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Can progressive and non-progressive behavioral variant frontotemporal dementia be distinguished at presentation?

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ABSTRACT

Background: Recent findings suggest that behavioral variant frontotemporal dementia (bv-FTD) patients differ in their disease progression (progressive vs. non-progressive patients). The current study investigates whether the two groups can be discriminated by their clinical features at first presentation.

Methods: Archival clinical data of the Early Onset Dementia Clinic, Cambridge, UK were analyzed of 71 bv-FTD patients: 45 progressive and 26 non-progressive cases with more than 3 years follow-up.

Results: The subgroups were largely indistinguishable on the basis of the presenting clinical features but could be distinguished on general cognitive (ACE-R) and selected supportive diagnostic features (distractibility, stereotypic speech, impaired activities of daily living (ADLs) and current depression).

Conclusions: Progressive and non-progressive patients are difficult to differentiate on the basis of current clinical diagnostic criteria for FTD but a combination of general cognitive, executive dysfunction and impaired ADL measures appear to be the most promising discriminators.

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INTRODUCTION

Frontotemporal dementia (FTD) is a common cause of young onset dementia (<65 years).[1] Clinical diagnostic criteria have been proposed [2] but the differentiation from other dementias remains problematic,[3, 4] particularly for the behavioral variant of FTD (bv-FTD) in which patients present with changes in personality and social conduct [5, 6], with considerable impact on carers [7].

Recent findings have shown variation in disease progression of bv-FTD. Some patients progress rapidly over few years, others show barely change over a decade [8-10]. This raises important issues concerning current diagnostic criteria which appear not to distinguish patients with definite FTD from those with little or no progression. The aetiology of these non-progressors is a matter of ongoing debate; it seems increasingly unlikely that they have true FTD but rather a “phenocopy”, which mimics the behavioral symptoms of bv-FTD [8, 9].

The current study aimed to differentiate progressors and non-progressors on the basis of their behavioral profiles at presentation by analysing 1) the clinical features of the FTD consensus criteria [2], 2) caregiver information from the Cambridge Behavioural Inventory (CBI).

METHODS

Case Selection

Review of the Cambridge Clinic database (1991-2007) yielded 123 patients with a clinical diagnosis of bv-FTD. 52 patients were excluded for the following reasons: follow-up of less than 3 years; no independent informant; limited clinical data; patients referred late in their illness. All patients were assessed by the same behavioral neurologist (JRH), neuropsychiatrist (Prof. G. Berrios) and underwent neuropsychological evaluation and MRI scanning. None met the criteria for major depression, schizophrenia, obsessive compulsive disorder, or substance abuse. All caregivers were interviewed independently [11] and reported an insidious change in behaviour and social function characteristic of bv-FTD. Diagnosis at the time of presentation was made at a consensus multi-disciplinary meeting and patients were followed in a dedicated clinic.

Prior to attendance at the clinic, all caregivers completed the Cambridge Behavioural Inventory (CBI) [12], which assesses several domains (see Table1). The CBI items are scored by frequency of occurrence (0-4), and have been validated against the Neuropsychiatric Inventory [12, 13]. Only data from the first assessment were included in the analyses.

A neurologist (CK), not involved in the initial evaluation and blind to subgroup membership, classified the cases into progressive vs. non-progressive based on decline in general cognitive function (i.e., Addenbrooke’s Cognitive Examination (ACE-R [14]), and everyday abilities over 3 years. The MRI scans were rated for atrophy using a semi-quantitative visual rating scale [8, 9]. These selection criteria yielded 45 progressive and 26 non-progressive cases. Of the progressive cases, 32 were dead, including 18 cases with available postmortem investigations confirming FTD pathology (tau or TDP-43

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positive) in all cases. The research program was approved by the Addenbrooke's Hospital Local Research Ethics Committee.

Selection of clinical features

Clinical features were coded into core, supportive (history, physical, behaviour, language and other) and exclusion features from letters and clinical notes by a neurologist (BS), not involved in their diagnosis and was blind to the progressor vs. non-progressor status.

Statistics

Data were analyzed using SPSS15.0 (SPSS Inc., USA). Parametric variables (age, education, ACE-R, MMSE, CBI) were compared across the groups via independent t-tests. Non-parametric categorical clinical data were analyzed with Chi-Square tests and Mann-Whitney tests, respectively.

RESULTS

Demographic and global cognitive function (Table 1)

Comparisons between progressors and non-progressors revealed no significant difference in demographic variables, except sex distribution with a higher percentage of men in the non-progressor group ($p < .025$). The two groups differed in their performance on the ACE-R total score ($p < .01$), which was lower in the progressive group. Baseline MRI scans were rated as 0-1 in all non-progressors while all progressors had at least one region rated as 2 [8, 9].

Cambridge Behavioural Inventory

On the CBI significant inter-group differences were present for the Everyday Skills ($p < .025$); Self-care ($p < .01$) and Sleep ($p < .01$) subscores which were abnormal in the progressors. All other CBI subscores showed similar performance in the two groups.

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Table 1. Mean scores (SD in brackets) for progressive and non-progressive patients on demographics, general cognitive and clinical tests.

	Progressors	*Non-progressors*	*Progressors vs Non-progressors*
N	45	26	-
Age	68.9 (8.3)	67.4 (7.7)	n.s.
Education	11.5 (2.2)	12.2 (2.4)	n.s
Age at onset	57.6 (8.5)	54.1 (7.6)	n.s
Length of history	3.9 (3.4)	2.9 (1.8)	n.s.
Handedness (R/L)	33 / 2	20 / 2	n.s
Sex (M/F)	28 / 17	24 / 2	*
ACE (100)	67.1 (20.6)	82.6 (20.4)	**
MMSE (30)	24.5 (4.9)	26.4 (6.2)	n.s.
CBI (316)	71.4 (67.1)	61.5 (57.9)	n.s.
Memory	11.9 (5.7)	10.8 (5.8)	n.s.
Attention/Orientation	9.1 (5.5)	8.1 (7.2)	n.s.
Everyday Skills	11.3 (8.7)	4.9 (6.9)	*
Self Care	6.2 (6.8)	1.2 (1.3)	**
Mood	11.7 (6.7)	12.4 (7.8)	n.s.
Abnormal Beliefs	2.6 (3.4)	3.7 (4.7)	n.s.
Challenging Behavior	3.8 (3.5)	3.7 (4.2)	n.s.
Disinhibition	6.3 (4.7)	4.6 (4.6)	n.s.
Eating Habits	6.8 (4.3)	5.5 (4.7)	n.s.
Sleep	4.2 (2.2)	2.2 (1.6)	**
Stereotypicality	16.6 (9.2)	13.8 (7.4)	n.s.
Motivation	21 (8.1)	17.2 (9.6)	n.s.

n.s. = non significant.
** = $p < .01$.
* = $p < .05$.

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Core and supportive diagnostic criteria
No differences between progressors and non-progressors were present for any core feature (Table 2). Decline in personal and social conduct was equally high in both groups. Less frequent for both groups were loss of insight and emotional blunting, although over 60% of cases presented with these clinical features. Excluding insidious onset which was universally present, 80% of progressors and 70% of non-progressors exhibited 3 or more core diagnostic features at first presentation.

Distractibility and stereotypic speech were the only supportive features that were significantly more common in the progressive cases. The other supportive feature that approached significance was current depression ($p = .065$) which was more frequent in non-progressors. Incontinence, hyperorality, speech pressure, extra-pyramidal abnormalities and bulbar palsy were present in less than 8% of cases.
A binary logistic regression (using: distractibility; stereotypical speech; current depression; personal hygiene; impaired ADLs) showed that none of the factors discriminated the groups. We also collapsed the clinical features into core, physical supportive, behavioral supportive and language supportive features. Non-parametric analyses showed a difference for the language features only ($p < .025$) which were more common in progressors.

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Table 2. Percentage of progressors vs. non-progressors with consensus criteria clinical features at presenation.

N	*Progressors (45)*	*Non-progressors (26)*	*Progressors vs Non-progressors*
	% of cases		
Core features			
Insidious Onset	100	100	n.s.
Personal conduct decline	98	92	n.s.
Social conduct decline	89	83	n.s.
Loss of insight	76	68	n.s.
Emotional blunting	67	65	n.s.
Supportive features			
History			
Onset < 65 years	81	96	n.s.
Physical			
Dietary changes	51	42	n.s.
Personal hygiene	30	12	n.s.
Loss of manners	29	23	n.s.
Gluttony	27	19	n.s.
Incontinence	11	0	n.s.
Hyperorality	2	0	n.s.
Behavioral			
Loss of empathy	71	58	n.s.
Distractibility	66	35	*
Mental rigidity	57	54	n.s.
Restlessness	53	35	n.s.
Perseveration	48	42	n.s.
Preoccupations	16	19	n.s.
Utilization	2	0	n.s.
Language			
Stereotypic speech	36	12	*
Speech aspontaneity	16	8	n.s.
Speech pressure	0	0	n.s.
Other			
Primitve reflexes	32	16	n.s.
Extra Pyramidal	5	0	n.s.

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abnormalities			
Bulbar palsy	7	0	n.s.
Current depression	7	23	p = .065

n.s. = non-significant.
* = p < .05.

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Exclusion clinical features

Analysis of the exclusion features (i.e., abrupt onset, seizures, head trauma at onset, severe amnesia, history spatial disorientation, myoclonus, pyramial signs, cerebellar ataxia, alcohol, vascular disease) showed no significant difference between the two groups. These features were generally absent in both groups, except amnesia, which was present in 11.1% and 3.8% of progressors and non-progressors, respectively.

DISCUSSION

Using the current diagnostic criteria it is difficult to distinguish progressive from non-progressive bv-FTD patients at first presentation. Both groups show high levels of endorsement for insidious onset, decline in personal and social conduct, loss of insight and emotional blunting. Three or more core diagnostic criteria were present in over 70% of cases. It is also interesting that not all of the progressing bv-FTD patients present all 5 core criteria at first presentation.[2] Of note is the fact that the diagnoses in all cases were made in a multidisciplinary clinic setting by an experienced team.

For the supportive features [2], distractibility and stereotypic speech were the only factors showing significant inter-group difference. A binary logistic regression confirmed that none of the consensus criteria distinguished the groups. When the supportive features were collapsed, the speech subcomponent was found to discriminate between the groups; probably due to the higher prevalence of stereotypic speech in the progressors.

The issue of exclusion features is complex. In this study, we permitted the diagnosis in patients with a typical presentation, even in the presence of one excluding feature, usually alcohol abuse or amnesia. Signs of alcohol abuse might be a secondary manifestation of social disinhibition in bv-FTD and a prior clinicopathological study [15] showed that 10% of FTD patients present with severe amnesia.

In addition to the information gained from clinical interviews of family members, the CBI showed a group separation for Everyday Skills, Self-care and Sleep subscores. This reflects the underlying deficit in activities of living in progressors.[16] Unfortunately, there are only two questions in the Sleep section of the CBI (poor nocturnal sleep and day-time sleepiness). Sleep and circadian rhythms require more systematic exploration in bv-FTD.

Poor differentiation of progressors and non-progressors at presentation presents a problem. If the clinical features are identical, how can non-progressors be distinguished without waiting for three years for a more definite diagnosis? Our study suggests that activities of daily living (ADL) impairment and general cognitive function may distinguish the subgroups. This is supported by recent work [16] showing that progressive and non-progressive bv-FTD can be separated on the basis of their ADL performance. The lower ACE-R scores in progressors presumably reflects executive dysfunction, which has been shown to distinguish progressive and non-progressive patients [17].

Together with tests of executive function, structural brain imaging, provide the clearest method of distinguishing patients with true FTD [8, 9]. The results of

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the present study, together with other recent parallel investigations, suggest that a combination of MRI quantification of brain atrophy, measurement of executive function and assessment of ADLs allow the most promising distinction between progressive and non-progressive bv-FTD patients.

The aetiology of the non-progressors remains unknown.[8, 9] Given their excellent long-term prognosis it seems unlikely that they have a neurodegenerative disorder. All were seen by an experienced neuropsychiatrist (Prof. G. Berrios), to exclude standard psychiatric diagnosis, although a proportion manifested a degree of mood disturbance and some may fit within the autism-Asperger's spectrum.

In conclusion, the widely used consensus diagnostic criteria [2] are in need of revision, as highlighted recently.[18] Supportive features were present in a minority of the cases, making their inclusion questionable. We support a revision of the criteria to incorporate levels of certainty: definite, probable and possible, depending on the combination of features present. Impairment in instrumental ADLs should be included as a core diagnostic feature given their ability to distinguish progressive from non-progressive bv-FTD cases.[16]

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REFERENCES

1. Ratnavalli E, Brayne C, Dawson K, et al. The prevalence of frontotemporal dementia. Neurology. 2002;58:1615-21.
2. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 1998;51:1546-54.
3. Wittenberg D, Possin KL, Rascovsky K, et al. The early neuropsychological and behavioral characteristics of frontotemporal dementia. Neuropsychol Rev. 2008;18:91-102.
4. Gregory CA, Orrell M, Sahakian B, et al. Can frontotemporal dementia and Alzheimer's disease be differentiated using a brief battery of tests? Int J Geriatr Psychiatry. 1997;12:375-83.
5. Snowden JS, Bathgate D, Varma A, et al. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. J Neurol Neurosurg Psychiatry. 2001;70:323-32.
6. Rankin KP, Kramer JH, Mychack P, et al. Double dissociation of social functioning in frontotemporal dementia. Neurology. 2003;60:266-71.
7. Mioshi E, Kipps CM, Dawson K, et al. Activities of daily living in frontotemporal dementia and Alzheimer disease. Neurology. 2007;68:2077-84.
8. Kipps CM, Davies RR, Mitchell J, et al. Clinical significance of lobar atrophy in frontotemporal dementia: application of an MRI visual rating scale. Dementia and geriatric cognitive disorders. 2007;23:334-42.
9. Davies RR, Kipps CM, Mitchell J, et al. Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging. Archives of neurology. 2006;63:1627-31.
10. Snowden JS, Neary D, Mann DMA. Fronto-Temporal Lobar Degeneration: Fronto-Temporal Dementia, Progressive Aphasia, Semantic Dementia. Churchill Livingstone; 1996.
11. Hodges JR. Cognitive Assessment for Clinicians. 2 ed.: Oxford University Press; 2007.
12. Wedderburn C, Wear H, Brown J, et al. The utility of the Cambridge Behavioural Inventory in neurodegenerative disease. Journal of neurology, neurosurgery, and psychiatry. 2008;79:500-3.
13. Nagahama Y, Okina T, Suzuki N, et al. The Cambridge Behavioral Inventory: validation and application in a memory clinic. J Geriatr Psychiatry Neurol. 2006;19:220-5.
14. Kipps CM, Nestor PJ, Dawson CE, et al. Measuring progression in frontotemporal dementia: implications for therapeutic interventions. Neurology. 2008;70:2046-52.
15. Graham A, Davies R, Xuereb J, et al. Pathologically proven frontotemporal dementia presenting with severe amnesia. Brain. 2005;128:597-605.
16. Mioshi E, Kipps CM, Hodges JR. Activities of daily living in behavioural variant frontotemporal dementia - Differences in caregiver and performance-based assessments. Alzheimer disease and associated disorders. In press.
17. Hornberger M, Piguet O, Kipps CM, et al. Executive function in progressive and non-progressive behavioral variant frontotemporal dementia. Neurology. In Press.

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18. Rascovsky K, Hodges JR, Kipps CM, et al. Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): current limitations and future directions. Alzheimer disease and associated disorders. 2007;21:S14-8.

Appendices: None