment of post-mortem specimens but was modified for the purpose of this study to rate MRIs obtained during life. The method involves assessment of 2 coronal slices, 1 at the level of the anterior temporal lobe and 1 at the level of the lateral geniculate nucleus, and produces a rating for frontotemporal atrophy from 0 to 4 (0=normal; 4=end-stage atrophy). Formal interrater and intrarater agreement were assessed using a larger sample of 273 MRIs of patients with FTD or Alzheimer disease, as well as control subjects, and showed good reliability (Cohen κ >0.7 and 0.8, respectively). Figure 1 shows the stages of the rating scale used to rank MRIs. Full details of the scale are available on request. For the analyses described later, the highest (worst) atrophy rating score, either frontal or temporal, was used in each case.

We used Kaplan-Meier survival analysis, grouped by atrophy score (0=normal MRI findings; 1=borderline atrophy; 2=definite atrophy), with log-rank post hoc testing. Discriminant analysis was also undertaken, comparing 2 groups defined by outcome at 3 years: those still living independently (favorable prognosis) and those who had died or were in institutional care (poor prognosis). Variables entered into the discriminant analysis were atrophy rating, sex, age, symptom duration, CDR, ACE score, and behavior score; the Wilks λ was used for significance testing. The CDR was also compared across the prognostic groups by a Mann-Whitney U test. All analyses were conducted in SPSS version 10 (SPSS Inc, Chicago, Ill).

The research program was approved by the Addenbrooke’s Hospital Local Research Ethics Committee.

RESULTS

The Table summarizes the baseline data according to prognosis. There were 16 patients in the favorable prognostic group and 15 in the group with poor prognosis. The latter included an equal number of men and women. All cases in the favorable prognostic group (living independently at 3 years), however, were male. Age at MRI was similar across the groups. The duration of symptoms to MRI was shorter in the poor prognosis group, although this difference was not significant. Cognitive and behavioral scores failed to differentiate the groups, but overall disability level at the time of MRI was marginally worse in those who went on to have a poor outcome (CDR 2 vs 1); again, this was not statistically sig-
significant (P = .25). The ratio of frontal to temporal lobe atrophy was comparable in the favorable and unfavorable prognostic groups (P = .56).

No consistent differences in medical history were found between the 2 groups. In particular, with reference to psychiatric symptoms, 4 patients had previously been diagnosed with depression, 2 in each group. None of these cases was considered to have active depression at the time of their dementia presentation. One quarter (4 of 16) of the poor prognosis patients had a family history of depression or anxiety, while the proportion in the favorable prognosis patients was closer to half (7 of 15). A family history of dementia was present in a similar number of cases in each group (2 of those with poor prognosis, and 3 with a favorable prognosis). One case with a family history of motor neuron disease was found to have a tau mutation; this individual had borderline atrophy on MRI and died within 3 years of presentation.

There was a highly significant relationship between time to loss of independence and MRI rating in the survival analysis. Fifteen of the 31 patients had not reached either of the predefined end points (death or institutional placement). The 15 included all the 0-rated (ie, normal) MRI results; survival could not, therefore, be estimated in this group.

Survival estimates did, however, differ greatly between those with borderline MRI results (rated 1, mean ± SE, 9.3 ± 1.7 years) and those with definitely abnormal MRI results (rated 2–4, mean ± SE, 3.0 ± 0.7 years), the difference being highly significant (Figure 2) (P = .003).

The discriminant analysis, with cases grouped by outcome, found atrophy rating to be the sole variable with significant power to predict prognosis (F to remove = 26.4; Wilks λ = 0.476; P < .001). All other variables (sex, age, symptom duration, CDR, behavioral score, ACE score) failed to show additional discriminating value.

### Table. Summary of Cross-Sectional Data According to Prognostic Group

<table>
<thead>
<tr>
<th>Prognostic Group</th>
<th>Sex, M/F</th>
<th>Age, y, Mean ± SD</th>
<th>Symptom Duration, y, Mean ± SD</th>
<th>CDR Median (Maximum, 3)</th>
<th>Behavior Score, Mean ± SD (Maximum, 13)</th>
<th>ACE Score, Mean ± SD (Maximum, 100)</th>
<th>No. of Cases Ascribed to Each MRI Rating Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>16/0</td>
<td>57.4 ± 7.8</td>
<td>5.9 ± 4.0</td>
<td>1</td>
<td>9.3 ± 1.8</td>
<td>81 ± 8.6</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Poor</td>
<td>8/7</td>
<td>59.9 ± 7.7</td>
<td>4.0 ± 3.4</td>
<td>2</td>
<td>7.9 ± 3.8</td>
<td>79 ± 4.9</td>
<td>0 3 3 9</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, Addenbrooke’s Cognitive Examination; CDR, Clinical Dementia Rating; MRI, magnetic resonance image.

Few longitudinal studies of disease progression have been reported in FTD, although a recent analysis of illness duration in cases that had reached autopsy gave a median survival from diagnosis of only 3 to 4 years. The patients with demonstrable frontotemporal atrophy included in the present study had a disease duration similar to that reported in the autopsy series.

Cases not showing brain atrophy, however, evolved quite differently. Length of follow-up in all cases was between 5 and 6 years. To reiterate, all patients were diagnosed using consensus criteria on the basis of a behavioral syndrome emerging in mid to late life and were indistinguishable in this respect. This is affirmed by the similarity of behavioral scores in cases with and without brain atrophy. Strikingly, no patient without brain atrophy died or entered residential care within the study period. Formal analysis showed markedly better survival in cases deemed to have normal brains or only borderline atrophy (mean ± SE, 9.3 ± 1.7 years) compared with those with unequivocal brain atrophy (mean ± SE, 3.1 ± 0.7 years). Furthermore, atrophy rating proved to be the only variable with power to discriminate between patients who would progress rapidly to institutionalization or death and those who would not.

A key question in interpreting the data is whether to consider the patients with normal MRI results as forming a continuum with the remainder. Frontotemporal dementia is pathologically heterogeneous, and this heterogeneity may encompass some of the cases described in whom initial MRI findings were normal, for instance, if they had presented very early in the natural history of their illness. Frontal hypometabolism and hypoperfusion have been demonstrated by functional imaging in cases with bvFTD showing no atrophy, the conventional interpretation being that the dysfunction would be followed, in due course, by structural change. Moreover, there is limited evidence that such cases, followed up for a decade or more, may eventually show frank brain atrophy.

The very different tempo of progression in the cases with normal MRI results in this study favors regarding them as a group apart. This is reinforced by our experience with MRIs in other clinical variants of FTD.
In contrast to cases with bvFTD, not 1 MRI result of the 52 cases with semantic dementia and 22 cases with progressive nonfluent aphasia we assessed (C.M.K., R.R.D., J.M., J.J.K., G.M.H., and J.R.H., unpublished data, 2006) was normal. Presumably, if a uniform range of pathologic substrates occurred across the clinical subtypes of FTD, one should see similar ranges of atrophy scores, albeit across different brain regions.

The challenge arises of proposing a specific pathologic mechanism to account for cases without apparent atrophy. The behavioral symptom profiles of these cases and those showing frank atrophy seem indistinguishable, as highlighted by their similar scores on behavioral rating scales, suggesting a similar distribution of pathologic features in both groups. In terms of pathogenesis, there would appear to be 2 major possibilities, the first being a very indolent form of neurodegeneration and the second, a biological basis akin to psychiatric disorders.

The proposed indolent neurodegeneration might have parallels with progressive supranuclear palsy where significant cortical deposition of tau protein, correlating with behavioral disturbance, occurs without substantial volume loss.22,23 Patients with progressive supranuclear palsy, of course, have significant subcortical tau deposits and marked disturbance of movement but behavioral changes occur in most and these correlate with the modest orbitofrontal atrophy that is also seen.21 Several cases with familial dementia associated with tau gene mutations can show very slight cortical atrophy,20,22 again suggesting that tau abnormalities can cause significant cortical dysfunction without loss of volume as well as causing gross atrophy. Intracellular tau processing has also been shown to differ between progressive supranuclear palsy and the latter group of tauopathies.28

Neurodegeneration is not typically invoked, by contrast, in discussions of FTD-like functional imaging abnormalities seen in depression and other psychiatric syndromes.29 Furthermore, alterations in serotonin function are described in FTD,24,31 while reduced serotonin function may explain both functional imaging changes and subtle neuropsychological changes in depression.29,32 Serotonergic therapies are long established in depression and may also improve behavioral problems in FTD.33-36 The 2 proposed pathogenic theories (neurodegeneration vs "psychiatric"), however, are not mutually exclusive; chronic neurochemical dysfunction may lead to degenerative changes and vice versa. Indeed, a recent study described “dementia” in 9 patients who met DSM-IV criteria for schizophrenia.37 The patients described in the present study did not meet criteria for specific psychiatric disorders, were in an older age bracket, and often had been referred to the neurology clinic by psychiatrists because of diagnostic uncertainty.

A final curiosity is the absence of women from the bvFTD group with normal MRI results while cases showing atrophy included equal numbers of both sexes. This may be a reflection of differential vulnerability between the sexes to the midlife behavioral changes described. Differences in health care–seeking behavior between the partners or families of male and female patients may be a further factor.

We have identified a subgroup of slowly progressing patients currently considered under the rubric of FTD and argued that they may not have a neurodegenerative process, in the traditional sense, causing their symptoms. The finding has major implications for the provision of prognostic information. Prolonged follow-up, however, with serial quantification of brain atrophy, functional imaging, and eventual histopathological examination will be required to resolve the controversy.

Accepted for Publication: April 13, 2006.

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Author Contributions: Drs Davies and Kipps provided an equal contribution to this work. Study concept and design: Davies, Kipps, Kril, Halliday, and Hodges. Acquisition of data: Davies, Kipps, Mitchell, and Kril. Analysis and interpretation of data: Davies, Kipps, Kril, Halliday, and Hodges. Drafting of the manuscript: Davies, Kipps, and Hodges. Critical revision of the manuscript for important intellectual content: Davies, Kipps, Mitchell, Kril, Halliday, and Hodges. Statistical analysis: Davies, Kipps, and Halliday. Obtained funding: Davies, Kril, and Hodges. Administrative, technical, and material support: Mitchell and Kril.

Study supervision: Hodges.

Financial Disclosure: None reported.

Funding/Support: This work was supported by a Wellcome Trust Clinical Training Fellowship (Drs Davies and Kipps), a program grant from the UK Medical Research Council (Dr Hodges), and a project grant from the National Health and Medical Research Council of Australia (Drs Kril and Halliday).

Role of the Sponsor: The funding sources had no involvement with the study design, collection of data, preparation of the manuscript, or decision to publish.

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