Clinical staging and disease progression in frontotemporal dementia

ABSTRACT

Objective: We aimed to develop a novel tool capable of staging disease severity in frontotemporal dementia (FTD) based upon functional dependence and behavioral changes, and to assess change over time in the 3 main FTD variants (behavioral variant FTD [bvFTD]; progressive nonfluent aphasia [PNFA]; and semantic dementia [SemD]).

Methods: The Frontotemporal Dementia Rating Scale (FRS) was developed in a validation cohort of 77 consecutive clinic attendees (bvFTD 29; PNFA 20; SemD 28) and applied to an independent sample of 75 patients (bvFTD 28; PNFA 21; SemD 26) to establish intergroup differences. Assessments from 42 patients followed up after 12 months were used to determine annual progression. Finally, a combined sample (n = 152) was used to determine length of symptoms in each severity category.

Results: Six severity stages were identified and operationalized based upon a 30-item questionnaire (very mild to profound). The cross-sectional study revealed much greater levels of impairment in bvFTD than in the language variants, with limited correlation with general cognitive measures. Patients with SemD showed the closest association between length of symptoms and stage, taking, on average, 10 years to reach the severe stage. Patients with bvFTD appear to move most quickly between stages and patients with PNFA were intermediate. The FRS was capable of detecting functional deterioration in all 3 variants over 12 months.

Conclusions: Disease progression differs across frontotemporal dementia (FTD) variants. Patients with behavioral variant FTD progress rapidly whereas those with semantic dementia progress more slowly. The Frontotemporal Dementia Rating Scale can aid in staging and determining disease progression. Length of symptoms and global cognitive assessments alone do not reflect disease severity and progression in FTD. Neurology® 2010;74:1591–1597

GLOSSARY

ACE-R = Addenbrooke’s Cognitive Examination Revised; AD = Alzheimer disease; ADL = activities of daily living; ANOVA = analysis of variance; bvFTD = behavioral variant frontotemporal dementia; CBI = Cambridge Behavioral Inventory; CDR = Clinical Dementia Rating Scale; DAD = Disability Assessment for Dementia; FRS = Frontotemporal Dementia Rating Scale; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; PCA = principal component analysis; PNFA = progressive nonfluent aphasia; SemD = semantic dementia.

Frontotemporal dementia (FTD) refers to 3 distinctive clinical syndromes with heterogeneous neuropathology: behavioral variant FTD (bvFTD), semantic dementia (SemD), and progressive nonfluent aphasia (PNFA).1 bvFTD patients present with marked change in personality and social conduct,2 whereas symptoms in SemD and PNFA remain language related, at least initially.3-6 Recent studies have established that FTD impacts considerably on everyday activities, which cannot be attributed to language deficits even in those with SemD and PNFA.7 These changes in behavior, language, and functional abilities lead to progressive disability7-10 and, consequently, high levels of stress and burden on carers.11-13

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There is no consistent method of determining disease stage or severity in FTD. Clinicians may use a combination of cognitive, behavioral, imaging, and activities of daily living (ADL)–based data. To complicate matters, patients with FTD present at different stages in terms of severity of dementia but these stages have not been well-defined to date. Moreover, no tool has yet been developed that is capable of delineating the stages of FTD severity, or its rate of disease progression. The majority of the FTD studies have relied on Alzheimer disease (AD) staging tools, such as the Clinical Dementia Rating Scale (CDR). An adapted CDR (FTLD-modified CDR) was recently developed for use in clinical trials, and showed superior ability to the standard CDR. The modified CDR, however, did not detect differences between FTD subgroups, or rates of progression in each variant.

The objectives of this study were to 1) identify stages or levels of dementia across the 3 main clinical variants of FTD using a novel staging tool, the Frontotemporal Dementia Rating Scale (FRS); 2) identify annual rate of decline in the FRS; and 3) investigate the relationship between length of symptoms and FRS stages.

**METHODS**

**Patient criteria.** Patients were included if they 1) fulfilled criteria for FTD; 2) had an informant who could give a reliable account of the patient’s routine; 3) had no physical disability that could confound assessment of activities of daily living; 4) had absence of major depression as assessed by a psychiatrist; and 5) had undergone an Addenbrooke’s Cognitive Examination Revised (ACE-R) and a CDR within 60 days of the functional assessment (patients were included irrespective of ACE-R scores). All patients underwent MRI scan and were excluded if they had evidence of significant cerebrovascular disease (infarcts or confluent white matter change). Cognitive testing was given by a senior research nurse or a research assistant. All patients were assessed by an experienced research occupational therapist (E.M.) and a senior behavioral neurologist (J.R.H.) at the research clinics in Cambridge or Sydney. Diagnoses were made on the basis of a multidisciplinary consensus (neurologist, neuropsychiatrist, and neuropsychologist), and measures described here were not included in the diagnostic process. Patients with clinical symptoms of bvFTD but without brain atrophy or progression, so called phenocopy cases, were also excluded.

Duration of disease was estimated by onset of symptoms as reported by the informant at the time of diagnosis. Note that in Cambridge and Sydney we have used the general label FTD to encompass all variants described above (bvFTD, SemD, PNFA), rather than frontotemporal lobar degeneration (FTLD).

An initial cohort of 77 patients with FTD was used to develop the FRS, as shown in figure 1 (sample 1). For this analysis the ratings on each FRS question were based on existent data from the Cambridge Behavioral Inventory (CBI) and the Disability Assessment for Dementia (DAD). An independent sample of 75 patients with FTD (sample 2: bvFTD = 28; SemD = 26; PNFA = 21) were included in the analysis. For the analysis of annual change, we used a subgroup of 42 patients with baseline and 1-year follow-up assessments (sample 3). Sample 2 and 3 caregivers were interviewed by an occupational therapist (E.M.) or neurologist (J.R.H.) who administered the FRS. Finally, to investigate the impact of the length of symptoms on FRS staging, we combined 2 sets of data: the sample that validated the scale (n = 77) and the sample mentioned above (n = 75), resulting in 152 patient assessments (sample 4).

**Controls.** Twenty age-matched controls (10 male and 10 female) were recruited at the MRC Cognition and Brain Science Unit, Cambridge, UK (table 1).

**Instruments. FRS.** A total of 77 patients with FTD were included (sample 1: bvFTD = 29; SemD = 28; PNFA = 20), following the same inclusion criteria reported in Methods. The 77 patients represented a consecutive sample assessed in Cambridge. Patients were matched for age and length of disease (table e-1 on the Neurology Web site at www.neurology.org). We intended to create a staging scale specific for FTD, capable of characterizing disease severity and nuances of change with disease, avoiding the floor effects inherent in standard cognitive tests. These can be misleading in moderate patients, especially those with language problems.
A total of 75 questions were initially identified from the CBI and DAD, which had previously been shown to capture the behavioral changes and impairment in ADLs that characterize FTD syndromes. Rasch modeling was applied to the set of 75 questions in 77 patients (sample 1). Rasch analysis converts ordinal raw data to interval measures, placing questions and patients along the same hierarchy. In other words, Rasch analysis ranks patients according to their level of ability (from able to disabled), while examining the hierarchy of questions according to their level of complexity (from difficult to easy). In this way it identifies which questions best describe patient capacity based on the whole sample, eliminating those questions that do not capture the sample characteristics as a continuum.

The Rasch analysis was conducted iteratively until the initial 75 items were reduced to a smaller set that would demonstrate construct validity, unidimensionality, and good internal reliability. To verify construct validity, items were excluded if they failed to fit recommended limits of infit and outfit values (MNSQ = 0.60 to 1.49 and Z = −2 to 2).

The resulting scale comprises 30 questions. Mean infit statistics (M = 1.01; Z = 0.0, SD = 0.8) and outfit statistics (M = 0.94; Z = 0.0, SD = 0.7) confirmed that, overall, this choice of items produced a smooth continuum without outliers.

To verify unidimensionality, which is a trait that assures that the scale is measuring one construct only, in this case disease severity, a principal component analysis (PCA) of the residuals was performed. This produced good Eigen values for the 5 contrasts (1.8–3.5). The raw variance explained was 46.4%, which was very close to the desired 50%.

Further comparison of positive and negative loaded variables confirmed the unidimensionality of the scale.

Test consistency was 0.93, almost reaching the desirable Cronbach’s α = 0.95. The item separation index of the scale was 3.68, which was close to the desired level of 3.0. Interrater test-reliability was conducted on a subsample of 23 patients, whose FRSs were scored by 4 independent raters (94 ratings). The intraclass reliability coefficient was 0.994 (absolute agreement), with figures closer to 1 demonstrating high agreement.

To verify construct validity, unidimensionality, and good internal reliability was conducted on a subsample of 23 patients, whose FRSs were scored by 4 independent raters (94 ratings). The intraclass reliability coefficient was 0.994 (absolute agreement), with figures closer to 1 demonstrating high agreement.

In the resultant scale, a score of 30 denotes full functional ability and no behavior change, whereas lower scores denote decline in everyday abilities and marked behavior change. Item difficulty is shown in figure e-1. Item difficulty was defined by logit values, with higher logit values representing more difficult items.

Once a score is obtained, it has to be converted to a percentage (raw score/number of applicable questions). This step avoids gender or cultural bias, respecting a patient’s premorbid abilities (e.g., no points are lost if the person has never managed finances or if cooking was not part of his or her routine prior to disease onset). This percentage score is then checked against a logit table, where a logit score is obtained. This step aids in spreading the patients across the different severity categories. Logit scores were subdivided into 6 equal categories to facilitate clinical interpretation: very mild (>4.12), mild (4.11 to 1.92), moderate (1.91 to −0.40), severe (−0.39 to −2.58), very severe (−2.57 to −4.99), and profound (below −4.99). Higher scores on the FRS denote higher functioning.

The FRS is available for free download via the Frontier Web site (http://www.frdg.org).

**ACE-R.** The ACE-R assesses 5 cognitive domains: attention/orientation, memory, verbal fluency, and language and visuospatial abilities. The total score is 100; higher scores reflect better ability. The ACE-R was designed to be sensitive to early stages of dementia, and incorporates the MMSE. Not all patients could perform an ACE-R due to disease severity (n = 56).

**CDR.** The CDR is a clinical staging instrument of dementia that combines 6 domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. An algorithm allows the calculation of a total score; a score of zero reflects no dementia and higher scores denote greater impairment. Not all patients had a CDR administered (n = 53).

**Standard protocol approvals, registrations, and patient consents.** The study was approved by the Addenbrooke’s Hospital Ethics Committee in Cambridge and the South Eastern Sydney/Illawara Area Health Service in Sydney. Patient or family consent was obtained from each participant.

**Statistical analysis.** Data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL). A priori, variables were plotted and checked for normal distribution by Kolmogorov-Smirnov tests. Parametric demographic data (age, education), as well as scores on the FRS, were compared via one-way analyses of variance (ANOVA), followed by Tukey HSD post hoc tests. Correlations between the FRS, cognitive assessments, CDR, and length of symptoms were done via Spearman correlation because ACE-R and MMSE scores were not normally distributed for PNFA and bvFTD. Change on FRS scores was analyzed using t tests.

### RESULTS Profiles of FTD variants on the FRS.

Data from 75 patients with FTD were used to compare profiles across clinical variants (bvFTD = 28; SemD = 26; PNFA = 21). As shown in the table, the patient groups were well-matched for age and length of disease.

Profiles of impairment according to logit scores are shown in figure 2A. A one-way ANOVA identified a group effect (F = 12.509, df = 74, p < 0.001) and post hoc tests revealed that the bvFTD group scored lower than the SemD (p < 0.001) and PNFA groups (p < 0.05), with no difference between the 2 language variants. For controls, mean logit staging score was 5.07 (SD = 0.56).

### Table 1 Demographics (SD), length of disease, and ACE-R scores of FTD patient subgroups and controls (n = 95)

<table>
<thead>
<tr>
<th></th>
<th>bvFTD (n = 28)</th>
<th>PNFA (n = 21)</th>
<th>SemD (n = 26)</th>
<th>Controls (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>82</td>
<td>62</td>
<td>62</td>
<td>50</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.8±(8.7)</td>
<td>67 (8.3)</td>
<td>63.3±(6.9)</td>
<td>70.9±(4.9)</td>
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<tr>
<td>Education, y</td>
<td>13 (3)</td>
<td>12.3±(3.7)</td>
<td>13.3±(3.4)</td>
<td>14.5±(3.3)</td>
</tr>
<tr>
<td>Symptoms, y</td>
<td>5.2±(3.5)</td>
<td>5.6±(2.4)</td>
<td>6 (2.7)</td>
<td>NA</td>
</tr>
<tr>
<td>ACE-R (max 100)</td>
<td>66.8±(20.1)</td>
<td>55.3±(21.4)</td>
<td>49.6±(19.1)</td>
<td>95.4±(3.2)</td>
</tr>
<tr>
<td>CDR (0–3)</td>
<td>1.1±(0.6)</td>
<td>0.93±(0.8)</td>
<td>0.6±(0.3)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-R = Addenbrooke's Cognitive Examination Revised; bvFTD = behavioral variant frontotemporal dementia; CDR = Clinical Dementia Rating Scale; FTD = frontotemporal dementia; NA = not applicable; PNFA = progressive nonfluent aphasia; SemD = semantic dementia.

* Controls were significantly older than patients with bvFTD and patients with SemD.

* Controls’ ACE-R scores were significantly higher than those of all patient subgroups.

* Scores of patients with bvFTD were significantly higher than those of patients with SemD (p < 0.05).
We also examined the groups according to their distribution of severity scores.

As shown in figure 3A, virtually all patients with bvFTD fell within the moderate, severe, very severe, or profound categories, whereas for the PNFA and SemD groups 25% fell within the mild category, and none were very severe or profound. The proportion of patients with PNFA in the severe category was about double in comparison to patients with SemD.

The FRS and cognitive measures, CDR, and length of symptoms. There was a correlation between the FRS and MMSE for bvFTD ($r = 0.482; p < 0.05$) and PNFA ($r = 0.675; p < 0.05$) groups. The PNFA group also showed a correlation between the FRS and ACE-R ($r = 0.695; p < 0.05$).

To verify concurrent validity, we compared FRS and CDR scores. There was an overall negative association between the FRS and the CDR ($r = -0.713, p < 0.001$). Figure 3B compares performance on the FRS and CDR. Interestingly, a proportion of patients with minimal or mild dementia on the CDR (0.5 or 1) had moderate or even severe ratings on the FRS.

In terms of disease progression and length of symptoms, only patients with SemD showed a correlation ($r = -0.556; p < 0.03$).

Nature of disease staging and progression. As in AD, overall FTD affects complex ADLs (instrumental ADLs) initially, with changes in basic ADLs later in the course of the disease. Table e-2 outlines the basic and instrumental ADL loss and changes in behavior at the various stages of FTD.

Length of symptoms in each severity category. To analyze the relationship between length of symptoms and staging, we combined the FRS assessments from the initial cohort (sample 1: $n = 77$) and the second cohort (sample 2: $n = 75$), resulting in a total of 152
assessments (sample 4). As shown in figure 4, the SemD group showed the clearest relationship between length of symptoms and severity categories, whereas the bvFTD and PNFA groups showed greater variability.

Since none of the patients with language variants were beyond severe, we have considered the time between symptom onset and reaching mild, moderate, and severe across the variants. It can be seen from figure 4 that for bvFTD the time to reach mild, moderate, and severe was very similar, and that by 5 years the vast majority have severe impairment. By contrast, progression in SemD appears much slower, taking on average 10 years to reach the severe stage. PNFA was somewhat intermediate, with an average around 3 years between mild, moderate, and severe stages.

Rate of decline. Twelve-month follow-up data were available for 42 patients (sample 3; bvFTD = 17; SemD = 15; PNFA = 10). Mean follow-up time was 13.1 months (6–27 months). All subgroups showed marked decline on the FRS ($p < 0.005$ for all), which was greater for the bvFTD group (figure 2B).

DISCUSSION

We were able to identify 6 clinical severity stages in FTD, and to characterize the features of each stage based on a novel instrument, the FRS. These behavioral and functional changes were identified using Rasch modeling. The bvFTD group were the most severely impaired and showed the most rapid progression through the stages.

This study confirms the devastating nature of bvFTD, which produces greater functional loss and behavioral change than SemD and PNFA, even after controlling for length of symptoms. Patients with SemD were the least impaired, with 70% of patients within very mild, mild, and moderate stages, although a recent study using different measures found PNFA to be the least impaired FTD variant. Our results showed that the functional level of the PNFA group was intermediate between bvFTD and SemD, perhaps in line with the pathologic heterogeneity; those presenting with lower scores may have underlying AD pathology. It is notable that half of the patients with PNFA fell in the severely impaired stage, which strengthens the case to use an ADL and behavioral scale. The reasons for this marked decline are unclear: one plausible explanation is the development of apraxia, which is common in PNFA and likely to impact everyday life. A proportion of patients with PNFA develop full-blown corticobasal syndrome as the disease progresses. The severity level of the PNFA group highlights the disabling nature of this variant, and that patients with PNFA have more general cognitive impairment than is commonly recognized.

Determining disease severity is controversial. There is currently a lack of consensus in how to define severity in dementia—different studies use cog-
Cognitive measures, length of disease, or even AD staging tools. Our study shows that severity can be measured using a unidimensional tool, which appears to characterize FTD well as a condition that ultimately causes loss of ability and changes in behavior. In addition, the FRS provided further understanding of disease progression in FTD by showing which abilities are lost first and last, without the limitation of cognitive assessments that are language driven.

The FRS also demonstrated statistically significant decline over a 12-month period in all 3 clinical variants. Longitudinal studies are few in FTD, and have reached varied conclusions especially in terms of survival. One study showed that patients with bvFTD declined faster than those with AD, but the SemD group did not differ from AD. Another study showed a similar rate of deterioration in both bvFTD and AD. The slow progression in SemD is in keeping with the prolonged survival shown in a consecutive series of 100 patients from Cambridge.

The lack of consistent correlation between the FRS and cognitive measures is of interest. It shows that our staging tool is not biased toward language abilities. For instance, several patients were mute but still high-functioning and independent, and therefore obtained scores within the mild stage. More importantly, it highlights the relevance of a staging tool that focuses on functional decline, which, as shown in AD studies, can be very sensitive to change in drug trials. In addition, the detailed clinical information provided by the FRS can guide families and clinicians in making important practical decisions in financial, legal, and long-term care issues.

There was, as expected, a negative association between the CDR and FRS in that advanced stages on the FRS correlated with worsening dementia on the CDR. More interestingly, it appears that the CDR underestimates disease severity since a proportion of patients rated as having minimal or mild dementia (CDR = 0.5 or 1.0) had moderate or severe levels of disability as rated by the FRS. There was an overall trend for length of symptoms to correlate with severity levels on the FRS: most patients with long disease history fall into the severe categories. Conversely, however, not everyone within these categories had a long disease history. This is especially true for patients with bvFTD, who may be at a moderate stage early in the disease. Moreover, this finding demonstrates that length of symptoms does not necessarily reflect dementia severity in FTD, and should be used with caution when matching different dementia groups.

Our study had certain limitations. We did not have pathologic confirmation of the patients assessed, which would clearly take a number of years, but prior studies have demonstrated that the majority of patients with bvFTD and SemD have pathology within the FTLD spectrum although a proportion of those with PNFA have Alzheimer pathology. In addition, a longer follow-up period would provide even more detailed information on disease staging and progression. We have established excellent interrater reliability but retest data should ideally be collected to verify test stability.

This is the first study to describe the specific aspects of disease staging in the variants of FTD. The loss of these abilities can be captured in the FRS, a novel staging tool, which in turn can guide clinicians in determining disease severity and in making prognosis for patients and families.

AUTHOR CONTRIBUTIONS
Statistical analysis was conducted by Dr. E. Mioshi.

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DISCLOSURE
Dr. Mioshi serves on the editorial board of Dementia and Geriatric Cognitive Disorders. Dr. Hsieh, Dr. Savage, and Dr. Hornberger report no disclosures. Dr. Hodges serves on editorial boards of Alzheimer’s Disease and Geriatric Cognition and Aphasia, Cognitive Neuropsychiatry, and Cognitive Neuropsychology; receives royalties from publication of Cognitive Assessment for Clinicians (Oxford University Press, 2007) and Frontotemporal Dementia Syndromes (Cambridge University Press, 2007); and receives fellowship support from the Australian Research Council Federation.

REFERENCES


