Progression in Behavioral Variant Frontotemporal Dementia: A Longitudinal Study

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**IMPORTANCE** A gap in the literature exists regarding progression in behavioral variant frontotemporal dementia (BVFTD). Guidance is needed concerning markers that will enable clinicians to discriminate FTD more effectively from phenocopies and to identify factors that determine progression and thereby prognosis.

**OBJECTIVES** To observe longitudinal outcomes and progression in probable and possible BVFTD in accordance with international diagnostic criteria and to identify features that may aid clinicians to prognosticate better in cases of possible BVFTD.

**DESIGN, SETTING, AND PARTICIPANTS** Longitudinal cohort study performed in a specialist tertiary FTD research clinic. Fifty-eight consecutive patients were followed up longitudinally from January 1, 2008, through December 31, 2013, and classified as having possible, probable, or definite BVFTD at presentation and latest review. Final follow-up was completed on December 31, 2013, and data were analyzed from January 1 to August 1, 2014.

**MAIN OUTCOMES AND MEASURES** Clinical, pathological, genetic, neuropsychological, and neuroimaging data were analyzed to categorize patients, to compare differences between groups with changed and unchanged diagnoses, to determine rates of progression in BVFTD, and to identify prognostic features in possible BVFTD.

**RESULTS** At presentation, 38 of the 58 patients fulfilled criteria for probable BVFTD; of these, 36 continued to satisfy probable criteria or underwent conversion to definite criteria over time. The remaining 20 patients satisfied possible criteria only, and 11 of these patients changed categories over time to probable or definite BVFTD and showed progression on cognitive and functional measures (termed *changed status*). Of these 11 patients, 8 (73%) carried the C9orf72 expansion. A positive family history, memory impairment, and clinical abnormalities at presentation were key features of progression (*P* < .05). A continuum of neuropsychological scores, progression rates, and atrophy severity emerged across patients in probable, possible, changed status, and nonchanged status groups; patients with probable BVFTD exhibited the most severe abnormalities.

**CONCLUSIONS AND RELEVANCE** Behavioral variant FTD shows variable progression over time. Clinicians can use a detailed neurologic and cognitive assessment to identify key predictive features of progression when faced with possible BVFTD, whereas a diagnosis of probable BVFTD is accurate in a clinical setting.


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he past 2 decades have seen a revolution in the characterization of behavioral variant frontotemporal dementia (BVFTD), which culminated in the development of internationally accepted diagnostic consensus criteria in 2011. Despite this progress, predicting the prognosis of BVFTD remains challenging. Many patients without atrophy on magnetic resonance imaging (MRI) only satisfy criteria for possible BVFTD and remain in this category for years. Some of these patients are described as phenocopy cases.

The C9orf72 (NG_031977) genetic expansion adds a level of complexity to the diagnosis. In the absence of genetic testing, many patients who carry this expansion satisfy diagnostic criteria for possible but not probable BVFTD at the first presentation. The wealth of case reports emerging that detail protracted and indolent cases with apparently normal neuroimaging results and relatively normal neuropsychological profiles testify to the complex nature of this expansion. Although considerable refinements in diagnostic criteria have been made, pieces of the puzzle are missing. How many cases of possible BVFTD evolve to probable or definite disease, and where does the C9orf72 expansion fit into current diagnostic criteria?

With these questions in mind, the present study explored the outcomes in a large BVFTD cohort. This longitudinally recruited cohort is ideal to address these issues because each participant underwent a detailed workup that included a comprehensive clinical assessment, a neuropsychological test battery, genetic testing, and long-term follow-up. With these questions in mind, the present study explored the outcomes in a large BVFTD cohort. This longitudinally recruited cohort is ideal to address these issues because each participant underwent a detailed workup that included a comprehensive clinical assessment, a neuropsychological test battery, genetic testing, and long-term follow-up.

Methods

Patients

Each patient was assessed by the Frontotemporal Dementia Research (FRONTIER) group from January 1, 2008, through December 31, 2013. Patients were included in the study if they satisfied criteria for possible, probable, or definite BVFTD and if they were (1) seen on at least 2 occasions during a 6-year period or (2) seen on at least 2 occasions over a 1-year period with a change in diagnosis over that time. Patients with FTD and concurrent motor neuron disease were excluded from the study, but those who developed motor neuron disease with disease progression were included. Ethical approval was obtained from the ethics committees of the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales. Participants or their responsible surrogates provided written informed consent in accordance with the Declaration of Helsinki.

Patients were classified as having possible, probable, or definite BVFTD according to diagnostic criteria. The diagnosis was reviewed at presentation and at the most recent examination. To meet possible criteria, 3 of the following 6 core behavioral features were present: apathy, disinhibition, stereotypic and/or compulsive behaviors, sweet preference, loss of empathy and/or sympathy, and a frontal-dysexecutive cognitive profile. To reach probable BVFTD, criteria for possible BVFTD were met with additional evidence of functional decline and frontal or temporal abnormalities on findings of MRI or fludeoxyglucose F 18–labeled positron emission tomography (FDG-PET). For the purpose of classification and to determine whether atrophy was present, MRIs were reviewed using a validated visual rating scale by means of a Likert scale (range, 0-4; 0 and 1 indicate within normal limits and 2-4 indicate atrophy) that assessed the orbitofrontal cortex, anterior temporal poles, and insular cortex according to previously published data. The rater (E.D.) was trained on an independent data set, and the intraclass correlation coefficient to assess intrarater reliability on the independent dataset was very high (Cronbach α = 0.9). Definite BVFTD criteria were met when pathological findings at autopsy or genetic findings during life confirmed the diagnosis. Data were then compared between (1) the entire BVFTD group and control individuals, (2) the groups with probable and possible BVFTD, and (3) those with possible BVFTD in whom the diagnosis became probable or definite (changed status) and those with possible BVFTD cases in whom the diagnosis remained possible (unchanged status). Final follow-up occurred on December 31, 2013.

Clinical Assessment

Clinical information was recorded on a standardized form. Behavioral symptoms were explored systematically during the caregiver interview based on the Cambridge Behavioral Inventory. Features of motor neuron disease, Parkinsonism, apraxia, ataxia, and eye movement abnormalities were documented.

A family history was obtained and the Goldman score was calculated (range, 1-4). A score of 3 or below was considered a family history positive for neurodegeneration. Family history of psychiatric illness in first-degree relatives is not included in the Goldman score but was also obtained. A psychiatric family history was considered present if a psychiatric diagnosis (eg, schizophrenia, mood disorder) was made by a psychiatrist and required treatment or affected function. Global cognitive function was measured using the Addenbrooke’s Cognitive Examination–Revised (ACE-R) (range, 0-100; scores >88 indicate normal function). Disease staging was assessed with the Frontotemporal Dementia Functional Rating Scale (FRS) (Rasch score range, −6.66 to 5.39; higher scores indicate higher function).

Neuropsychological Assessment

The Delayed Recall component of the Rey-Osterrieth Complex Figure Test, the Rey Auditory Verbal Learning Test, and the Doors and People test examined episodic memory. Visuospatial ability was measured with the Copy component of the Rey-Osterrieth Complex Figure Test. Digit Span Backward subtest of the Wechsler Memory Scale–Third Edition, the Hayling test of inhibitory response, and the Trail Making Test assessed working memory and executive function. Naming was assessed using the Sydney Language Battery. The Ekman 60 Faces Test and The Awareness of Social Inference Test (TASIT) evaluated emotional processing.

Genetic Screening

We extracted DNA from whole-blood samples. The repeat primed polymerase chain reaction analysis was performed
using the procedure described previously\textsuperscript{23} based on the protocol of Renton and colleagues.\textsuperscript{24} Patients with a family history of neurodegenerative disorder were also screened for other common genetic mutations (GRN [\textit{NG_007886}] and MAPT [\textit{NG_007398}]) using Sanger sequencing of genomic DNA corresponding to all coding exons.\textsuperscript{25,26}

### Neuropathology
We systematically classified cases into the major molecular classes of frontotemporal lobar degeneration (FTLD). These included FTLD-tau, FTLD-TRANsactive response DNA binding protein of 43 kDa, FTLD-fused in sarcoma, FTLD–ubiquinated inclusion bodies, and FTLD without inclusions\textsuperscript{27} in addition to criteria for other neurodegenerative disorders\textsuperscript{28} using immunohistochemical techniques.\textsuperscript{29}

### Neuroimaging
### Imaging Acquisition
Patients underwent whole-brain T1-weighted imaging using a 3-T MRI scanner with standard quadrature head coil (Phillips). The 3-dimensional T1-weighted sequences were acquired as follows: coronal orientation, matrix of 256 × 256, 200 sections, 1-mm\textsuperscript{2} in-plane resolution, section thickness of 1 mm, and echo time/repetition time of 2.6/5.8 milliseconds.

### Voxel-Based Morphometry Analysis
Three-dimensional T1-weighted sequences were analyzed with FSLVBM, a voxel-based morphometry analysis\textsuperscript{30} and part of the FMRIB Software Library (FSL) package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM/). Tissue segmentation was performed using FMRIB’s Automatic Segmentation Tool from brain-extracted images. The resulting gray matter, partial volume maps were aligned to the Montreal Neurological Institute standard space (MNI 152) using the nonlinear registration approach with FNIRT (part of the FSL package), which uses a b-spline representation of the registration warp field. The registered partial volume maps were divided (to correct for local expansion or contraction) by the Jacobian determinant of the warp field. These images were smoothed with an isotropic gaussian kernel with an SD of 3 mm (full-width at half-maximum, 8 mm). A voxelwise general linear model was applied, and permutation-based nonparametric testing was used to form clusters with the threshold-free cluster enhancement method, tested for significance at \( P < .05 \), and corrected for familywise error.

### Statistical Analysis
We analyzed the data from January 1 through August 1, 2014, with the SPSS statistical package (version 22.0; SPSS, Inc). Results of Kolmogorov-Smirnoff tests determined whether variables were normally distributed. We compared parametric variables across groups via independent \( t \) tests and analysis of variance. Nonparametric data were analyzed using Mann-Whitney and Kruskal-Wallis tests, and \( \chi^2 \) tests compared categorical data. Linear mixed-effect models examined change in performance across groups over time.\textsuperscript{31}

### Results

#### BVFTD Cohort
Of the 89 patients with BVFTD, 58 met our inclusion criteria. Of the 31 patients who failed to meet the inclusion criteria owing to insufficient follow-up, 12 had probable BVFTD and 19 had possible BVFTD. Follow-up ranged from 1.0 to 5.2 years, with a mean follow-up of 3.1 years. Demographic data are represented in Table 1.

When the diagnostic criteria for BVFTD were applied at presentation, before the genetic and pathological examinations, 20 patients met criteria for possible BVFTD and 38 patients met criteria for probable BVFTD. The \textit{C9orf72} expansion was subsequently found in 15 patients (26%). A family history of neurodegenerative disorder was present in 18 of 58 patients (31%). Of these familial cases, the \textit{C9orf72} expansion was present in 10 (56%); a \textit{GRN} mutation, in 5 (28%); and an \textit{MAPT} mutation, in 1 (6%). Known genes were not present in 2 familial cases.

### Table 1. Demographic Characteristics for Patients With Probable and Possible BVFTD and Patients With Changed and Unchanged Disease Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants</th>
<th>Probable (n = 38)</th>
<th>Possible (n = 20)</th>
<th>P Value</th>
<th>Changed (n = 11)</th>
<th>Unchanged (n = 9)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. M:F</td>
<td>46.12</td>
<td>14.11</td>
<td>.03</td>
<td></td>
<td>28.10</td>
<td>18.2</td>
<td>.12</td>
</tr>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>58.5 (7.9)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>59.1 (8.2)</td>
<td>57.4 (4.2)</td>
<td>.46</td>
</tr>
<tr>
<td>Educational level, mean (SD), y</td>
<td>12 (3.1)</td>
<td>13.4 (2.3)</td>
<td>.08</td>
<td></td>
<td>12.5 (3.2)</td>
<td>10.8 (2.7)</td>
<td>.03</td>
</tr>
<tr>
<td>Disease duration, mean (SD), y</td>
<td>4.5 (3.0)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>3.5 (2.4)</td>
<td>5.4 (3.6)</td>
<td>.02</td>
</tr>
<tr>
<td>ACE-R score, mean (SD)\textsuperscript{4}</td>
<td>76.1 (13.7)</td>
<td>94.5 (3.1)</td>
<td>&lt; .001</td>
<td></td>
<td>72.4 (14.9)</td>
<td>83 (8)</td>
<td>.01</td>
</tr>
<tr>
<td>FRS Rasch score, mean (SD)\textsuperscript{5}</td>
<td>-0.5 (1.4)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>-0.7 (0.2)</td>
<td>0.2 (0.3)</td>
<td>.11</td>
</tr>
<tr>
<td>No. of patients with \textit{C9orf72} present</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>7</td>
<td>8</td>
<td>.12</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-R, Addenbrooke’s Cognitive Examination–Revised; BVFTD, behavioral variant frontotemporal dementia; FRS, Functional Rating Scale; NA, not applicable.

\textsuperscript{4} Scores range from 0 to 100; scores higher than 88 indicate normal function.

\textsuperscript{5} Scores range from -6.66 to 5.39; higher scores indicate higher function.
(11%). Five of the 40 patients with apparently sporadic disease (13%) harbored the C9orf72 expansion. Three of these patients with the C9orf72 expansion had a family history of psychiatric disease, which was present in 6 of the 15 patients with the C9orf72 expansion (40%).

Of the 38 probable cases, 17 (45%) changed status to definite BVFTD at follow-up, whereas 19 (50%) remained probable and 2 (5%) had pathologically findings of Alzheimer disease at autopsy (eFigure 1 in the Supplement). The C9orf72 expansions were found in familial (n = 5) and sporadic (n = 2) disease. A family history of psychiatric disease was present in 1 of the 2 patients with C9orf72 sporadic disease. In 2 of 13 familial cases (15%), no known gene was found.

In the group with possible BVFTD at presentation, failure to meet criteria for probable BVFTD was owing to the absence of imaging abnormalities on MRI (based on the visual atrophy rating scale) and FDG-PET in all cases. Each patient displayed a degree of functional disability. Of these 20 patients with possible BVFTD at baseline, 11 changed status over time to probable or definite BVFTD (eFigure 1 in the Supplement). Five patients with a family history of neurodegenerative disorder and 3 patients with sporadic disease in the changed status group had the C9orf72 expansion and were classified as definite cases based on this finding. Two of the 3 sporadic cases with the C9orf72 expansion had a family history of psychiatric disease. The final 3 cases in the changed status group were diagnosed as having probable BVFTD after the development of brain atrophy on MRIs. Brain atrophy on MRIs was also observed in 5 of 8 carriers of the C9orf72 expansion at follow-up. Illustrative coronal images at baseline and follow-up for those in the changed status category are demonstrated in eFigure 2 in the Supplement.

Figure 1. Behavioral Features Across the Spectrum of Behavioral Variant Frontotemporal Dementia (BVFTD)

Behavioral features at presentation in patients with probable and possible BVFTD and patients with changed and unchanged disease status expressed as percentages of the total group.

- *P < .05, χ² test, compared with probable BVFTD.
- *P < .05, χ² test, compared with changed disease status.

Comparison of Patients With BVFTD and Controls
Abnormalities on clinical examination findings (16 patients [28%]), a family history of neurodegenerative disorder (18 patients [31%]), and high rates of core behavioral symptoms were found in patients with BVFTD. Neuropsychological testing revealed significantly poorer scores than among controls across the board. Voxel-based morphometry analysis showed the typical BVFTD atrophy pattern involving frontal, temporal, and subcortical regions (P < .01, corrected).

Comparison of Patients With Probable and Possible BVFTD
Abnormal clinical findings were present in patients with probable (n = 11) and possible (n = 5) BVFTD (P < .05). Stereotypic and/or compulsive behaviors were more prevalent in the probable group (P < .05) whereas other behavioral features were similar across groups (Figure 1). On a group level, patients with probable BVFTD had significantly poorer scores across all cognitive domains, except for naming (P = .18) and visuospatial function (P = .23), than patients with possible BVFTD (P < .05; eTable 1 in the Supplement).

Figure 2 demonstrates atrophy patterns in patients with probable and possible BVFTD compared with controls. Patients with probable BVFTD showed significantly more atrophy in the frontal and subcortical regions compared with those with possible BVFTD, whereas no areas of significant atrophy were found in the converse (eTable 2 in the Supplement).

Longitudinal Data
On the ACE-R and the FRS, the groups combined showed significant deterioration over time (P < .001). We found a significant interaction between disease group and time for changes in the ACE-R score (P < .05), which indicated a faster rate of decline in patients with probable BVFTD (Figure 3). No significant interaction between disease group and time (P = .26) was identified for the FRS.
Comparison of Groups With Changed and Unchanged Status

Clinical Assessment
Abnormal clinical findings were found only in the group with changed status (P < .05; parkinsonism [n = 3]; frontal release signs [n = 2]). The changed status group showed more abnormal stereotypic and/or compulsive behaviors than the unchanged status group (P < .05; Figure 1).

Neuropsychological Assessment
Compared with controls and in keeping with the BVFTD profile of cognitive function, the group with changed status scored significantly worse across the range of cognitive tasks (P < .05 for all; Table 2). When we compared the groups with changed and unchanged status, the most striking difference was in episodic memory. All aspects of memory differed significantly be-
between groups, including visual, verbal, and recognition memory, with the changed status group having significantly poorer scores than the unchanged status group ($P < .05$). On some tests of executive function, we found evidence of poorer performance in the changed status group compared with the unchanged status group, but findings were inconsistent across tasks. Visuospatial functioning, emotion processing, and naming scores did not differ significantly between the changed status group and unchanged status group ($P > .2$). The profile in the group with unchanged status was variable for executive tasks and emotion processing but was consistently in the control range across the memory indices.

### Longitudinal Data

On the ACE-R and the FRS, the groups combined showed significant deterioration over time ($P < .05$ and $P < .001$, respectively), with significant interactions between disease group and time ($P < .05$ and $P < .001$, respectively) that indicated a faster rate of decline in the changed status group compared with the unchanged status group (Figure 3). The unchanged status group remained stable on both measures.

### Neuroimaging Data

The group with changed status showed widespread atrophy predominantly in the anterior insula, striatum, orbitofrontal cortex, and temporal poles, with a left-sided predominance compared with controls (Figure 2 and eTable 3 in the Supplement). The group with unchanged status showed minimal frontotopolar atrophy only. Direct comparisons between the changed status and unchanged status groups revealed no significant differences; however, at an uncorrected threshold of $P < .001$, greater left thalamic and right insular volume loss was seen in the changed status group compared with the unchanged status group (eFigure 3 in the Supplement).

### Discussion

This novel study provides fresh insights into the progression of BVFTD over time. The results of this study show 2 distinct trajectories for patients with possible BVFTD. In the group with changed BVFTD, cognitive and functional deterioration over time was seen and patients were likely to carry the C9orf72 expansion, whereas the group with unchanged BVFTD remained stable for several years. The chance at presentation of following either trajectory is almost 50:50, but a number of predictive features have been identified. A family history of neurodegeneration, clinical abnormalities on results of an examination, stereotypic and compulsive behaviors, and deficits on the ACE-R score are associated with progression, with memory deficits also emerging as a marker of progression. Our results indicate that the likelihood of progression may be determined during a routine neurologic consultation by means of a detailed clinical interview and examination and a brief test of global cognition. Brain atrophy analyses show subtle but widespread cortical atrophy in the group with changed status compared with the controls, in keeping with true BVFTD in the changed group. Most patients with probable BVFTD have FTLD pathological findings at autopsy, suggesting that a probable BVFTD diagnosis in the clinic is accurate. Finally, a continuum of neuropsychological and neuroimaging abnormalities are seen across probable and possible BVFTD and changed

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**Figure 3. Mixed-Model Analyses Showing Progression in Global Cognition and Function Across the Behavioral Variant Frontotemporal Dementia (BVFTD) Spectrum**

A) Probable vs possible BVFTD

B) Probable vs BVFTD

C) Changed vs unchanged status

D) Changed vs unchanged status

Results of changes in scores in patients with probable and possible BVFTD and patients with changed and unchanged disease status. Error bars indicate 95% CIs. A and C, Estimated marginal means based on the percentage of change in the Addenbrooke's Cognitive Examination–Revised (ACE-R) score (range, 0-100; scores > 88 indicate normal function) over time. Difference for time and time × diagnosis in probable vs possible BVFTD and changed vs unchanged status, $P < .05$ and $P < .001$, respectively; changed vs unchanged status, $P < .05$ and $P = .26$, respectively; changed vs unchanged status, $P < .001$. P values were calculated using linear mixed effect models.
More than one-third of the cohort had possible BVFTD at presentation. These patients exhibit key features of BVFTD yet showed little or no atrophy on MRI findings as judged using a visual ratingscale. Although the sample size is small and validation in an independent center is desirable, nonetheless almost one-half of all possible cases were subsequently found to have the C9orf72 expansion, and all possible cases with a family history of neurodegeneration carried this expansion. A careful clinical history to unearth a family history of a neurodegenerative disorder (especially motor neuron disease), clinical examination, and cognitive evaluation could identify most cases likely to progress, many of whom have the C9orf72 expansion, and may guide clinicians to appropriately identify patients for referral to genetic services. Also, one-half of cases with this expansion initially met criteria for possible rather than probable BVFTD.

Memory, traditionally considered to be unimpaired in BVFTD, appears as a hallmark neuropsychological deficit in the group with changed disease status. The deficit spans verbal and nonverbal components and perhaps testifies to the true nature of neurodegeneration in this group. A recent study identified 2 distinct amnestic profiles in BVFTD, including one with severe memory deficits comparable to Alzheimer disease and another with subnormal and normal memory scores. Extensive memory circuits involving the thalamus have also been implicated in memory deficits in BVFTD. Considering that most patients in the changed status category carried the C9orf72 expansion, we find it compelling that some studies comparing C9orf72 and sporadic BVFTD linked memory problems with expansion carriers. Our data indicate that memory tests may best distinguish possible cases likely to progress from those whose condition will remain stable. In contrast, performance on executive tasks is impaired in patients with changed and unchanged disease status. This finding raises a fundamental question: What is the underlying abnormality in the patients with unchanged disease status? These patients show mild deficits on tests previously found to be sensitive markers of BVFTD, such as inhibitory control and emotion processing. Patients with little or no progression over time and normal imaging findings have been

### Table 2. Neuropsychological Test Results in Patients With Changed and Unchanged Disease Status and Controls at Presentation

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Score, Mean (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Changed</td>
<td>Unchanged</td>
</tr>
<tr>
<td>General domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-R**</td>
<td>78.4 (7.5)</td>
<td>87.0 (6.6)</td>
</tr>
<tr>
<td>Executive domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT time differenceb</td>
<td>129.9 (62.4)</td>
<td>108.7 (55.2)</td>
</tr>
<tr>
<td>Digit Span Test Backwardsd</td>
<td>3.8 (0.9)</td>
<td>4.4 (1.5)</td>
</tr>
<tr>
<td>Hayling test of inhibitory responsed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category A errors</td>
<td>4.7 (4.5)</td>
<td>1.3 (1.6)</td>
</tr>
<tr>
<td>Category B errors</td>
<td>2.9 (2.6)</td>
<td>2.4 (1.7)</td>
</tr>
<tr>
<td>Letter fluencyd</td>
<td>8.1 (4.4)</td>
<td>9.8 (5.9)</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>7.0 (2.7)</td>
<td>10.0 (4.0)</td>
</tr>
<tr>
<td>Delayed</td>
<td>5.7 (3.6)</td>
<td>9.5 (4.0)</td>
</tr>
<tr>
<td>RCF 3-min recallg</td>
<td>8.7 (5.7)</td>
<td>15.5 (6.7)</td>
</tr>
<tr>
<td>Doors and People Test: Combinedh</td>
<td>6.9 (8.3)</td>
<td>16.0 (6.3)</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCF Copy scorei</td>
<td>25 (6)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Emotional domain</td>
<td></td>
<td></td>
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<tr>
<td>Ekman 60 Faces Test†</td>
<td>39.0 (5.8)</td>
<td>41.5 (6.3)</td>
</tr>
<tr>
<td>TASIT†</td>
<td>19.0 (3.4)</td>
<td>18.6 (3.3)</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
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<tr>
<td>Sydbatl</td>
<td>23.0 (2.7)</td>
<td>23.4 (3.5)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-R, Addenbrooke's Cognitive Examination–Revised; TMT, Trail Making Task; RAVLT, Rey Auditory Verbal Learning Test; RCF, Rey-Osterrieth Complex Figure Test; Sydbat, Sydney Language Battery; TASIT, The Awareness of Social Inference Test.

** Scores range from 0 to 100; scores higher than 88 indicate normal function.

b Longer times indicate greater impairment (maximum, 600 min).

c Scores range from 0 to 9; higher scores indicate better performance.

d Scores range from 0 to 15; higher scores indicate greater impairment.

The lowest score possible is 0 (no words), with no upper limit.

Scores range from 0 to 15; higher scores indicate better performance.

Scores range from 0 to 36; higher scores indicate greater ability.

Scores range from 0 to 24; higher scores indicate better performance.

Scores range from 0 to 24; higher scores indicate better performance.

Scores range from 0 to 60; higher scores indicate better performance.

Scores range from 0 to 28; higher scores indicate better performance.

Scores range from 0 to 30; higher scores indicate better performance.
termed phenocopy cases.37-39 These patients are predominantly male and present with a collection of behavioral features indistinguishable from true BVFTD. This presentation has been hypothesized to represent a decompensated developmental disorder in the Asperger-autism spectrum appearing in later life. The results from the present study partly corroborate this theory because mild executive impairments and emotion recognition deficits are seen in patients with unchanged BVFTD and patients on the Asperger-autism spectrum.40,41 A proportion of such cases may have a sporadic form of neurodegeneration with extremely slow progression, although this seems less likely. A clinicopathological study of patients with unchanged status is clearly needed; until then, the uncertainty regarding the underlying mechanism will remain.

Subgroup analyses reveal a dissociation between functional and cognitive progression in probable compared with possible BVFTD. Although having a shorter duration of illness, patients with probable BVFTD show worse cognitive deficits at presentation and more rapid progression of cognitive changes than those with possible BVFTD. In contrast, on a functional measure, both groups deteriorated at a similar rate. The lack of progression in the group with unchanged disease status over time was striking. A longitudinal study of neuropsychological test scores would determine whether progression differed within the various cognitive domains.

As in other studies of BVFTD, C9orf72 is the most common gene abnormality and together with GRN and MAPT mutations they account for most familial disease. However, a minority of familial cases do not have a known gene defect, whereas the C9orf72 expansion is also present in a number of sporadic cases. The nature of referrals to our tertiary center might have inflated the number of C9orf72 sporadic cases in our cohort, and rates should be generalized with caution. Previous studies have shown that familial psychiatric illness is associated with C9orf72,42,43 and we have demonstrated that when familial mental health disorders are considered as evidence of neurodegeneration, we account for most sporadic cases.

Conclusions

These findings have repercussions for the reliability of current diagnostic criteria, which state that to conform to the cognitive profile of BVFTD, “relative sparing of episodic memory” should be present.1(p2462) Contrary to current recommendations, this study and numerous others32-35 have found that memory deficits in BVFTD are often present and constitute an important component of the phenotype. Given that pathologically based pharmaceutical treatments are on the horizon, the differentiation of FTLD from the pathological features of Alzheimer disease seems to be imperative. When we consider recent diagnostic advances, amyloid PET imaging or sampling of cerebrospinal fluid might be useful in cases in which the patients’ memory is affected. Finally, important information can be gleaned from the routine neurologic consultation, and clinicians should consider this when faced with difficult questions of prognosis and referral for genetic testing.
Progression in Behavioral Variant Frontotemporal Dementia

Original Investigation  Research


