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A short neuropsychologic and cognitive evaluation of frontotemporal dementia

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ABSTRACT

Objective: To elaborate a brief but efficient neuropsychological assessment of frontotemporal dementia (FTD), selecting the most specific and sensitive cognitive and behavioural items for distinguish between AD and FTD in the earlier dementia stages.
Methods: Retrospective study with three groups, 35 patients with FTD, 46 with AD and 36 normal subjects, were administered the MMSE, FAB, Tower of London and Stoop's test along with a 98 items behavioural and cognitive questionnaire. The most sensitive items were selected and validated internally for diagnosis by lineal discriminant analysis.
Results: From the 98 items in the questionnaire, 29 showed significant discriminatory power. Non-cognitive symptoms with higher odd-ratio for FTD compared to AD were impairment in social behaviour (disinhibition, aggressiveness), loss of insight and inappropriate acts. Language disorders, such as echolalia, verbal apraxia or aggramatism, dominate in the cognitive profile of FTD. FAB was confirmed as the best cognitive instrument to differentiate FTD and AD. A linear discriminant function with the combination of the FAB score and the items from our questionnaire with higher OR for FTD accurately classified 97% of individuals.
Conclusions: The neuropsychological tests allow the differentiation between FTD and AD. The combination of FAB test with the assessment of key behavioural and cognitive symptoms appears helpful in this distinction.

1. Introduction

Frontotemporal dementia (FTD) accounts for 3–10% of dementia in post-mortem investigations [1–4], while clinical series on presenile dementia have reported a frequency of FTD up to 20% [5,6]. Although FTD has become increasingly recognized by clinicians, in earlier stages its clinical diagnosis is sometimes blurred with Alzheimer's disease (AD). Moreover, despite striking neuropsychological differences between AD and FTD, NINCDS–ADRDA criteria often fail to distinguish between these diseases, since many FTD patients fulfill criteria for AD [7]. Heterogeneity of the clinical forms of FTD and the lack of a classification of FTD until recent years add uncertainty to this differentiation.

Lund and Manchester criteria for FTD diagnosis [4], with the later modification by Neary et al. [5], are currently unanimously accepted as the "gold standard" for the clinical diagnosis of these patients. Nevertheless, difficulties in ascertaining some cases with FTD are common [8–10]. Therefore, additional clinical or neurobiological markers are still needed in this regard. Neuropsychological assessment has been used in several studies to differentiate these diseases by looking into either cognitive or behavioural traits of each disease [3,11–16]. However, the importance of considering both types of symptoms jointly has been only recently stressed [17,18]. Considering the aforementioned issues we conducted a retrospective study using a clinical assessment that included both cognitive and behavioural testing, intended to select the most specific and sensitive items in order to get an efficient and direct discrimination of FTD patients from AD.

2. Patients and methods

We carried out a retrospective chart review and database search of the patients diagnosed with FTD in an outpatient Neurology department of a Community Hospital during a 3-year period. The study included 35 subjects in the FTD group, which had a previous clinical diagnosis based on Neary et al. criteria [4,5], and 46 subjects in the AD group that met a diagnosis of probable AD by NINCDS-ADRDA criteria [19]. The control group comprised 36 subjects cognitively normal and without previous history of

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neurological or psychiatric illness. Age and sex distributions were similar in the three groups. Neuropsychological tests were done by staff that were independent from those that participated in the clinical diagnosis. Additional information was obtained through an interview of the patient and its main caregiver, as well as supplemented by behavioural observation. Random autopsy confirmation was possible in about 10% of cases with exact clinicopathological correspondence.

Dementia was staged according to the Clinical Dementia Rating (CDR) [20]. Cognitive assessment included MMSE in its version validated for the Spanish population [21] and specific frontal tests as Frontal Assessment Battery (FAB) [11], Stroop's [22] and Tower of London [23] tests. In order to use a homogeneous set of cases for comparison, only patients with an MMSE score higher than 12 and CDR 1–2 were included in the study.

FAB [11] and its six different items, conceptualization, mental flexibility, motor programming, resistance to interference, inhibitor control, and environmental autonomy [24–26] were assessed. Each item was scored from 0 to 3 (0 = none; 3 = maximum correct) [11,14]. Stroop's test [22] was scored considering the number of failures and the time required to complete the test. The test was interrupted if the patient reached an upper limit of 20 failures or 120 seconds to moderate the ceiling effect. The Tower of London test [23] was undertaken using a computer version in MS-DOS TBasic, developed specifically for this study. This software program allows the examiner to select the model to be tested (from 1 to 5 minimal movements) and scores the initial latency or time until the patient made the first movement, number of movements and total time employed in the task. The evaluator keys into the program the patient commands. The test was interrupted if the patient reached an upper limit set at twice the minimal movements plus one, or plus two when the minimal movements were five. There was no time limit. Patients who could not finish the test or who made more movements than the maximum allowed were computed as unable to complete the test. As this study was retrospective, Stroop's and Tower of London test could only be assessed in a sub-set of patients.

In addition, we developed a 98-item questionnaire with behavioural and cognitive sections. It was based on the Frontal Behavioural Inventory (FBI) [27], Lund and Manchester items [4] and the Spanish version of the CAMDEX interview for the caregiver [28]. If the caregiver did not understand the question as it was constructed, a different question related to the same target was asked. The language testing was based not only on the caregiver's report, but also on data obtained during the patient evaluation. Each item was scored on a 0–3 scale, with 0 designating absence of the symptom and 3 its maximum severity (see Appendix A).

Statistical data was analyzed with the software SPSS 10.0. Non-numerical data (sex, items from the behavioural and cognitive questionnaire) was examined using the Chi-square (χ^2) test. For numerical data (age distribution, MMSE score, FAB score and Tower of London test results) the Kruskal–Wallis test, a non-parametric alternative to ANOVA test, was used. Dichotomy comparisons (e.g., age at onset) were done with the Student's *t*-test. The behavioural and cognitive questionnaire data was grouped in normal (score 0–1) and abnormal (2–3) for odd-ratio calculations. Cut-off points of FAB, Tower of London and Stroop's tests were determined by Receiver Operator Characteristics (ROC) curves and calculating the area under the receiver operator curve (AUC). Correlation between items in the behavioural and cognitive questionnaire and the different items of the FAB test was examined with the Spearman correlation coefficient.

Finally, for internal validation of the results we calculated the power to classify patients into two groups according to a linear discrimination function. Two models were calculated using the diagnosis of FTD or AD as the non-numerical variable. The first one used only the FAB score as a predictor variable, and the second one included the FAB score and those items of the behavioural questionnaire which were statistical significant.

The study was approved by the Research Ethics Committee of the Ramon y Cajal Hospital. Informed consent was obtained from a surrogate decision maker.

Table 1
Mean age, age at onset and MMSE score for all the groups.

Item	FTD	AD	Control
Mean age	67 ± 9.23	73.48 ± 5.64	64.72 ± 11.02
Age at onset	63.57 ± 9.58	70.33 ± 5.54	
MMSE	18.71 ± 9.39	22.35 ± 5.69	32.69 ± 2.56

3. Results

3.1. Sociodemographic variables

Forty-nine men and sixty-eight women were enrolled, without statistical differences in gender between the three groups ($\chi^2_{(2)}$ 0.305; $p > 0.05$). The age at onset was lower in the FTD group compared to the AD group (Student's *t*; $p = 0.000$). There were no statistical differences in the CDR score (FTD: 1.23 ± 0.77; AD: 1.24 ± 1.35) (Student's *t*; $p = 0.965$) or the MMSE between the FTD and AD groups (Student's *t*; $p = 0.061$) (Table 1).

3.2. Non-cognitive symptoms

The more frequent non-cognitive symptoms in the FTD group were mental rigidity (84%), apathy (79%), loss of insight (76%), disorganization (76%) and aspontaneity (73%).

The symptoms with highest sensitivity for FTD (highest OR) were loss of social awareness (disinhibition, aggressiveness), loss of insight, inappropriateness and mental rigidity (Table 2). The variables of the behavioural and cognitive questionnaire, which better correlated with the FAB items were loss of insight (Spearman's $r = -0.444$; $p = 0.01$) and inappropriateness (Spearman's $r = -0.338$; $p = 0.01$).

Table 2
Behavioural and cognitive questionnaire. Odds-ratio FTD vs. AD. NC: odd ratios not calculable because one of the groups (Alzheimer) is 0. Numbers in italics are the numbers of the questions on Appendix A.

Item	Odds ratio	95% CI
Inappropiateness (*1*)	8.182	1.660–40.317
Aggresiveness (*2*)	14.826	1.785–123.151
Loss of social awareness (*3*)	3.375	1.186–9.605
Poor organization (*6*)	2.579	0.835–7.969
Mental rigidity (*7*)	5.400	1.067–27.328
Perseveration (*8*)	3.818	1.081–13.486
Inappropiateness (*9*)	5.273	1.325–20.984
Loss of insight (*10*)	9.900	3.025–32.395
Dietary changes (*11*)	9.538	1.119–81.335
Memory impairment (*12*)	0.257	0.049–1.346
Disorientatión (*14*)	0.938	0.124–7.083
Confusion episodes (*15*, *16*)	5.984	1.513–23.675
Economy of utterance	1.095	0.393–3.049
Agrammatism (*17*)	6.840	2.123–22.038
Anomia (*18*)	5.769	1.946–17.103
Fluent aphasia (*19*)	6.075	1.889–19.534
Disprosody (*20*)	NC	NC
Sluttering (*21*)	13.333	2.741–64.855
Perseveration (*22*)	NC	NC
Agrammatism (*23*)	11.160	1.323–94.111
Paraphasias (*24*, *25*, *26*)	NC	NC
Loss of word meaning (*27*, *28*)	1.261	0.476–3.338
Echolalia (*29*)	19.190	2.331–157.983

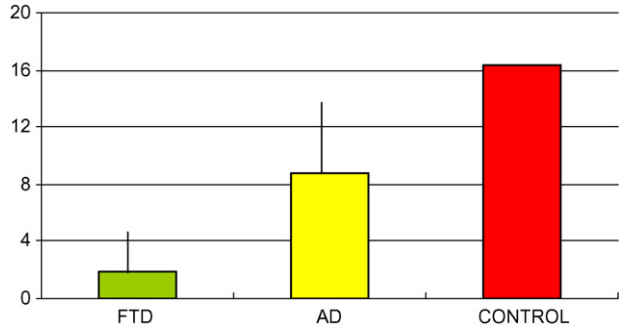

Fig. 1. FAB test results.

3.3. Cognitive symptoms

Language disorders dominated in the cognitive profile of FTD. They included anomia, semantic aphasia, echolalia, palilalia, dysprosody, fluent aphasia, phonemic or semantic paraphasias, aggramatism and stuttering. On the other hand, memory impairment, spatial disorientation or confusional spells were very rare in the FTD group (Table 2). Patients with FTD showed a significantly lower score on every item and on the total score of FAB, compared to AD and normal controls (Kruskal–Wallis; $p = 0.01$) (Fig. 1). The most sensitive FAB item for the diagnosis of FTD was resistance to interference (97%) followed by mental flexibility and inhibitor control (94% each). The first one was also the most specific (100%). Environmental autonomy reached this specificity as well. According to ROC curves, resistance to interference was the most valuable item for FTD diagnosis with an AUC ± CI of 0.985 ± 0.15.

The Tower of London test was applied to 13 patients with FTD (but only three were able to complete it), 39 patients with AD, and 31 healthy controls. This test showed a low capability to discriminate between FTD and AD but was useful to distinguish dementia cases from controls. Although this test did not allow discrimination between the two groups, according to the ROC results the most useful items for the evaluation of patients with FTD were the number of movements in the two movement paradigm (AUC ± CI 95% = 0.799 ± 0.081) and the total time of execution in the five movement paradigm (AUC ± CI 95% = 0.806 ± 0.082).

Stroop's test was performed by 29 cases with FTD, 40 with AD, and 36 normal controls. As with the Tower of London test, Stroop's test was accurate for the diagnosis of dementia, but could not differentiate FTD from AD. Nevertheless, execution time for all the items (reading, colour identification, attention and sensitivity to interference) had a higher discrimination power than number of mistakes.

3.4. Discriminant analysis

With a linear discriminant function, the FAB score classified correctly only 79% of the patients, while the combination of the FAB score and the items from our questionnaire with higher OR for FTD accurately classified 97% of individuals (sensitivity 100%, specificity 93%, negative predictive value 100%, positive predictive value 94%). Only two cases, AD patients that were allocated in the FTD group, were incorrectly classified using this function. The graphical representation of the discriminant function named "*L*" (Fig. 2) was utilized to define a decision rule, so that for $L > 0.5$ the proposed diagnosis was FTD and for $L < -0.1$ the proposed diagnosis was AD.

4. Discussion

We recommend the use of a neuropsychological evaluation to discriminate FTD from AD, as previous studies have done [18,29]. Among the 98 questions taken from previously reported inventories, we selected 29 based on their higher OR for FTD or better correlation with FAB items. These 29 selected questions are listed in Appendix A. The validity of this reduction was proven internally with the discriminant analysis.

Similar scales have been reported to diagnose FTD and differentiate it from AD with high diagnostic accuracy [11,27,30]. The FBI [27], specifically designed to quantify the behavioural disorder of FTD, is particularly useful in early stages. Its discriminating power decreases as disease progresses, due to the disappearance of some symptoms and the appearance of others [30]. The Middelheim Frontal Score [30] is also a helpful assessment tool that detects mainly behavioural symptoms. Although these appear more sensitive than cognitive testing in FTD [31], it also includes cognitive items [18]. The FAB [11] accurately discriminates between patients with frontal lobe dysfunction from normal controls, but the sensitivity and specificity to differentiate FTD from AD are not very high (77% and 87%, respectively) in mildly demented groups [14,32].

Our scale endeavoured to join the more reliable behavioural items of previous scales with specific cognitive characteristics to improve the differential diagnosis of FTD and AD. The assessment was performed in a clinical series. This may be considered a flaw, since several items of the scale were taken from the clinical diagnostic criteria of FTD [4,5], potentially indicating a risk of a circular evaluation. In this regard, random cases of this series with necropsy study showed concordance with the established clinical diagnosis. Additionally, formerly published studies showed high diagnostic accuracy in clinically diagnosed patients [30]. Power calculations

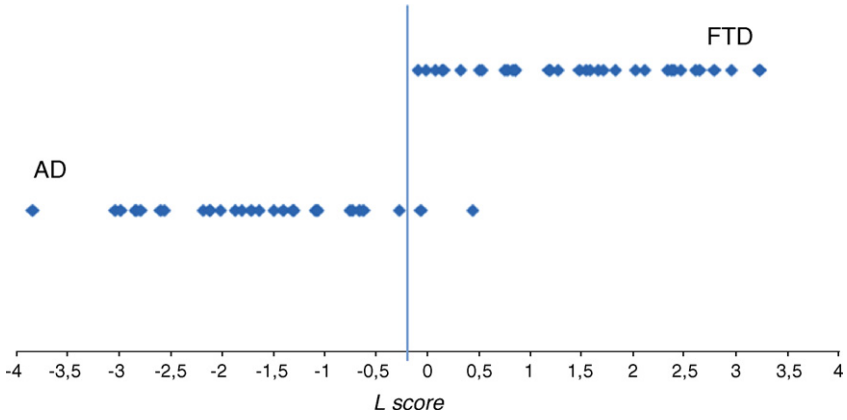

Fig. 2. Graphical representation of the discriminant function.

were not considered necessary for a retrospective study, but lack of differences in some items could be due to underpower for some outcomes.

Solely cognitive tests undertaken in isolation are valid for the examination of executive function and attention deficits. However, they are unable to discriminate AD from FTD [32]. Despite the different pattern of brain damage, both groups showed a poor performance on Stroop's and Tower of London tests, secondary to an inhibitory dysfunction related to the disconnection within the network of cerebral areas recruited during the performance of these tests [33,34]. In our series, only specific criteria subsets of the FAB test were useful, such as the mental flexibility, which indicated a good sensitivity and the environmental autonomy which had high specificity, confirming established reports [35].

The most prevalent behavioural and cognitive symptoms for the FTD group were apathy, loss of insight, perseveration, personal neglect, logopenia, anomia and semantic aphasia as described previously [3]. Among these, loss of insight and anomia were the most sensitive, along with inappropriateness and aggramatism.

We point to the importance of assessing language performance, as this function is affected in all FTD phenotypes [36]. Moreover, the typical aphasic profile of FTD is different from AD, so it may have additional usefulness to distinguish between these two types of dementia [36].

In conclusion, our study supports that the neuropsychological study of FTD must include a behavioural questionnaire together with frontal lobe function tests. Selected questions from the battery used for the diagnosis of FTD along with the FAB test can be use with a good clinical reliability in distinguishing FTD from AD.

Appendix A

A.1. FTD questionnaire (applied to the caregiver)

Inform the caregiver that we are looking for changes in previous status. Score will be done according to the following: 0 = none; 1 = mild, occasional; 2 = moderate; 3 = severe, most of the time.

1. Has s/he kept social rules or has s/he said or done things that are unacceptable?
2. Has s/he shown physical or verbal aggression?
3. Does his/her behaviour have serious social consequences (e.g., separation, lose of job, imprisonment, etc.)?
4. Does s/he deny any problems when discussed?
5. Is s/he aware if s/he does anything wrong (e.g., inappropriate conduct such as behaving rudely or childishly)?
6. Is s/he able to finish the activities that s/he initiates?
7. Does s/he have recurrent ideas that s/he cannot avoid?
8. Does s/he do acts without sense, unnecessarily or ritualistically?
9. Does s/he look into the rubbish or likes keeping unnecessary things?
10. Is s/he worried because of any repetitive acts or ideas?
11. Has s/he changed her/his diet?
12. Does s/he have difficulty in remembering a small list of things?
13. Does s/he have difficulty in remembering recent events?
14. Does s/he have any difficulty in finding her/his way home?
15. Does s/he have spells of confusion?
16. Is her/his level of impairment fluctuant during a given day (or during the course of the day)?
17. Has her/his conversational fluency decreased?
18. Does s/he have any difficulty in naming objects?
19. Does s/he use fluent, effortless language but without meaning?
20. Is her/his voice monotonous and constant?
21. Is there stuttering or hesitation in her/his speech?
22. Does s/he repeat phonemes quickly, effortlessly?
23. Does s/he construct sentences correctly?
24. Does s/he reverses words?
25. Does s/he make mistakes during conversations (phonemes changes)?
26. Does s/he use correct words but with a personal and wrong meaning?
27. Has s/he had more difficulty in understanding words than in the past?
28. Has s/he had any difficulty in understanding orders or a simple conversation?
29. Does s/he repeat the last words said by another person?

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