Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the ‘bvFTD phenocopy syndrome’

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\textbf{Introduction}

Behavioural variant frontotemporal dementia (bvFTD) is the most common presentation of frontotemporal dementia (FTD) \cite{1,2}. Patients usually present with changes in behaviour and personality, including alterations of mood, motivation and inhibition, which are recognized in the current diagnostic criteria \cite{3} (Table 1). These clinical diagnostic criteria have, in the past, been shown to reliably detect and discriminate bvFTD from other dementias \cite{4}; however, recent work has identified patients fulfilling diagnostic criteria for the disease who do not appear to progress clinically. This review describes means of distinguishing this group at an early stage from patients who are likely to deteriorate.

\textbf{Phenocopy syndrome}

Researchers at the Cambridge Dementia Group became aware of a group of bvFTD patients in whom there did not appear to be disease progression following clinical diagnosis despite a clear history from caregivers of initial personality and behavioural changes. Using a visual scale to rate the degree of atrophy in frontal and temporal lobes, it became clear that there was a distinct lack of frontotemporal atrophy on structural imaging in many of those patients \cite{6}. Crucially, imaging changes are not currently mandatory for definite bvFTD diagnosis. More importantly, Kipps and colleagues \cite{6} noted that other frontotemporal syndromes (particularly semantic dementia, but also progressive nonfluent aphasia), invariably showed significant atrophy by the time of diagnosis. By contrast, over half of the bvFTD patients had scans that overlapped with the control range (0–1) (see Fig. 1).

\textbf{Purpose of review}

The clinical features of behavioural variant frontotemporal dementia (bvFTD) are well established; however, recent work has identified patients fulfilling diagnostic criteria for the disease who do not appear to progress clinically. This review describes means of distinguishing this group at an early stage from patients who are likely to deteriorate.

\textbf{Recent findings}

Despite indistinguishable clinical profiles, studies in a cohort of bvFTD patients showed a particularly good prognosis in a subgroup of predominantly male patients in whom initial structural imaging was normal. This could not be explained by differences in disease duration, and was confirmed by subsequent PET studies. Retrospective review of clinical data in these groups verified that the current clinical diagnostic criteria are both insensitive to true progressive bvFTD, particularly in the early stages, and also poorly specific. In contrast, measures of activity of daily living performance, executive function and tests of social cognition appear to have better discriminatory value for patients who show clear clinical progression, with many individual diagnoses verified by post mortem examination in this group.

\textbf{Summary}

It remains doubtful that the nonprogressive group have a neurodegenerative disease. The implication for the current clinical diagnostic criteria and their proposed revision is discussed.

\textbf{Keywords}

diagnosis, frontotemporal dementia, imaging, neuropsychology, phenocopy

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Moreover, a retrospective survival analysis of a bvFTD cohort [5] showed that those patients with abnormal scans were largely dead or institutionalized within 3 years, in line with median survival time in pathologically proven cases of bvFTD [7]. However, patients with scan ratings in the control range had a significantly better disease prognosis, with some patients surviving for 10 years or longer. Importantly, disease duration was controlled for between both groups and therefore was unlikely to contribute to the findings. To our knowledge, there are no pathologically verified studies of such bvFTD phenocopy cases; however, two cases from the Cambridge sample have since come to autopsy and did not show frontotemporal lobar degeneration (FTLD) specific pathology. In addition, two single cases diagnosed clinically as bvFTD, but lacking pathological changes at post mortem, have been reported as asides in other studies [8,9] highlighting again the importance of detecting such phenocopy cases at a clinical level.

Clinical features
Nonprogressive bvFTD cases are a concern as they mimic the clinical characteristics of frank bvFTD. A study by Hornberger and colleagues [10] investigated whether the diagnostic criteria for the Cambridge bvFTD patients were inappropriately applied, or whether the clinical diagnosis in the nonprogressive group of patients was insufficiently rigorous. The entire bvFTD cohort of the Cambridge Dementia Group was assessed retrospectively [10], including 71 patients in whom follow-up information was available for at least 3 years to be certain of the disease progression. Importantly, clinical features at presentation were extracted blind to knowledge about imaging and subsequent outcome. Characteristics defined by the consensus criteria, those from earlier lists of diagnostic formulations, and a number of frontal behavioural characteristics derived from behavioural rating scales were noted. Of these patients, 32 had died, and 18 of these had post mortem data which confirmed the clinical diagnosis. The results confirmed the inability of the clinical diagnostic criteria to separate progressive cases from those that remained stable after clinic presentation. More specifically, progressive bvFTD and phenocopy cases were virtually identical on the core bvFTD diagnostic criteria and only showed significant differences for a few supportive diagnostic features [distractibility, stereotypic speech, impaired activities of daily living (ADLs) and current depression].

Carer and functional information
One factor which is likely to have influenced the identical behavioural presentation in both groups is the lack of insight many bvFTD patients show. Clinicians need to rely heavily on information provided by carers to corroborate symptoms, and in few other diseases is the clinician so dependent on the carer in reaching a diagnosis. In the studies mentioned above, behavioural symptoms reported by carers, and rated using behavioural inventories such as the Cambridge Behavioural Inventory and Neuropsychiatric Inventory, were indistinguishable in real and phenocopy bvFTD patients [11], with all caregivers being adamant that there had been both a distinct change in behaviour, and progression over time. By contrast, functional assessments of ADLs show differential performance in phenocopy and bvFTD cases. Mioshi et al. [12] showed that a detailed assessment of ADLs was effective at identifying those patients in whom performance was truly compromised; this group overwhelmingly comprised patients from the progressive bvFTD patient group. In a follow-up study [13], it was shown that only bvFTD patients with significantly impaired ADLs decline functionally over a 12-month period, whereas phenocopy patients do not deteriorate functionally over the same time frame.

Neuroimaging
In addition to the sensitivity of visual scan ratings, functional imaging studies have shown excellent...
Neuropsychology and social cognition

Sophisticated imaging modalities such as PET and MRI are not always readily available, and although patients with bvFTD often end up in specialist dementia clinics, diagnosis may be delayed, or confused with psychiatric syndromes [15]. Neuropsychological assessments are often performed as a means of establishing whether a neurodegenerative process is occurring or not. In particular, executive function performance in phenocopy and real bvFTD patients has provided useful insights into which tests are most useful in diagnosing each group at clinic presentation.

In a retrospective study of executive tests, phenocopies performed at control levels, whereas real bvFTD patients were usually impaired [16]. In particular, the Verbal (letter) Fluency task, Digit Span Backwards, the Hayling test of Inhibition and the Trail making Test Part B ( Trails B ) were good discriminators [16], with Hayling and Digit Span Backwards alone correctly classifying 85% of patients at first clinic presentation. Global cognitive screening measures such as the Addenbrooke’s Cognitive Examination ( ACE-R ) [17] were also capable of monitoring cognitive decline, with 10–12 points expected loss per annum on this scale in progressors, compared with comparative stability in those patients with normal imaging [18]. On a cautionary note, up to 25% of patients shown to subsequently progress had normal neuropsychology at clinic presentation [16], implying that normal neuropsychological performance is not a reliable exclusion criterion for the disease and that such measures should be corroborated by imaging or ADL performance when possible.

Interestingly, the admixture of phenocopy and real bvFTD patients might have contributed to earlier contradictory neuropsychology findings in bvFTD as the ratio of each group in a study would have the potential to affect the outcome. This might explain the previously mixed results in executive functioning in bvFTD, and was recently proposed as an explanation for the variability of reported memory problems at presentation in bvFTD. For example, a study by Hornberger and colleagues [19] showed that real bvFTD patients were impaired to a similar degree as Alzheimer disease patients on episodic memory tests, whereas phenocopies showed near normal performance.

Measurement of performance on tasks assessing social dysfunction has provided a further means for discriminating both patient groups at presentation. Patients with bvFTD have well-documented impairment of their ability to interpret emotion in others – they lack empathy, and have defective ability to represent the mental states of others ( Theory of Mind ) [20,21]. A behavioural study looking at emotion and sarcasm interpretation showed that there was particularly impaired negative emotion recognition in those bvFTD patients who had imaging changes [22]. Similarly, sarcasm interpretation, requiring mental state attribution and the interpretation of emotion signals, showed that bvFTD patients with imaging changes on MRI and PET performed badly on this measure as well [22]. It is not clear at this stage whether such social cognition tests can be applied in everyday clinical practice, as normative age-related data are not available for most tests, however social cognition assess-

Figure 2 Flowchart of a possible diagnostic approach to discriminate phenocopy from real behavioural variant frontotemporal dementia patients at clinic presentation

<table>
<thead>
<tr>
<th>Fulfill clinical criteria for bvFTD?</th>
<th>No</th>
<th>Exclude bvFTD diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired on executive function tests and ADLs?</td>
<td>Yes</td>
<td>Probable bvFTD</td>
</tr>
<tr>
<td>MRI atrophy (frontotemporal)</td>
<td>No</td>
<td>Probable bvFTD</td>
</tr>
<tr>
<td>FDG-PET hypometabolism (frontotemporal)</td>
<td>Yes</td>
<td>Probable bvFTD</td>
</tr>
<tr>
<td>If female → possible phenocopy If male → probable phenocopy</td>
<td>Monitor progression</td>
<td></td>
</tr>
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ADLs, activities of daily living; bvFTD, behavioural variant frontotemporal dementia.
ment seems a promising avenue for future bvFTD diagnostic assessment.

Clinical diagnosis
On a purely practical level, how should the above pheno-
copy evidence guide or influence clinical diagnostic practice? Since these patients have not yet come to post mortem in convincing numbers, we cannot state with certainty that there is no neurodegenerative process occurring. However, it would seem unlikely in view of the normal imaging many years after symptoms onset; the lack of clinical progression when under medical review; and near-normal neuropsychological and ADL performance. Identification on clinical characteristics alone is problematic, and should be supported by the results of executive function tests, ADL assessment and concordant imaging changes in the frontal and/or temporal lobes (see Fig. 2). In those bvFTD patients with globally abnormal executive function and impaired ADLs as well as clear imaging evidence, the diagnosis is likely to be a pathological form of bvFTD. In patients who do not show impairment in these domains, despite a convincing set of other clinical criteria, one should maintain a strong degree of caution if the imaging findings are normal (see Fig. 2). In these patients, it would be sensible to carefully re-visit the history and attempt to corroborate it independently. Where doubt remains, a period of monitoring without confirming a degenerative process seems sensible, followed by re-examination of executive function and imaging measures to verify disease progression after an interval of at least 12 months.

Implications for bvFTD diagnostic criteria
The studies reported above have important implications for the current diagnostic criteria and their recently proposed revision [23]. As mentioned earlier, the current criteria do not reliably distinguish real bvFTD and pheno-
copy patients [10**], with limitations of both sensitivity and specificity [3]. Importantly, they also miss the most salient features in real bvFTD patients. In a study by Piguet and Hornberger [24**], it was shown that of 45 bvFTD patients for whom there was clear clinical progression and imaging evidence of frontotemporal dysfunction or atrophy, only half exhibited all five core diagnostic criteria needed for diagnosis at presentation, with some patients never showing some of the core criteria over the entire disease history. Of the supportive features, only impaired executive function, hyperorality, mental inflexibility and distractibility were present in over half the patients at presentation.

New diagnostic bvFTD criteria have been proposed (see Table 2) [23] and are in the process of being validated across multiple sites worldwide. These criteria incorporate levels of clinical certainty into the diagnosis (possible, probably, definite) and more rigorously define the nature of the included clinical characteristics. Work is still ongoing as to how many criteria are needed for diagnosis, but both imaging findings and neuropsychological performance on executive tests will have more weight in the diagnosis. Tests of social cognition and assessment of ADLs, however, are not included in the revision.

Conclusion
The underlying explanation for the pheno-copy cases remains unclear, but is quite likely to be heterogeneous. At this point, very few pheno-copy cases have come to post mortem, and none of those that have died appear to have evidence of FTLD neuropathology. In view of the apparent normal life expectancy of these patients, it may be some time before there is a full understanding of the pathological basis of their disorder. Many of the features of FTD overlap with those seen in neuropsychiatric conditions, and it is likely that a number of the pheno-copy

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**Table 2 Revised diagnostic criteria [23] for behavioural variant frontotemporal dementia; currently under validation**

<table>
<thead>
<tr>
<th>Revised bvFTD diagnostic criteria</th>
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<tbody>
<tr>
<td><strong>Neurodegenerative disease</strong></td>
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<tr>
<td>Shows progressive deterioration of behaviour and/or cognition by observation or history</td>
</tr>
<tr>
<td><strong>Possible bvFTD</strong></td>
</tr>
<tr>
<td>Early (3 years) behavioral disinhibition</td>
</tr>
<tr>
<td>Early (3 years) apathy or inertia</td>
</tr>
<tr>
<td>Early (3 years) loss of sympathy and empathy</td>
</tr>
<tr>
<td>Early (3 years) perseverative, stereotyped or compulsive/ritualistic behavior</td>
</tr>
<tr>
<td>Hyperorality and dietary changes</td>
</tr>
<tr>
<td>Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions</td>
</tr>
<tr>
<td><strong>Probable bvFTD</strong></td>
</tr>
<tr>
<td>Meets criteria for possible bvFTD</td>
</tr>
<tr>
<td>Exhibits significant functional decline</td>
</tr>
<tr>
<td>Imaging results consistent with bvFTD</td>
</tr>
<tr>
<td><strong>bvFTD with definite FTLD disorder</strong></td>
</tr>
<tr>
<td>Meets criteria for possible or probable bvFTD</td>
</tr>
<tr>
<td>Histopathological evidence of FTLD on biopsy or at post mortem</td>
</tr>
<tr>
<td>Presence of a known pathogenic mutation</td>
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bvFTD, behavioural variant frontotemporal dementia.
cases have decompensated personality disorders, or autism spectrum disorders such as Asperger’s syndrome manifest at a level below the threshold for formal psychiatric diagnosis. In the absence of biological markers for these conditions, this is, however, difficult to prove.

More importantly, the evidence for such phenocopy patients has influenced both the sensitivity and specificity of the clinical diagnosis of bvFTD, which is reflected in the revised diagnostic criteria. On a clinical level, clinicians can be reasonably confident that patients who display a bvFTD-like syndrome with normal imaging and neuropsychological profile have a low risk of progression and good life expectancy. This is vitally important prognostic information for both patients and carers.

Acknowledgements
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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest


This large retrospective study demonstrated that the current diagnostic criteria lack sensitivity in detecting bvFTD features at presentation and at later follow-up.