Measuring progression in frontotemporal dementia: Implications for therapeutic interventions
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Measuring progression in frontotemporal dementia
Implications for therapeutic interventions

C.M. Kipps, FRACP
P.J. Nestor, FRACP, PhD
C.E. Dawson, RGN
J. Mitchell, BSc
J.R. Hodges, FMedSci

ABSTRACT

Background: There is a need for instruments which can measure progression of disease in frontotemporal dementia (FTD), particularly with respect to the assessment of potential therapeutic agents.

Methods: The Cambridge Early Onset Dementia Clinic database was reviewed for all prospectively enrolled cases of FTD with documented scores on the Mini-Mental State Examination (MMSE) or Addenbrooke’s Cognitive Examination (ACE) on at least two occasions. We identified 50 cases fulfilling these criteria: pathologic confirmation was present in 11 of 16 patients who had died, 12 of the remainder had imaging abnormalities on their initial scans, and 22 had structural scans no different from controls. We compared these groups to a cohort with early AD (n = 25) and healthy controls (n = 10).

Results: There was clear cognitive decline (measured by the MMSE and ACE) in patients who had died, and those with documented atrophy on initial MRI scan. In contrast, patients with FTD with normal scans showed no change in cognitive scores over a much longer interval, and serial ACE measurements paralleled those of controls. Power calculations showed that the inclusion of these patients with FTD would significantly increase the number of cases needed in any therapeutic trial.

Conclusion: Addenbrooke’s Cognitive Examination is a simple monitoring tool which can detect progression of disease in frontotemporal dementia over a 1- to 2-year interval without the need for serial imaging. We estimated that a clinical trial that enrolled subjects with abnormal MR scans would require 135 subjects per group to detect a small effect, and 35 for a medium effect.

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GLOSSARY

ACE = Addenbrooke’s Cognitive Examination; ANOVA = analysis of variance; bvFTD = behavioral variant of frontotemporal dementia; CBI = Cambridge Behavioral Inventory; CDR = Clinical Dementia Rating; DLDH = dementia lacking distinctive histology; FTD = frontotemporal dementia; FTDc = clinically similar FTD cases; FTDp = patients with FTD who have imaging abnormalities and require increasing levels of care or institutionalization; FTP = FTP cases pathologically verified at postmortem; MMSE = Mini-Mental State Examination.

The ability to confidently measure disease progression is vital in any future trials of therapeutic agents in frontotemporal dementia (FTD).1 The ideal instrument should be simple to administer, could be used across multiple sites without difficulty, and would be sensitive to changes in relatively small groups of patients. Furthermore, in a randomized controlled trial, it is of great importance to identify and enroll subjects at greatest risk of disease progression to maximize power to detect a therapeutic effect.

The Addenbrooke’s Cognitive Examination (ACE) is a well-validated scale which has been shown to be useful for the assessment of patients with dementia.2,3 The test measures performance in five cognitive domains (attention and orientation, memory, verbal fluency, language, and visuospatial) and incorporates the Mini-Mental State Examination (MMSE).4

Here we report the use of the ACE in prospectively enrolled subjects with a clinical diagnosis of the behavioral variant of FTD (bvFTD), followed with serial assessments.
We also examine the influence of baseline structural imaging on the rate of cognitive deterioration in bvFTD subgroups, and provide estimated sample sizes for future therapeutic trials.

**METHODS Identification of patients and controls.**

The database of the Cambridge Early Onset Dementia Clinic was interrogated to ascertain cases of bvFTD, followed prospectively where there had been at least two assessments, 6 months apart or more, using the ACE and the MMSE. The diagnosis of FTD was made on the basis of published criteria. The 50 cases of FTD identified in this manner were then matched with 25 patients with clinically diagnosed AD (disease controls) and 10 age-matched healthy controls who had been serially assessed using the same instruments. Patients diagnosed with clinical FTD-MND were excluded from this study.

FTD patient group assignment. The 50 patients with clinically diagnosed FTD were divided into three groups: 1) 16 deceased cases, 11 of whom were pathologically verified at postmortem (designated FTDp+), 2) an additional 12 individuals with clear evidence of brain atrophy on a validated, semiquantitative rating scale or changes on functional imaging scans (FDG-PET, SPECT), and who had clearly deteriorated since diagnosis, requiring increasing levels of care or institutionalization (FTDp), 3) a cohort of 22 patients with FTD in whom MRI or functional imaging was normal throughout their disease course (FTDc [clinically similar FTD cases]). Scores on cognitive test batteries were not taken into account when assigning patients to groups. The pathologic diagnoses in the FTDp group included six patients with tau-positive inclusions, four with ubiquitinated inclusions, and one with a diagnosis of dementia lacking distinctive histology (DLDH).

Cognitive and behavioral evaluation. The ACE (and MMSE) was administered to all patients at the time of their regular clinic follow-up by a nurse or research assistant trained in its administration who was unaware of the MRI ratings (see below). For this study, the original version of the ACE was used on both occasions. Copies of the test are available from the authors at no charge. At the same time, the Clinical Dementia Rating (CDR) was scored and the Cambridge Behavioral Inventory was completed by caregivers. The Neuropsychiatric Inventory was also completed in the majority of cases.

MRI ratings. A clinical quality MRI scan was present in most cases for the patients with FTD (n = 46), and was rated blind to all clinical information including scores on the MMSE, ACE, and CBI using a recently published rating scale. On this 5-point scale, template images are used to rate standard coronal images of the frontal and anterior temporal lobes of the brain at the point where the temporal stem joins the inferior frontal region. The level of atrophy is graded with reference to sulcal widening in frontotemporal cortical regions and the degree of ventricular dilatation. Full details of this scale, the two independent raters who rated the images used in this and previous studies including intra- and inter-rater reliability statistics are available elsewhere. A score of 0 or 1 overlaps with the controls range, and is regarded as normal, although a rating of 1 can be considered borderline abnormal. Ratings between 2 and 4 are regarded as definitely abnormal as they were never seen in age-matched controls. Image ratings were used to dichotomize the group into normal (rating scale 0–1) or abnormal (rating scale 2–4) subgroups, and MMSE and ACE progression was compared between groups.

Data analysis. Demographic variables were analyzed using one-way analysis of variance (ANOVA) (age at first assessment, CBI-Behavior, Neuropsychiatric Inventory) when normally distributed and Kruskal-Wallis with post hoc Mann-Whitney U test where non-normality was present (years education, CDR, duration of illness, interval between initial and final reviews) (table 1).

Initial MMSE scores and annualized change in MMSE were analyzed using nonparametric Kruskal Wallis chi square tests with Dunn corrected post hoc contrasts comparing groups of interest (FTDp+, FTDp, and FTDc).

Initial ACE scores were analyzed using one-way ANOVA with Bonferroni corrected post hoc group contrasts. A mixed two-way repeated measures ANOVA (condition: ACE at onset, review × group: FTDp+, FTDp, FTDc, AD, Control) was used for the analysis of serial ACE scores. Duration of follow-up (i.e., interval between initial and last ACE testing sessions) differed widely between groups, so this variable was used initially as a covariate in the analyses. Pairwise post hoc contrasts were corrected for multiple comparisons (reported at Bonferroni corrected significance p < 0.05) and interactions were interpreted by inspection of interaction graphs. The analyses were repeated for the FTD subjects with normal and abnormal MRI scans on the basis of the image ratings described above. Power calculations for future studies at different effect sizes were performed using customized software for all FTD subjects with an abnormally rated initial MRI scan and combining all FTD subjects irrespective of MRI scan rating.

**RESULTS**

Mini-Mental State Examination. The MMSE differed between patient groups at the outset (Kruskal Wallis: \( H[4] = 39.03, p < 0.001 \)), see table 2. Post hoc tests showed that the FTDc group and controls had better performance on the MMSE than any of the other groups which did not differ from each other. The annual decline in the FTDp and AD groups, but not FTDp patients, was worse than in the FTDc patients and controls (Kruskal-Wallis: \( H[5] = 22.27, p < 0.001 \)).

Addenbrooke’s cognitive examination. One-way ANOVA disclosed that the FTDp+, FTDp, and AD groups were worse than the FTDc group and controls on the ACE at initial presentation \( [F(4,80) = 10.10, p < 0.001] \); post hoc contrasts Bonferroni corrected, \( p < 0.05 \); see table 2.

Change in ACE score using a repeated measures ANOVA design showed a significant effect of condition (i.e., in general ACE scores declined across the testing interval \([F(1,80) = 41.35, p < 0.001]\)). There was also a main effect of group \([F(4,80) = 17.63, p < 0.001]\); pairwise
post hoc comparisons, Bonferroni corrected, showed that the FTD groups and AD patients (all \( p < 0.001 \)) performed worse across the two conditions than either the FTDc group or controls (who did not differ from each other). Importantly, there was a strong group \times\ condition interaction \([F(3,54) = 3.93, p < 0.05]\). Examination of interaction graphs showed that the source of this interaction was that the FTDp+, FTDp, and AD groups had deteriorating ACE performance over time compared with the FTDc and control groups.

In order to compensate for the possible confounding effect of illness duration at the time of ACE testing and differences in interval between cognitive testing, these variables were entered as covariates in a repeated measures ANOVA: change in ACE × diagnostic group. There was no effect of duration of illness at initial testing or of interval between onset and follow-up, and there was no interaction with change in cognitive performance. There was, however, a group \times\ ACE change interaction \([F(3,54) = 3.93, p < 0.05]\). Inspection of interaction graphs showed that the extent of cognitive decline in the FTDp+, FTDp, and AD groups was far greater than that in the FTDc group, which remained stable. The annualized rate of decline on the ACE is shown in figure 1 for the combined FTDp group (pathologically confirmed plus FTD patients with imaging changes), FTDc group, patients with AD, and controls.

Analysis using image ratings only in FTD cases. The annual change in MMSE for FTD cases with im-

### Table 1  Demographic data

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<th>FTDc</th>
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<tbody>
<tr>
<td>n</td>
<td>Mean</td>
<td>(SD)</td>
<td>n</td>
<td>Mean</td>
<td>(SD)</td>
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<td>Age at ACE*</td>
<td>16</td>
<td>58.8</td>
<td>(7.3)</td>
<td>12</td>
<td>63.4</td>
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<tr>
<td>Education</td>
<td>14</td>
<td>11.8</td>
<td>(2.4)</td>
<td>12</td>
<td>11.8</td>
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<tr>
<td>CDR†</td>
<td>16</td>
<td>1.3</td>
<td>(0.7)</td>
<td>12</td>
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<td>NPI total‡</td>
<td>13</td>
<td>39.5</td>
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<td>CBI-Behavior§</td>
<td>12</td>
<td>79.4</td>
<td>(29.4)</td>
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<td>65.8</td>
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<tr>
<td>Interval (months)¶</td>
<td>16</td>
<td>15.9</td>
<td>(9.3)</td>
<td>12</td>
<td>19.9</td>
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<tr>
<td>Duration of illness [y]¥</td>
<td>13</td>
<td>4.9</td>
<td>(4.2)</td>
<td>12</td>
<td>2.9</td>
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### Table 2  Mini-Mental State Examination (MMSE) and Addenbrooke’s Cognitive Examination (ACE) scores at onset and review

<table>
<thead>
<tr>
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<th>bvFTD groups</th>
<th>Control groups</th>
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<tbody>
<tr>
<td></td>
<td>FTDp+, n = 16</td>
<td>FTDp, n = 12</td>
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<tr>
<td></td>
<td>Mean</td>
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<tr>
<td>MMSE (initial)*</td>
<td>24.2</td>
<td>(4.8)</td>
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<tr>
<td>MMSE (final)*</td>
<td>18.1</td>
<td>(6.6)</td>
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<tr>
<td>ACE (initial)*</td>
<td>73.6</td>
<td>(17.4)</td>
</tr>
<tr>
<td>ACE (final)*</td>
<td>52.9</td>
<td>(21.1)</td>
</tr>
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</table>

*\(F(4,80) = 3.77, p < 0.01\); post hoc FTDp+, FTDc, < AD.
†\(F(3,31) = 2.83, p < 0.06\); post hoc AD < FTDp+, FTDp, FTDc, but note relatively small number of AD cases with NPI.
‡\(F(3,63) = 12.58, p < 0.001\); post hoc AD < FTDp+, FTDp, FTDc.
§\(H(4) = 35.26, p < 0.01\); post hoc FTDp+, FTDp < FTDc, AD, Ctrl.
¶\(H(3) = 8.98, p < 0.05\); post hoc FTDp+, FTDp, FTDc < AD.
¥FTDp+ = frontotemporal dementia (FTD) confirmed pathologically; FTDp = clinical diagnosis of FTD with structural or functional imaging changes; FTDc = clinically similar FTD cases where structural imaging is normal; AD = Alzheimer disease controls; NC = age-matched healthy controls; ACE = Addenbrooke’s Cognitive Examination; CDR = Clinical Dementia Rating; NPI total = Neuropsychiatric Inventory total score (frequency \(\times\) severity); CBI Behavior = Cambridge Behavioural Inventory; Interval = the time between the first and last cognitive tests; duration illness = time from onset to time of initial ACE testing.
ages rated as normal (n = 24) or abnormal (n = 22) was analyzed using nonparametric Wilcoxon signed ranks test. Note that two patients from the FTDP group had imaging changes on SPECT but had structural imaging rated within the control range, so for the purpose of this assessment were included in the group with a normal MRI. In those cases where imaging was assessed as normal, the median MMSE showed no pairwise change over the time period (median = 29.0 on both occasions), whereas in patients with FTD with abnormal MRI scans, there was a marked drop in MMSE scores (initial MMSE: median = 26 vs follow-up MMSE: median = 19, Wilcoxon T = 21.5, p < 0.01). This was despite the duration of follow-up being only half as long in the FTDp and AD groups.

A preliminary analysis using the interval between initial and follow-up ACE scores as a covariate in a repeated measures ANOVA showed that despite an overall group difference in duration between the initial and final ACE testing, this covariate was not significant in the model. The data were therefore further analyzed without the covariate which showed a main effect of condition [F(1,44) = 28.75, p < 0.001]; in general, performance on the ACE was worse at follow-up testing. There was also a main effect of group: [F(1,44) = 48.99, p < 0.001]; those with abnormal scans were worse on overall ACE performance across the two time periods. Importantly, there was an interaction [F(1,44) = 9.92, p < 0.01]; inspection of interaction graphs showed that this was due to the relative stability in ACE scores over time in the imaging normal group compared to the imaging abnormal group who deteriorated quite markedly between first and final testing session. The changes in MMSE and ACE scores are shown in figure 2 for both groups; annualized change in the ACE for cases with normal imaging was 2.8 points (SD = 6.4), while for those with imaging abnormality, there was a decline of 13.4 points per year [SD = 13.8, F(1,44) = 11.45, p < 0.01]. The duration of symptoms at first ACE assessment was no different between these two groups (normal MRI: M = 4.4 years, SD = 3.6, abnormal MRI: M = 4.0 years, SD = 3.1; U = 176.5, p > 0.1).

The majority of patients underwent imaging within 6 months of their first cognitive assessment [normal imaging: mean = 3.8 months, SD = 14.5; abnormal imaging: mean = 2.7 months, SD = 15.9; t(44) = 1.4, NS]. The interval between cognitive assessment and imaging, duration of illness at time of ACE, and interval between first and follow-up testing on the ACE were included as covariates in the repeated measures ANOVA. None of these covariates was significant in the model, and there was no covariate interaction with change in ACE scores. A strong interaction was again seen between imaging group and change in ACE [F(1,33) = 11.90, p < 0.01].

The initial score on the ACE was included as a covariate in a repeated measures ANOVA (change in ACE × group) and showed an interaction between the change in ACE performance and the initial ACE score [F(1,43) = 9.21, p < 0.01] but an even stronger interaction between the change in ACE and imaging group [F(1,43) = 20.61, p < 0.001]. Although patients with abnormal imaging had worse initial ACE scores than those with normal imaging (t(44) = 4.47, p < 0.001), there was substantial overlap. In other words, imaging abnormality and not initial ACE score was most predictive of subsequent decline on the ACE.

Scores on the Cambridge Behavioral Inventory (CBI) were measured longitudinally in 36 of the patients with FTD (normal imaging = 22, abnormal imaging = 14). Similar to the ACE, the duration of follow-up was almost twice as long in the

![Figure 1](image-url)
normal imaging group (38.5 months [SD 24.4] vs 19.8 months [SD 11.8]). Interestingly, the extent of the behavioral disturbance in both groups remained high across the time interval, and a repeated measures ANOVA (CBI × group) showed no effect of time period or group, and no group × time period interaction. In other words, measurement of the behavioral disturbance correlated poorly with progression of disease over time, and did not separate out those patients with abnormal imaging from those with normal scans.

**DISCUSSION**

Two factors are crucial for the purpose of clinical trials: the effects of a disease-modifying drug must be measurable within a reasonable timeframe, and, most importantly, only individuals with the disease of interest should be included in the trial. In this work we demonstrate the utility of the ACE in monitoring disease progression and also highlight the importance of carefully screening the entry of patients into any future trials of therapeutic agents for FTD, which can be achieved using a standardized MRI rating scale.11

There was clear progression of deficits on the ACE in patients with pathologically confirmed FTD and in cases where there was evidence of structural abnormality at presentation. This was despite a wide range of ACE scores and a degree of overlap with control values at baseline. Little progression could be demonstrated on the ACE when structural imaging at baseline in FTD subjects was rated as normal, despite a much longer period of follow-up than for the other patient groups. Although these individuals performed worse than controls at presentation, they had a course which paralleled them over time.

The ACE was better at defining cognitive deterioration than the MMSE. Perhaps this is unsurprising since the ACE was designed to be more sensitive to cognitive deficits within the FTD spectrum.3,4 Earlier work demonstrated that verbal fluency (words beginning with P and animals in 1 minute) is a particularly valuable component of the ACE. It is also quick to administer, and can be performed with minimal training. Defined cut-offs exist for neurodegenerative disease,2,3 which would also help facilitate the selection of subjects. It is easily distributed across multiple sites (at no cost), and there are few obstacles to combining

**Power calculations.** In the group of 46 FTD subjects where imaging findings were available, the number of subjects required in a study to show a small, medium, and large effect size, corresponding to a 25%, 50%, and 75% reduction in the annual change in ACE scores, is shown in table 3. In those subjects with an abnormal MRI at baseline, a medium effect size, i.e., 50% reduction in the annual change on the ACE could be detected with 35 FTD subjects. The inclusion of subjects with normal MRI scans at baseline results in a doubling of the sample size needed to show an equivalent reduction in the ACE score over 1 year. This would increase further if patients with FTD with normal imaging at trial entry were overrepresented in the study.
In this study we were not attempting to differentiate clinical cases of FTD from AD using the ACE although earlier studies have shown that it is also useful for this purpose.1,3,16,17

We do not report the results of additional neuropsychological tests such as executive function measures and those using assessment of social cognition.1 It has been argued that most commonly used measures of cognitive function are insensitive to orbitofrontal and mesial frontal pathology which is where the initial pathology may occur in FTD.18-20 Despite this concern, in the monitoring of disease progression for the purposes of a trial, our findings suggest it may be quite reasonable to focus on general cognitive measures such as the ACE. Tests of social cognition and aspects of executive function may be of more utility in early cases, and in separating true FTD cases from those that mimic it, but it remains to be seen whether they are of use in monitoring longitudinal changes. With respect to behavioral ratings, previous work has highlighted the complete overlap of behavioral rating scores in FTD groups with, and without, imaging abnormalities.21 We showed a similar finding in this study, and in addition, behavioral features, unlike the cognitive scores, did not change differentially in the two groups. Reliance on such measures is unlikely to identify individuals at risk of rapid progression.

Patients with bvFTD form the largest group of patients within the FTLD spectrum,22,23 and most trials are likely to concentrate on this group.1 There is also a high frequency of normal imaging findings within this group, a finding contrary to that seen in semantic dementia, which shares a common underlying neuropathology.3,9,11 The failure to detect progression on the ACE despite a longer duration of follow-up in the FTDc group is concordant with our earlier findings reporting a different disease trajectory and enhanced progression in this group.10 Whether this group is non-neurodegenerative or a particularly slowly progressive group remains controversial21,22; this study cannot fully address this issue, although the results are suggestive of a lack of progressive neuropathology in the group of patients with bvFTD with normal imaging at baseline. These patients seldom come to autopsy, yet are likely to be overrepresented in any clinical trial in view of their extended survival.

The power calculations (see table 3) provide preliminary data on the numbers of subjects needed for a clinical trial in FTD using the ACE as an outcome measure. For therapies with a large effect size, as few as 17 subjects in each of the treatment and placebo arms may be needed, although this increases to 135 subjects per arm with smaller predicted effect sizes (i.e., a 25% reduction in ACE change per year, which would constitute a reduction in the decline on the ACE by 3 points per year). Sample size, however, increases dramatically when patients with bvFTD with normal imaging are included in the power calculations, particularly if they are over-represented for any reason. The lack of progression of cognitive scores in these subjects suggests that for the purposes of a clinical trial they should either be excluded, or, at the very least, analyzed separately so as to reduce the chance of type II error in therapeutic trials.

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REFERENCES


Table 3 Power calculations

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<tr>
<td></td>
<td>Mean (SD)</td>
<td>Small (125%)</td>
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<tr>
<td>MRI abnormal</td>
<td>13.4 (13.8)</td>
<td>n=135</td>
</tr>
<tr>
<td>MRI normal</td>
<td>2.8 (6.4)</td>
<td>n=895</td>
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<tr>
<td>Combined MRI normal and MRI abnormal</td>
<td>7.2 (11.9)</td>
<td>n=281</td>
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Small, medium, and large effect sizes correspond to 25%, 50%, and 75% reductions in ACE scores. A therapeutic intervention with a medium effect size in the MRI abnormal group would reduce the mean annual ACE change by 6.7 points (50%), whereas a similar effect in the combined group would require double the number of patients in order to show a reduction of 3.6 points on the ACE. MRI abnormal and MRI normal groups are defined by ratings on structural image rating scale without reference to clinical data. ACE = Addenbrooke’s Cognitive Examination; FTD = frontotemporal dementia.

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