

## New Diagnostic Criteria for the Behavioural Variant of Frontotemporal Dementia

Yolande AL Pijnenburg

Neurologist, Department of Neurology and Alzheimer Centre, VU University Medical Centre

### Abstract

In September 2011, the International Behavioural Variant Frontotemporal Dementia Criteria Consortium established a new set of clinical diagnostic criteria for the behavioural variant of frontotemporal dementia (bvFTD). Following the 1998 criteria by Neary et al., where five core items had to be present to make a diagnosis of bvFTD, the new criteria incorporate six clinical hallmarks and demand that at least three of these are present. Moreover, a degree of probability and a role for neuroimaging findings are introduced within the criteria. The new diagnostic criteria have a sensitivity of 76 % for probable bvFTD and a sensitivity of 86 % for possible bvFTD. They provide a good starting point for a more accurate diagnosis of bvFTD.

### Keywords

Frontotemporal dementia, diagnosis, clinical, sensitivity, pathology

**Disclosure:** The author has no conflicts of interest to declare.

**Received:** 31 October 2011 **Accepted:** 10 November 2011 **Citation:** *European Neurological Review*, 2011;6(4):234–7 DOI:10.17925/ENR.2011.06.04.234

**Correspondence:** Yolande AL Pijnenburg, Department of Neurology and Alzheimer Centre, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands. E: y.pijnenburg@vumc.nl

Frontotemporal dementia (FTD) is a neurodegenerative disorder mainly affecting the frontal and/or temporal lobes, leading to dementia with prominent behavioural and/or language disturbances. Symptom onset is most often between 45 and 65 years. Arnold Pick described the disease with remarkably focal lobar atrophy in 1892 and it was later termed Pick's disease by Alois Alzheimer.<sup>1,2</sup> At present, it is known that frontotemporal lobar degeneration (FTLD) with Pick bodies consisting of tau-positive intraneuronal inclusions is not the only pathological correlate of FTD. A variety of tau-positive abnormalities are responsible for about 45 % of FTLD (FTLD-tau), whereas another 45–50 % of FTD cases are associated with ubiquitin-positive, TAR DNA-binding protein-43 (TDP-43)-positive pathology (FTLD-TDP).<sup>3–5</sup> Lastly, about 5–10 % of FTLD cases have ubiquitin-positive, TDP-43-negative, fused in sarcoma protein (FUS)-positive pathology (FTLD-FUS).<sup>6</sup> FTD has a relatively high degree of heritability. Mutations in the tau gene, progranulin gene and the recently discovered C9orf72 gene are responsible for up to 25 % of FTD cases.<sup>7–11</sup>

In the late 1980s, renewed interest in non-Alzheimer dementias arose as it became evident that, among patients who had died from dementia, 10 % suffered from frontotemporal cortical degeneration without Alzheimer's disease pathology.<sup>12</sup> Subsequently, the clinical characteristics of these patients were described in more detail.<sup>13,14</sup> In 1994, the Lund and Manchester groups published clinical and neuropathological criteria for FTD, whereby clinical symptoms were merely listed and pathological syndromes were subdivided into a frontal lobe degeneration type consisting of non-specific neurodegenerative changes, the Pick type including Pick bodies and the motor neurone disease type which at the time was non-specific as well.<sup>15</sup> The clinical symptoms of FTD were refined into a stricter corpus

of criteria in 1998.<sup>16</sup> Here the term FTLD was used as an umbrella for three main clinical syndromes: FTD, semantic dementia (SD) and progressive non-fluent aphasia (PNFA). Whereas the latter two present with language disturbances, FTD is characterised by five core clinical criteria, all of which had to be present to make a diagnosis of FTD. These included an insidious onset and gradual progression, an early decline of social interpersonal behaviour, an early decline in the regulation of personal behaviour, early emotional blunting and an early loss of insight. Furthermore, a number of supportive features such as pre-senile onset were formulated. Exclusion features included, among others, severe amnesia and spatial disorientation.

With some adaptations by an American working group on FTD, proposing that the term FTLD be reserved for the pathological spectrum and the term FTD for the clinical spectrum, including both language variants (SD and PNFA) and the behavioural variant (bvFTD), the 1998 criteria have remained widely used until very recently.

Some shortcomings and unmet needs, however, have ultimately led to the development of a new set of clinical diagnostic criteria for FTD by a large international consortium, which will be described in detail in this article.<sup>17,18</sup>

Although the five core criteria for bvFTD intuitively fit very well with the clinical picture of a typical bvFTD patient, one of the practical problems these criteria raise is the interpretation of rather abstract descriptions such as 'disturbed regulation of personal behaviour'. Obviously, this type of description leaves room for free interpretation by the clinician. Moreover, due to lack of insight bvFTD patients will not complain about their behavioural and emotional changes spontaneously and clinicians

**Table 1: The International Behavioural Variant Frontotemporal Dementia Criteria Consortium Diagnostic Criteria for Behavioural Variant Frontotemporal Dementia**

<b>I. Neurodegenerative Disease</b>
The following symptom must be present to meet criteria for bvFTD:
A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant)
<b>II. Possible bvFTD</b>
Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events
<b>A. Early behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:</b>
A.1. Socially inappropriate behaviour
A.2. Loss of manners or decorum
A.3. Impulsive, rash or careless actions
<b>B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:</b>
B.1. Apathy
B.2. Inertia
<b>C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:</b>
C.1. Diminished response to other people’s needs and feelings
C.2. Diminished social interest, interrelatedness or personal warmth
<b>D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:</b>
D.1. Simple repetitive movements
D.2. Complex, compulsive or ritualistic behaviours
D.3. Stereotypy of speech
<b>E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:</b>
E.1. Altered food preferences
E.2. Binge eating, increased consumption of alcohol or cigarettes
E.3. Oral exploration or consumption of inedible objects
<b>F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:</b>
F.1. Deficits in executive tasks
F.2. Relative sparing of episodic memory
F.3. Relative sparing of visuospatial skills
<b>III. Probable bvFTD</b>
All of the following symptoms (A–C) must be present to meet criteria:
A. Meets criteria for possible bvFTD
B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
C.1. Frontal and/or anterior temporal atrophy on MRI or CT
C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT
<b>IV. bvFTD with Definite FTLD Pathology</b>
Criterion A and either criterion B or C must be present to meet criteria.
A. Meets criteria for possible or probable bvFTD
B. Histopathological evidence of FTLD on biopsy or at <i>post mortem</i>
C. Presence of a known pathogenic mutation
<b>V. Exclusionary Criteria for bvFTD</b>
Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.
A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
B. Behavioural disturbance is better accounted for by a psychiatric diagnosis
C. Biomarkers strongly indicative of Alzheimer’s disease or other neurodegenerative process

*bvFTD = behavioural variant frontotemporal dementia; CT = computed tomography; FTLD = frontotemporal lobar degeneration; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography.*

rely to a large extent on the information supplied by caregivers. As all five core criteria need to be present for a diagnosis of bvFTD, cases with FTLD that fulfil fewer than five criteria would have to be diagnosed alternatively. The sensitivity of the 1998 clinical diagnostic criteria for bvFTD lies between 36.5 and 79 % with relatively higher specificities (90–100 %).<sup>19–22</sup> In particular, emotional blunting and loss of insight may be lacking at initial presentation.<sup>21</sup> A study in 34 pathologically proven FTLD cases revealed a sensitivity of 79 % for the clinical criteria for

bvFTD. With additional use of neuropsychological and neuroimaging findings, sensitivity increased to 85 % with a specificity of 99 %.<sup>19</sup> Snowden et al. found a sensitivity of 100 % and specificity of 97 % for the 1998 clinical criteria for bvFTD in combination with neuropsychological examination in a large series of pathologically proven FTLD cases.<sup>5</sup>

Thus, within dementia cohorts a diagnosis of bvFTD can be made with fair diagnostic accuracy by experienced clinicians. Due to their

focus on behavioural and emotional symptoms, it is conceivable that sensitivity and specificity of the clinical diagnostic criteria decreases when applied to a population with neuropsychiatric symptoms, including, for example, subjects with late-onset schizophrenia or depression, but this has never been investigated.

In recent years, a subgroup of patients has been described, in whom behavioural characteristics are indistinguishable from bvFTD, but who are characterised by a relative absence of functional decline and, in general, have normal findings on neuroimaging.<sup>23-26</sup> By far the largest proportion of these patients is male. It is still a matter of debate whether these patients really suffer from a neurodegenerative disorder or whether this so-called phenocopy syndrome is part of a spectrum of psychiatric disorders. The current clinical diagnostic criteria provide no means to distinguish this benign subgroup from patients with a more degenerative course.

Other arguments for updating the clinical diagnostic criteria for bvFTD consisted of a need for a more structured categorisation of individual items and a more flexible approach to fulfil the criteria. Moreover, it was felt that adding a degree of probability to the clinical diagnosis and acknowledging the role of biomarkers and genetics in the diagnosis would be of great benefit.<sup>17,27</sup>

## Development and Description of New Clinical Diagnostic Criteria for the Behavioural Variant of Frontotemporal Dementia

The International Behavioural Variant Frontotemporal Dementia Criteria Consortium (FTDC) comprises 46 members with extensive experience in bvFTD. A conceptual set of criteria based on the international literature was discussed and refined during the course of three years. The result consists of six behavioural, emotional or neuropsychological main features, including several clinical aspects that are summarised within the criteria.<sup>28</sup> These include early behavioural disinhibition, early apathy or inertia, early loss of sympathy or empathy, early perseverative, stereotyped or compulsive/ritualistic behaviour, hyperorality and dietary changes and a neuropsychological profile consisting of executive/ generation deficits with relative sparing of memory and visuospatial functions. When patients fulfil a minimum of three main features, they receive a diagnosis of possible bvFTD. A diagnosis of probable bvFTD can subsequently be established when functional decline is observed in the presence of frontotemporal hypometabolism on positron emission tomography (PET), hypoperfusion on single-photon emission computed tomography (SPECT) or atrophy on computed tomography (CT) or magnetic resonance imaging (MRI). A definite diagnosis of bvFTD can be made in the presence of pathological verification through cerebral biopsy or *post-mortem* confirmation or in the presence of a pathogenic mutation. Exclusion criteria consist of a better alternative diagnosis for the clinical presentation and biomarkers pointing in the direction of another disease. The FTDC criteria for bvFTD are displayed in *Table 1*.

The sensitivity of the newly established criteria was then tested in a cohort of 137 pathologically verified FTL cases yielded by 16 brain banks. The sensitivity of the 1998 criteria was 60 %, as opposed to 86 % with the newly developed diagnostic criteria for possible bvFTD and 76 % for probable bvFTD.

## Discussion

With this new set of criteria, one of the main shortcomings of the 1998 criteria, namely that all five core criteria had to be present for a diagnosis of bvFTD, has been bypassed. Instead, a flexible scoring system, whereby at least three out of six hallmarks have to be present, has been introduced. The six items are easy to memorise and easily applicable for clinicians. Moreover, it appears that the newly introduced rating system has a higher sensitivity for bvFTD than the criteria that were used up till now.

The introduction of a degree of probability to the diagnosis of bvFTD is in line with diagnostic criteria for other main causes of dementia.<sup>29-31</sup> Again, analogous to, for example, the new diagnostic criteria for Alzheimer's disease,<sup>31</sup> with the assignment of a role to biomarkers such as atrophy patterns, hypoperfusion or hypometabolism patterns, profiles of cerebrospinal fluid (CSF) proteins, or mutations, the new criteria have been modernised and important findings of the last decade have been integrated.

This approach is important for prognostic reasons. Moreover, by demanding both neuroimaging abnormalities and functional decline for a diagnosis of probable bvFTD, a group of subjects with the benign phenocopy syndrome of bvFTD may correctly be excluded from research studies such as clinical trials.

The other side of the coin is that approximately a quarter of subjects with pathologically proven bvFTD do not fulfil the criteria for probable bvFTD. They are either lacking one or more clinical hallmarks or fulfil one or more exclusion criteria. In the study cohort, particularly older bvFTD patients with a presentation of severe amnesia could not be classified according to the revised criteria.

Ten per cent of bvFTD patients did fulfil the criteria for possible bvFTD, but did not reach the criteria for probable bvFTD. This means that they either had no functional decline, or their neuroimaging findings, including PET or SPECT, were negative. Pathologically proven bvFTD patients with a disease duration of up to 17 years have been described.<sup>13</sup> Functional decline in these patients might therefore not be noticeable over a short term. It is an interesting question whether these patients can be distinguished from subjects with the phenocopy syndrome on clinical grounds. The sensitivity of MRI for bvFTD has been found to be 50 % in *post-mortem* verified cases.<sup>19</sup> The yield of functional neuroimaging after normal structural neuroimaging was high in the study of Knopman et al., where seven out of eight bvFTD patients with normal MRI had abnormal PET or SPECT findings. These findings are contradicted by the finding that fluorodeoxyglucose (FDG)-PET findings in nine patients with the clinical picture of bvFTD but normal MRI were all negative.<sup>25</sup> The additive role of FDG-PET after negative MRI in suspected bvFTD has to be studied in larger cohorts with pathological confirmation. Of course, it remains of great importance that subjects with possible bvFTD receive long-term clinical follow-up and, if possible, *post-mortem* examination in order to identify the ultimate outcome in these patients.

In the future, prospective validation of the new criteria should take place, to determine the sensitivity but also the specificity of the revised criteria. As bvFTD is a behavioural disorder, apart from validation in dementia cohorts, it is important to study the value of the new criteria among cohorts with psychiatric symptoms as well. ■

1. Alzheimer A, [On certain peculiar diseases of old age], *Zeitschrift für die gesamte Neurologie und Psychiatrie* (Berlin),

1911;4:356-85.

2. Pick A, [On the relations of senile brain atrophy to aphasia],

*Prager Medizinische Wochenschrift*, 1892;15:165-7.

3. Cairns NJ, Bigio EH, Mackenzie IR, et al., *Neuropathologic*

- diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration, *Acta Neuropathol*, 2007;114:5–22.
4. Rohrer JD, Lashley T, Schott JM, et al., Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration, *Brain*, 2011;134:2565–81.
  5. Snowden JS, Thompson JC, Stopford CL, et al., The clinical diagnosis of early-onset dementias: diagnostic accuracy and clinicopathological relationships, *Brain*, 2011;134:2478–92.
  6. Mackenzie IR, Neumann M, Bigio EH, et al., Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update, *Acta Neuropathol*, 2010;119:1–4.
  7. Poorkaj P, Bird TD, Wijsman E, et al., Tau is a candidate gene for chromosome 17 frontotemporal dementia, *Ann Neurol*, 1998;43:815–25.
  8. Baker M, Mackenzie IR, Pickering-Brown SM, et al., Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17, *Nature*, 2006;442:916–9.
  9. Cruts M, Gijssels I, van der Zee J, et al., Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21, *Nature*, 2006;442:920–4.
  10. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al., Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS, *Neuron*, 2011;72:245–56.
  11. Renton AE, Majounie E, Waite A, et al., A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-Linked ALS-FTD, *Neuron*, 2011;72:257–68.
  12. Brun A, Frontal lobe degeneration of non-Alzheimer type. I. neuropathology, *Arch Gerontol Geriatr*, 1987;6:193–208.
  13. Gustafson L, Frontal lobe degeneration of non-Alzheimer type II. Clinical picture and differential diagnosis, *Arch Gerontol Geriatr*, 1987;6:209–23.
  14. Neary D, Snowden JS, Northen B, Goulding P, Dementia of frontal lobe type, *J Neurol Neurosurg Psychiatry*, 1988;51:353–61.
  15. The Lund and Manchester Groups, Clinical and neuropathological criteria for frontotemporal dementia, *J Neurol Neurosurg Psychiatry*, 1994;57:416–8.
  16. Neary D, Snowden JS, Gustafson L, et al., Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria, *Neurology*, 1998;51:1546–54.
  17. Rascovsky K, Hodges JR, Kipps CM, et al., Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): Current limitations and future directions, *Alzheimer Dis Assoc Disord*, 2007;21:S14–8.
  18. Rascovsky K, Hodges JR, Knopman D, et al., Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia, *Brain*, 2011;134(Pt 9):2456–77.
  19. Knopman DS, Boeve BF, Parisi JE, et al., Antemortem diagnosis of frontotemporal lobar degeneration, *Ann Neurol*, 2005;57:480–8.
  20. Mendez MF, Shapira JS, McMurtry A, et al., Accuracy of the clinical evaluation for frontotemporal dementia, *Arch Neurol*, 2007;64:830–5.
  21. Piguet O, Hornberger M, Shelley BP, et al., Sensitivity of current criteria for the diagnosis of behavioral variant frontotemporal dementia, *Neurology*, 2009;72:732–7.
  22. Pijnenburg YAL, Mulder JL, Van Swieten JC, et al., Diagnostic accuracy of consensus diagnostic criteria for frontotemporal dementia in a memory clinic population, *Dement Geriatr Cogn Disord*, 2008;25:157–64.
  23. Davies RR, Kipps CM, Mitchell J, et al., Progression in frontotemporal dementia - Identifying a benign Behavioral variant by magnetic resonance imaging, *Arch Neurol*, 2006;63:1627–31.
  24. Hornberger M, Shelley BP, Kipps CM, et al., Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation?, *J Neurol Neurosurg Psychiatry*, 2009;80:591–3.
  25. Kipps CM, Hodges JR, Fryer TD, Nestor PJ, Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype, *Brain*, 2009;132:2566–78.
  26. Koedam EL, Van der Flier WM, Barkhof F, et al., Clinical characteristics of patients with frontotemporal dementia with and without lobar atrophy on MRI, *Alzheimer Dis Assoc Disord*, 2010;24:242–7.
  27. Vandenberghe R, Sense and sensitivity of novel criteria for frontotemporal dementia, *Brain*, 2011;134:2450–3.
  28. Rascovsky K, Hodges JR, Knopman D, et al., Sensitivity of Diagnostic Criteria in Autopsy-Confirmed Patients with Behavioral Variant Frontotemporal Dementia (bvFTD): First Report of the International bvFTD Criteria Consortium (FTDC), *Neurology*, 2011;76:A262–3.
  29. Roman GC, Tatemichi TK, Erkinjuntti T, et al., Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop, *Neurology*, 1993;43:250–60.
  30. McKeith IG, Dickson DW, Lowe J, et al., Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium, *Neurology*, 2005;65:1863–72.
  31. McKhann GM, Knopman DS, Chertkow H, et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement*, 2011;7:263–9.