Frontal Assessment Battery and Differential Diagnosis of Frontotemporal Dementia and Alzheimer Disease

Andrea Slachevsky, MD, PhD; Juan Manuel Villalpando, MD; Marie Sarazin, MD; Valerie Hahn-Barma, MSc; Bernard Pillon, PhD; Bruno Dubois, MD

Background: The different distribution of pathologic features in frontotemporal dementia (FTD) and Alzheimer disease (AD) predicts a predominant dysexecutive syndrome in FTD. The Frontal Assessment Battery (FAB) has previously been validated in diseases associated with a frontal lobe dysfunction.

Objective: To evaluate the sensitivity of the FAB to differentiate FTD and AD.

Design: Comparison study.

Setting: Memory Clinic of the Salpêtrière Hospital, Paris, France.

Patients: Twenty-six patients with FTD and 64 patients with AD.

Main Outcome Measures: Comparison of FAB and Mini-Mental State Examination (MMSE) scores between patients with FTD and those with AD.

Results: The mean±SD FAB scores significantly differed between patients with FTD (7.6±4.2) and those with AD (12.6±3.7) (P<.001), but not MMSE scores. The FAB correctly identified 78.9% of the patients. These results were maintained in a subgroup of mildly demented patients (MMSE score, ≥24). In these patients, a cutoff score of 12 on the FAB was optimal to differentiate both disorders (sensitivity, 77%; specificity, 87%).

Conclusions: The FAB takes less than 10 minutes to administer and provides an objective measure to distinguish FTD from AD in mildly demented patients.

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A mong the primary degenerative diseases, Alzheimer disease (AD) accounts for 50% to 70% of cases and frontotemporal dementia (FTD) for 5% to 20%, according to the age of the population studied.1 In neuroimaging (cerebral computed tomography or magnetic resonance imaging), patients with FTD presented predominant anterior atrophy, mainly localized in the frontal and frontotemporal areas, contrasting with the predominant mesial temporal lobe atrophy in patients with AD.2 Functional studies with positron emission tomography or single-photon emission computed tomography confirmed these data, with hypometabolism or hypoperfusion in the frontal, temporal, or frontotemporal cortex in FTD and decreased regional cerebral blood flow or hypometabolism predominantly located in the parieto-occipital cortex in AD.3 Such a different distribution of pathologic features would predict a differential cognitive pattern on mental status examination and, notably, a predominant dysexecutive syndrome in FTD.4,5 Nevertheless, the differential diagnosis is not always easy, especially in patients with mild dementia. Indeed, most patients with FTD also fulfilled the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD.6

Actually, because of the aging of the population, physicians are increasingly confronted with the management of dementia.7 Considering that AD and FTD have different prognosis and treatment, there is a need for tasks that could help physicians to make the differential diagnosis. The Frontal Assessment Battery (FAB), which can be used at the bedside and takes approximately 10 minutes to administer, has previously been validated and shown to identify a dysexecutive syndrome in neurodegenerative diseases.8 The aim of this study was to assess whether the
FAB could contribute to the differential diagnosis of FTD and AD, especially in mildly demented subjects, to serve as a tool that could help clinicians.

 METHODS

 POPULATION

The study evaluated the FAB in 90 consecutive patients referred to the Memory Clinic of the Salpêtrière Hospital, Paris, France, in whom the diagnosis of probable FTD or AD was made. Patients were excluded if they had a history of cerebral stroke, alcohol abuse, major head injury, or other major medical illnesses or psychiatric disorders that could account for their mental status. Twenty-six patients were diagnosed as having probable FTD according to the Lund and Manchester criteria. Their symptoms corresponded to dementia of frontal type, ie, mainly changes in behavior and personality without semantic dementia or progressive aphasia. Functional (single-photon emission computed tomography) and/or structural (computed tomography or magnetic resonance imaging) imaging demonstrating frontal hypoperfusion and/or frontal atrophy was available for all patients. One of the patients had a postmortem examination that confirmed the diagnosis of FTD. Sixty-four patients had probable AD according to the NINCDS-ADRDA criteria. Performance on the FAB was not considered for establishing the diagnosis of FTD or AD. Patients with FTD and AD were comparable in sex ratio and educational level. However, as expected, patients with FTD were significantly younger than patients with AD (Table 1).

FRONTAL ASSESSMENT BATTERY

The FAB consists of 6 subtests exploring different functions related to the frontal lobes and correlated with frontal metabolism, as measured with the regional distribution of fluoroxyglucose F 18 in a positron emission tomography study of patients with frontal lobe damage of various causes. The 6 subtests of the FAB explore the following: (1) conceptualization and abstract reasoning (similarities test); (2) mental flexibility (verbal fluency test); (3) motor programming and executive control of action (Luria motor sequences); (4) resistance to interference (conflicting instructions); (5) inhibitory control (go–no go test); and (6) environmental autonomy (prehension behavior). Each subtest is scored from 3 (better score) to 0, for a maximum score of 18. The FAB has shown a good validity (correlation of $r = 0.82$ with the Mattis Dementia Rating Scale) and interrater reliability ($k = 0.87$).

 STATISTICAL ANALYSIS

Age, years of education, and Mini-Mental State Examination (MMSE) scores were compared by unpaired $t$ tests. The sex ratio was assessed by a $\chi^2$ test. To determine whether the FAB contributes to the differential diagnosis of FTD and AD, the following tests were applied: (1) $1$-way analyses of covariance with the FAB scores and subscores as the dependent variable and age as covariate; and (2) a logistic regression analysis using the FAB and the MMSE scores as independent variables to ensure that the discriminative value of the FAB is not related to the severity of global intellectual deterioration. To determine the cutoff score of the FAB that would yield the highest sensitivity and specificity for differentiating FTD and AD, FAB scores were subjected to a receiver operating characteristic (ROC) curve analysis. For this purpose, the clinical diagnosis of either FTD or AD served as the gold standard against which the results of FAB were compared to calculate sensitivity and specificity. The area under the curve was also calculated to estimate the discriminant ability of the FAB.

The same analyses were performed in a subset of patients with mild dementia (MMSE score, $\geq 24$) to determine whether the FAB contributes to the differential diagnosis even at an early stage of dementia.

RESULTS

FAB SCORES IN PATIENTS WITH FTD AND AD

The 2 groups of patients significantly differed in the FAB scores, but not the MMSE scores (Table 1). Patients with FTD performed worse in each of the subtests of the FAB except motor sequences (Table 2).

VALUE OF THE FAB IN THE DIFFERENTIAL DIAGNOSIS OF FTD AND AD

A logistic regression analysis using the FAB and the MMSE scores as independent variables showed a highly significant influence of the FAB ($\chi^2 = 18.40, P < .001$), but not of the MMSE ($\chi^2 = 3.55, P = .06$).

The ROC curve showed that a cutoff score of 11 on the FAB yielded the highest sensitivity and specificity with regard to differentiating patients with FTD and AD (Figure). Moreover, the area under the ROC curve was

<table>
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<tr>
<th>Table 1. Characteristics of Patients</th>
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<td><strong>Whole Groups</strong></td>
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<tr>
<td><strong>Characteristics</strong></td>
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<tr>
<td>Sex, No. M/F</td>
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<tr>
<td>Age, y†</td>
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<td>Education, y†</td>
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<tr>
<td>MMSE†</td>
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<td>FAB†</td>
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Abbreviations: AD, Alzheimer disease; FAB, Frontal Assessment Battery (18 points possible); FTD, frontotemporal dementia; MMSE, Mini-Mental State Examination (30 points possible).
*Significant differences between groups in the whole population ($P < .001$) and in the early demented group ($P < .001$). Other differences are not significant.
†Results are expressed as mean ± SD (range).
The results of this study show that the FAB is helpful for the differential diagnosis of patients with FTD and AD even at early stages of dementia. The diagnosis of FTD was mainly based on clinical evidence. Lund and Manchester criteria have, however, a high specificity and sensitivity, ensuring that the clinical diagnosis of FTD was as accurate as possible. Moreover, neuroimaging, available for all patients with FTD, confirmed the presence of frontotemporal atrophy and/or hypoperfusion in all patients with FTD, a strong argument in favor of FTD, and the diagnosis was confirmed post mortem in 1 patient in the study. Another issue to consider is that patients with FTD were significantly younger than patients with AD. This was expected, since a clinical characteristic of FTD is earlier occurrence than AD. Several studies have demonstrated that normal aging is accompanied by a decline in executive skills and degenerative changes in the prefrontal cortex. This would limit the discriminative power of the FAB in the study. However, the FAB scores differentiated the 2 groups of subjects independently of age. Another possible limitation of our study is the use of the MMSE to assess level of dementia, because it has no items of executive function (an area of primary dysfunction in FTD) but is heavily weighted on orientation and memory (areas more likely to be affected in AD). Consequently, patients with FTD may be more impaired than their MMSE scores reflect, which could contribute to the differences, especially in the early demented group. Finally, our population had a relatively low level of education (range, 4–14 years) and the results of the study may not be applicable to a population with a higher level. Nevertheless, that the performance of patients with FTD on the FAB was significantly lower argues in favor of more predominant dysexecutive deficits in FTD than in AD and underlines the usefulness of the FAB for distinguishing these 2 degenerative diseases.

Either behavioral or cognitive scales have been proposed for differential diagnosis. The Frontal Behavioral Inventory correctly classified 92.7% of patients with FTD, but patients with vascular dementia and manic-depressive psychosis had scores similar to those of patients with FTD. The Frontotemporal Behavioral Scale had a specificity of 93% and a sensitivity of 100% for the diagnosis of FTD. Finally, the Neuropsychiatry Inventory correctly classified 77% of patients with FTD and AD. However, these behavioral scales require the presence of a caregiver and are dependent on his or her reliability, whereas a cognitive evaluation can be used in all patients.

Some screening tests of cognitive functions have been proposed for the differential diagnosis of FTD and AD,

**VALUE OF THE FAB IN THE DIFFERENTIAL DIAGNOSIS OF PATIENTS WITH EARLY DEMENTIA**

To study the power of the FAB to discriminate patients with FTD and AD with early dementia, we performed the same analysis on a subset of patients with mild impairment according to the MMSE (MMSE score, ≥24). There were 9 patients with FTD and 24 with AD. Patients with FTD and AD were comparable in education level and MMSE scores, but significantly differed in age (Table 1). One-way analyses of covariance with age as covariate showed that patients with FTD performed worse on the global scale and on each subtest, except motor sequences and go–no go (Table 2). Moreover, a logistic regression analysis using the FAB and the MMSE scores as independent variables showed a significant influence of the FAB (χ² = 5.95, P = .02), but not of the MMSE (χ² = 2.47, P = .12).

The ROC curve showed that a cutoff score of 12 on the FAB yielded the highest sensitivity and specificity with regard to differentiating patients with FTD and AD. Moreover, the area under the ROC curve was 0.81, indicating that the FAB had a good discriminant ability.

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Table 2. Value of the FAB and Each of Its Subtests

<table>
<thead>
<tr>
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<th>Whole Groups</th>
<th>Early Demented</th>
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<tr>
<td></td>
<td>AD</td>
<td>FTD</td>
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<tr>
<td>FAB global score (30)†‡</td>
<td>12.6 ± 3.7</td>
<td>7.6 ± 4.2</td>
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<tr>
<td>Similarities (3)†‡</td>
<td>2.2 ± 1.0</td>
<td>1.1 ± 1.2</td>
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<tr>
<td>Verbal fluency (3)†‡</td>
<td>1.9 ± 0.9</td>
<td>1.0 ± 1.1</td>
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<tr>
<td>Motor series (3)</td>
<td>1.5 ± 0.9</td>
<td>1.1 ± 0.9</td>
</tr>
<tr>
<td>Conflicting</td>
<td>2.4 ± 1.0</td>
<td>1.5 ± 1.1</td>
</tr>
<tr>
<td>Instructions (3)†‡</td>
<td>1.9 ± 1.2</td>
<td>1.2 ± 1.1</td>
</tr>
<tr>
<td>Go–no go (3)†</td>
<td>2.5 ± 0.9</td>
<td>2.0 ± 1.1</td>
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</table>

Abbreviations: AD, Alzheimer disease; FAB, Frontal Assessment Battery; FTD, frontotemporal dementia.

*Results are expressed as mean ± SD. Numbers in parentheses are total possible points.
†Significant differences between groups in the whole population (P < .001).
‡Significant differences between groups in the early demented group (P < .001).

Receiver operating characteristic curve in all patients and in patients with a Mini-Mental State Examination (MMSE) score of 24 or greater. In the whole population, a cutoff score of 11 on the Frontal Assessment Battery differentiated the frontotemporal dementia and Alzheimer disease groups with a sensitivity of 81% and specificity of 72%. In patients with early dementia, a cutoff score of 12 on the Frontal Assessment Battery differentiated the frontotemporal dementia and Alzheimer disease groups with a sensitivity of 77% and specificity of 87%.

0.81, indicating that the FAB had a good discriminant ability.
including the Addenbrooke Cognitive Examination.\textsuperscript{22} The FAB, because of its thorough assessment of frontal lobe functions, could have a higher power of discrimination. To the best of our knowledge, other bedside instruments for differentiating FTD and AD, including the Executive Interview\textsuperscript{23} and the Alzheimer Disease Scale and Pick Disease Scale,\textsuperscript{24} have not been studied in patients in the early stages of dementia.

In conclusion, the FAB is a short, quick, and easy battery that can be used by neurologists at the bedside. It is an objective measure that allows them to identify patients with predominant dysexecutive syndrome and to follow the evolution of this dysfunction as the disease progresses. Poor performance on the FAB in conjunction with the presence of behavioral abnormalities could be an important factor indicating the diagnosis of FTD.\textsuperscript{16}

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