This is a summary of three American Academy of Neurology (AAN) guidelines on dementia. Although the guidelines address all forms of dementia, this summary focuses on Alzheimer’s disease, for which current evidence is strongest and clearest. The guidelines conclude that AD should be detected and treated early. Patients with Mild Cognitive Impairment should be identified and monitored for progression to AD—a likely event. The clinical criteria for diagnosing AD are reliable and valid. Although AD is not curable, there are treatment and care options available today that can manage symptoms, improve quality of life and delay time to nursing home placement.

Please refer to the full guidelines for more information at www.aan.com/professionals/practice/index.cfm.

**PRACTICE PARAMETER: DETECTION OF DEMENTIA—MILD COGNITIVE IMPAIRMENT**

- **Dementia is common in the elderly.** 10% of persons over age 65 and up to 50% over 85 have dementia.
- **AD and MCI differ from normal aging.** Know the ten warning signs of AD. Communicate the warning signs to your community, your colleagues, your patients, and their families. Contact the AAN or the Alzheimer’s Association for tools or ideas on how to do so.
- **Identify and monitor Mild Cognitive Impairment patients for progression to AD.** MCI is a classification of persons with memory impairment who are not demented (normal general cognitive function; intact activities of daily living). Between 6 and 25% of MCI patients progress to dementia or AD each year. MCI patients should be evaluated regularly for progression to AD using the assessment tools listed below.
- **Be alert to cognitive impairment in all your patients.** screen for dementia if cognitive impairment is suspected.

**Good evidence supports using:**
- General cognitive screening instruments:
  - Mini Mental Status Exam (adjusted for age/education)
  - Memory Impairment Screen
- Neuropsychological batteries

**Weak evidence supports using:**
- Other general cognitive screening instruments:
  - Kokmen Short Test of Mental Status
  - 7-Minute Screen
- Interview based techniques:
  - Blessed Dementia Rating Scale
  - CDR
  - IQCODE
- Brief cognitive assessment instruments*:
  - Clock Drawing Test
  - Time and Change Test

*Caution should be used; these tools are limited in scope

**Ten Warning Signs of AD**

1. Memory loss that affects job skills
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time and place
5. Poor or decreased judgment
6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative

Used with the permission of the Alzheimer’s Association.

**PRACTICE PARAMETER: DIAGNOSIS OF DEMENTIA**

- The clinical criteria for AD are reliable (DSM-III-R definition; NINCDS-ADRDA and DSM-IV diagnostic criteria)
- Vascular dementia, dementia with Lewy Bodies and fronto-temporal dementia should be excluded, but the current diagnostic criteria for those diseases are imperfect.
- Structural neuroimaging is appropriate to detect lesions which may result in cognitive impairment.
- The CSF-14-3-3 protein is useful when CJD is suspected and recent stroke or viral encephalitis can be excluded.

**Evidence supports the following tests in the routine evaluation of the demented patient:**
- Complete blood cell count
- Glucose
- Depression screening
- Thyroid function tests
- Serum electrolytes
- BUN/creatinine
- Serum B12 levels
- Liver function tests

**Evidence indicates the following tests should not be included in the routine evaluation of the demented patient**
- Screening for syphilis (unless patient has a specific risk factor, e.g., living in a high-incidence region)
STRATEGIES TO IMPROVE FUNCTIONAL PERFORMANCE AND REDUCE PROBLEM BEHAVIORS

- To improve functional performance
  - Behavior modification, scheduled toileting, prompted voiding to reduce urinary incontinence
  - Graded assistance, practice and positive reinforcement to increase functional independence
  - Low lighting levels, music and simulated nature sounds to improve eating behaviors
  - Intensive multi-modality group training may improve activities of daily living

- To reduce problem behaviors
  - Music, particularly during meals and bathing
  - Walking or other forms of light exercise
  - Simulated presence therapy, such as use of videotapes of family
  - Massage
  - Comprehensive psychosocial care programs
  - Pet therapy
  - Utilizing commands issued at the patient's comprehension level
  - Bright light, white noise
  - Cognitive remediation
  - Massage
  - Walking or other forms of light exercise
  - Music, particularly during meals and bathing

**Strength Of Evidence**

- Behavior modification, scheduled toileting, prompted voiding to reduce urinary incontinence: Strong
- Graded assistance, practice and positive reinforcement to increase functional independence: Good
- Low lighting levels, music and simulated nature sounds to improve eating behaviors: Weak
- Intensive multi-modality group training may improve activities of daily living: Weak
- Music, particularly during meals and bathing: Good
- Walking or other forms of light exercise: Good
- Simulated presence therapy, such as use of videotapes of family: Weak
- Massage: Weak
- Comprehensive psychosocial care programs: Weak
- Pet therapy: Weak
- Utilizing commands issued at the patient's comprehension level: Weak
- Bright light, white noise: Weak
- Cognitive remediation: Weak

This is an evidence-based educational service of the American Academy of Neurology. It is designed to provide members with evidence-based guideline recommendations to assist with decision-making in patient care. It is based on an assessment of current scientific and clinical information, and is not intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on the circumstances involved. Physicians are encouraged to carefully review the full AAN guidelines so they understand all recommendations associated with care of these patients.

Copies of this summary and a companion patient version are available at www.aan.com/professionals/practice/index.cfm or through AAN Member Services at (800) 879-1960.
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

Guy M. McKhann a,b,*, David S. Knopman c, Howard Chertkow d,e, Bradley T. Hyman f, Clifford R. Jack, Jr. g, Claudia H. Kawas h,i,j, William E. Klunk k, Walter J. Koroshetz l, Jennifer J. Manly m,n,o, Richard Mayeux m,n,o, Richard C. Mohs p, John C. Morris q, Martin N. Rossor r, Philip Scheltens s, Maria C. Carrillo t, Bill Thies t, Sandra Weintraub u,v, Creighton H. Phelps w

aDepartment of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
bZanvyl Krieger Mind/Brain Institute, Johns Hopkins University, Baltimore, MD, USA
cDepartment of Neurology, Mayo Clinic, Rochester, MN, USA
dDepartment of Neurology, McGill University School of Medicine, Montreal, QC, Canada
eBloomfield Centre for Research in Aging, Lady Davis Institute, Montreal, QC, Canada
fDepartment of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
gDepartment of Radiology, Mayo Clinic, Rochester, MN, USA
hDepartment of Neurology, University of California, Irvine, CA, USA
iDepartment of Neurobiology and Behavior, University of California, Irvine, CA, USA
jAlzheimer Disease Research Center, University of California, Irvine, CA, USA
kDepartment of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
lNational Institute of Neurological Disorders and Stroke, Bethesda, MD, USA
mTaub Institute for Research on Alzheimer’s Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA
nGertrude H. Sergievsky Center, Columbia University Medical Center, New York, NY, USA
oDepartment of Neurology, Columbia University Medical Center, New York, NY, USA
pEli Lilly and Company, Indianapolis, IN, USA
qDepartment of Neurology, Washington University School of Medicine, St. Louis, MO, USA
tAlzheimer’s Association, Chicago, IL, USA
tDementia Research Centre, Department of Neurodegeneration, UCL Institute of Neurology, University College London, Queen Square, London, United Kingdom
uDepartment of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands
vAlzheimer’s Association, Chicago, IL, USA
wDepartment of Psychiatry, Northwestern Feinberg School of Medicine, Chicago, IL, USA
xDepartment of Neurology, Northwestern Feinberg School of Medicine, Chicago, IL, USA
yAlzheimer’s Disease Centers Program, National Institute on Aging, Bethesda, MD, USA

Abstract

The National Institute on Aging and the Alzheimer’s Association charged a workgroup with the task of revising the 1984 criteria for Alzheimer’s disease (AD) dementia. The workgroup sought to ensure that the revised criteria would be flexible enough to be used by both general healthcare providers without access to neuropsychological testing, advanced imaging, and cerebrospinal fluid measures, and specialized investigators involved in research or in clinical trial studies who would have these tools available. We present criteria for all-cause dementia and for AD dementia. We retained the general framework of probable AD dementia from the 1984 criteria. On the basis of the past 27 years of experience, we made several changes in the clinical criteria for the diagnosis. We also retained the term possible AD dementia, but redefined it in a manner more focused than before. Biomarker evidence was also integrated into the diagnostic formulations for probable and possible AD dementia.

*Corresponding author: Tel.: 410-516-8640; Fax: 410-516-8648.
E-mail address: guy.mckhann@jhu.edu

1552-5260/ - see front matter © 2011 The Alzheimer’s Association. All rights reserved.
doi:10.1016/j.jalz.2011.03.005
dementia for use in research settings. The core clinical criteria for AD dementia will continue to be the cornerstone of the diagnosis in clinical practice, but biomarker evidence is expected to enhance the pathophysiological specificity of the diagnosis of AD dementia. Much work lies ahead for validating the biomarker diagnosis of AD dementia.

© 2011 The Alzheimer’s Association. All rights reserved.

Keywords: Alzheimer’s disease; Dementia; Diagnosis; Magnetic resonance brain imaging; Positron emission tomography; Cerebrospinal fluid

1. Introduction

In the fall of 1983, a group was convened by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA) to establish criteria and to describe the clinical diagnosis of Alzheimer’s disease (AD). The group addressed issues of medical history, clinical examination, neuropsychological testing, and laboratory assessments and then produced a report, which was published in July 1984 [1]. The criteria in this report, commonly referred to as the NINCDS–ADRDA criteria, have been quite successful, surviving for over 27 years. These criteria have been reliable for the diagnosis of probable AD, and across more than a dozen clinical pathological studies have had a sensitivity of 81% and specificity of 70% [2]. They have been widely used in clinical trials and clinical research.

However, now 27 years later, these criteria require revision. Therefore, the National Institute on Aging and the Alzheimer’s Association charged a workgroup with the task of revising the 1984 criteria for AD dementia. Details of the charge to the workgroup are described in the Introduction that accompanies this article [3]. The characterization of the preclinical [4] and mild cognitive impairment (MCI) [5] phases of the AD pathophysiological processes is described in the companion articles.

Our knowledge of the clinical manifestations and biology of AD has increased vastly. The features of the original criteria that required revision include the following:

1. The fact that the histological pathology of AD (or surrogates for this pathology) may be found across a broad clinical spectrum (including individuals who are cognitively normal, those with MCI, and those with dementia) [6,7]. Therefore, throughout this article, we use the term AD pathophysiological process to encompass the antemortem biological changes that precede the postmortem neuropathological diagnosis of AD as well as the neuropathological substrate. AD dementia refers to the clinical syndrome that arises as a consequence of the AD pathophysiological process.

2. Lack of acknowledgment of distinguishing features of other dementing conditions that occur in a similarly aged population, which were not completely recognized decades ago. For example, Dementia with Lewy bodies [8], vascular dementia [9], behavior variant frontotemporal dementia [10–12], and primary progressive aphasia [13] have been characterized extensively.

3. No inclusion of results of magnetic resonance imaging, positron emission tomography (PET) imaging, and cerebrospinal fluid (CSF) assays (that we will refer to subsequently as biomarkers) in decision-making. Initial efforts to incorporate biomarkers into the diagnosis of AD dementia and MCI [14] need to be coupled with a more comprehensive approach to the diagnostic process.

4. The implication that memory impairment is always the primary cognitive deficit in all patients with AD dementia. Experience has shown that there are several nonamnestic presentations of the pathophysiological process of AD, the most common ones being the syndrome of posterior cortical atrophy [15] and the syndrome of logopenic–primary progressive aphasia [16].

5. Lack of information about genetics of AD. Mutations in three genes—amyloid precursor protein, presenilin 1, and presenilin 2—cause an early onset, autosomal dominantly inherited AD [17].

6. Proposed age cutoffs for the diagnosis of AD dementia. Work over the past decades has established that AD dementia in those aged <40 years, although rare, does not differ in its pathophysiology from older persons [18]. AD dementia in persons aged >90 years is also part of that same spectrum as that of younger persons, even though clinical–pathological correlations are attenuated [19].

7. Extreme heterogeneity of the “Possible” AD dementia category, including a group of patients who would now be diagnosed as “Mild cognitive impairment (MCI).”

The objective of our committee was to focus on the criteria for AD dementia, that is, dementia secondary to the pathophysiology of AD. It was our intention to first review the NINDS–ADRDA criteria and then to update them, incorporating more modern innovations in clinical, imaging, and laboratory assessment. We will first propose (1) Criteria for all-cause dementia and then, (2) Criteria for dementia caused by AD. We set ourselves the goal of ensuring that the revised criteria would be flexible enough to be used by both general healthcare providers without access to neuropsychological testing, advanced imaging, and CSF measures, as well as specialized investigators involved in research or in clinical trial studies who would have these measures available.
2. Criteria for all-cause dementia: Core clinical criteria

In this section, we outline core clinical criteria to be used in all clinical settings. Because there are many causes of dementia, we will first outline the criteria for all-cause dementia.

The diagnosis of dementia is intended to encompass the spectrum of severity, ranging from the mildest to the most severe stages of dementia. The methodology for staging of dementia severity was beyond the charge of the workgroup. Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
   a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
   b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
   c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
   d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
   e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

The differentiation of dementia from MCI (see companion article [5] on the diagnosis of MCI) rests on the determination of whether or not there is significant interference in the ability to function at work or in usual daily activities. This is inherently a clinical judgment made by a skilled clinician on the basis of the individual circumstances of the patient and the description of daily affairs of the patient obtained from the patient and from a knowledgeable informant.

3. Proposed classification criteria for AD dementia

We propose the following terminology for classifying individuals with dementia caused by AD: (1) Probable AD dementia, (2) Possible AD dementia, and (3) Probable or possible AD dementia with evidence of the AD pathophysiological process. The first two are intended for use in all clinical settings. The third is currently intended for research purposes.

4. Probable AD dementia: Core clinical criteria

4.1. Probable AD dementia is diagnosed when the patient

1. Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics:
   A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
   B. Clear-cut history of worsening of cognition by report or observation; and
   C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
      a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
      b. Nonamnestic presentations:
         ● Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
         ● Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
         ● Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.
   D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by
a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Note: All patients who met criteria for “probable AD” by the 1984 NINCDS–ADRDA criteria [1] would meet the current criteria for probable AD dementia mentioned in the present article.

4. Possible AD dementia: Core clinical criteria

A diagnosis of possible AD dementia should be made in either of the circumstances mentioned in the following paragraphs.

5. Atypical course

Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline.

Or

5.2. Etiologically mixed presentation

Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.

Note: A diagnosis of “possible AD” by the 1984 NINCDS-ADRDA criteria [1] would not necessarily meet the current criteria for possible AD dementia. Such a patient would need to be re-evaluated.

6. Probable AD dementia with evidence of the AD pathophysiological process

The rationale for including biomarkers for the pathophysiological process of AD in the diagnostic criteria is summarized in the Introduction to this series of articles [3]. The major AD biomarkers that have been widely investigated at this time (see [21] for review) may be broken into two classes based on the biology which they measure. Biomarkers of brain amyloid-beta (Aβ) protein deposition are low CSF Aβ42 and positive PET amyloid imaging [22,23]. The second category is that of biomarkers of downstream neuronal degeneration or injury. The three major bio-markers in this category are elevated CSF tau, both total tau and phosphorylated tau (p-tau); decreased 18fluorodeoxyglucose (FDG) uptake on PET in temporo-parietal cortex; and disproportionate atrophy on structural magnetic resonance imaging in medial, basal, and lateral temporal lobe, and medial parietal cortex. Total tau and p-tau are treated equivalently in this study, although p-tau may have more specificity for AD than other dementing diseases.

In persons who meet the core clinical Criteria for probable AD dementia biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. However, we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. There are several reasons for this limitation: (1) the core clinical criteria provide very good diagnostic accuracy and utility in most patients; (2) more research needs to be done to ensure that criteria that include the use of biomarkers have been appropriately designed, (3) there is limited standardization of biomarkers from one locale to another, and (4) access to biomarkers is limited to varying degrees in community settings. Presently, the use of biomarkers to enhance
certainty of AD pathophysiological process may be useful in three circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician.

Biomarker test results can fall into three categories—clearly positive, clearly negative, and indeterminate. We envision that application of biomarkers for the AD pathophysiological process would operate as outlined in the Table 1.

7. Possible AD dementia with evidence of the AD pathophysiological process

This category is for persons who meet clinical criteria for a non-AD dementia but who have either biomarker evidence of AD pathophysiological process, or meet the neuropathological criteria for AD. Examples would include persons who meet clinical criteria for dementia with Lewy bodies or for a subtype of frontotemporal lobar degeneration, but who have a positive AD biomarker study or at autopsy are found to meet pathological criteria for AD. In the biomarker table, we indicate that both categories of biomarkers must be positive for an individual who presents clinically with a non-AD phenotype to meet criteria for possible AD. This is a conservative approach that may change as more information is gained concerning the long-term outcomes of different combinations of biomarker findings. A diagnosis of possible AD dementia with evidence of AD pathophysiological process does not preclude the possibility that a second pathophysiological condition is also present.

8. Considerations related to the incorporation of biomarkers into AD dementia criteria

As described in the two companion articles on the preclinical [4] and MCI [5] phases of the AD pathophysiological process, AD dementia is part of a continuum of clinical and biological phenomena. AD dementia is fundamentally a clinical diagnosis. To make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied.

According to their nature, CSF biomarkers rely on a quantitative interpretation in comparison with normative standards. Imaging biomarkers can be interpreted in both a qualitative or quantitative manner. In many cases, biomarker results will be clearly normal or abnormal. In these cases, a qualitative interpretation of a biomarker test will unequivocally identify “positive” findings that imply the presence of the underlying AD pathophysiological process, or negative findings that unequivocally imply absence of an AD pathophysiological process. However, in some cases, ambiguous or indeterminate results will be obtained. This is inevitable given that all biomarkers are continuous measures, and the diagnostic labels of “positive” or “negative” require that cutoff values be applied to continuous biological phenomena. Although sophisticated quantitative and objective image analysis methods do exist, at present, accepted standards for quantitative analysis of AD imaging tests are lacking. Standard clinical practice in diagnostic imaging is qualitative in nature. Therefore, quantification of imaging biomarkers must rely on local laboratory specific standards. The same holds true for CSF biomarkers, although standardization efforts are more advanced for CSF biomarkers than for the imaging tests. Quantitative analytic techniques are, and will continue to be in evolution for some time. Therefore, practical use of biomarkers must follow best-practice guidelines within laboratory-specific contexts, until standardization has been fully accomplished.

A sequence of events has been described with Aβ pathophysiological processes becoming abnormal first and downstream neuronal injury biomarkers becoming abnormal later [6,7]. This might imply a hierarchical ranking of Aβ biomarkers over downstream neuronal injury biomarkers for diagnostic purposes. However, at this time, the reliability of such a hierarchical scheme has not been sufficiently well established for use in AD dementia. Given the number of

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (CSF tau, FDG-PET, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD dementia</td>
<td>Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>With three levels of evidence of AD pathophysiological process</td>
<td>Intermediate (PET or CSF)</td>
<td>Intermediate</td>
<td>Unavailable or indeterminate</td>
</tr>
<tr>
<td>Possible AD dementia (atypical clinical presentation)</td>
<td>Based on clinical criteria</td>
<td>High</td>
<td>Positive</td>
</tr>
<tr>
<td>With evidence of AD pathophysiological process</td>
<td>High but does not rule out second etiology</td>
<td>High</td>
<td>Positive</td>
</tr>
<tr>
<td>Dementia-unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, 18fluorodeoxyglucose; MRI, magnetic resonance imaging.
different AD biomarkers, it is inevitable that different combinations of test results can occur. For example, individual cases might be encountered with a positive Aβ and negative neuronal injury biomarker, or a positive FDG PET and negative tau measure, and so on. At present, the data are insufficient to recommend a scheme that arbitrates among all different biomarker combinations. Further studies are needed to prioritize biomarkers and to determine their value and validity in practice and research settings.

9. Pathophysiologically proved AD dementia

The diagnosis of pathophysiologically proved AD dementia would apply if the patient meets the clinical and cognitive criteria for AD dementia outlined earlier in the text, and the neuropathological examination, using widely accepted criteria [24], demonstrates the presence of the AD pathology.

10. Dementia unlikely to be due to AD

1. Does not meet clinical criteria for AD dementia.
2. a. Regardless of meeting clinical criteria for probable or possible AD dementia, there is sufficient evidence for an alternative diagnosis such as HIV dementia, dementia of Huntington’s disease, or others that rarely, if ever, overlap with AD.
   b. Regardless of meeting clinical criteria for possible AD dementia, both Aβ and neuronal injury biomarkers are negative (see section 6, earlier in the text).

Acknowledgment

The authors acknowledge the assistance of Dr. Cerise Elliott at the National Institute on Aging. Guy McKhann serves on a Data Safety Monitoring Board for Merck. David Knopman serves on a Data Safety Monitoring Board for Lilly Pharmaceuticals and is an investigator for clinical trials sponsored by Elan Pharmaceuticals, Forest Pharmaceuticals, and Baxter Healthcare; he is deputy editor of Neurology and receives compensation for editorial activities. Howard Chertkow serves as a consultant to Pfizer Canada, Lundbeck Canada, Janssen Ortho, Novartis Canada, and Bristol-Myers Squibb; he receives a research grant from Pfizer Canada. Bradley Hyman serves as a consultant to EMD Serrano, Janssen, Takeda, BMS, Neurophage, Pfizer, Quanterix, foldrx, Elan, and Link, and receives funding from the NIH, the Alzheimer’s Association, and Fidelity Biosciences. Clifford Jack serves as a consultant for Eli Lilly, Eisai, and Elan; he is an investigator in clinical trials sponsored by Baxter and Pfizer Inc., and owns stock in Johnson and Johnson. Claudia Kawas serves on a Data Safety Monitoring Board for Lilly Pharmaceuticals, Elan Pharmaceuticals, and Lundbeck; she is an investigator in a trial sponsored by Avid Radiopharmaceuticals. William Klunk serves as a consultant to GE Healthcare and receives research grants from the same; he also receives royalties from GE Healthcare for PiB PET technology and owns stock or options in Neuroptix, a company seeking to commercialize detection of amyloid in the eye. Walter Koroshetz are employees of the U.S. Government and report no conflicts. Jennifer Manly reports no conflicts of interests. Richard Mayeux serves on scientific advisory board of Psychogenics. Richard Mohs is a full-time employee of Eli Lilly and Company and holds stock in Lilly. Avid Radiopharmaceuticals is a wholly owned subsidiary of Eli Lilly and Co. John Morris serves as a consultant to Astra Zeneica, Bristol-Myers Squibb, Eisai, Janssen, Genetic, Eli Lilly, Merck, Novartis, Otsuka, Pfizer, and Schering Plough. University College London receives payment for Martin Rossor serving on the Safety Monitoring Committees for Janssen and Servier trials in AD. Philip Scheltens serves as a consultant to Pfizer Pharmaceuticals, Genetech, Danone Research, Lundbeck Pharmaceuticals, GE Healthcare, Roche, and Novartis; he also serves on speakers bureau for Lundbeck Pharmaceuticals. Maria Carrillo and Bill Thies are employees of the Alzheimer’s Association and reports no conflicts. Sandra Weintraub reports no conflicts of interest and Creighton Phelps.

References


Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

ABSTRACT

The Dementia with Lewy Bodies (DLB) Consortium has refined its recommendations about the clinical and pathologic diagnosis of DLB, updating the previous report, which has been in widespread use for the last decade. The revised DLB consensus criteria now distinguish clearly between clinical features and diagnostic biomarkers, and give guidance about optimal methods to establish and interpret these. Substantial new information has been incorporated about previously reported aspects of DLB, with increased diagnostic weighting given to REM sleep behavior disorder and 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. The diagnostic role of other neuroimaging, electrophysiologic, and laboratory investigations is also described. Minor modifications to pathologic methods and criteria are recommended to take account of Alzheimer disease neuropathologic change, to add previously omitted Lewy-related pathology categories, and to include assessments for substantia nigra neuronal loss. Recommendations about clinical management are largely based upon expert opinion since randomized controlled trials in DLB are few. Substantial progress has been made since the previous report in the detection and recognition of DLB as a common and important clinical disorder. During that period it has been incorporated into DSM-5, as major neurocognitive disorder with Lewy bodies. There remains a pressing need to understand the underlying neurobiology and pathophysiology of DLB, to develop and deliver clinical trials with both symptomatic and disease-modifying agents, and to help patients and carers worldwide to inform themselves about the disease, its prognosis, best available treatments, ongoing research, and how to get adequate support. Neurology® 2017;89:1–13

GLOSSARY

AD = Alzheimer disease; CHEI = cholinesterase inhibitor; DAT = dopamine transporter; DLB = dementia with Lewy bodies; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LB = Lewy body; MCI = mild cognitive impairment; MIBG = metaiodobenzylguanidine; MMSE = Mini-Mental State Examination; MTL = medial temporal lobe; PD = Parkinson disease; PSG = polysomnography; RBD = REM sleep behavior disorder.

The Dementia with Lewy Bodies (DLB) Consortium last reported on diagnosis and management in December 2005, and its recommendations have been widely cited for both clinical and research use.1,2 Changes made to the diagnostic criteria at that time increased diagnostic sensitivity for DLB,3 but detection rates in clinical practice remain suboptimal,4 with many cases missed or misdiagnosed, usually as Alzheimer disease (AD). The revised DLB criteria presented here incorporate new developments since then and result from a review process that combined the reports of 4 multidisciplinary, expert working groups with a meeting that included patient and care partner participation (appendix e-1 at Neurology.org). The Consortium recognizes increasing interest in detecting early-stage disease; prodromal DLB criteria are in development and will be reported separately.

SUMMARY OF CHANGES While maintaining their previous structure, the revised DLB clinical diagnostic criteria improve on earlier versions1,2 by distinguishing clearly between clinical features and diagnostic

Author affiliations are provided at the end of the article.

Members of the DLB Consortium are listed at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was paid by NIHR Newcastle Biomedical Research Centre in Ageing and Long-Term Conditions.

This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
bionarkers, with guidance about optimal methods to establish and interpret these. Clinical signs and symptoms are weighted as core or supportive, and biomarkers as indicative or supportive, based upon their diagnostic specificity and the volume of good-quality evidence available. Although carrying less diagnostic weight, supportive items are often valuable in clinical decision-making, acting as signposts to or adding evidence for a DLB diagnosis. The previous category of suggestive features is no longer used and those items, namely REM sleep behavior disorder (RBD), severe neuroleptic sensitivity, and low dopamine transporter (DAT) imaging, have been reassigned in the new scheme.

The revised criteria (Table 1) generate categories of probable and possible DLB, corresponding to terminology previously used, describing the clinical presentations most typical of dementia associated with underlying Lewy-related pathology. Because of considerable pathologic heterogeneity, some dementia presentations associated with Lewy-related pathology are atypical, e.g., if abundant neocortical neuritic plaques and tangles are present in addition to Lewy bodies (LB), the clinical profile may more closely resemble AD than DLB.4,5 Such mixed pathology cases are common, explaining why up to half of carefully research-diagnosed patients with AD may have unsuspected Lewy-related pathology at autopsy.6 Criteria for the detection of such patients, previously characterized as the LB variant of AD,7 remain to be formulated.

Clinical features. Dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities, is an essential requirement for DLB diagnosis.

Although dementia screens such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment are useful to characterize global impairment in DLB, neuropsychological assessment should include tests covering the full range of cognitive domains potentially affected. Disproportionate attentional, executive function, and visual processing deficits relative to memory and naming are typical.8,9,10 Measures of attention/executive function that differentiate DLB from AD and normal aging and that predict progression from mild cognitive impairment (MCI) to DLB include tests of processing speed and divided/alternating attention, e.g., Stroop tasks, trail-making tasks, phonemic fluency, and computerized tasks of reaction time. The spatial and perceptual difficulties of DLB often occur early; examples of useful probes include tasks of figure copy, e.g., intersecting pentagons, complex figure copy; visual assembly, e.g., block design, puzzle tasks; spatial matching, e.g., line orientation, size matching tasks; and perceptual discrimination, e.g., incomplete figures, incomplete letters, pareidolia tasks.10,11

Memory and object naming tend to be less affected in DLB, and are best evaluated through story recall, verbal list learning, and confrontation naming tasks, although some patients’ difficulties may be secondary to speed or retrieval task demands.

No DLB-specific assessment batteries have been developed, although recommendations have been made about suitable existing instruments12 and a composite risk score tool has been published.12

Core clinical features. Fluctuation. DLB fluctuations have been described in detail previously1–2 and are typically delirium-like,3 occurring as spontaneous alterations in cognition, attention, and arousal. They include waxing and waning episodes of behavioral inconsistency, incoherent speech, variable attention, or altered consciousness that involves staring or zoning out. Direct questioning of an informant about fluctuations may not reliably discriminate DLB from AD, but questions about daytime drowsiness, lethargy, staring into space, or episodes of disorganized speech do. These have been incorporated into scales that either score the severity and frequency of fluctuations derived from a clinical interview or use informant reports from semi-structured questionnaires.13–16 Recording variations in attentional performance using repeated computer-based tests offers an independent method.10 At least one measure of fluctuation should be documented when applying DLB diagnostic criteria. Fluctuations may also occur in advanced stages of other dementias, so they best predict DLB when they are present early.17

Visual hallucinations. Recurrent, complex visual hallucinations occur in up to 80% of patients with DLB and are a frequent clinical signpost to diagnosis. They are typically well-formed, featuring people, children, or animals, sometimes accompanied by related phenomena including passage hallucinations, sense of presence, and visual illusions.18 Patients are typically able to report these experiences, as are observant caregivers. Patient responses to their hallucinations vary both in degree of insight and emotional reaction to them. Assessment scales for characterizing and quantifying visual hallucinations are available.17

Parkinsonism. Spontaneous parkinsonian features, not due to antiparkinsonian medications or stroke, are common in DLB, eventually occurring in over 85%.19 Parkinsonism in Parkinson disease (PD) is defined as bradykinesia in combination with rest tremor, rigidity, or both.18 Many DLB patients’ parkinsonism falls short of this, so documentation of only one of these cardinal features is required. Care should be taken particularly in older patients not to misinterpret physical signs due to comorbidity, e.g.,
Table 1  Revised\textsuperscript{1,2} criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

| Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent and occur early. |
| Core clinical features (The first 3 typically occur early and may persist throughout the course.) |
| Fluctuating cognition with pronounced variations in attention and alertness. Recurrent visual hallucinations that are typically well formed and detailed. REM sleep behavior disorder, which may precede cognitive decline. |
| One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity. |
| Supportive clinical features |
| Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hyposmia; dysphagia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression. |
| Indicative biomarkers |
| Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. Abnormal (low uptake) \textsuperscript{123}I-iodine-MIBG myocardial scintigraphy. Polysomnographic confirmation of REM sleep without atonia. |
| Supportive biomarkers |
| Relative preservation of medial temporal lobe structures on CT/MRI scan. Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity: the cingulate island sign on FDG-PET imaging. Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range. |
| Probable DLB can be diagnosed if: |
| a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or |
| b. Only one core clinical feature is present, but with one or more indicative biomarkers. |
| Probable DLB should not be diagnosed on the basis of biomarkers alone. |
| Possible DLB can be diagnosed if: |
| a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or |
| b. One or more indicative biomarkers is present but there are no core clinical features. |
| DLB is less likely: |
| a. In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or |
| b. If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia. |

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

Biomarkers. Although direct biomarker evidence of LB-related pathology is not yet available for clinical diagnosis, several useful indirect methods are.

**Indicative biomarkers.** If one or more of these is found, associated with one or more core clinical features, probable DLB should be diagnosed. Dementia without any core clinical features, but with one or more indicative biomarkers, may be classified as possible DLB. Probable DLB should not be diagnosed on the basis of biomarkers alone.

**Reduced DAT uptake in basal ganglia demonstrated by SPECT or PET imaging.** The utility of DAT imaging in distinguishing DLB from AD is well-established, with sensitivity (78%) and specificity (90%).\textsuperscript{19} Figure 1 shows \textsuperscript{123}I-iodine FP-CIT SPECT images in patients with AD, patients with DLB, and normal controls. When parkinsonism is the only core clinical feature of DLB in a patient with dementia, reduced DAT uptake warrants a probable DLB diagnosis provided that other disorders associated with cognitive impairment and reduced DAT uptake can be excluded, e.g., progressive supranuclear palsy, multisystem atrophy, corticalbasal degeneration, and frontotemporal dementia. Normal DAT uptake may be reported in autopsy-confirmed DLB.
either because of minimal brainstem involvement and limited nigral neuron loss or a balanced loss of dopamine across the whole striatum, rather than predominantly in the putamen.

Reduced uptake on metaiodobenzylguanidine myocardial scintigraphy. 123Iodine-MIBG myocardial scintigraphy quantifies postganglionic sympathetic cardiac innervation, which is reduced in LB disease.\(^{22}\) Images from patients with AD, DLB, and age-matched normal controls are shown in figure 2. Useful sensitivity (69%) and specificity (87%) values for discriminating probable DLB from probable AD rise to 77% and 94% in milder cases (MMSE >21).\(^{28}\) Studies have generally excluded patients with comorbidities, or taking medicines, which can produce abnormal MIBG images. Clinicians should carefully interpret MIBG results in the light of possible confounding causes, including ischemic heart disease, heart failure, diabetes mellitus, peripheral neuropathies, and medications that may cause reduced uptake including labetalol, reserpine, tricyclic antidepressants, and over-the-counter sympathomimetics.\(^{29,e14,e15}\)

PSG confirmation of REM sleep without atonia. PSG demonstration of REM sleep without atonia\(^{e16,e17}\) is desirable whenever feasible, since it is a highly specific predictor of Lewy-related pathology. If the PSG shows REM sleep without atonia in a person with dementia and a history of RBD, there is a ≥90% likelihood of a synucleinopathy,\(^{22}\) sufficient to justify a probable DLB diagnosis even in the absence of any other core feature or biomarker (figure 3).

Supportive biomarkers. These are biomarkers consistent with DLB that help the diagnostic evaluation, but without clear diagnostic specificity.

Relative preservation of medial temporal lobe structures on C/T MRI scan. Patients with AD show greater atrophy of medial temporal lobe (MTL) structures than patients with DLB (figure 1), particularly the hippocampus, which is strongly correlated at autopsy with tangle rather than plaque or LB-related pathology.\(^{30}\) Absent or minimal MTL atrophy is therefore consistent with DLB, but unusual in AD. A multisite study with autopsy confirmation found sensitivity (64%) and specificity (68%) for separating AD from DLB.\(^{34}\) MTL atrophy in DLB may, however, signal substantial additional AD neuropathologic change, and predict a more rapid clinical course.\(^{32}\)

Generalized low uptake on SPECT/PET perfusion/metabolism scan, reduced occipital activity, and the posterior cingulate island sign on FDG-PET imaging. FDG-PET occipital hypometabolism correlates with visual cortex neuropathology in DLB\(^{33}\) and a small, autopsy-confirmed study suggested this could distinguish DLB from AD with
high accuracy.\textsuperscript{34} Larger studies, earlier in disease, suggest sensitivity (70%) and specificity (74%) slightly lower than needed for an indicative biomarker, although better than that reported for HMPAO-SPECT (65% and 64%).\textsuperscript{35,36} Relative preservation of posterior or midcingulate metabolism on FDG-PET (the cingulate island sign) has been described in DLB,\textsuperscript{37} associated with less concurrent neurofibrillary pathology, but with no difference in A\textbeta load relative to AD (figure 4).\textsuperscript{38}

Prominent posterior slow-wave EEG activity with periodic fluctuations in the pre-alpha/theta range. Evidence is building to support quantitative EEG as a DLB biomarker, characterized by specific abnormalities in posterior derivations. These include a pre-alpha-dominant frequency, either stable or intermixed with alpha/theta/delta activities in pseudoperiodic patterns,\textsuperscript{39} which together have a predictive value >90% for the diagnosis of DLB compared with AD.\textsuperscript{41} These specific EEG patterns also correlate positively with the severity of clinically observed cognitive fluctuations\textsuperscript{42} and may be seen at the MCI stage.\textsuperscript{43}

Other imaging biomarkers. PET imaging shows increased A\textbeta brain deposition in >50% of patients with DLB, limiting its value to distinguish between AD and DLB.\textsuperscript{40} Combining biomarkers in a multimodal approach can improve diagnostic accuracy in distinguishing DLB and AD\textsuperscript{41} and provides information about mixed pathology and multisystem involvement. Tau PET imaging may have an important role, along with MTL atrophy, as a key indicator of coexisting AD pathology in DLB, predictive of clinical phenotype and progression.

**Genetic and fluid biomarkers.** The development of broadly applicable CSF, blood, peripheral tissue, or genotypic biomarkers for DLB remains elusive. Although it is clear that there is a substantial genetic contribution to DLB\textsuperscript{42,43} and that different genetic markers even within the \alpha-synuclein gene (\textit{SNCA}) may be associated with different LB syndromes,\textsuperscript{44} our understanding of the core genes involved remains limited. CSF \alpha-synuclein is not yet proven as a biomarker, while A\textbeta, tau, and phospho-tau measurements may be more useful in determining concomitant AD pathology or predicting cognitive decline.\textsuperscript{45} Glucocerebrosidase (\textit{GBA}) mutations are overrepresented in DLB\textsuperscript{46} but most individuals with DLB do not have them. It is premature to recommend genetic testing in a clinical setting, either for confirmation of diagnosis or for prediction of disease, and genetic studies should currently be limited to research settings.
Clinical management. The management of patients with DLB is complex, requiring a multifaceted approach. Key elements include a thorough initial evaluation to ensure accurate diagnosis; early identification of signs and symptoms requiring intervention; engagement, education, and support of care providers; and a multidisciplinary team approach. Patients with DLB are prone to mental status worsening, including delirium, in the face of comorbid medical disorders. Dopaminergic therapies and anticholinergic medications can adversely affect cognition and behavior, leading to confusion and psychosis. Treatment of DLB is focused on the cognitive, psychiatric, motor, and other nonmotor symptoms that represent the core or most common features of the disorder. A combination of pharmacologic and nonpharmacologic approaches is optimal. As the evidence base to support particular treatments remains limited, the recommendations outlined below remain based, in part, upon consensus expert opinion.

Nonpharmacologic interventions. Given both the limited evidence for efficacy and the potential increased morbidity and mortality risks associated with pharmacologic treatments in DLB, there is a need to develop and test nonpharmacologic management strategies. Interventions can be patient- or caregiver-focused, or both. More research in this area has been conducted in AD and PD than in DLB, with promising preliminary evidence for exercise (both motor and cognitive benefits), cognitive training, and caregiver-oriented education and training to manage psychiatric symptoms including agitation and psychosis.

Pharmacologic management. Cognitive symptoms. Meta-analyses of Class I clinical trials of rivastigmine and donepezil support the use of cholinesterase inhibitors (CHEIs) in DLB for improving cognition, global function, and activities of living, with evidence that even if patients do not improve with CHEIs they are less likely to deteriorate while taking them. The efficacy of memantine in DLB is less clear, but it is well-tolerated and may have benefits, either as monotherapy or adjunctive to a CHEI.

Neuropsychiatric symptoms. CHEIs may produce substantial reduction in apathy and improve visual...
hallucinations and delusions in DLB.49 Since anxiety and agitation are sometimes driven by psychosis, there may be secondary benefits in these. The use of antipsychotics for the acute management of substantial behavioral disturbance, delusions, or visual hallucinations comes with attendant mortality risks in patients with dementia, and particularly in the case of DLB they should be avoided whenever possible, given the increased risk of a serious sensitivity reaction.50 Low-dose quetiapine may be relatively safer than other antipsychotics and is widely used, but a small placebo-controlled clinical trial in DLB was negative.51 There is a positive evidence base for clozapine in PD psychosis, but efficacy and tolerability in DLB have not been established. Newer drugs targeting the serotonergic system, such as pemovastatin,52 may be alternatives, but controlled clinical trial data in DLB are needed. Although depressive symptoms are common in DLB, trial data are scant. In alignment with general advice on depression in dementia, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and mirtazapine are options in DLB with treatment guided by individual patient tolerability and response.

Motor symptoms. Parkinsonism is often less responsive to dopaminergic treatments in DLB than in PD and their use may be associated with an increased risk of psychosis, although some patients may benefit from levodopa preparations introduced at low doses and increased slowly to the minimum required to minimize motor disability without exacerbating psychiatric symptoms.53-56 Patients at risk of falling may benefit from safety assessments, as well as bone mineral density screening, and assessment of vitamin D status, to manage risk of traumatic fractures.

Other symptoms. A wide range of other symptoms can occur in DLB, including autonomic and sleep/wakefulness disturbances, which have profound negative sequelae for quality of life in both patients and their families. In the absence of DLB-specific trial data for these symptoms, clinicians base their treatment decisions on clinical experience, expert opinion, or evidence-based recommendations developed in other diseases, e.g., cautious bedtime use of clonazepam may reduce the risk of sleep-related injuries in...
patients with DLB with RBD but carries a risk of worsening cognition and gait impairment, melatonin being a possibly safer option.54

Pathology. Pathologic assessment and diagnostic criteria for DLB. The previously published methods for pathologic assessment and diagnosis of DLB should continue to be used with only a few modifications, shown in table 2, which predicts the likelihood that the pathologic findings will be associated with a typical DLB clinical syndrome, i.e., cases with high likelihood are expected to fulfill clinical criteria for probable DLB, whereas low likelihood cases may have few or no DLB clinical features.

Table 2 assigns categories of AD neuropathologic change according to National Institute on Aging–Alzheimer’s Association criteria (no, low, intermediate, and high),55 and adds previously omitted categories of Lewy-related pathology including olfactory bulb only56 and amygdala predominant.57,58 Both of these are considered to be low-likelihood DLB but may in the future be useful in assessing prodromal disease. Further efforts are required to develop better interrater reliability59 for Lewy-related disease subtypes (olfactory bulb only, amygdala predominant, brainstem, limbic [transitional], and diffuse neocortical). Table 2 also includes an assessment of substantia nigra neuronal loss (none, mild, moderate, and severe) in order to subclassify cases into those likely or not to have parkinsonism (DLB-P and DLB-no P).60

**FUTURE DIRECTIONS.** Since publication of the 2005 consensus report, DLB has been confirmed as a major dementia subtype, categorized in DSM-529 as neurocognitive disorder with LB, and distinguished from neurocognitive disorder due to PD. The consensus group remains supportive of the 1-year rule distinguishing DLB from PD dementia, because as originally stated1,2 this arbitrary cutoff remains useful, particularly in clinical practice. Based as it is on expert opinion, the time period may need modification when the genetic underpinnings, pathophysiologic mechanisms, and prodromal states of these disorders are sufficiently understood to enable a data-driven solution.e30,e31

There is an urgent need to develop guidelines and outcome measures for clinical trials in DLB, both symptomatic and disease-modifying, nonpharmacologic and pharmacologic. DLB researchers can build upon experience gained in AD and PD; additional issues for them to consider include subtyping of patients on the basis of clinical or biomarker criteria and selecting target symptoms and outcome measures appropriate to DLB. It will be necessary to manage potential confounding factors that are common in DLB, e.g., fluctuations in alertness and fatigue, active hallucinations, and concomitant use of cognitive enhancing and psychiatric medications. Such considerations will need to be applied when designing clinical trials across the spectrum of clinical syndrome of DLB from prodromal and presymptomatic stages, still to be identified, to overt dementia.

Suggested strategies to progress critical areas of biological research include collecting samples from large population-based cohorts and developing a publicly available DLB genetic database and a repository for DLB exome data. Family studies are needed to find and confirm genes, requiring clinicians to take detailed family histories seeking evidence not only of DLB, PD, and AD and other dementias, but also of RBD and supportive features.

In order to make progress in deciphering biological mechanisms at play in DLB including GBA32 and inflammatory pathways,35 it will be necessary to develop robust animal models that capture the true neuropathologic and behavioral abnormalities of DLB, and to identify possible disease-specific

### Table 2

<table>
<thead>
<tr>
<th>Alzheimer disease neuropathologic change</th>
<th>NIA-AA none/low (Braak stage 0-II)</th>
<th>NIA-AA intermediate (Braak stage III-IV)</th>
<th>NIA-AA high (Braak stage V-VI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewy-related pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse neocortical</td>
<td>High</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Limbic (transitional)</td>
<td>High</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Brainstem-predominant</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Amygdala-predominant</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Olfactory bulb only</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Substantia nigra neuronal loss to be assessed (as none, mild, moderate, and severe)60 in order to subclassify cases into those likely or not to have parkinsonism.

Abbreviation: NIA-AA = National Institute on Aging–Alzheimer’s Association guidelines for the neuropathologic assessment of Alzheimer disease.56
molecular differences in α-synuclein, tau, and Aβ among DLB, PD, PD dementia, and AD. The latter includes characterization of possible molecular strains of misfolded or pathologic α-synuclein, posttranslational modifications in degradation and clearance processes, and transmission and propagation. It will be increasingly important to study protein interactions among α-synuclein, Aβ, and tau. Finally, there is an unmet need to characterize biological effects of identified genetic risk factors, including APOE, GBA, and SNCA, as well as to model and analyze gene–environmental interactions.

In order to best advance DLB research, global harmonization efforts are required to create networks of researchers and research participants who share common platforms for data and biomarker collection, outcome measures for clinical–translational research, and shared terminology across language, cultures, and traditions. Consideration might be given to creating an international patient and caregiver association to serve as advocates for private and public funding; identifying obstacles to the pharmaceutical industry sponsoring DLB research; bridging relationships with the PD and AD world research communities; creating a plan for reimbursement for DLB clinical care, drugs/devices, and biomarkers; and increasing interdisciplinary and interprofessional communication regarding the challenges facing clinicians, patients, and caregivers. Finally, priority needs to be given to helping patients and carers to inform themselves about the disease, its prognosis, best available treatments, ongoing research, and how to get adequate support.

AUTHOR AFFILIATIONS

From the Institute of Neuroscience (I.G.M., J.-P.T., J.A., D.B., A. Thomas), Newcastle University, UK; Departments of Neurology (B.F.B.) and Radiology (K. Kantarcı), Mayo Clinic (A.L.), Rochester, MN; Neuropathology Laboratory (D.W.D., M. Murray) and Departments of Psychiatry and Psychology (T.J.F.), Neurology (N.R.G.-R.), and Neuroscience (P.M., O.A.R.), Mayo Clinic, Jacksonville, FL; Brain and Mind Centre (G.H.), University of Sydney (S.L.), Australia; Department of Neurology (J.E.D.) and Center for Neurodegenerative Disease Research (V.M.Y.L., J.Q.T.), Perelman School of Medicine at the University of Pennsylvania (D.W., A.C.-P., J.B.T.), Philadelphia; Parkinson’s Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC) (D.W.), Philadelphia Veterans Affairs Medical Centre, PA; Institute of Psychiatry, Psychology, and Neuroscience (D.A., D.f.), King’s College London, UK; Centre for Age-Related Diseases (D.A.), Stavanger University Hospital, Norway; Institute for Healthy Aging and Lifespan Studies (I-HeAL) (J.G.), Florida Atlantic University, Boca Raton; Medical School (C.G.B.), University of Exeter; Lewy Body Society (A.B.), Edinburgh, UK; Banner Sun Health Research Institute (T.G.B.), San Cay, AZ; University Hospital of Strasbourg (F.B.); ICube Laboratory (F.B.), CMI2 Geriatrics Department and University of Strasbourg-CNRS, France; Departments of Radiology & Neurology (N.R.B.), University of Michigan; Department of Veterans Affairs (N.B.), Ann Arbor, MI; Department of Neuroscience, Imaging and Clinical Sciences (L.B.), University G. d’Annunzio of Chieti-Pescara, Chieri, Italy; Department of Molecular Neuroscience (J.B.), Institute of Neurology, UCL, London, UK; Center for Neurodegenerative Science (P.B.), Van Andel Research Institute, Grand Rapids, MI; Neurological Disorders Research Center (O.E.-A.), Qatar Biomedical Research Institute (QBBRI), Ar-Rayyan; Department of Neurosciences (H. Feldman, D.G., D.P.S.), University of California, San Diego; Department of Psychiatry (H. Fujiished, Nagoya University Graduate School of Medicine, Japan; Department of Neurological Sciences (J.G.G.), Rush University Medical Center, Chicago, IL; Department of Neurology (S.N.G.), Massachusetts General Institute for Neurodegenerative Disease, Massachusetts General Hospital, Boston; Department of Neurology and Taub Institute (L.S.H.), Columbia University, New York, NY; Neurology Service (A.L.), Hospital Clinic de Barcelona, Spain; Departments of Neurology and Psychiatry (D.K.), University of North Carolina at Chapel Hill; Department of Epidemiology (W.K.), University of Washington, Seattle; Lou Ruvo Center for Brain Health (J.B.T.), Neurologic Institute, Cleveland Clinic, OH; Thomas Jefferson University (C.L.), Philadelphia, PA; Department of Medicine (M. Maellimo), Sunnybrook Health Sciences Centre, University of Toronto, Canada; Division of Neuroscience (E.M.), National Institute on Aging, Baltimore, MD; Paracelsus-Elena-Klinik (B.M.), Kasel, Germany; Department of Pathology (T.J.M.),Stanford University, CA; GE Healthcare (E. Moreto), Medical Affairs, London, UK; Department of Behavioral Neurology and Cognitive Neuroscience (E. Morl), Tohoku University Graduate School of Medicine, Sendai, Japan; Department of Psychiatry (J.T.O.), University of Cambridge, UK; Department of Neurology (S.O.), Kanto Central Hospital, Tokyo, Japan; Department of Neurology (R.B.P.), Montreal General Hospital, Canada; Axovant Sciences, Inc. (S.R.), New York, NY; Laboratory of Neurogenetics (A.S.), NIH, Bethesda, MD; Lewy Body Dementia Association (A. Taylor), Lübum, GA; Neurology Department (J.B.T.), Houston Methodist Hospital, TX; Division of Neurology/Neuropathology (P.T.), Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy; VA Puget Sound Health Care System (D.T.), Seattle, WA; University College London & North Essex Partnership University NHS Foundation Trust (Z.W.), UK; Department of Neurology and Neurobiology of Aging (M.Y.), Kanazawa University Graduate School of Medical Sciences; and Yokohama City University Medical Center (K. Kosaka), Japan.

AUTHOR CONTRIBUTIONS

Ian McKeith: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Bradley Boeve: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Dennis Dickson: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Glenda Halliday: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Thomas Beach: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Daniel Weintraub: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Dag Aarsland: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. James Galvin: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Johannes Arntzen: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Clive Ballard: analysis or interpretation of the data, drafting or revising the manuscript. Ashley Bayston: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Laura Bonanni: analysis or interpretation of the data, drafting or revising the manuscript. Nicolaas Bohnen: analysis or interpretation of the data, drafting or revising the manuscript. Jose Bras: analysis or interpretation of the data, drafting or revising the manuscript. Patrick Brundin: analysis or interpretation of the data, drafting or revising the manuscript. David Burn: analysis or interpretation of the data, drafting or revising the manuscript. Alice Chen-Plotkin: analysis or interpretation of the data, drafting or revising the manuscript. Ian McKeith: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript. Dennis Dickson: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript.

Neurology 89 July 4, 2017 9
provided administrative support to the consortium meeting in Fort Lauderdale. I.G.M., D.B., J.-P.T., J.A., and A.T. receive support from the UK NIHR Biomedical Research Centre awarded to the Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University. Travel grant support was provided by the Alzheimer’s Research UK ARUK NE Network Centre. B.F.B., D.W.D., K.K., and T.J.F. are supported by the NIH (P50-AG016574) and the Mangurian Foundation for Lewy Body Research. G.H. is a senior principal research fellowship holder from the National Health and Medical Research Council of Australia (1079679). D.A. is a Royal Society Wolfson Research Merit Award Holder and thanks the Wolfson Foundation and the Royal Society for their support. C.G.B. thanks the Maudsley BRC for Mental Health and BRU dementia for supporting his involvement in the work. A.C.-P. receives research support from the NIH (RO1 NS082826, U01 NS082134, P50 NS053488), the Burroughs Wellcome Fund, the Alzheimer’s Association/Michael J. Fox Foundation/Weston Biomarkers Across Neurodegenerative Disease initiative, and the Pechenik Montague Award Fund. D.F. acknowledges support from NIHR Programme Grants for Applied Research (RP-PG-0610-10100 SHAPED). O.E.-A. acknowledges support for OE laboratory from the Michael J. Fox Foundation for Parkinson’s Research (New York). S.N.G. receives support from R21 NS 090243 and the National Parkinson’s Foundation. O.A.R. is supported through the Mayo Clinic: A Morris K. Udall Parkinson’s Disease Research Center of Excellence (NINDS P50 NS072187), NINDS R01 NS078086, the Michael J. Fox Foundation for Parkinson’s Research, the Mayo Clinic AD and Related Dementias Genetics Program, and the Sacks-Carlberg Research Fund, supported in part by a P50 NS053488 Morris K. Udall Parkinson’s Disease Research Center of Excellence grant from NINDS. P.T. acknowledges support from the Italian Ministry of Health “Ricerca Corrente.” M.Y. acknowledges support from the Japan Foundation for Neuroscience and Mental Health.

DISCLOSURE
I. McKeith receives support from the UK NIHR Biomedical Research Centre awarded to the Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University. He has consulted for Axovant Sciences, Takeda, Eisai, and GE Healthcare. B. Boeve has served as an investigator for clinical trials sponsored by GE Healthcare, FORUM Pharmaceuticals, C2N Diagnostics, and Axovant Sciences. He receives royalties from the publication of Behavioral Neurology of Dementia (Cambridge Medicine, 2009). He serves on the Scientific Advisory Board of the Tau Consortium. He receives research support from the NIH and the Mangurian Foundation. D. Dickson receives research support from the NIH (P50-AG016574, P50-NS072187, P01-AG003949) and CurePSP. Foundation for PSP/CBD and Related Disorders. Dr. Dickson is an editorial board member of Acta Neuropathologica, Annals of Neurology, Brain, Brain Pathology, and Neuropathology, and he is editor-in-chief of American Journal of Neurodegenerative Disease and International Journal of Clinical and Experimental Pathology. G. Halliday consults for the National Health and Medical Research Council of Australia (NHMRC); received travel funds from AHIC, International Society of Neurochemistry, International DLB Conference, AAN, International MSA Conference, NHMRC National Institute for Dementia Research, 2nd Chinese Brain Banking Meeting, and Japanese Neurosociety Society; is on the editorial boards of Acta Neuropathol, J Neural Transm, J Parkinson’s Dis, Transl Neurodegen, and Neuropathol Appl Neurobiol; receives royalties from Academic Press, Elsevier, and Oxford University Press; receives research grant funding from NHMRC (1080307, 1077746, and 1079679), the Michael J. Fox Foundation, Shake-it-up Australia, Parkinson’s NSW, and University of NSW (infrastructure and equipment); and holds stock in Cochlear (2004 on) and NIB Holdings (2007 on). J. Taylor is a consultant of Lundbeck and received honoraria for talks from GE Healthcare and Flynn Pharmaceuticals. D. Weintraub has received research funding or support from Michael J. Fox Foundation for Parkinson’s Research, NIH (NINDS), Novartis Pharmaceuticals, Department of Veterans Affairs, Aid Radiopharmaceuticals, Alzheimer’s Disease Cooperative Study.
and the International Parkinson and Movement Disorder Society; honorary from AbbVie, Acadia, Biogen, Biotie, Clintree LLC, Janssen, Merck, Novartis, Pfizer, Teva Pharmaceuticals, UCB, and the CHDI Foundation; license fee payments from the University of Pennsylvania for the QUIP and QUIP-RI; royalties from Wolters Kluwer; and fees for legal consultation for a lawsuit related to antipsychotic prescribing in a patient with Parkinson disease. D. Aarsland has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, and GE Health, and serves as a paid consultant for H. Lundbeck and Axovant. J. Galvin receives research support from Biogen, Axovant, NIH, Association for Frontotemporal Degeneration, and Florida Department of Health, and is a consultant for Biogen and Eisai. J. Attie reports no disclosures relevant to the manuscript. C. Ballard has received honoraria and grant funding from Acadia Pharmaceuticals, which manufactures pemaminexerin. Other financial disclosures in the last 2 years include the following: contract grant funding from Lundbeck, Takeda, and Axovant pharmaceutical companies and honoraria from Lundbeck, Lilly, Orasqua, and Orthon pharmaceutical companies. A. Bayston reports no disclosures relevant to the manuscript. T. Beach is a consultant to GE Healthcare and Avid Radiopharmaceuticals, performs contracted research for Avid Radiopharmaceuticals and Navidea Biopharmaceuticals, and receives research funding from NIH grant (P30AG019610), the Arizona Department of Health and Human Services, and the Michael J. Fox Foundation for Parkinson’s Research. F. Blanc has received speaker’s honoraria and travel expenses from Roche, Biogen Idec; Novartis, and Merck Serono. N. Bolhem receives research support from the NIH, Outside of this work, Outside of this work, Dr. J. Fox Foundation. L. Bonanni reports no disclosures relevant to the manuscript. J. Bras was supported by a fellowship from the Alzheimer’s Society and funding from the Lewy Body Society and Parkinson’s UK. P. Brundin has received commercial support as a consultant to Renovo Neural, Inc., Roche, Teva/Lundbeck, and AbbVie. He has received commercial support for grants/research from Renovo and Teva/Lundbeck. D. Brundin has ownership interests in Acousart AB and Parkcell AB. D. Burn and A. Chen-Potkin report no disclosures relevant to the manuscript. J. Duda serves on the Editorial Board for npj Parkinson’s Disease and has received research support from the US Department of Veterans Affairs, NIH, and the Michael J. Fox Foundation for Parkinson’s Research. O. El-Agnaf reports no disclosures relevant to the manuscript. H. Feldman receives research funding from the NIH, the Canadian Institutes of Health Research, the Weston Foundation, UC Cures for Alzheimer’s Disease, and Heart and Stroke Foundation of Canada. He has served as coinvestigator on clinical trials supported by TauRx, Hoffman LaRoche, and Lilly. He currently serves on the scientific advisory board for the Tau Consortium, Tau Rx, and the Alzheimer Society of Canada Research Policy. He has performed service agreements for UCSDD/UBC with Genentech Banner Health, Eisai, Arena, and Merck. He receives royalties for the publication of An Atlas of Alzheimer’s Disease (Informa Health, 2007). He has a US patent: PCT/US 2007/070008. T. Ferman, D. flynce, and H. Fujishiro report no disclosures relevant to the manuscript. D. Galasko is funded by NIH grant AG15313, the Michael J. Fox Foundation, and the California Institute for Regenerative Medicine. He has received funding from TV Pharmaceuticals and Eli Lilly, Inc., for consultation, from Eli Lilly and Prothera for service on Data Safety Boards, and payment from Biomed Central as Editor for Alzheimer’s Research and Therapy. J. Goldman has received grant/research support from the NIH, Michael J. Fox Foundation, Rush University, Parkinson Disease Foundation, Acadia, and Bootie (site PI), consulting fees from Acadia, Biogen, Pfizer, and Teva, and honoraria from the International Parkinson and Movement Disorder Society, American Academy of Neurology, MedEdicus, and Peri-Med. S. Gomperts reports no disclosures relevant to the manuscript. N. Graf-Radford is in a multicenter study on Lewy body disease for Axovant and is taking part in multicenter studies with Eli Lilly, Biogen, and TauRx. He has consulted for Cytos. L. Honig has performed consulting for Bristol-Myers Squibb, Forum, Lilly, and Lundbeck pharmaceutical companies; has performed clinical drug trials research funded by AbbVie, Axovant, Bristol-Myers Squibb, C2N, Forum, Genentech, Lilly, Lundbeck, Merck, Pfizer, Roche, TauRx, and TV pharmaceutical companies; receives compensation from editorial board activities of JAMA Neurology, and receives research support from NIH. A. Ianzo reports no disclosures relevant to the manuscript. K. Kantarci serves on the Data Safety Monitoring Board for Takeda Pharmaceuticals. She is funded by the NIH. D. Kauser served as a consultant to Janssen Research and Development and was a member of the Scientific Advisory Board for Takeda/Zinfindel. He serves as a consultant to Axovant Sciences, Inc., is a member of the Scientific Advisory Board of the FTD Disorders Registry, is a member of the Scientific Advisory Council of the Lewy Body Dementia Association, and is a member of the Board of Directors of Alzheimer’s North Carolina. He receives research support from NIH, TauRx Therapeutics, Navidea Biopharmaceuticals, Axovant Sciences, Neurim Pharmaceuticals, and AbbVie. W. Kukull is funded primarily by NIH grant U01 AG016976 “National Alzheimer’s Coordinating Center” and has no other relevant disclosures. He is a Senior Associate Editor for Alzheimer’s and Dementia and is also on the editorial board of Alzheimer’s Disease and Associated Disorders (nonrenumerated positions). V. Lee may accrue revenue in the future on patents submitted by the University of Pennsylvania wherein she is coinventor and she received revenue from the sale of Avid to Eli Lilly as coinventor on imaging-related patents submitted by the University of Pennsylvania. She receives research support from the NIH, GSK, Janssen, Biogen, and several nonprofits. J. Leverenz has served as a consultant for Axovant, GE Healthcare, Navidea Biopharmaceuticals, and Takeda and is funded by grants from the Alzheimer’s Drug Discovery Fund, Gennzyme/Sanoft, Jane and Lee Seidman Fund, Lewy Body Dementia Association, Michael J. Fox Foundation, and NIH (RF1AG169145, P50NS062684, U01NS061061). S. Lewis, C. Lippa, and A. Lande report no disclosures relevant to the manuscript. M. Masellis has a pending patent and provisional for the same title. Outside of this work, Dr. Masellis has served as an Associate Editor for Current Neuropharmacogenomics and Personalized Medicine; served as an advisor to Bioscape Medical Imaging CRO, UCB, and GE Healthcare; received honoraria and travel/accommodations/meeting expenses from Novartis and Teva; received royalties from Henry Stewart Talks Ltd.; received peer-reviewed research grants from Canadian Institutes of Health Research, Early Researcher Award—Ministry of Economic Development and Innovation of Ontario, Ontario Brain Institute, Sunnybrook AFP Innovation Fund, Alzheimer’s Drug Discovery Foundation (ADDF), Brain Canada, Heart and Stroke Foundation Centre for Stroke Recovery, Weston Brain Institute, and Washington University; received investigator-initiated research support from Teva; received contract research support from Axovant; and received salary support from the Department of Medicine at Sunnybrook Health Sciences Centre and University of Toronto and from the Sunnybrook Foundation. In addition, Dr. Masellis has a patent US 14/674,466 pending, a patent PCT/TU5/023618 pending, a patent AR 2015010101 pending, and a patent CA 270666 pending. A. McLean and V. Lee report no disclosures relevant to the manuscript. B. Mollenhauer has received independent research grants from TEVA-Pharma, Desitin, Boehringer Ingelheim, and GE Healthcare, and honoraria for consultancy from Bayer Schering Pharma AG, Roche, AbbVie, TEVA-Pharma, and Biogen, and for presentations from GlaxoSmithKline, Orion Pharma, and TEVA-Pharma, and travel costs from TEVA-Pharma. B.M. is a member of the executive steering committee of the Parkinson Progression Marker Initiative of the Michael J. Fox Foundation for Parkinson’s Research and has received grants from the BMBF, EU, Deutsche Parkinson Vereinigung, Michael J. Fox Foundation for Parkinson’s Research, and Stifterverband für die deutsche Wissenschaft, and has scientific collaborations with Roche, Bristol-Myers Squibb, Eli Lilly, Covance, and Biogen. T. Montine reports no disclosures relevant to the manuscript. E. Moreno is a full employee of GE Healthcare and has been involved in the clinical development of DaTSCAN for the diagnosis of DLB. E. Mori received honoraria from serving on the scientific advisory board of Eisai, grants and personal fees from Eisai, Daichi Sankyo, Novartis, and FUJIFILM RI, and personal fees from Johnson & Johnson, Ono, and NIH Bio-Physics. M. Murray is funded by the Ed and Ethel Moore Alzheimer’s Disease Research Program (6AZ01) and Gerstner Family Career Development Award. J. O’Brien has acted as a consultant for GE Healthcare, Cytox, TauRx, Axona, Piramal, and Lilly and has received grants from Avid (Lilly). S. Orimo received honoraria for sponsored lectures from FUJIFILM RI Pharma Co Ltd. R. Postuma received grants from the Fonds de la Recherche en Sante Quebec, the Canadian Institute of Health Research, the Parkinson Society, the Weston-Garfield Foundation, and the Webster Foundation, as well as funding for consultancy.
REFERENCES


Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium
Ian G. McKeith, Bradley F. Boeve, Dennis W. Dickson, et al.
Neurology published online June 7, 2017
DOI 10.1212/WNL.0000000000004058

This information is current as of June 7, 2017
Updated Information & Services
including high resolution figures, can be found at:
http://www.neurology.org/content/early/2017/06/07/WNL.000000000004058.full.html

Supplementary Material
Supplementary material can be found at:
http://www.neurology.org/content/suppl/2017/06/07/WNL.000000000004058.DC1
http://www.neurology.org/content/suppl/2017/06/07/WNL.000000000004058.DC2

Citations
This article has been cited by 2 HighWire-hosted articles:
http://www.neurology.org/content/early/2017/06/07/WNL.000000000004058.full.html##otherarticles

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Assessment of cognitive disorders/dementia
http://www.neurology.org/cgi/collection/assessment_of_cognitive_disorders_dementia
Dementia with Lewy bodies
http://www.neurology.org/cgi/collection/dementia_with_lewy_bodies
Parkinson's disease with dementia
http://www.neurology.org/cgi/collection/parkinsons_disease_with_dementia

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://www.neurology.org/misc/addir.xhtml#reprintsus
Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia


1 Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, 19104 PA, USA
2 Neuroscience Research Australia and University of New South Wales, Randwick, NSW 2031, Australia
3 Department of Neurology, Mayo Clinic, Rochester, 55905 MN, USA
4 Department of Neurology, UCLA School of Medicine, 90095 Los Angeles, CA, USA
5 Department of Psychiatry, UCLA School of Medicine, 90095 Los Angeles, CA, USA
6 Memory and Aging Center, University of California, 94143 San Francisco, CA, USA
7 Department of Epidemiology and Biostatistics, University of California, 94107 San Francisco, CA, USA
8 Department of Neurology, Erasmus Medical Centre, 3015 CE Rotterdam, Netherlands
9 Division of Neuropsychiatry and Geriatric Psychiatry, Johns Hopkins University School of Medicine, Baltimore, 21287 MD, USA
10 Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, 21287 MD, USA
11 Department of Neurology, University of Western Ontario, London, N6A 4V2 ON, Canada
12 Institute for Health and Aging, University of California, San Francisco, 94143 CA, USA
13 Wessex Neurological Centre, Southampton University NHS Trust, Southampton, SO16 6YD, UK
14 Department Clinical Neurosciences, Southampton University, Southampton, SO16 6YD, UK
15 Dementia Research Centre, UCL Institute of Neurology, London, WC1n 3BG, UK
16 Department of Neurosciences, University of California, San Diego, 92093 CA, USA
17 VA Medical Centre, University of California, San Diego, 92161 CA, USA
18 Department of Medicine (Neurology), Sunnybrook Health Sciences Centre, University of Toronto, Toronto, M4N 3M5 ON, Canada
19 Cognitive Neurology and Alzheimer’s Disease Centre, Northwestern University Feinberg School of Medicine, Chicago, 60611 IL, USA
20 Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, 02129 MA, USA
21 Department of Psychiatry, Technische Universitaet Muenchen, 81675 Munich, Germany
22 Departments of Neurology and Histology, University Lille Nord de France, 59000 Lille, France
23 Alzheimer Centre and Department of Neurology, VU University Medical Centre, PO Box 7057, 1007 MB, Amsterdam, the Netherlands
24 Rotman Research Institute, Baycrest, Toronto, M6A 2E1 ON, Canada
25 Departments of Medicine and Psychiatry, University of Toronto, Toronto, M6A 2E1 ON, Canada
26 Institute of Cognitive Neurology, Favaloro University, 1126 Buenos Aires, Argentina
27 Traumatic Brain Injury Research Laboratory, Kessler Foundation Research Centre, West Orange, 07052 NJ, USA
28 Department of Psychology, Universita Vita-Salute San Raffaele, 20132, Milan, Italy
29 Department of Neuroscience, Universita Vita-Salute San Raffaele, 20132, Milan, Italy
30 Department of Medicine, Division of Neurology, Baycrest and University of Toronto, Toronto, M6A 2E1 ON, Canada

© The Author (2011). Published by Oxford University Press on behalf of the Guarantors of Brain. All rights reserved.
For Permissions, please email: journals.permissions@oup.com
Based on the recent literature and collective experience, an international consortium developed revised guidelines for the diagnosis of behavioural variant frontotemporal dementia. The validation process retrospectively reviewed clinical records and compared the sensitivity of proposed and earlier criteria in a multi-site sample of patients with pathologically verified frontotemporal lobar degeneration. According to the revised criteria, ‘possible’ behavioural variant frontotemporal dementia requires three of six clinically discriminating features (disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviours, hyperorality and dysexecutive neuropsychological profile). ‘Probable’ behavioural variant frontotemporal dementia adds functional disability and characteristic neuroimaging, while behavioural variant frontotemporal dementia ‘with definite frontotemporal lobar degeneration’ requires histopathological confirmation or a pathogenic mutation. Sixteen brain banks contributed cases meeting histopathological criteria for frontotemporal lobar degeneration and a clinical diagnosis of behavioural variant frontotemporal dementia, Alzheimer’s disease, dementia with Lewy bodies or vascular dementia at presentation. Cases with predominant primary progressive aphasia or extra-pyramidal syndromes were excluded. In these autopsy-confirmed cases, an experienced neurologist or psychiatrist ascertained clinical features necessary for making a diagnosis according to previous and proposed criteria at presentation. Of 137 cases where features were available for both proposed and previously established criteria, 118 (86%) met ‘possible’ criteria, and 104 (76%) met criteria for ‘probable’ behavioural variant frontotemporal dementia. In contrast, 72 cases (53%) met previously established criteria for the syndrome ($P < 0.001$ for comparison with ‘possible’ and ‘probable’ criteria). Patients who failed to meet revised criteria were significantly older and most had atypical presentations with marked memory impairment. In conclusion, the revised criteria for behavioural variant frontotemporal dementia improve diagnostic accuracy compared with previously established criteria in a sample with known frontotemporal lobar degeneration. Greater sensitivity of the proposed criteria may reflect the optimized diagnostic features, less restrictive exclusion features and a flexible structure that accommodates different initial clinical presentations. Future studies will be needed to establish the reliability and specificity of these revised diagnostic guidelines.

**Keywords:** behavioural variant frontotemporal dementia; diagnostic criteria; frontotemporal lobar degeneration; FTD; pathology

**Abbreviations:** bvFTD = behavioural variant frontotemporal dementia; FTDC = International Behavioural Variant FTD Criteria Consortium; FTLD = frontotemporal lobar degeneration; SPECT = single-photon emission computed tomography

**Introduction**

The behavioural variant of frontotemporal dementia (bvFTD) is a clinical syndrome characterized by a progressive deterioration of personality, social comportment and cognition. These changes result from frontotemporal lobar degeneration (FTLD) associated with a range of heterogeneous pathologies (Mackenzie et al., 2009, 2010). Despite recent advances in the characterization of bvFTD, the diagnosis of the syndrome remains challenging; while some patients are dismissed as ‘normal’ others may be misdiagnosed as suffering from psychiatric disorders or Alzheimer’s disease (Mendez et al., 1993, 2007; Varma et al., 1999). Early and accurate differential diagnosis of bvFTD is critical, as it has implications for heritability (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998; Watts et al., 2004; Skibinski et al., 2005; Baker et al., 2006; Cruts et al., 2006; Kumar-Singh and Van Broeckhoven, 2007), prognosis (Rascovsky et al., 2005; Roberson et al., 2005; Chow et al., 2006), therapeutics (Swartz et al., 1997; Moretti et al., 2003; Pasquier et al., 2003; Lebert et al., 2004; Huey et al., 2006; Boxer and Boeve, 2007; Mendez, 2009) and environmental management of patients (Perry and Miller, 2001; Robinson, 2001; Talerico and Evans, 2001; Merrilees and Miller, 2003; Merrilees, 2007; Boutoleau-Bretonniere et al., 2008).

In the absence of definitive biomarkers, the diagnosis of bvFTD is dependent on clinical diagnostic criteria; in other words, the identification of the syndrome’s core or necessary symptoms. The publication of consensus criteria by Neary and colleagues (1998) was a major development in the field. These criteria are widely used in research and practice, but some limitations have become apparent. Among these are the ambiguity of behavioural descriptors and inflexibility in the application of criteria (i.e. the requirement that all five core features be manifest).
Most importantly, a number of studies have established the relative insensitivity of these criteria in the early stages of bvFTD when disease-modifying treatments are likely to be most effective (Mendez and Perryman, 2002; Mendez et al., 2007; Rascovsky et al., 2007a; Piguet et al., 2009).

Based on the empirical knowledge accumulated in the past 12 years (Mendez and Perryman, 2002; Mendez et al., 2007; Rascovsky et al., 2007a; Piguet et al., 2009), the International Behavioural Variant FTD Criteria Consortium (FTDC) developed revised guidelines for the diagnosis of bvFTD. The FTDC is comprised of 46 members with extensive experience in bvFTD. After reviewing the world literature, the FTDC developed an initial draft of the bvFTD criteria. This document was further refined over 3 years through correspondence, a web-based interactive forum and in-person meetings. In this report, we propose a revision of diagnostic and research criteria for bvFTD and provide results of an autopsy-confirmed analysis of the sensitivity of these revised diagnostic guidelines.

Materials and methods

Participants

Sixteen brain banks with special interest in clinical assessments of patients with FTLD pathology were identified (see Supplementary Table 1 for participating sites). Sites were asked to select cases who met modified Mackenzie criteria for FTLD (Mackenzie et al., 2009, 2010) (Table 1), and were clinically diagnosed with bvFTD, Alzheimer’s disease, vascular dementia, dementia with Lewy bodies or other neurological or psychiatric conditions at presentation. Cases were excluded if they had concomitant pathology such as Alzheimer’s disease (defined as Braak > 2; CERAD plaque score > sparse), Lewy body disease or significant vascular pathology (defined as large vessel infarct or more than one lacune). Cases were also excluded if they presented with predominant primary progressive aphasia or extra-pyramidal syndromes (e.g. corticobasal syndrome or progressive supranuclear palsy). Patients with multiple syndromes (e.g. bvFTD and corticobasal syndrome) were only included in the study if they were considered bvFTD at initial presentation.

A description of participant selection can be seen in Fig. 1. A total of 406 cases were enrolled in the FTDC registry. Cases were split in half by random allocation to create an original and a replication set. The original set was designated as a sensitivity sample (n = 203), and the replication set was chosen for future specificity studies. The 203 cases in the original sample were reviewed in the context of the proposed FTDC criteria (Table 3). As a result, 11 had pathology exclusion criteria (e.g. concomitant pathology), 13 had clinical exclusion criteria (e.g. primary/predominant aphasic or extra pyramidal presentations) and three cases did not have enough clinical information for inclusion in the study (defined as < 3 of the clinical ratings needed to be evaluated for possible bvFTD). All cases in the total sample (n = 176) had enough clinical ratings to potentially meet criteria for possible bvFTD. Of the total sample, 154 cases had functional disability and neuroimaging ratings, and 152 cases had complete core ratings for established 1998 criteria. The common sample (n = 137) had sufficient information to potentially evaluate all bvFTD criteria (FTDC possible bvFTD, FTDC probable bvFTD and 1998 criteria for bvFTD). Clinical and demographic characteristics did not differ depending on the sample used (Table 2).

FTDC diagnostic and research criteria for behavioural variant frontotemporal dementia

The FTDC simplified the existing diagnostic criteria and attempted to focus on features that best distinguish bvFTD from psychiatric disorders, Alzheimer’s disease and other dementing conditions. Some of the major advances reflected in the new criteria include: (i) reduced number of diagnostic features; (ii) no arbitrary distinctions between core and supportive features; (iii) greater flexibility in how patients can meet diagnostic criteria; (iv) clearer operational definitions; (v) incorporation of genetic and neuroimaging findings; and (vi) diagnostic hierarchy (distinction between possible, probable or definite bvFTD with FTLD pathology depending on level of diagnostic certainty).

Table 3 presents the proposed FTDC criteria for behavioural variant FTD. Criteria for possible, probable and bvFTD with definite FTLD pathology are described in detail in Appendix 1.

Procedure

For the purpose of pilot validation, a structured criteria rating form was created. This form included general demographics, FTDC criteria (Table 3) and previously established 1998 criteria (referred to below as the 1998 criteria) (Neary et al., 1998). A summary of the 1998 criteria
is provided in Supplementary Table 2. A complete version of the rating form is available from the authors.

Un-blinded neurologists or psychiatrists with expertise in bvFTD retrospectively reviewed patient charts from their respective sites. Any clinical information contained in the charts was considered, including history and clinical impressions, caregiver information, standard cognitive and behavioural measures, as well as laboratory and imaging findings. Raters used a web-based version of the criteria rating form to ascertain items of established (Neary et al., 1998) and proposed FTDC criteria at presentation. Individual features were rated as present if the feature was clearly present, absent if clearly absent and ‘don’t know’ if the information contained in the chart was insufficient to make a clear determination. Raters were also asked to estimate the time of symptom onset for FTDC behavioural features. No interrater reliability data were available, as criteria were ascertained by single raters.

In order to avoid exclusion of cases with ‘don’t know’ responses, we employed rules set a priori for fulfilment of criteria. Patients were considered to meet established 1998 criteria if all five core features were rated as present and no exclusion features were rated as present. Patients were considered to meet possible bvFTD if they met criteria for a neurodegenerative disease (i.e. progressive deterioration of behaviour and/or cognition) and presented with three of six possible bvFTD features with no exclusion features rated as present (i.e.

**Figure 1** Case selection and description of samples. bvFTD = behavioural variant FTD; F&I = functional disability and neuroimaging.

**Table 2** Mean (± SD) demographic characteristics by sample

<table>
<thead>
<tr>
<th></th>
<th>Total sample (n = 176)</th>
<th>Functional disability and neuroimaging sample (n = 154)</th>
<th>1998 Criteria sample (n = 152)</th>
<th>Common sample (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>72/104</td>
<td>65/89</td>
<td>64/88</td>
<td>60/77</td>
</tr>
<tr>
<td>Age at onset</td>
<td>58.1 (10.9)</td>
<td>58.4 (11.1)</td>
<td>57.8 (10.9)</td>
<td>58.1 (11.1)</td>
</tr>
<tr>
<td>Age at initial evaluation</td>
<td>61.5 (10.9)</td>
<td>61.7 (11.0)</td>
<td>61.3 (10.9)</td>
<td>61.5 (11.0)</td>
</tr>
<tr>
<td>Age at death</td>
<td>66.1 (11.6)</td>
<td>66.4 (11.7)</td>
<td>65.8 (11.6)</td>
<td>65.8 (11.6)</td>
</tr>
<tr>
<td>Education</td>
<td>14.2 (3.5)</td>
<td>14.3 (3.4)</td>
<td>14.2 (3.5)</td>
<td>14.2 (3.5)</td>
</tr>
<tr>
<td>MMSE</td>
<td>22.2 (7.0)</td>
<td>22.5 (6.9)</td>
<td>22.2 (7.1)</td>
<td>22.3 (7.1)</td>
</tr>
<tr>
<td>Duration: onset–initial evaluation</td>
<td>3.2 (2.7)</td>
<td>3.2 (2.6)</td>
<td>3.2 (2.6)</td>
<td>3.3 (2.6)</td>
</tr>
<tr>
<td>Duration: onset–death</td>
<td>7.8 (3.9)</td>
<td>7.6 (3.9)</td>
<td>7.7 (3.9)</td>
<td>7.6 (3.9)</td>
</tr>
<tr>
<td>Duration: initial evaluation–death</td>
<td>4.6 (3.3)</td>
<td>4.4 (3.1)</td>
<td>4.5 (3.3)</td>
<td>4.3 (3.1)</td>
</tr>
</tbody>
</table>

The classification was modified from existing FTLD criteria (Mackenzie et al., 2009, 2010) to accommodate cases with incomplete immunohistochemistry.

MMSE = Mini-Mental State Examination.
medical or psychiatric conditions that could explain the pattern of behavioural or cognitive deficits). Patients met probable bvFTD if they met criteria for possible bvFTD, had functional disability and neuroimaging findings consistent with bvFTD, and had no biomarkers strongly indicative of Alzheimer’s disease or other degenerative process. Given that the entire sample met pathological criteria for FTLD, all cases that met FTDC criteria for possible bvFTD also met criteria for bvFTD with definite FTLD pathology.

The ethics committee at each participating centre approved the research programme.

### Table 3 International consensus criteria for behavioural variant FTD (FTDC)

<table>
<thead>
<tr>
<th>I. Neurodegenerative disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following symptom must be present to meet criteria for bvFTD</td>
</tr>
<tr>
<td>A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Possible bvFTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:</td>
</tr>
<tr>
<td>A.1. Socially inappropriate behaviour</td>
</tr>
<tr>
<td>A.2. Loss of manners or decorum</td>
</tr>
<tr>
<td>A.3. Impulsive, rash or careless actions</td>
</tr>
<tr>
<td>B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:</td>
</tr>
<tr>
<td>B.1. Apathy</td>
</tr>
<tr>
<td>B.2. Inertia</td>
</tr>
<tr>
<td>C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:</td>
</tr>
<tr>
<td>C.1. Diminished response to other people’s needs and feelings</td>
</tr>
<tr>
<td>C.2. Diminished social interest, interrelatedness or personal warmth</td>
</tr>
<tr>
<td>D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:</td>
</tr>
<tr>
<td>D.1. Simple repetitive movements</td>
</tr>
<tr>
<td>D.2. Complex, compulsive or ritualistic behaviours</td>
</tr>
<tr>
<td>D.3. Stereotypy of speech</td>
</tr>
<tr>
<td>E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:</td>
</tr>
<tr>
<td>E.1. Altered food preferences</td>
</tr>
<tr>
<td>E.2. Binge eating, increased consumption of alcohol or cigarettes</td>
</tr>
<tr>
<td>E.3. Oral exploration or consumption of inedible objects</td>
</tr>
<tr>
<td>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]:</td>
</tr>
<tr>
<td>F.1. Deficits in executive tasks</td>
</tr>
<tr>
<td>F.2. Relative sparing of episodic memory</td>
</tr>
<tr>
<td>F.3. Relative sparing of visuospatial skills</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Probable bvFTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the following symptoms (A–C) must be present to meet criteria.</td>
</tr>
<tr>
<td>A. Meets criteria for possible bvFTD</td>
</tr>
<tr>
<td>B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)</td>
</tr>
<tr>
<td>C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:</td>
</tr>
<tr>
<td>C.1. Frontal and/or anterior temporal atrophy on MRI or CT</td>
</tr>
<tr>
<td>C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. Behavioural variant FTD with definite FTLD Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion A and either criterion B or C must be present to meet criteria.</td>
</tr>
<tr>
<td>A. Meets criteria for possible or probable bvFTD</td>
</tr>
<tr>
<td>B. Histopathological evidence of FTLD on biopsy or at post-mortem</td>
</tr>
<tr>
<td>C. Presence of a known pathogenic mutation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>V. Exclusionary criteria for bvFTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders</td>
</tr>
<tr>
<td>B. Behavioural disturbance is better accounted for by a psychiatric diagnosis</td>
</tr>
<tr>
<td>C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process</td>
</tr>
</tbody>
</table>

*As a general guideline ‘early’ refers to symptom presentation within the first 3 years (for further discussion see Supplementary material, Appendix 1).

bvFTD = behavioural variant FTD.
Data analysis

SPSS 18 and STATA® were used for all statistical analyses. Demographic characteristics are reported as means and standard deviations or proportions when appropriate. Frequency of symptoms is reported as proportions. We compared the sensitivity of the FTDC and 1998 criteria in the common sample using statistical methods for matched binary data (McNemar’s test with each case as a matched pair). Sensitivity of criteria by demographical features was analysed using chi-square tests.

Results

Sample characteristics

All cases in the study (n = 176) met modified Mackenzie criteria for FTLD (see Table 1 for pathology glossary). Pathology classifications were as follows: 70 cases were classified as FTLD tau, 48 FTLD-TDP, 32 FTLD-UPS NOS, 17 FTLD-ni NOS, 6 FTLD-FUS, 1 FTLD-IF NOS and 2 cases with incomplete immuno-histochemistry were classified as ‘other’ (FTLD-NOS). Within the tau-positive sample, some cases were specifically identified in the notes as corticobasal degeneration (n = 7), progressive supranuclear palsy (n = 4), argyrophilic grain disease (n = 1), one case with tangle-predominant pathology and argyrophilic grain disease, and one case with an unclassified tauopathy. One of the cases classified as FTLD-TDP had secondary pathological features of argyrophilic grain disease. Within the total sample, 46 cases (26.3%) had a positive family history of a similar primary dementia in a first-degree relative. Of 104 cases with genetic screening, 23 (22.1%) had a pathogenic mutation (16 cases with MAPT and seven cases with PGRN mutations).

The demographic characteristics of each sample can be seen in Table 2. The total sample was primarily Caucasian (96%) with a slight male predominance (59%). Patients were highly educated (14.2 years) and had mild dementia at initial evaluation (average Mini-Mental State Examination = 22.2). Of 172 cases with age of onset reported, 71% had onset before the age of 65 years (average age of onset = 58 years). The average survival from first evaluation was 3.2 years and from symptom onset was 7.8 years. Within the total sample, 26 cases (14.8%) developed features of motor neuron disease while 22 cases (12.5%) exhibited motor features similar to corticobasal syndrome or progressive supranuclear palsy. Some behavioural variant patients with FTD in the total sample demonstrated additional language features such as impaired word or object knowledge (20.4%), motor speech deficits (15.3%) and grammatical deficits in language production or comprehension (7.9%).

At initial presentation, 122/176 (69.3%) of cases received a clinical diagnosis of bvFTD, but this number decreased to 112/176 (63.6%) at the last evaluation. The second most common clinical diagnosis was Alzheimer’s disease in 26/176 (14.8%). First and last clinical diagnoses can be seen in Supplementary Table 3.

Sensitivity of FTDC criteria for behavioural variant frontotemporal dementia

Sensitivity of FTDC and 1998 criteria can be seen in Fig. 2. Of 176 pathology-confirmed FTLD cases, 149 met FTDC criteria for possible bvFTD [sensitivity = 0.85, 95% confidence interval (95% CI) (0.79–0.90)]. Of 154 cases with functional disability and neuroimaging ratings, 115 met criteria for probable bvFTD [sensitivity = 0.75, 95% CI (0.68–0.82)]. In contrast, of 152 cases with complete ratings for 1998 criteria, 79 met criteria for bvFTD [sensitivity = 0.52, 95% CI (0.44–0.60)].

We compared the sensitivity of 1998 and FTDC criteria in the common sample using the McNemar’s test for matched binary data (with each case as a matched pair). This smaller sample includes patients with ratings for both FTDC and 1998 criteria, and is highly representative of the larger samples where patients were evaluated with FTDC criteria (Table 2). Of 137 cases in the common sample, 118 (86%) met criteria for possible bvFTD, 104 (76%) met criteria for probable bvFTD and only 72 (53%) cases met 1998 criteria for bvFTD. Of note, while 65 patients in the common sample failed to meet 1998 criteria, 34 of these cases were nevertheless diagnosed clinically with bvFTD, while six cases were diagnosed with FTD/motor neuron disease at initial presentation. Sensitivity differences between FTDC and 1998 criteria in the common sample were statistically significant (possible bvFTD versus 1998 criteria: McNemar’s χ² = 44.08, P < 0.0001; probable bvFTD versus 1998 criteria: McNemar’s χ² = 18.75, P < 0.0001). We focus below on the common sample, as both FTDC and 1998 criteria were ascertainable in this group, and these findings closely reflected observations in the larger samples.

Sensitivity of behavioural variant frontotemporal dementia criteria by demographic characteristics

Within the common sample, sensitivity rates for FTDC and 1998 criteria did not differ according to the presence or absence of tau pathology, pathogenic mutations or family history of a similar primary dementia. Both FTDC and 1998 criteria were more sensitive in cases with early onset (onset < 65 years) compared with cases with late onset of the disease (Supplementary Fig. 1). This difference was significant for possible bvFTD (0.92 versus 0.73, χ² = 8.4, P < 0.01), probable bvFTD (0.85 versus 0.54, χ² = 14.2, P < 0.001) and 1998 criteria (0.61 versus 0.32, χ² = 8.6, P < 0.01). Patients with early onset bvFTD had significantly higher rates of disinhibition, loss of sympathy and empathy, perseverative behaviours and imaging findings consistent with bvFTD.

Frequency of individual features

The frequency of individual diagnostic features for 1998 and FTDC criteria can be seen in Fig. 3. All cases in the common sample...
had progressive deterioration of behaviour or cognition consistent with a neurodegenerative disease. Within the common sample, the frequency of possible bvFTD features ranged from 59% (hyperorality) to 84% (early apathy). We were able to ascertain whether these behavioural symptoms were present at onset in a subset of patients; this information can be seen in the Supplementary material, Appendix 1. Closer inspection of ratings for the neuropsychological criterion showed that 120/137 cases in the common sample had unambiguous ratings for a neuropsychological profile consistent with bvFTD (i.e. ‘yes’ or ‘no’ responses, indicating sufficient information to rate this criterion). Of these 120 cases, 114 had ‘deficits in executive tasks’, 89 had ‘relative sparing of episodic memory’ (compared with executive dysfunction) and 99 had ‘relative sparing of visuospatial skills’ (compared with executive deficits). In total, 82/120 cases (68%) had a complete neuropsychological profile most consistent with bvFTD (i.e. executive/generation deficits with relative sparing of memory or visuospatial functions). For probable bvFTD features, 82% of the cases had imaging findings consistent with bvFTD, while 99% exhibited functional decline by history or caregiver report. Within the common sample, individual core features for the 1998 criteria ranged from 78% (decline in social interpersonal conduct) to 99% (insidious onset and gradual progression). By comparison, Supplementary Fig. 2 shows the frequency of supportive features for the 1998 bvFTD criteria. Within the common sample, features such as decline in hygiene, mental rigidity and distractibility were present in 50–57% of cases. Fifty-nine per cent of the cases exhibited altered speech output, with specific language alterations ranging from mutism (13%) to perseveration of speech (35%). Physical signs were relatively uncommon and ranged from low and labile blood pressure (0.7%) to presence of primitive reflexes (26%).

**Frequency of behavioural variant frontotemporal dementia exclusionary features**

The presence of exclusionary features for FTDC and 1998 criteria can be seen in Fig. 4. In the common sample, 2/137 (1.5%) cases exhibited one or more exclusion features for possible bvFTD criteria. In these two cases, the pattern of cognitive and behavioural deficits was better accounted for by other non-degenerative or medical disorders. Of the 137 cases in the common sample, 26 (19%) presented one or more exclusion features for 1998 criteria. Of note, 15 cases (11%) presented with early, severe amnesia while nine cases (7%) exhibited spatial disorientation. Cases rated as having early, severe amnesia had an older age at onset compared with cases that did not exhibit this exclusion feature [age at onset: 64 versus 57 years, \( t(133), \ P < 0.05 \)].

**Sensitivity of behavioural variant frontotemporal dementia by number of features**

Diagnostic accuracy reflects a combination of diagnostic and exclusion features. This is summarized in Fig. 5, which shows the sensitivity of FTDC and 1998 criteria by number of features present. When taking exclusion features into account, 69% of the patients in the common sample met four of six features for possible bvFTD, 86% met three of six features for possible bvFTD (required to meet criteria) and 90% of cases met two of six features for possible bvFTD. In contrast, only 53% of cases met the
five core features required to meet 1998 criteria when taking exclusion features into account.

**Cases that failed to meet FTDC criteria**

Within the common sample, 19 cases failed to meet FTDC criteria for possible bvFTD. A summary of observations related to criteria failure for possible bvFTD can be seen in Table 4. Patients who failed to meet criteria were significantly older than patients who met criteria (age at onset: 64 versus 57 years, $P < 0.05$; age at initial evaluation: 66 versus 61 years, $P < 0.05$). Six cases presented with early, severe amnesia and were diagnosed with probable Alzheimer’s disease at presentation (mean age at initial evaluation = 72). An additional three cases with rare pathologies (argyrophilic grain disease, argyrophilic grain disease and tangle-predominant pathology, argyrophilic grain disease and TAR DNA binding protein pathology) were significantly older (mean age at initial evaluation = 82 years), and two of three had significant episodic memory deficits. Although the requirement that patients exhibit three of six diagnostic features at presentation was based on prior experience of the Consortium, only six cases were falsely diagnosed because they had only two of six diagnostic features at presentation. Of these six cases, four were initially diagnosed as either ‘non-amnestic mild cognitive impairment’ or bvFTD, and two were diagnosed as bvFTD at last evaluation. Of the remaining cases, two presented with prominent delusions, one presented with prominent spatial disorientation (diagnosed with dementia NOS at presentation, bvFTD at last evaluation) and one case was a PGRN mutation carrier with a known family history. In total, 10/19 patients had marked

![Figure 3](https://brain.oxfordjournals.org/)

Figure 3 Frequency of individual features for (A) possible bvFTD, (B) probable bvFTD and (C) 1998 core criteria. Frequency is shown as percentage of cases in the corresponding sample (white bars) or the common sample (black bars). bvFTD = behavioural variant FTD; F&I = functional disability and neuroimaging.
memory problems at presentation. Failure to meet criteria for possible bvFTD was not due to insufficient information or ‘don’t know’ responses.

Of the 118 cases in the common sample that met criteria for possible bvFTD, 14 cases failed to meet criteria for probable bvFTD. All 14 cases had imaging findings inconsistent with bvFTD at presentation (e.g. no apparent lobar atrophy or significant posterior atrophy). Compared with cases who met the criteria for probable bvFTD, cases that failed to meet criteria were significantly older (age at onset: 63 versus 56 years, \( P < 0.05 \); age at initial evaluation: 67 versus 60 years, \( P < 0.05 \)), and male predominant (12/14 males = 0.86 versus 54/104 males = 0.52, \( X^2 = 5.7, P < 0.05 \)).

**Discussion**

The proposed FTDC criteria are the result of a 3-year multinational effort to develop empirically derived diagnostic criteria for bvFTD. The present study found that FTDC criteria provide greater sensitivity than previously established criteria in a multi-site sample with known FTLD pathology. Of 137 cases where sufficient clinical data were available to evaluate both FTDC and previously established 1998 criteria, known as the common sample, 118 (86%) met criteria for possible bvFTD, and 104 (76%) met criteria for probable bvFTD. In contrast, the proportion of cases meeting 1998 criteria (53%) was significantly lower. These sensitivity rates were comparable with those found in the larger sample, in which either the FTDC or 1998 criteria could be evaluated. Thus, of 176 pathology-confirmed FTLD cases, 149 (85%) met FTDC criteria for possible bvFTD, while 113/154 (75%) with functional disability and neuroimaging ratings met criteria for probable bvFTD. The increased sensitivity of FTDC criteria is thought to reflect the optimized diagnostic features, less restrictive exclusion features and crucially, a flexible structure that accommodates variation in the symptom profile at presentation. Use of FTDC criteria for bvFTD diagnosis will improve identification of the syndrome, particularly in the earliest stages when disease-modifying therapies are most likely to be effective.
Three sets of bvFTD diagnostic criteria have been published over the past two decades that reflect our evolving knowledge about the presentation and progression of the disease (Brun et al., 1994; Neary et al., 1998; McKhann et al., 2001). Among these, most dementia centres adopted the 1998 consensus criteria as the norm for bvFTD diagnosis (Neary et al., 1998). Based on the accumulated experience with the 1998 criteria (Mendez and Perryman, 2002; Mendez et al., 2007; Rascovsky et al., 2007a; Piguet et al., 2009), the International Behavioural Variant FTD Criteria Consortium developed revised guidelines for the diagnosis of bvFTD. Recognizing that the optimum level of diagnostic certainty depends on the clinical and research requirements, the revised
FTDC criteria are now structured as a diagnostic hierarchy. Diagnosis of possible bvFTD is based solely on the clinical syndrome and aims to identify patients at the mildest stages of disease. This classification relies on the flexible combination of three of six clinically discriminating features: disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviours, hyperorality and a dysexecutive neuropsychological profile. Compared with earlier 1998 criteria, possible bvFTD eliminates the distinction between core and supportive features and significantly reduces the number of exclusionary features. Diagnosis of probable bvFTD is based on the clinical syndrome, plus demonstrable functional decline and the frontotemporal imaging findings that reflect the principal anatomical location of neurodegeneration in bvFTD. Furthermore, a diagnosis of probable bvFTD may be withheld if other biomarkers are strongly indicative of Alzheimer’s disease or other degenerative processes. This classification aims to capture patients with a high probability of underlying FTLD pathology and will be useful in studies where high diagnostic certainty is sought (such as clinical trials). The conclusive classification of bvFTD with definite FTLD pathology is limited to patients who exhibit the bvFTD clinical syndrome and who also have a pathogenic mutation or histopathological evidence of FTLD. Patients with the ‘definite’ diagnosis would usually be included in retrospective studies where pathology-proven FTLD cases are needed.

Possible and probable FTDC criteria are applied most usefully in the early stages of bvFTD, when there is less overlap with other FTLD phenotypes or neurodegenerative conditions. It may be useful in this context to distinguish between a primary behavioural syndrome using these criteria, a predominant aphasis syndrome using recently published criteria for primary progressive aphasia (Gorno-Tempini et al., 2011), or a predominant amnestic presentation using NIA-Alzheimer’s Association criteria for Alzheimer’s disease (McKhann et al., 2011).

Sensitivity of possible behavioural variant frontotemporal dementia

As a first step in the validation of bvFTD criteria, we compared the sensitivity of proposed FTDC and previously established 1998 criteria in a multi-site sample of patients with bvFTD with known FTLD pathology. This is the largest pathology-confirmed sample of patients with bvFTD reported to date, and sheds some light on the typical presentation of the syndrome. The clinical and demographic characteristics are similar to those of other large bvFTD samples (Johnson et al., 2005; Le Ber et al., 2006).

At initial evaluation, individual features for possible bvFTD were frequent, but not necessarily always present: in the total sample of 176 cases, apathy (84%) and disinhibition (76%) were the most common features, while hyperorality was the least common (59%). This is not surprising, as patients with bvFTD differ in their presentation, particularly at early stages of the disease. For example, while most patients with bvFTD exhibit both disinhibition and apathy well into their disease course, patients may initially present as primarily disinhibited or primarily apathetic (Le Ber et al., 2006). This variable presentation may reflect differences in the earliest localization of disease and/or underlying neuropathological features (Hu et al., 2007; Massimo et al., 2009). The flexible structure of possible bvFTD criteria attempts to account for this variability at initial presentation. Sensitivity of possible bvFTD was further enhanced by the use of less restrictive exclusionary features. Within the common sample, only two cases (1.5%) exhibited a pattern of deficits that was better explained by other medical conditions, and no cases were better explained by a psychiatric diagnosis. The specification of three core features for a possible diagnosis was based on the consortium experience but appears to be optimal. In the common sample, 86% of the patients had three of the six required clinical features. Increasing the number to four features decreased sensitivity to 69%, while relaxing the requirement to two features increased sensitivity only by 4%, with potential detriment to specificity. The question of the optimal criterion will need to be addressed in prospective studies that evaluate the combined sensitivity and specificity of the proposed FTDC criteria.

Within the common sample, we found a significant difference in sensitivity according to age of disease onset. The criteria for possible bvFTD were significantly more sensitive in cases with early onset (onset < 65 years of age) compared with those with late onset of the disease (0.92 versus 0.73, respectively). Compared with patients with early onset, patients with late onset bvFTD had significantly lower rates of disinhibition, loss of sympathy/empathy and perseverative, compulsive behaviours. The lower sensitivity of possible bvFTD in older patients may be due to the presence of unusual FTLD-spectrum pathologies or primarily amnestic presentations. Although included in the FTLD spectrum, cases with argyrophilic grain disease pathology (argyrophilic grain disease, argyrophilic grain disease and tangle-predominant pathology, argyrophilic grain disease and TAR DNA binding protein pathology) may not present with a typical behavioural syndrome. Further studies are required to examine the cognitive and behavioural characteristics of patients with rare FTLD pathologies such as these. On the other hand, the occurrence of amnestic presentations in this sample is not surprising, as marked anterograde amnesia has been documented as either the sole or dominant symptom in up to 10% of pathology-confirmed bvFTD cases (Hodges et al., 2004; Graham et al., 2005; Knopman et al., 2005; Piquet et al., 2009). The preponderance of primarily amnestic (versus behavioural) presentations in elderly subjects with bvFTD may be related to hippocampal sclerosis, for example, which was recently reported in 43% of FTLD cases with late onset of disease (> 65 years of age) (Baborie et al., 2010). On a cautionary note, the preponderance of memory deficits in the elderly may bias overall clinical impressions by increasing the salience of prominent amnesia while downplaying the patient’s behavioural symptoms. Future prospective studies will need to confirm these preliminary observations regarding age differences in amnestic versus behavioural presentations.

Only six cases failed to be diagnosed as possible bvFTD because they exhibited only two of six diagnostic features. Prospective studies are needed to determine whether cases with two diagnostic features for possible behavioural variant FTD warrant increased vigilance for the eventual emergence of the typical bvFTD syndrome. Since a reduced number of diagnostic criteria may
et al.

Mendez and Perryman (2002) examined the sensitivity of 1998 FTDC criteria in a sample of 53 patients with a clinical diagnosis of bvFTD and frontal hypoperfusion on SPECT. Only a third of these patients met 1998 criteria at presentation, but this number increased to 83% at a 2-year follow-up. This low initial sensitivity was replicated by the same authors in a sample of 134 patients with a suspected diagnosis of bvFTD (Mendez et al., 2007). Another retrospective study (Piguet et al., 2009) evaluated the sensitivity of 1998 criteria in a well-characterized cohort of 45 patients with bvFTD with a 3-year follow-up (18 with confirmed FTLD pathology). Only 58% of the patients in this sample met 1998 criteria for bvFTD at presentation. In contrast to sensitivity rates reported in retrospective studies, a prospective study (Pijnenburg et al., 2008) found a much higher sensitivity of 1998 criteria for bvFTD (79%), but there was no pathological confirmation in the majority of cases. Of note, diagnostic features in the above study were ascertained by a caregiver questionnaire about the 1998 clinical features and patients were diagnosed based on 1998 criteria (with 1-year clinical follow-up as gold standard). As expected, the restrictions that lower the sensitivity of 1998 criteria also lead to increased levels of specificity. This is particularly true when attempting to discriminate bvFTD from Alzheimer’s disease or other dementing conditions. In studies with dementia comparison groups, the specificity of 1998 criteria ranged from 90 to 100% (Mendez et al., 2007; Pijnenburg et al., 2008).

Comparison of FTDC and 1998 criteria

The consensus criteria published by Neary and colleagues (1998) greatly advanced the field of frontotemporal degenerations, and have been widely used in research and clinical practice. In an effort to further refine criteria by incorporation of recent empirical knowledge, the FTDC developed revised guidelines for the diagnosis of bvFTD. Both the 1998 and revised FTDC criteria rely on the presence of distinct clinical features for the diagnosis of bvFTD. A major difference, however, is that the 1998 criteria require the presence of all five core diagnostic features: insidious onset and gradual progression, early decline in personal and social interpersonal conduct, emotional blunting and loss of insight. Although individual core features are common at presentation, they are not ubiquitous. In the present sample, for example, the frequency of 1998 core features at initial presentation ranged from 78% for emotional blunting, to 99% for insidious onset and gradual progression. The ambiguity in behavioural descriptions (e.g. ‘emotional blunting’, ‘regulation of personal conduct’), and the need for inferences about a patient’s cognitive or emotional state (e.g. ‘loss of insight’), also have the potential to lower interrater reliability and the ultimate validity of these items for diagnosis (Rascovsky et al., 2007b). The 1998 criteria are further restricted by a large number of exclusion features (11 exclusion features and three relative exclusion features). Of 137 cases in the common sample, 26 (19%) presented one or more exclusion features for these diagnostic guidelines. Our observations show that the presence of early severe amnesia or spatial disorientation should not be exclusionary, and elimination of these exclusions improved the sensitivity of the FTDC criteria compared with the 1998 criteria. Exclusion based solely on impaired neuropsychological memory performance can lead to underdiagnosis of bvFTD (Hornberger et al., 2010), while spatial disorientation (when applied without reference to timing) may result in erroneous rejection of the diagnosis in patients who are in the late stages of their illness.

The strict, five-feature core requirement, coupled with the number and nature of exclusion features, may be responsible for the low sensitivity of 1998 criteria observed in the present study. When taking exclusion features into account, only 53% of patients met all five core features at initial presentation. Even when the number of core features was relaxed, only 72% of the patients met three of the five core features required for diagnosis. Furthermore, the three most common 1998 core features were insidious onset and gradual progression, loss of insight and impairment in regulation of personal conduct. These three features are very common in neurodegenerative diseases and may yield suboptimal discrimination when attempting to differentiate bvFTD from other forms of dementia (IHii et al., 2009; Orfei et al., 2010; Starkstein et al., 2010).

The low sensitivity of 1998 criteria found in the present study mirrors the findings in recent retrospective studies. For instance, Mendez and Perryman (2002) examined the sensitivity of 1998 criteria in a sample of 53 patients with a clinical diagnosis of bvFTD and frontal hypoperfusion on SPECT. Only a third of these patients met 1998 criteria at presentation, but this number increased to 83% at a 2-year follow-up. This low initial sensitivity was replicated by the same authors in a sample of 134 patients with a suspected diagnosis of bvFTD (Mendez et al., 2007). Another retrospective study (Piguet et al., 2009) evaluated the sensitivity of 1998 criteria in a well-characterized cohort of 45 patients with bvFTD with a 3-year follow-up (18 with confirmed FTLD pathology). Only 58% of the patients in this sample met 1998 criteria for bvFTD at presentation. In contrast to sensitivity rates reported in retrospective studies, a prospective study (Pijnenburg et al., 2008) found a much higher sensitivity of 1998 criteria for bvFTD (79%), but there was no pathological confirmation in the majority of cases. Of note, diagnostic features in the above study were ascertained by a caregiver questionnaire about the 1998 clinical features and patients were diagnosed based on 1998 criteria (with 1-year clinical follow-up as gold standard). As expected, the restrictions that lower the sensitivity of 1998 criteria also lead to increased levels of specificity. This is particularly true when attempting to discriminate bvFTD from Alzheimer’s disease or other dementing conditions. In studies with dementia comparison groups, the specificity of 1998 criteria ranged from 90 to 100% (Mendez et al., 2007; Pijnenburg et al., 2008).

Sensitivity of probable behavioural variant frontotemporal dementia

The designation of probable bvFTD by the FTDC criteria restricts diagnosis to patients with demonstrable functional decline and typical bvFTD anatomical findings. These criteria are particularly suited for studies where high diagnostic certainty is required (such as clinical trials). Although 86% of patients in the common sample met criteria for possible bvFTD, only 76% of cases met criteria for probable bvFTD. Patients who failed to meet criteria for probable bvFTD were significantly older (age at onset: 63 versus 56; age at initial evaluation: 67 versus 60), and all 14 cases had imaging findings inconsistent with bvFTD at presentation (e.g. no apparent lobar atrophy or significant posterior atrophy). Although disproportionate atrophy in medial frontal, orbital–insular and anterior temporal regions may help distinguish bvFTD from other conditions (Frisoni et al., 1996; Rosen et al., 2002a; Varma et al., 2002; Grossman et al., 2004; Boccardi et al., 2005; Short et al., 2005; Whitwell and Jack, 2005; Bocii et al., 2006; Perry et al., 2006; Du et al., 2007; Mendez et al., 2007; Richards et al., 2008; Schroeter et al., 2008; Seeley et al., 2008; Davies et al., 2009; Kipps et al., 2009a; Lindberg et al., 2009; Whitwell et al., 2009), this imaging pattern is not necessarily present in all cases or at very early stages of disease (Perry et al., 2006). In fact, structural imaging in the form of frontal or anterior temporal lobe atrophy has been reported in 50–64% of cases with bvFTD (Knopman et al., 2005; Mendez et al., 2007; Pijnenburg et al., 2008). Low sensitivity of structural imaging may be particularly related to age at disease onset. A recent study of pathology-confirmed FTLD cases showed that, while a majority of prese...
(onset < 65) showed moderate to severe frontotemporal atrophy and ventricular dilation at autopsy, only 12/30 (40%) of elderly patients showed severe frontotemporal atrophy (Baborie et al., 2010). Compared with structural imaging, functional imaging changes (e.g. predominant frontotemporal hypometabolism or hypoperfusion in SPECT or PET, or perfusion changes observed with arterial spin labelling MRI) may provide additional sensitivity (Mendez et al., 2007; Hu et al., 2010), suggesting that behavioural and functional abnormalities may precede structural imaging changes in bvFTD. Of interest, there was a striking male predominance in cases that failed the imaging requirements for probable bvFTD compared with those who did (12/14 males = 0.86 versus 54/104 males). The reasons behind this gender difference are unclear, but may relate to ascertainment bias or greater reliance on imaging features to diagnose females with ambiguous behavioural profiles.

Strengths and caveats

The present study is the result of a multinational effort to devise empirically derived criteria for bvFTD, and represents the largest pathology-confirmed bvFTD sample reported to date. Although the study design makes our findings representative and generalizable, some caveats of the study should be kept in mind. The greatest limitation of the present study was the absence of appropriate neurological or psychiatric comparison groups to assess specificity of the FTDC criteria. In our stepwise approach to criteria development, we are pursuing the strategy of evaluating the specificity of FTDC criteria once sensitivity has been established. Validation of any diagnostic criteria is an iterative process, and we acknowledge that the FTDC criteria may require revisions in light of future specificity findings. Unfortunately, appropriate specificity studies may require a prospective design with considerable time requirements. Constructing a suitable comparison group retrospectively to estimate specificity is challenging and prone to bias for several reasons. First, the sample of pathologically proven non-FTLD cases would have to be very large. Second, it is likely that information relevant to the FTDC criteria would never have been collected in cases where FTLD was not suspected clinically. For example, information about the core behavioural symptoms characteristic of bvFTD is generally not recorded in patients with typical amnestic Alzheimer’s disease or other forms of dementia. Patients with the phenocopy syndrome also present problems. These patients are behaviourally indistinguishable from patients with true bvFTD when the 1998 criteria are applied (Hornberger et al., 2009; Kipps et al., 2009a). Phenocopy cases should be distinguishable in that they do not have functional decline or imaging changes. Given these factors, it is possible that specificity could be erroneously under or over-estimated. In order to assess specificity properly, a prospective study of a large number of unselected patients with dementia should be carried out in which the elements of the FTDC criteria are sought at the time of initial diagnosis. Ideally, such a study should have independent biomarker confirmation of the pathological diagnosis, a very considerable logistic undertaking.

The use of autopsy-confirmed cases ensures that our patients had FTLD pathology, but we acknowledge that retrospective autopsy-based samples can be prone to selection bias. It should be noted, however, that most participating brain banks were associated with Alzheimer’s centres or memory clinics treating a range of degenerative conditions where autopsy is generally pursued for all types of dementia. While individuals erroneously diagnosed with a psychiatric illness may have been less likely to undergo autopsy, in our experience, it is unlikely for patients with dementia to retain a primary psychiatric diagnosis late in their disease course. Another caveat of the present study is the ascertainment of diagnostic features based on retrospective and unblinded review of records. Although raters were instructed to rate features as positive only when clearly present, a priori knowledge of the underlying pathology may have sensitized raters to features consistent with bvFTD. Conversely, some FTDC features were not known at the time of patient evaluation, so the retrospective nature of the study may have underestimated the true frequency of such diagnostic criteria (e.g. loss of sympathy or empathy). The variability of information across centres may also contribute to low frequency rates, particularly when evaluating features such as imaging and neuropsychological profiles. Prospective studies that include standardized tests, questionnaires and imaging parameters may help elucidate the utility of the revised FTDC criteria. Finally, while we relied on easily observable features with clear operational definitions, prospective studies with multiple, blinded raters with different levels of expertise will be needed to determine the reliability of the FTDC criteria.

Summary

In summary, early and accurate diagnosis of bvFTD is crucial for the appropriate care of patients afflicted with this devastating disorder. In the absence of definitive biomarkers, diagnosis of bvFTD should be made on the basis of sensitive clinical criteria coupled with diagnostic methods that are practical and easily available. Even as sensitive and specific biomarkers for FTLD become a reality, definition of the bvFTD clinical syndrome is important for routine screening, as well as optimal management of patients and their families. The proposed FTDC criteria provide a sensitive standard for bvFTD diagnosis, allowing for early recognition of the syndrome when disease-modifying therapies are expected to be most effective. Future reliability and specificity studies will ultimately clarify the relative strength of these revised diagnostic guidelines.

Funding

National Institutes of Health (P01-AG17586, R01-NS44266, P01-AG32953, R01-AG15116, P50-AG016574, P01-AG019724, P50-AG023501, R01-AG034499-02); Department of Health Services grant from the state of California (CA DHS 07-65807).

Supplementary material

Supplementary material is available at Brain online.
References


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 2009a; 132: 2566–78.


I. Neurodegenerative disease

In order to meet criteria for any bvFTD diagnosis, the patient must show a progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant). This core symptom aims to distinguish bvFTD from acute medical events or stable conditions such as long-standing psychiatric disease.

II. Possible bvFTD

The diagnosis of possible bvFTD is based on personality, social comportment and cognitive features that discriminate bvFTD from other conditions. While it is important to interpret diagnostic features of a case in the clinical context, ratings of behavioural features can be difficult and potentially open to observer bias. As such, we encourage ratings that are based on overt behaviours, as opposed to inferences about a patient’s cognitive or emotional state. For quantification of these behaviours, scales such as the Neuropsychiatric Inventory (Cummings et al., 1994), the Cambridge Behavioural Inventory (Boz et al., 2000; Wedderburn et al., 2008) or the Frontal Behavioural Inventory (Kertesz et al., 2000) are available to guide behavioural ratings. For some patients, standard psychiatric evaluation will be required. Determination of a cognitive profile should be based on formal neuropsychological testing. Tests of social cognition, assessing emotion, theory of mind and decision-making can provide further objective markers of cognitive dysfunction (Gregory et al., 2002; Snowden et al., 2003; Rosen et al., 2004b; Lough et al., 2006; Elsinger et al., 2007, 2011; Torralva et al., 2009a; Kipps et al., 2009b). However, these are not yet widespread in clinical practice and have not therefore been incorporated into the neuropsychological criterion for bvFTD.

In order to meet criteria for possible bvFTD, three of the following behavioural or cognitive symptoms (A–F) must be present. We selected this threshold to accommodate individual differences in clinical presentation. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events. As a general guideline ‘early’ refers to symptom presentation within the first 3 years (for further discussion see Supplementary material, Appendix 1).

A. Early behavioural disinhibition

Early behavioural disinhibition is a hallmark feature of the bvFTD clinical syndrome. Many comparative studies show that disinhibition discriminates bvFTD from Alzheimer’s disease, dementia with Lewy bodies and vascular dementia (Brun et al., 1994; Barber et al., 1995; Levy et al., 1996; Mendez et al., 1998; Hirono et al., 1999; Boz et al., 2000; Kertesz et al., 2000; Bathgate et al., 2001; Rosen et al., 2002b; De Deyn et al., 2005; Srikanth et al., 2005; de Vugt et al., 2006; Blair et al., 2007; Heidler-Gary et al., 2007; Liscic et al., 2007; Rankin et al., 2008). Disinhibition may present as one of the following (A.1–A.3):

A.1. Socially inappropriate behaviour

Examples of behaviours that violate social norms include inappropriately approaching, touching or kissing strangers, verbal or physical aggression, public nudity or urination, inappropriate sexual acts and criminal behaviour (such as theft or shoplifting).

A.2. Loss of manners or decorum

This category includes a range of behaviours that violate social graces. Examples include inappropriate laughter, cursing or loudness, offensive jokes or opinions, or crude or sexually explicit remarks. Patients may also display a general lack of etiquette (e.g.

Appendix 1: FTDC diagnostic and research criteria for behavioural variant frontotemporal dementia

I. Neurodegenerative disease

In order to meet criteria for any bvFTD diagnosis, the patient must show a progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant). This core symptom aims to distinguish bvFTD from acute medical events or stable conditions such as long-standing psychiatric disease.
failing to wait in line, eating with mouth open), loss of respect for interpersonal space and a lack of response to social cues (e.g. patient will continue talking despite other’s attempts to end a conversation). Some bvFD patients with FTD exhibit poor hygiene or grooming (e.g. wearing malodorous, stained, torn or inappropriate clothing) or impulsive physical behaviours (e.g. flatulence, scratching or fondling private parts, picking teeth, belching or spitting).

A.3. Impulsive, rash or careless actions
The revised criteria acknowledge that not all behavioural disinhibition leads to obvious breaches in social or interpersonal conduct; in fact, it can manifest as impulsive behaviours that may or may not be performed in a social context. These include reckless driving, new-onset gambling, stealing (usually food or ‘shiny’ objects), buying or selling objects without regard for consequences, or indiscriminate sharing of personal information (e.g. credit card information, social security number).

B. Early apathy or inertia
Apathy/inertia is the most common initial symptom in bvFTD (Diehl-Schmid et al., 2006; Le Ber et al., 2006; Mendez et al., 2008a), and appears to be more severe and pervasive in bvFTD than in other dementias (Levy et al., 1996; Kertesz et al., 2000; Boone et al., 2003; Liu et al., 2004; Engelborghs et al., 2005; Perri et al., 2005; Srikanth et al., 2005; de Vugt et al., 2006; Jenner et al., 2006; Shinagawa et al., 2006; Blair et al., 2007; Chow et al., 2009). In order to meet this criterion, one of the following symptoms (B.1–B.2) must be present:

B.1. Apathy
Apathy is defined as a loss of motivation, drive or interest (Robert et al., 2009). It can manifest as passivity or lack of spontaneity. The patient may lack initiative and cease to engage in important or previously rewarding activities (e.g. job, hobbies).

B.2. Inertia
Inertia refers to decreased initiation of behaviour (i.e. the patient requires prompts or cues to initiate or continue routine activities). For example, it may be reported that a patient requires specific directives to start and finish brushing his teeth, or that a patient no longer starts or sustains conversation.

C. Early loss of sympathy or empathy
Loss of empathy refers to an inability to read the emotional expressions of others or imagine their experiences (Rankin et al., 2006). It is a common feature at initial presentation, and is often coupled with indifference and a general decrease in social engagement (Le Ber et al., 2006). This feature is especially useful in the differentiation of bvFTD from Alzheimer’s disease (Barber et al., 1995; Kertesz et al., 2000; Boone et al., 2003; Rankin et al., 2005; Mendez et al., 2006). In everyday life, loss of sympathy or empathy may present as one of the following (C.1–C.2):

C.1. Diminished responsiveness to other people’s needs and feelings
A positive rating on this feature should be based on specific examples that reflect a lack of understanding or indifference to the feelings of others—e.g. hurtful comments or inexplicable disregard for others pain or distress.

C.2. Diminished social interest, interrelatedness or personal warmth
While the preceding feature referred to overt behaviours that denote a marked loss of empathy, this feature refers to a more general decline in social engagement, with emotional detachment, coldness, lack of eye contact, etc. Relatives and friends might experience the patient as uncharacteristically distant (e.g. no longer touches, hugs or seeks out their company).

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour
Perseverative, stereotyped or compulsive behaviours have been added to the revised criteria, as they are commonly observed in pathology confirmed cases (Ames et al., 1994), and consistently discriminate bvFTD from other primary dementias (Miller et al., 1997; Hirono et al., 1999; Bozeat et al., 2000; Kertesz et al., 2000; Bathgate et al., 2001; Shigenobu et al., 2002; Nyatsanza et al., 2003; Liu et al., 2004; Mendez et al., 2005; Srikanth et al., 2005; de Vugt et al., 2006; Shinagawa et al., 2006; Blair et al., 2007). A positive rating on this feature can occur if the patient exhibits any one of the following (D.1–D.3):

D.1. Simple repetitive movements
These movements include tapping, clapping, rubbing, scratching, picking at skin or clothing, humming, rocking, throat clearing, pursing of lips or lip smacking.

D.2. Complex, compulsive or ritualistic behaviours
Examples include counting and cleaning rituals, collecting or hoarding, checking, repetitive trips to the bathroom (without need), ordering objects and walking fixed routes. Pacing (without a compulsive quality) should not be included, as it can occur in other primary dementias or as a psychotropic medication effect.

D.3. Stereotypy of speech
These are single words, phrases or entire themes or stories that the patient habitually repeats despite their lack of communicative value.

E. Hyperorality and dietary changes
Changes in dietary and eating behaviour are common manifestations of bvFTD (Passant et al., 2005; Diehl-Schmid et al., 2006), and can range from altered food preferences to oral exploration of inedible objects. Although this feature is shared with other FTLD syndromes (Snowden et al., 2001; Ikeda et al., 2002; Liscic et al., 2007; Whitwell et al., 2007), dietary changes consistently discriminate bvFTD from Alzheimer’s disease (Miller et al., 1997; Bozeat et al., 2000; Bathgate et al., 2001; Ikeda et al., 2002; Rosen et al., 2002).
et al., 2002b; Liu et al., 2004; Srikanth et al., 2005; Jenner et al., 2006; Blair et al., 2007; Mendez et al., 2008b). This combined feature can present as one of the following symptoms (E.1–E.3):

E.1. Altered food preferences
In the context of bvFTD, this change in food habits usually presents as carbohydrate cravings (particularly sweets), or food fads (i.e. rigid, stereotyped or idiosyncratic food preferences).

E.2. Binge eating, increased consumption of alcohol or cigarettes
Patients consume excessive amounts of food and continue to eat despite (in some cases) acknowledging satiety (Woolley et al., 2007). Some patients exhibit new, resumed or compulsive smoking or ingestion of alcohol.

E.3. Oral exploration or consumption of inedible objects
In extreme cases, hyperorality may manifest as oral exploration, chewing or ingestion of inedible objects, a feature consistent with the Kluver-Bucy syndrome (Mendez and Foti, 1997).

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions

The neuropsychological profile of bvFTD is now treated as a criterion in its entirety. Features such as ‘early and severe amnesia’ and ‘spatial disorientation’ (poor spatial localization and disorientation in highly familiar surroundings) cease to be exclusion criteria, as that would disqualify a significant proportion of patients with bvFTD. Some studies have demonstrated marked anterograde amnesia in pathologically confirmed cases (Graham et al., 2005; Knopman et al., 2005; Piguet et al., 2009), while ‘spatial disorientation’ without reference to time from disease onset may erroneously reject patients in the late stages of their illness. Although deficits in specific cognitive functions alone are unlikely to reliably differentiate bvFTD from other conditions (Hutchinson and Mathias, 2007), the overall pattern of impairments (specifically, relative sparing of memory and visuospatial functions in comparison to executive dysfunction) may aid in differential diagnosis (for review see Grossman, 2002; Wittenberg et al., 2008). Determination of a cognitive profile should be based on formal neuropsychological testing. In order to meet this criterion, patients must present with all three of the following features (F.1–F.3):

F.1. Deficits in executive tasks
Patients with bvFTD often present with deficits in executive function, a term that encompasses complex cognitive abilities such as working memory, planning, generation, abstraction, problem solving and mental flexibility. In order to meet this criterion, the patient must demonstrate cognitive impairment on at least one standardized test of executive ability (defined as performance at or below the fifth percentile compared with age- and education-matched norms). Although patients with bvFTD may perform within normal limits on traditional executive function tests (e.g. Wisconsin Card Sorting Test, Stroop), they consistently fail verbal and non-verbal generation tasks, and may show deficits in planning, mental flexibility, response inhibition and reversal learning (Lindau et al., 1998; Hodges et al., 1999; Perry and Hodges, 2000; Rascovsky et al., 2002, 2008; Slachter et al., 2004; Perri et al., 2005; Walker et al., 2005; Heidler-Gary et al., 2007; Hornberger et al., 2008; Huey et al., 2009; Krueger et al., 2009; Libon et al., 2009; Mendez et al., 2009; Torralva et al., 2009a, b). The presence of errors in the performance of various cognitive tests (e.g. perseverations or rule violations) is considered an item of this criterion, as it can aid in the differential diagnosis of bvFTD (Kramer et al., 2003; Thompson et al., 2005; Libon et al., 2007b; Carey et al., 2008).

F.2. Relative sparing of episodic memory
Preservation of episodic memory relative to executive dysfunction, can be valuable in differential diagnosis, particularly when the distinction involves bvFTD and Alzheimer’s disease (Elfgen et al., 1994; Pachana et al., 1996; Lindau et al., 1998; Perry and Hodges, 2000; Rascovsky et al., 2002; Kramer et al., 2003; Rosen et al., 2004a; Walker et al., 2005; Heidler-Gary et al., 2007; Libon et al., 2007a, b; Giovagnoli et al., 2008). This relative preservation can be observed in both verbal and non-verbal domains, and is most evident when memory tests lack a heavy retrieval or executive burden (e.g. long list of words, reproduction of complex figures).

F.3. Relative sparing of visuospatial skills
Most patients with bvFTD retain the ability to navigate their environment, copy simple and complex line drawings, assemble blocks and judge spatial positions until very late in their disease (Elfgen et al., 1994; Mendez et al., 1996, 2009; Miller et al., 1997; Rascovsky et al., 2002, 2008; Perri et al., 2005; Giovagnoli et al., 2008). When evaluating patients with known executive impairments, care should be taken to avoid complex constructional tasks with heavy executive demands.

III. Probable bvFTD

The diagnosis of probable bvFTD is based on functional and imaging findings that discriminate this disorder from other dementias, psychiatric disorders and non-degenerative conditions such as the phenocopy syndrome. Individuals with a phenocopy syndrome may have identical clinical features to those with bvFTD, but the phenocopy syndrome is not progressive: functional abilities are preserved and imaging abnormalities are absent (Davies et al., 2006; Kipps et al., 2007b, 2009a; Mioshi et al., 2009; Piguet et al., 2009). The aetiology of ‘phenocopy’ cases remains unknown (Hornberger et al., 2009; Piguet et al., 2011). Given their good long-term prognosis, it seems less likely that they have a neurodegenerative disorder. Although some authors speculate that phenocopy cases may fit the autism–Asperger’s spectrum or psychiatric disorder, there is currently no published evidence to support this claim (Piguet et al., 2011). In order to meet criteria for probable bvFTD, a patient must first meet criteria for possible bvFTD (A), plus both of the following (B and C):
IV. bvFTD with definite FTLD pathology

This conclusive diagnostic category is based on the presence of a known pathogenic mutation or histopathological evidence of FTLD (on biopsy or autopsy). In order to meet criteria for bvFTD with definite FTLD pathology, a patient must present with possible or probable bvFTD (A), plus one of the one of the following (B–C):

B. Histopathological evidence of FTLD on biopsy or at post-mortem

Although distinguished by the selective degeneration of frontal and anterior temporal lobes, FTLD is histopathologically heterogeneous. Recent consensus criteria (Mackenzie et al., 2009, 2010) classify FTLD on the basis of the presumed molecular defect (i.e. the protein abnormality presumed to be pathogenic or most characteristic). In general terms, FTLD can be assigned to one of three major molecular subgroups: FTLD with tau inclusions (FTLD tau), FTLD with TAR DNA-binding protein inclusions (FTLD-TDP) or cases immunoreactive for fused in sarcoma protein (FTLD-FUS). For the purpose of this study, consensus criteria have been modified to accommodate cases with incomplete immunohistochemistry. Please refer to Table 1 for pathology glossary and descriptions.

C. Presence of a known pathogenic mutation

Under the new framework, an individual presenting with the bvFTD clinical syndrome and a verified pathogenic mutation is now considered to meet criteria for bvFTD with definite FTLD pathology. Autosomal dominant bvFTD may be caused by mutations in several genes, including those encoding the microtubule-associated protein tau (MAPT) (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998), charged multi-vesicular body protein 2B (CHMP2B) (Skibinski et al., 2005), valosin-containing protein (VCP) (Watts et al., 2004) and progranulin (PGRN) (Baker et al., 2006; Cruts et al., 2006).

V. Exclusionary criteria for bvFTD

In order to diagnose bvFTD, one should exclude medical, neurological and psychiatric conditions that could otherwise account for the behavioural and cognitive changes presented by the patient. A
A diagnosis of bvFTD may not be given if the patient presents with any one of the following (A–B):

**A. Pattern of deficits is better accounted for by other non-degenerate nervous system or medical disorders**

These comprise a variety of conditions including delirium, cerebrovascular disease, cerebellar disorder, trauma, infections, systemic disorders (e.g. hypothyroidism) or substance-induced conditions.

**B. Behavioural disturbance is better accounted for by a psychiatric diagnosis**

The behavioural syndrome should not be better accounted for by psychiatric conditions such as depression, schizophrenia, bipolar disorder, late-onset psychosis or a pre-existing personality disorder.

In the absence of definitive biomarkers, criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

To clarify, a diagnosis of probable bvFTD does not require biomarker or genetic screening for Alzheimer's disease or other degenerative conditions. However, when available, the presence of sensitive and specific biomarkers indicative of other degenerative conditions will preclude a diagnosis of probable bvFTD.

**C. Biomarkers strongly indicative of Alzheimer’s disease or other neurodegenerative process**

These include pathogenic mutations for other conditions (e.g. Presenilin, APP), extensive amyloid related radioligand binding (e.g. PIB) (Rabinovici et al., 2007), or the presence of sensitive and specific CSF markers (Dubois et al., 2000; Rowe et al., 2007; Shaw et al., 2009). Biomarker studies are rapidly evolving, and this criterion will require revisions once sensitive and specific biomarkers are determined for Alzheimer’s disease and other degenerative conditions. Similarly, a positive FTLD biomarker criterion should be added to the diagnosis of probable bvFTD once additional FTLD biomarkers become available.