Dementia

she sits
eyes almost closed
a small Buddha —
my mother
still teaching

Marilyn Sandall
Seattle

Clinical Guidelines and Related Research for Dementia Diagnoses

Prepared for the Rural and Remote Memory Clinic

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2010 Revisions

Table of Contents

Definition of Terms and Overview of Sections

Criteria Sources: This section compares, and contrasts the different sets of criteria (e.g., DSM-IV, *NINCDS-ADRDA*) that are typically used in clinical and research settings.

Validity: Validity is the extent to which something is true. In this manual, the validity section addresses the degree of agreement or level of controversy associated with the diagnosis or phenomenon, and by implication, the criteria.

Sensitivity: Sensitivity is the ability (of the given set of criteria) to correctly identify those who have the disease. Sensitivity = ("true positives"/ ("true positives" + "false negatives")) multiplied by 100. When the "false negatives" is a small number relative to the "true positives", sensitivity approaches 100%.

Specificity: Specificity is the ability (of the given set of criteria) to correctly identify those who do not have the disease. Specificity = ("true negatives" divided by ("true negatives" + "false positives")) multiplied by 100. When the "false positives" is a small number relative to the "true negatives", specificity approaches 100%.

Prevalence: Prevalence measures the commonality of a disease. Prevalence involves all affected individuals, regardless of the date of contraction. It is calculated by dividing the number of cases of a disease present in a population at a specified time by the number of individuals in the population at that specified time. This section gives prevalence rates when available.

Neuropsychological Profile: This section of the manual gives an overview taken from research and review papers of the neuropsychological profile typically seen in a given type of dementia.

Neuroanatomical Profile: This section of the manual gives an overview taken from research and review papers of the neuroanatomical profile (e.g., autopsy and structural and functional neuroimaging) typically seen in a given type of dementia.

Differential Diagnosis: This section compares and contrasts the neuropsychological and neuroanatomical evidence for that particular type of dementia against other types of dementia (and other disorders) to help guide diagnoses.

Sources of Criteria and Related Research for Dementia

Consensus Criteria: Clinicians and researchers gather to determine criteria for a given disorder for clinical and research purposes when more comprehensive manuals (e.g., DSM) are outdated.

DSM-IV-(TR): Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (TR: Text Revision without criteria revision). This is the most commonly used criteria manual in Canada and the U.S and is consequently used in many research studies and appears often in this manual.

ICD-10: International Classification of Diseases, 10th edition is used in the United Kingdom but does not appear often in the literature or in the manual.

NINDS-AIREN: The National Institute of Neurological Disorders and Stroke National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences is commonly used in the literature and thus appears in the manual.

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Alzheimer's Disease and Related Disorders Association is also commonly used in the literature.

Literature Searches from 1998-present: Most of the information in this manual was from literature searches (Medline and PsychInfo from 1998-July 2009). Back searches from articles were performed when warranted.

CCCDTD3: Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia, March 10, 2006.

Mild Cognitive Impairment

Mild Cognitive Impairment

This set of criteria is from Petersen et al. (1999) and was renamed in "MCI-amnestic" by the same authors in 2001.

1. Complaint of defective memory (preferably corroborated by an informant)
2. Normal activities of daily living
3. Normal general cognitive functioning
4. Abnormal memory function for age
5. Absence of dementia (Petersen et al., 1997).

An objective level of impairment of either 1.0 s.d. or 1.5 s.d. below published norms on memory measures is commonly used (Petersen, 2001). MCI has also been subgrouped into amnestic MCI (only memory impairment), amnestic multiple MCS (impairment extending beyond memory) and a third subgroup for individuals who show a single non-memory cognitive impairment. Individuals with MCI may demonstrate subtle functional changes but the TCCCDTC recommends that these changes should only occur in higher functions and not represent significant impairment in daily life.

Subclinical Cognitive Impairment

This set of criteria is taken from Ritchie, Atero & Touchon (2001).

MCI is indicated by scores that are more than one standard deviation below the mean of age-matched controls on any area of cognition:

1. Attention
2. Primary Memory (immediate recall)
3. Secondary Memory (delayed recall)
4. Visuospatial Ability
5. Language
6. Reasoning

Age-Related Cognitive Decline

This set of criteria is taken from DSM-IV (American Psychiatric Association, 1994)

This category can be used when the focus of clinical attention is an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age. Individuals with this condition may report problems remembering names or appointments or may experience difficulty in solving complex problems. This category should be considered only after it has been determined that the cognitive impairment is not attributable to a specific mental disorder or neurological condition.

Cognitive Impairment, no dementia

This set of criteria is taken from the Canadian Study of Health and Aging (2000).
One standard deviation below the mean on the MMSE. Also use a consensus conference to decide which persons are cognitively impaired.

Related Research on Mild Cognitive Impairment

Criteria Sources:

The Petersen et al. (1999) criteria appear to be used the most often in the literature. A consensus conference has resulted in updating this set of criteria to specify three subtypes: amnestic, impairment in multiple domains, and impairment in one domain other than memory. Petersen's original criteria have memory as the central deficit while all other cognitive functioning is normal, which is in contrast to other criteria (e.g., Ritchie's criteria are broader than Petersen et al). The CSHA criteria are often seen in the literature. DSM-IV's description is not used. The CCCDTD3 does not recommend one label over another (MCI, CIND) as all have limitations (e.g., lack of diagnostic specificity).

Prevalence:

Prevalence of cognitive impairment, no dementia in an Italian study was 10.7% (DiCarlo et al., 2000). The Canadian Study of Health and Aging documented a 16.8% prevalence of cognitive impairment without dementia (Tuokko, 2003). In general, people with CIND have higher rates of dementia progression as compared to those without CIND (Tuokko et al., 2003). According to the CCCDTD3 between 19% and 50% of MCI individuals progress to dementia.

Validity:

This is a controversial area, as there is lack of agreement in the literature as to whether MCI is normal aging, early stage dementia, or something in between. There are many different conceptualizations of MCI (Davis & Rockwood, 2004), which is problematic when attempting to establish the validity of the criteria/diagnosis. Also, Ritchie et al. (2001) recognize that the diagnosis lacks temporal stability, which is problematic for validation. Neuropsychological and neuroimaging profiles were not found, which makes it difficult to validate.

MCI is an area of interest because of the findings that people with MCI are more likely than people with normal profiles to progress to dementia (for example, Palmer, Fratiglioni & Winblad (2003) compared several studies and found that persons with cognitive impairment have a higher risk of developing dementia over a three year period, at which point the risk decreases). Of Petersen's three subtypes of MCI, amnestic MCI is thought to lead to AD, multiple cognitive deficits MCI is thought to lead to normal aging, AD, or vascular dementia, and non-memory MCI has a wide variety of outcomes (Peterson et al., 2001b).

The CCCDTD3 argues that the use of MCI is more applicable in a clinical setting due to the use of subjective memory complaints as criteria while CIND is more appropriate for population studies because of the use of objective test cut-off scores. The diagnosis of MCI has limitations, however, specifically the operationalization of MCI and the lack of cut-off criteria.

Specificity and Sensitivity:

Ritchie et al. (2001) suggest that Petersen et al.'s (1999; 2001) criteria may be too strict and miss cases of MCI. Specific numbers for sensitivity and specificity were not found but percentages of false positives and false negatives were found.

Hong, Zarit & Johansson (2003) examined the two main sets of criteria for their ability to predict subsequent dementia and found that in an older sample (80-85+) neither Ritchie's nor Petersen's criteria were great at predicting subsequent dementia cases. Ritchie's criteria resulted in more cases of MCI but more false positive error, whereas Petersen's criteria resulted in more false negative error.

Hong et al. (2003) found that of the people that developed dementia, Petersen's criteria successfully classified 31% of the cases (69% were false negatives) and Ritchie's correctly identified 54% of the cases (46% were false negatives). Of those who did not develop dementia, Petersen's criteria identified 75% of the cases correctly (25% were false positives) and Ritchie's criteria identified 55% of the cases correctly (45% were false positives).

Neuropsychological Profile:

None found. Petersen et al. classify it mainly as a memory disorder but others suggest it can affect any type of cognitive functioning. Typically the objective level of impairment for MCI is assigned at either 1.0s.d or usually 1.5 s.d. below published norms on memory tests. As well, MCI has been divided into amnestic MCI (only memory impairment), amnestic multiple MCI (impairment beyond memory including subtle changes in executive function, attention, naming etc.) and those with impairment in one non-memory domain.

Neuroanatomical Profile:

Some MCI subjects show very early stages of AD including neurofibrillary tangles in the hippocampus and entorhinal cortex. The CCCDTD3 stresses, however, that this profile is non-specific as many healthy older adults show evidence of AD like pathology but never show dementia like symptoms.

Alzheimer's Disease (AD)

NINDS-ADRDA criteria for Probable AD

This set of criteria for probable AD is taken from NINDS-ADRDA (McKhann et al., 1984) and is recommended by the CCCDTD3.

I. Criteria for probable AD

- Dementia established by clinical examination and documented by the Mini-Mental Status Test; Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- Deficits in two or more areas of cognition;
- Progressive worsening of memory and other cognitive functions;
- No disturbance of consciousness;
- Onset between ages 40 and 90, most often after age 65; and
- Absence of systemic disorders or other brain diseases that in and of themselves could
- account for the progressive deficits in memory and cognition

II. The diagnosis of *probable* Alzheimer`s disease is supported by:

- Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia);
- Impaired activities of daily living and altered patterns of behaviour;
- Family history of similar disorders, particularly if confirmed neuropathologically;
- Laboratory results of: normal lumbar puncture as evaluated by standard techniques, normal pattern or non-specific changes in EEG, such as increased slow-wave activity, and evidence of cerebral atrophy on CT with progression documented by serial observation

III. Other clinical features consistent with the diagnosis of *probable* Alzheimer`s disease, after exclusion of causes of dementia other than Alzheimer`s disease, include:

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease; and
- CT normal for age

IV. Features that make the diagnosis of *probable* Alzheimer`s disease uncertain or unlikely include:

- sudden, apoplectic onset; although recent CCCDTD3 recommendations state an acute onset should not necessarily excluded a diagnosis of AD
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

- seizures or gait disturbances at the onset or very early in the course of the illness.

Dementia of the Alzheimer's Type (294.1x)

This set of diagnostic criteria is taken from DSM-IV-TR (APA, 2000).

A. The development of multiple cognitive deficits manifested by both
(1) memory impairment (impaired ability to learn new information or to recall previously learned information)
(2) one (or more) of the following cognitive disturbances:
(a) aphasia (language disturbance)
(b) apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) agnosia (failure to recognize or identify objects despite intact sensory function)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
(1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
(2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
(3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Episode, Schizophrenia).

Code based on presence or absence of a clinically significant behavioral disturbance:
294.10 Without Behavioral Disturbance: if the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.
294.11 With Behavioral Disturbance: if the cognitive disturbance is accompanied by a clinically significant behavioral disturbance. (e.g., wandering, agitation)

Specify subtype:
With Early Onset: if onset is at age 65 years or below
With Late Onset: if onset is after age 65 years

Coding note: Also code 331.0 Alzheimer's disease on Axis III. Indicate other prominent clinical features related to the Alzheimer's disease on Axis I (e.g., 293.83 Mood Disorder Due to Alzheimer's Disease, With Depressive Features, and 310.1 Personality Change Due to Alzheimer's Disease, Aggressive Type).

Related Research on Alzheimer's Disease

Criteria Sources:

The criteria for DSM-IV-TR and NINCDS-ADRDA are similar regarding cognitive deficits, course, and functional impairment. The criteria differ in one respect: NINCDS requires confirmation of AD through clinical history and psychometric testing. The exclusionary criteria also differ slightly, as NINCDS includes exclusionary ages (under forty or over ninety) and DSM-IV requires exclusion of substance abuse or other major mental disorder. The CCCDTD3 recommends the NINCDS-ADRDA criteria. Updated criteria released in June, 2010 from the National Institute on Aging and the Alzheimer's Association divide AD dementia into amnestic presentation and non-amnestic presentation (language presentation, visual presentation, or executive dysfunction)
Consider that none of the AD criteria have been fully operationalized and depend on subjective judgment (with the partial exception of NINCDS criteria, which requires an MMSE score with confirmation of neuropsychological testing) (Storey, Slavin, & Kinsella, 2002).

Prevalence:

At age 65, 0.6% in males and 0.8% in females have AD, and the numbers increase exponentially with age (at age 85, 11% for males and 14% in females; at age 90, 21% in males and 25% in females; and at age 95, 36% in males and 41% females). (APA, 2000). AD accounts for approximately 60% of all cases of dementia. Lisa the CSHA papers of prevalence should likely be included here.

Validation of criteria:

There have not been recent studies validating AD; however, the criteria appear to be universally accepted and thus validity is not a concern.

Sensitivity and specificity:

The CCCDTD3 gives sensitivity and specificity for the NINCDS-ADRDA criteria. Probable AD from this criteria source is reported as having good sensitivity (average 81%, range 47% to 100%) at the expense of specificity (average 70%, range 47% to 100%). Possible AD as a category achieves higher sensitivity (average 93%) but lower specificity (average 48%).

Neuropsychological Profile:

Dunn, Owen and Sahakian (2001) write that the first deficit typically seen is difficulty with anterograde verbal and nonverbal episodic memory (delayed recall is more affected than

immediate recall). The next typical deficit is impairment in semantic memory (i.e., semantic fluency word lists and confrontational naming deficits). Note that the difficulty in semantic fluency is in contrast with relatively intact letter fluency. For example, a deficit in animal naming may be observed with intact letter naming.
Lee, Rahman, Hodges, Sahakian & Graham (2003) found that episodic memory, particularly for object location (visuo-spatial paired associates learning test), is very useful for early diagnosis of AD and differentiation of AD from FTD.
The CCCDTD3 identify early memory deficits for recent events or names in AD with progression to more remote memory problems and semantic memory deficits at later stages. Measures of executive functioning tend to be relatively well preserved in early stage AD compared to other dementia subtypes, while language deficits (including word finding difficulties) occur in about 8-10% of early AD cases.

Neuroanatomical Profile:

Kantarci and Jack (2003) performed a literature review on neuroimaging in AD and found that for structural imaging, changes initially involve atrophy in anteromedial temporal lobe and limbic cortex (particularly the hippocampus and entorhinal cortex), after which atrophy spreads to neocortex and finally to primary sensory cortices. Regarding functional imaging, the authors suggest that at this time, SPECT and PET are not more sensitive or specific for detecting AD than the clinical criteria.

Differential Diagnosis:

Varma et al. (1998) compared FTD to AD and found that difficulty in praxis and orientation to time and place indicates AD over FTD; in contrast, a deficit in problem solving indicates FTD over AD. Deficits in attention, perception, memory, and language do not indicate one over the other.

Lee et al. (2003) found that the Paired Associates Learning (a visuo-spatial object location episodic memory task) differentiated AD from SD and fvFTD. Kramer, Jurik, Rankin et al., (2003) found that both AD and Semantic Dementia (SD) patients were impaired on verbal memory as compared to fvFTD patients, but only AD patients were impaired on visual memory. fvFTD patients performed worse on backward digit span and had more executive errors as compared to AD and SD patients. SD patients were more impaired than AD and fvFTD patients on confrontation naming.

Visual hallucinations and parkinsonism features might not differentiate AD from dementia with Lewy body (DLB). Although visual hallucinations and parkinsonism features are typical of DLB, they can also occur in AD and do not always occur in DLB (Storey et al., 2002). AD is characterized by episodic memory deficits, whereas DLB is characterized by a fluctuating cognitive state, and visuospatial, visuoconstructional, and visuoperceptual difficulties as compared to AD. Note that semantic memory is similar in AD and DLB. Simard, van Reekem, and Cohen (2000) write that impairment of spatial working memory in DLB may be the most consistent distinguishing feature between AD and DLB.

Vascular Cognitive Impairment

According to Rockwood (2002), Vascular Cognitive Impairment (VCI) is increasingly accepted as a broader description encompassing all forms of cognitive loss due to cerebrovascular disease (CVD). Subtypes of VCI include vascular CIND, cortical VaD (multi-infarct dementia), subcortical VaD, hypoperfusion or cardiogenic dementia, hemorrhagic dementia, hereditary VaD and "mixed" dementia (AD with evidence of CVD).

The CCCDTD3 recognizes three subtypes: VCI-no dementia (VCI-ND), a subcortical vascular dementia with a prominent dysexecutive profile and white matter changes on neuroimaging and VaD with multiple or single strategic infarcts.

Vascular Cognitive Impairment – no dementia

This set of criteria is from Wentzel, Darvesh, MacKnight & Rockwood (2000)

1. Patients should have acquired cognitive impairment, discernable from the history as a decline in the prior level of cognitive function, and demonstrated by cognitive testing.
2. Clinical features which suggest a vascular cause include:
    a. Sudden onset
    b. Stepwise course
    c. A course marked by prolonged plateaus
    d. A course marked by periods of spontaneous improvement
    e. Onset or worsening in relation to stroke or to episode of hypoperfusion (e.g., dysrhythmia, intraoperative hypotension)
    f. Focal neurological symptoms
    g. Focal neurological signs
    h. Evidence of patchy cognitive deficits during formal cognitive testing
3. Radiographic features which suggest a vascular contribution to cognitive impairment include:
    a. One or more cortical or subcortical strokes or hemorrhages
    b. Lacunar infarction
    c. White matter ischemic changes
    d. VCI can be seen alone or in combination with another dementing illness
    e. VCI may or may not meet the (AD-based) criteria for dementia. the typical presentation for a mixed diagnosis is when a patient presents with AD and is found to have ischemic lesions clinically and/or radiographically
4. VCI can conform to any one or a combination of the following radiographic patterns:
    a. Multiple cortical strokes
    b. Multiple subcortical strokes
    c. Single strategic stroke
    d. Perventricular white matter changes
    e. No identified lesions

The severity of the impairment can be expressed in terms of its impact on patient functioning, and must be individualized to reflect variation in premorbid fashion:

Very Mild: Patients are obliged to use cuing strategies or assistive devices, but the use of these devices compensates for the deficit. Alternatively, impairment prevents the performance of complex occupational tasks such as maintaining employment or engaging in detailed hobbies.

Mild: Impairment in complex instrumental self-care activities in which the patient was previously competent (e.g., driving, paying bills, using the telephone, taking medications).

Moderate: Inability to perform intermediate self-care activities such as bathing, walking, housework, meal preparation, shopping or walking outside.

Severe: Inability to perform basic self-care activities such as toileting, dressing, eating, transferring or grooming.

Vascular Dementia (VaD)

NINDS-AIREN Criteria for the Probable Vascular Dementia

This set of criteria is taken from Roman et al. (1993)

I. The criteria for the clinical diagnosis of *probable* vascular dementia include *all* of the following:

1. *Dementia* defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferable established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.

Exclusion criteria: cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.

2. *Cerebrovascular disease*, defined by the presence of focal signs on neurological examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of not irrelevant CVD by brain imaging (CT or MRI) including *multiple large vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as *multiple basal ganglia* and *white matter* lacunes, or extensive periventricular white matter lesions, or combinations thereof.
3. A relationship between the above two disorders, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II. Clinical features consistent with the diagnosis of probable vascular dementia include the following:

1. Early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait)

2. History of unsteadiness and frequent, unprovoked falls;
3. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease;
4. Pseudobulbar palsy; and
5. Personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include
1. Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging;
2. Absence of focal neurological signs, other than cognitive disturbance; and
3. Absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of possible vascular dementia may be made in the presence of dementia (section I-1) with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of definite vascular dementia are
1. Clinical criteria for probable vascular dementia;
2. Histopathologic evidence of CVD obtained from biopsy or autopsy;
3. Absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and
4. Absence of other clinical or pathological disorder capable of producing dementia.

VI. Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathologic features, for subcategories or defined conditions such as cortical vascular dementia, subcortical vascular dementia, Binswanger's Disease, and thalamic dementia.

DSM-IV-TR Criteria for Vascular Dementia (290.4x)

A. The development of multiple cognitive deficits manifested by both
1. memory impairment (impaired ability to learn new information or to recall previously learned information)
1. one (or more) of the following cognitive disturbances:
   a) aphasia (language disturbance)
   b) apraxia (impaired ability to carry out motor activities despite intact motor function)
   c) agnosia (failure to recognize or identify objects despite intact sensory function)
   d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.

D. The deficits do not occur exclusively during the course of a Delirium.

Code based on predominant features:
290.41 With Delirium: if delirium is superimposed on the dementia
290.42 With Delusions: if delusions are the predominant feature
290.43 With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.
290.40 Uncomplicated: if none of the above predominates in the current clinical presentation

Specify if: With Behavioral Disturbance
Coding note: Also code cerebrovascular condition on Axis III

Related Research on Vascular Dementia

Criteria Sources:

The CCCDTD3 recognizes four consensus criteria for VaD: The State of California AAD Diagnostic and Treatment Centers criteria (the California criteria), the National Institute of Neurologic Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, the Hachinski Hachinski Ischemic Score (HIS) modified by Rosen, and those found in the DSM-IV. According to the CCCDTD3 all these criteria have poor sensitivity at the cost of high specificity. The CCCDTD3 attributes the lack of sensitivity in diagnostic criteria partially to the overlap between vascular pathology and AD pathology (i.e., some vascular pathology exists in 29%-41% of dementias).
Note that the criteria among different sources are not interchangeable as they are for AD, and that DSM-IV is more liberal than NINDS criteria (Chui et al., 2000).

Validity:

There is controversy regarding the criteria for vascular dementia. The literature generally recognizes that DSM-IV and NINDS criteria are problematic because they require a memory deficit, which is not always the case in vascular dementia (Bowler, 2002); however, DSM-IV and NINDS criteria are often used as criteria for studies.

Erkinjuntti & Rockwood (2003), who seem to be influential in this field, explain that VCI is defined as cognitive impairment in the face of cerebrovascular disease, and that VaD is currently viewed as a subset of VCI.

Feldman and Kertesz (2001) list various subtypes of vascular dementia: Lacunar disease, multiinfarct type (large vessel), Binswanger's disease, watershed ischemia, strategic infarcts, anoxic encephalopathy, amyloid angiopathy, cerebral angiitits, CADASIL, and other.

Sensitivity and Specificity:

Gold et al. (2002) compared DSM-IV, ICD-10, ADDTC, and NINDS criteria using autopsy cases to assess the sensitivity and specificity. They found that ADDTC for possible (not probable) dementia may have the best balance of specificity and sensitivity; DSM-IV is good for excluding mixed cases but is not sensitive.

	Sensitivity	Specificity
DSM-IV for vascular dementia	.50	.84
ADDTC (possible vascular dementia)	.70	.78
NINDS-AIREN possible vascular dementia	.55	.84
ICD-10 vascular dementia	.20	.94
ADDTC probable vascular dementia	.25	.91
NINDS-AIREN for probable vascular dementia	.20	.93

Chui et al. (2000) found excellent inter-rater agreement for AD but not for vascular dementia among the various sets of criteria. For vascular dementia, the original Hachinski Ischemic Score had the highest inter-rater reliability (.65), followed by HIS modified. DSM-IV also had moderate inter-rater reliability for vascular dementia (.59).
The CCCDTD3 guidelines note that the NINDS-AIREN criteria for VaD are problematic due to the emphasis on memory impairment when executive dysfunction is often predominant. As well, cognitive decline may be slowly progressive rather than stepwise.

Prevalence:

There is also some controversy about the prevalence of vascular dementia but generally it is reported as a similar rate to dementia with Lewy body (~10%). The Canadian Study of Health and Aging (CSHA) found that vascular dementia comprised 29% of all dementia cases, but post mortem findings suggests this number is only 4% (Hebert et al., 2000). The CSHA found that incidence was between 2.5-3.8 cases per 1000 each year in people over age 65. The prevalence of VCI in CSHA is 5% of people over 65. This number includes vascular CIND (a subset of CIND). Prevalence of VaD was 1.5% (Hebert et al., 2000).
Hebert et al. (2000) found some interesting risk factors for vascular dementia (using NINDS criteria) that are relevant for this clinic: residing in a rural area (2.03), living in an institution (2.33), diabetes (2.15), depression (2.41), apolipoprotein E4 (2.34), hypertension in women (2.05), heart problems in men (2.52), taking aspirin (2.33), and occupational exposure to pesticides or fertilizers (2.05). Protective factors included eating shellfish (.46) and regular exercise for women (.46).

Neuropsychological Profile:

The idiopathic nature of vascular dementia makes it difficult to define a neuropsychological profile. Korczyn (2002) suggests that dysexecutive syndrome (e.g., goal formulation, initiation, planning, and organizing) may be the hallmark feature.
Rockwood (2002) divides vascular dementia into three main subtypes: cortical MID, strategic infarct, and subcortical/small vessel. The author describes that dysexecutive syndrome and difficulty with abstract thought is common to cortical vascular dementia. Rockwood suggests that the cognitive impairment resulting from strategic vascular dementia varies, but that memory problems, confusion, fluctuating consciousness, apathy, lack of spontaneity, perseveration, and mild dysphasia may occur. The cognitive deficits from subcortial dementia tend to affect the prefrontal subcortical circuit, so a loss of executive function, with mental slowing and impairment of goal formulation, initiation, planning, organizing, sequencing, executing, and abstracting can occur (Desmond et al., 1999, as cited in Rockwood, 2002). Memory deficits are less common, and mood changes with depression, personality changes, and emotional lability are common.

According to the CCCDTD3, VaD often presents with memory and executive difficulty but performance on neuropsychological measures can show a range of intact and impaired skills, largely dependent on the location of the vascular damage.

Garret and Cohen (2003) describe some of the myths surrounding the diagnosis of vascular dementia in a review paper:

1. VaD does not always result in a stepwise decline. Only 20% of patients' families describe a stepwise decline. Subcortical ischemic disease in particular can occur insidiously and result in a gradual rate of cognitive decline.
2. VaD is not always characterized by a patchy neuropsychological profile. Other forms of dementia (e.g., AD) can be uneven, and VaD can be global.
3. VaD is characterized by a primary memory deficit. Executive deficit (planning, cognitive flexibility, organization, etc.), rather than memory impairment, may be more characteristic of VaD.
4. Evidence of cardiovascular disease on structural MRI does not always provide evidence for the diagnosis of VaD. Many older patients have abnormal MRI so it is difficult to know whether CVD on MRI is clinically meaningful or simply part of an underlying degenerative disease.
5. VaD and AD may not be discrete disease entities. Evidence suggests that vascular pathology is a causative agent in the development of AD, and there is a potential overlap and interaction between these 2 conditions.

Neuroimaging Profile:

Corticosubcortical occipitotemporal infarct is typical of "cortical VaD" (Small, 2002). Brain areas typically affected by "strategic VaD" include hippocampal formation, angular gyrus, cingulated gyrus, thalamus, fornix, basal forebrain, caudate nucleus, globus pallidus, genu or interior limb of the internal capsule (Small, 2002). Brain areas typically affected in "subcortical

VaD" include prefrontal subcortical syndrome, prefrontal cortex, caudate nucleus, pallidum, thalamus, and thalamocortical circuit (Small, 2002).

There are no standards for clinicians to follow to determine the clinical significance of lacunar infarctions or white matter ischemic disease for vascular dementia. Lacunar infarctions will be more clinically relevant in some areas as compared to others (e.g., thalamus vs corona radiate), and some suggestion that 25% white matter damage to meet damage necessary for VaD (Garret & Cohen, 2003).

Mixed Dementia (MD)

Although most research studies focus on AD and VaD as separate clinical entities there is increasing evidence that the brain lesions associated with each disorder often co-occur, especially in older adults. As well, there is support for the notion that the interaction of AD and VaD pathology increases the likelihood of clinically significant cognitive decline. When AD and VaD pathology coexist it is often termed mixed dementia. The NINDS-AIREN diagnostic criteria do not include mixed dementia but suggest the term AD with cerebrovascular disease. Alternatively the Hachinski Ischemic Score, the ICD-10 and the DSM-IV all include a mixed dementia category.

NINDS-AIREN Criteria
Terminology: AD with cerebrovascular disease
Criteria: Typical AD associated with clinical radiological evidence of stroke

Hachinski Ischemic Score Criteria
Terminology: Mixed Dementia
Criteria: score based on clinical features; AD (less than or equal to 4), VaD (greater than or equal to 7), MD (intermediate score of 5 or 6)

ICD-10 Criteria
Terminology: Mixed Dementia
Criteria: Cases that met criteria for VaD and AD

Alzheimer's Disease Diagnostic and Treatment Center Criteria
Terminology: Mixed Dementia
Criteria: Presence of ischemic vascular disease and a second systemic or brain disorder

DSM-IV Criteria for Dementia Due to Multiple Etiologies

A. The development of multiple cognitive deficits manifested by both
    1. memory impairment (impaired ability to learn new information or to recall previously learned information)
    2. one (or more) of the following cognitive disturbances:
        a) aphasia
        b) apraxia
        c) agnosia
        d) disturbance in executive functioning
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. There is evidence from history, physical examination, or laboratory findings that the disturbance has more than one etiology (e.g., head trauma plus chronic alcohol use, Dementia of the Alzheimer's Type with the subsequent development of Vascular dementia).
D. The deficits due not occur exclusively during the course of a delirium.

Related Research on Mixed Dementia

Criteria Sources:

The NINDS-AIREN diagnostic criteria do not include mixed dementia but suggest the term AD with cerebrovascular disease. Alternatively the Hachinski Ischemic Score, the ICD-10, the Alzheimer's Disease Diagnostic Treatment Center (ADDTC) criteria, and the DSM-IV all include a mixed dementia category. These criteria sources are controversial and have not been well validated by neuropathological studies. One study found that the proportion of neuropathologically diagnosed MD cases clinically classified as VaD was 54% for the ADDTC, 29% for the NINDS-AIREN and 18% for the Hachinski Ischemic Score (Zekry et al., 2002). The ADDTC and NINDS-AIREN criteria have been reported as more sensitive but less able to differentiate VaD and MD. The use of mixed dementia to describe a combination of AD and VaD pathology is used most commonly in the literature.

Prevalence:

Autopsy supported prevalence rates of coexisting vascular pathology in AD range from 23% to 45% (Langa et al., 2004).

Neuropsychology

Subjects with MD have higher frequency of depressed mood, focal modor or sensory findings and gaid disorder. Few studies of neuropsychology in MD exist but one study reported the neuropsychological characteristics of MD are closer to those of VaD than AD (Zekry et al., 2002).

Neuropathology:

AD – extracellular amyloid plaques and intracellular neurofibrillary tangles
VaD – cerebral infarctions, multiple lacunar infarctions, ischemic periventricular leukoencephalopthy

Dementia with Lewy Body

The following criteria are taken from McKeith and colleagues (2005) and are accepted by the CCCDTD3.

1. *Central feature* (essential for possible or probable DLB):
   - progressive cognitive decline that interferes with daily functioning
   - prominent or persistent memory impairment may not occur in early stages but is evident with progression
   - deficits on tests of attention, executive function and visuospatial ability prominent
2. *Core feature* (two sufficient for probably DLB, one for possible DLB)
   - fluctuating cognition with pronounced variations in attention and alertness
   - recurrent visual hallucinations that are well formed and detailed
   - spontaneous features of parkinsonism
3. *Suggestive features* (If one or more present and one or more core feature probable DLB can be diagnosed. Possible DLB can be diagnosed if one or more suggestive feature present even if no core features present. Probable DLB not diagnosed on basis of suggestive features alone)
   - REM sleep behaviour disorder
   - Severe neuroleptic sensitivity
   - Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET
4. *Supportive features* (commonly present but no diagnostic specificity)
   - repeated falls and syncope
   - transient, unexplained loss of consciousness
   - severe autonomic dysfunction (e.g. orthostatic hypotension, urinary incontinence)
   - hallucinations in other modalities
   - systemized delusions
   - depression
   - relative preservation of medial temporal lobe structures on CT/MRI
   - generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
   - abnormal (low uptake) MIBG myocardinal scintigraphy
   - prominent slow wave activity on EEG with temporal lobe transient sharp waves
5. diagnosis of DLB is less likely
   - in presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
   - presence of any other physical illness or brain disorder sufficient to account in part or in total for clinical picture
   - if parkinsonism only appears for the first time at a stage of severe dementia
6. temporal sequence of symptoms
   - DLB diagnosed when dementia occurs before or concurrently with parkinsonism (if present).
   - Parkinson disease dementia (PDD) should be used to describe dementia that occurs in 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 LB 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 DLB continues to be recommended.

Related Research on DLB

Criteria Sources:

There are no DSM-IV-TR criteria for dementia with Lewy body. DSM-IV suggests that if DLB occurs with Parkinson's disease it should be coded under "dementia due to General Medical Condition (Parkinson disease). DSM-IV-TR does not currently recognize Lewy body dementia without Parkinson's disease but is investigating the possibility pending further research. The McKeith criteria are more commonly used in the literature and do not require Parkinson's disease as part of the criteria.

Prevalence:

Rahkonen et al (2003) found that DLB had a 5% prevalence rate in the general population in Finland of people over 75 years of age and 22% in all people with dementia. This rate is half the rate of AD and the same rate as vascular dementia. DLB accounts for 15-20% of cases of dementia in hospital autopsy studies (Weiner, 1999) and in community based samples (Holmes et al., 1999), with slightly higher prevalence for males than females (McKeith, 2002).
The approximate rate of decline in patients with DLB is 10% per year, which is similar to AD for dementia and similar to PD for parkinsonism symptoms (McKeith, 2002). McKeith also found that the age of onset for DLB is 50-83; the age of death from DLB ranges from 68-92 years, which suggests the disease has approximately 9--15 year expected mortality.

Validity:

Recent studies (1998-present) validating DLB do not exist; however, McKeith and colleagues criteria appear to be well received in the literature. Serby and Samuels (2001) performed a meta-analysis that tested the Consensus criteria and found that the most common symptom is parkinsonism (64%) and parkinsonism with dementia (66%), whereas only 39% had visual hallucinations and 29% had cognitive fluctuations. The authors suggest that parkinsonism is a hallmark feature of DLB rather than cognitive fluctuations, as is suggested by consensus criteria. Note that the authors report potential selection problems.

Specificity and Sensitivity:

The sensitivity and specificity of DLB appear to be quite high. DLB has a sensitivity of .83 and specificity of .91 (McKeith et al., 2000; Ballard, McKeith, Harrison, 1997). McKeith (2002) suggests that autopsy validation studies place high specificity (.9-1.0) but lower sensitivity (.22-.83). Other studies (retrospective) indicate lower sensitivity. Diagnostic accuracy of .50 has been reported (Hohl et al., 2000).

Neuropsychological Profile:

McKeith et al. (2005) state progressive mental impairment is a mandatory condition for a diagnosis of DLB with the cognitive profile of DLB including both cortical and subcortical impairments. Substantial impairments in areas of attention, executive functioning and visuospatial functioning are evident with relative preservation of confrontational naming and delayed recall as compared to individuals with AD.

The CCCDTD3 recommendations state DLB patients show more inattention, distractibility, difficulty with set shifting, incoherence, confabulation, perseveration and intrusions when compared to individuals with AD. As well, individuals with DLB show significantly improved performance when given memory recognition tests or are given semantic cues to aid retrieval. McKeith (2002) provides an overview of how DLB presents clinically. The author describes that the presenting concern of DLB is often dementia, but it can also present as Parkinsonism alone, a psychiatric disorder in absence of dementia, or orthostatic hypertension, falls, or transient disturbance in consciousness. The most common feature of DLB is fluctuation in consciousness, and 2/3 of cases also have visual hallucinations. Note that transient consciousness can be mistaken for transient ischemic attacks. Many patients with DLB will have depressive symptoms (40% have a major depressive episode), which is more prevalent than is found in AD. 70% have parkinsonism features, and falls and synocope are found in 1/3 of cases.

A systematic literature review performed by Collerton, Burn, McKeith and O'Brien (2003) found that DLB is primarily a visuo-perceptual and attentional-executive dementia, which the authors suggest is consistent with the prevalence of Lewy Bodies in the frontal, cingulate, and inferior temporal cortex.

McKeith et al. (2003) describe that the most common feature of DLB is fluctuation in consciousness, with may be manifested by a marked difference between best and worst performance. The authors suggest that there is often variability across cognitive tasks, particularly attention and executive tasks but short term memory may be intact (McKeith et al., 2003). The authors suggest the differential performance differentiates DLB from AD. McKeith et al. (2003) found patients with DLB have difficulty with visual perceptual and learning tasks, and visual semantic and praxis tasks.

The Clinician Assessment of Fluctuation or the One Day Fluctuation Scale, which are competed by caregivers, may provide more information on fluctuation in attention and arousal, which is often difficult to capture (Walker et al, 2000, in McKeith 2002).

Neuroanatomical Profile:

Barber and colleagues (1999; 2000) found that patients with DLB have generalized atrophy on structural imaging, but when compared with AD patients, DLB patients (40%) have relative intact medial temporal lobe structures on MRI, especially the hippocampus. White matter changes are similar in AD and DLB (which is still less than what is found in vascular dementia) and similar ventricular enlargement and frontal lobe atrophy is found in AD and DLB (Barber et al, 1999; 2000). SPECT imaging shows more subtle differences- although there is a similar pattern of blood flow changes in AD and DLB, there is more occipital hyperperfusion in DLB as compared to AD (review, Barber et al., 2001).

Collerton, Burn, McKeith and O'Brien (2003) suggest that DLB affects the frontal, cingulate, and inferior temporal gyrus, which explains the difficulty with visuo-perceptual and attentional-executive tasks.

Galasko, Katzman, Salmon, & Hansen (1996) examined patients with AD, patients with Lewy body variant of AD, and patients with Lewy body alone. They found that hallucinations were more common in the Lewy body patients (with or without AD) as compared to the AD patients. The Lewy body AD group had greater difficulty with executive and visuospatial tests than the AD group.

Differential Diagnosis:

Patients with DLB are better than patients with AD at verbal memory and orientation tasks, but performance on visual tasks (especially visual recognition) is more impaired in DLB than in AD (McKeith et al., 2003). McKeith and colleagues suggest that the most common feature of DLB is fluctuation in consciousness, which is often accompanied by visual hallucinations, and that a significant difference between best and worst performance on the neuropsychological tests differentiates DLB from AD.

Frontotemporal Dementia

Note:
FTD was once diagnosed as Pick's disease but has evolved because of the requirement to find Pick bodies which made it difficult to diagnose. Thus this dementia had a reputation for being rare and was consequently underdiagnosed (Kertesz, 2003). International consensus criteria support the division of frontal temporal dementia into three main subtypes: frontal variant FTD, progressive non-fluent aphasia, and semantic dementia (Neary et al., 1998), which are described on the following pages. Hodges et al. (2003) add corticobasal degeneration syndrome and motor neuron disease to the spectrum; these 5 main types described by Hodges et al. appear to correspond to the 5 main pathologies described by McKhann. However, certain authors view FTD as an overarching disorder, and McKhann et al. (2001) have proposed simplifying FTD into a single set of criteria. This subdivision of frontotemporal dementia into three dominant subtypes is supported by the CCCDTD3.

Clinical Criteria for Frontotemporal Dementia

This set of criteria is taken from McKhann et al. (2001).

1. The development of behavioral or cognitive deficits manifested by either
    a) Early and progressive change in personality, characterized by a difficulty in modulating behavior, often resulting in inappropriate responses or activities, or
    b) Early and progressive change in language, characterized by problems with expression of language or severe naming difficulty and problems with word meaning.
2. The deficits outlined in 1a or 1b cause significant impairment in social or occupational functioning and represent a significant decline from previous level of functioning
3. The course is characterized by a gradual inset and continuing decline in function.
4. The deficits outlined in 1a or 1b are not due to other nervous system conditions (e.g., cerebrovascular disease), systemic conditions (e.g., hypothyroidism) or substance-induced conditions.
5. The deficits do not occur exclusively during delirium.
6. The disturbance is not better accounted for by a psychiatric diagnosis (e.g., depression).

Frontotemporal Dementia (frontal variant)

The following is from consensus criteria from Neary et al.'s international consensus criteria (1998).

Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved.

I. Core diagnostic features

Insidious onset and gradual progression
Early decline in social interpersonal conduct
Early impairment in regulation of personal conduct
Early emotional blunting
Early loss of insight

II. Supportive diagnostic features

Behavioral disorder

1. Decline in personal hygiene and grooming
2. mental rigidity and inflexibility
3. distractibility and impersistence
4. hyperorality and dietary changes
5. perseverative and stereotyped behavior
6. utilization behavior

Speech and language

1. altered speech output (A. spontaneity and economy of speech; B. Press of speech)
2. stereotype of speech
3. echolalia
4. perseveration
5. mutism

Physical signs

1. primitive reflexes
2. incontinence
3. akinesia, rigidity, and tremor
4. low and labile blood pressure

Investigations

1. neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptual disorder
2. electroencephalography: normal on conventional EEG despite clinically evident dementia
3. brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

III. Supportive Features

Onset before age 65; positive family history of similar disorder in a first degree relative; Bulbar palsy, muscular weakness and wasting, fasciculations (associated motor neuron disease present in minority of patients)

IV. Diagnostic exclusion features
Historical and Clinical

1. Abrupt onset with ictal events
2. Head trauma related to onset
3. Early, severe amnesia
4. Spatial disorientation
5. Logoclonic, festinant speech with loss of train of thought
6. myoclonus
7. Corticospinal weakness
8. Cerebellar ataxia
9. choreoathetosis (dyskinesia)

Investigations (exclusionary)

1. Brainimaging, predominant postcentral structural or functional deficits; multifocal lesions on CT or MRI
2. Laboratory tests indicating brain involvement of metabolic or inflammatory disorder such as MS, syphilis, AIDS and herpes simplex encephalitis

V. Relative diagnostic exclusion features

Typical history of chronic alcoholism
Sustained hypertension
History of vascular disease (e.g., angina, claudication)

Related Research on fv-FTD

Criteria Sources:

DSM-IV-TR (APA, 2000) does not include criteria for any of the frontotemporal dementias; the closest equivalent is "Dementia due to a General Medical Condition (Pick's disease)". The DSM-IV set of criteria is problematic because a memory deficit is needed for a diagnosis of dementia (but typically does not occur in FTD until later stages) and the "frontal" symptoms are not specified.

The criteria used in the literature for FTD can be confusing. Some researchers still use the term "Pick's disease", and "frontal variant FTD" is often referred to as simply "FTD". Furthermore, "FTD" is often used as a blanket term for the various subtypes of FTD. Finally, Lund-Manchester criteria for FTD are also cited in the literature. This set of criteria is set up like a checklist and is the precursor to the current consensus guidelines, so is very similar to the consensus criteria. Adding to the confusion, some articles do not clearly define the use of the various terms. Regardless, the international consensus criteria appear to be accepted in the literature and are being applied in recent studies. McKhann's overarching FTD criteria are used less often.

Validity:

Mendez and Perryman (2002) found that only 1/3 of FTD (fv) met consensus criteria on presentation. Please see the table for features upon presentation- the features typically associated with fvFTD were not always present, but after 2 years, most features were present.

	At presentation	**2 years**
Core diagnostic features		
Insidious onset and gradual progression	100%	100%
Early decline in social interpersonal conduct	39.6%	83%
Early impairment in regulation of personal conduct	69.8%	88.7%
Early emotional blunting	35.8%	94.3%
Early loss of insight	58.5%	100%
Supportive diagnostic features		
Decline in personal hygiene and grooming	32.1%	100%
Mental rigidity and inflexibility	35.8%	83%
Distractibility and impersistence	28.3%	94.3%
Hyperorality and dietary changes	0	20.8%
Perseverative and stereotyped behavior	45.3%	88.7%
Utilization behavior	0	1.9%
Speech and language (sparse verbal output, reiterative speech, or anomia)	41.5%	96.2%
Physical signs such as primitive reflexes	0	7.5%

Sensitivity and Specificity:

Lopez, Litvan, Catt et al. (1999) found that sensitivity was .97 and specificity was .97 for clinician recognition of FTD (using Lund-Manchester criteria) when compared to AD, DLB, and progressive supranuclear palsy. Mendez and Perryman (2002) also recognize that both sensitivity and specificity are high in FTD. When incorrectly diagnosed, FTD is most likely to be confused with AD, as Varma et al. (1999) found that most patients with FTD fulfilled the requirements for the NINCDS criteria for AD. Varma et al. found the specificity for AD compared to FTD is only .23 (sensitivity was .91). The authors concluded that FTD is under-diagnosed and is most typically confused with AD.

Prevalence:

Overall, FTD comprises 10% of all dementias and 20% of all dementias under age 65 (cited in Mendez & Perryman, 2002). Note that Gislason et al. (2003) found that 3% of dementia patients aged 85+ had FTD, which is higher than expected in older adults. The authors also found that 19% of patients over 85 qualified for "frontal lobe syndrome"[1] (unspecified FTD), and that 87% of those patients had been diagnosed with other kinds of dementia. There is a strong familial

[1] Frontal Lobe Syndrome takes into consideration behavioral signs from neuropsychiatric interview, behavioral symptoms from informant interview, affective signs from neuropsychiatric interview, and affective symptoms from informant interview.

pattern in FTD, as 20-40% of patients have a clear family history of FTD (McKhann et al., 2001). Survival is 6 years (+/- 1.1) (Hodges et al., 2003).

Neuropsychological Profile:

Rahman et al. (1999) describe fv FTD as typically presenting with deficits on frontal lobe tests while severe amnesia, aphasia, perceptual or spatial disorders are absent. The authors explain that neuropsychological tests that are sensitive to the orbitofrontal/ventromedial cortex are able to detect impairment.

Mendez and Perryman (2002) also report that any test that is sensitive to the orbital-frontal lobes will detect fv FTD, such as increased decision making time, decreased visual discrimination, and increased risk taking. Failure on other tests of frontal lobe function (e.g., Wisconsin, Trails, Stroop) may reveal qualitative differences in performance for the patient with fv FTD, such as concreteness, poor set shifting, perseveration, failure to use one trial to guide subsequent trials, difficulty inhibiting over-learned responses, poor organization and difficulty with temporal sequencing. If memory, language, perceptual, and spatial deficits are revealed, it is typically due to inattention, lack of self-monitoring, and lack of concern for accuracy rather than a deficit in the higher brain function itself

Varma et al. (1999) found that deficits in orientation and praxis increased the odds of having a diagnosis of AD as compared to FTD, whereas deficits in problem solving *decreased* the odds of having AD as compared to FTD. Measures of executive functioning (e.g., perseveration, rule violations) tend to be more impaired in FTD than in individuals with AD (Wittenberg et al., 2008). On measures of delayed recall, visuoconstruction and word list learning individuals with FTD perform better than those with AD (Diehl & Kurz, 2002).
According to the CCCDTD3, orientation and episodic memory are relatively preserved in FTD, with subjective memory complaints likely being due to inattention. Working memory is often impaired. FTD- fv patients typically show anomia and reduction in spontaneous conversation.

Neuroanatomical Profile:

McKhann et al. (2001) found that FTD patients (identified using overarching criteria) had atrophy of anterior temporal lobes and frontal lobes on CT and MRI scans. Scans using SPECT, PET and perfusion MRI found decreased perfusion of the temporal and frontal lobes. McKhann et al. (2001) note that “striking asymmetry” between the hemispheres itself is common. The authors also noted that FTD is more specific than AD, as AD typically has more widespread atrophy and perfusion deficits, which, for example, often involve the parietal lobes or temporoparietal areas.

Pasquier et al. (2003) reviewed imaging in FTD and Primary Progressive Aphasia and found that FTD tends to affect frontal areas bilaterally whereas PPA tends to affect the left temporal area asymmetrically.

Gregory et al. (1999) did not find early indications of fv-FTD using CT, MRI and SPECT but only examined 2 patients. The authors found that frontal atrophy in both patients on MRI

developed after a couple of years, and then hypoperfusion developed a couple of years after that in the inferior frontal lobes.

Differential Diagnosis:

Bozeat et al. (2000) compared fv FTD to AD and found that stereotypic behavior, changes in eating preference, disinhibition and poor social awareness reliably differentiated the two groups. They also found that although deficits in executive function, poor self care, and restlessness were related to disease severity, these features did not differentiate disease.
McKhann et al. (2001) described that it is rare to have onset of FTD after age 75 whereas the incidence of AD increases with age (however, note that Gislason et al. found that 3% of people have FTD in adults 85+). The authors also stated that it is rare to have early behavior problems in AD but common in FTD. In AD, memory loss is apparent in the earlier stages but memory problems are not seen in FTD until much later, and the spatial deficits observed in AD in moderate stages are rarely observed in FTD. Furthermore, patients with AD do not typically have motor deficits in early and moderate stages, whereas FTD often have motor difficulties, such as weakness and muscle wasting. Note, however, that parkinsonism symptoms are common to both and cognitive inflexibility is similar in both.

Snowden (2001) described the difference between FTD and semantic dementia and found that emotion response differentiated the two groups: Global lack of emotion was found in FTD, whereas lack of emotion in semantic dementia patients was restricted to showing less fear. Snowden also found that social avoidance was more typical of FTD, whereas social seeking more typical of semantic dementia. Other differences included a diminished response to pain in FTD (in contrast semantic dementia patients showed an increased response to sensory stimuli) and increased gluttony in FTD (in contrast semantic dementia patients had increased food fads).

Progressive Non-Fluent Aphasia

This set of criteria is taken from Neary et al. (1998) international consensus criteria:

Disorder of language is the dominant feature initially and throughout the disease. Other aspects of cognition are relatively preserved.

I. Core Diagnostic Features

Insidious onset and gradual progression

Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphrasia, anomia

II. Supportive Diagnostic Features:

Speech and Language

1. stuttering or oral apraxia
2. impaired repetition
3. alexia, agraphia
4. early preservation of word meaning
5. late mutism

Behavior

1. early preservation of social skills
2. late behavioral changes similar to FTD

Physical signs

late contralateral primitive reflexes, akinesia, rigidity, tremor

Investigations

Neuropsychology: nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder

Electroencephalography: normal or minor asymmetric slowing

Brain imaging (structural and/or functional): asymmetrical abnormality predominantly affecting the dominant (usually left) hemisphere

III. Supportive Features

Onset before age 65; positive family history of similar disorder in a first degree relative; Bulbar palsy muscular weakness and wasting, fasciculations (associated motor neuron disease present in minority of patients)

IV. Diagnostic exclusion features

Historical and Clinical

1. Abrupt onset with ictal events
2. Head trauma related to onset
3. Early, severe amnesia
4. Spatial disorientation
5. Logoclonic, festinant speech with loss of train of thought
6. myoclonus
7. Corticospinal weakness

8. Cerebellar ataxia
9. choreoathetosis

Investigations
Brainimaging, predominant postcentral structural or functional deficits; multifocal lesions on CT or MRI
Laboratory tests indicating brain involvement of metabolic or inflammatory disorder such as MS, syphilis, AIDS and herpes simplex encephalitis

V. Relative diagnostic exclusion features
Typical history of chronic alcoholism
Sustained hypertension
History of vascular disease (e.g., angina, claudication)

Related Research on Progressive non-Fluent Aphasia

Criteria Sources:

There are no DSM-IV-TR criteria for progressive non-fluent aphasia. DSM-IV-TR simply states that frontotemporal dementia not due to Pick's disease warrants further research. As described in the fv FTD section, the consensus criteria are generally accepted in the literature, although many studies report using Mesulam's terminology "primary progressive aphasia" to denote a similar type of dementia, including the CCCDTD3. Subtypes of primary progressive aphasia are sometimes used: "primary progressive aphasia, non-fluent type" denotes a dementia similar to Neary et al.'s progressive non-fluent aphasia type of dementia, whereas primary progressive aphasia, fluent type is similar to Neary et al's semantic dementia).

Validity:

Validity studies specifically for progressive non-fluent aphasia were not found but the consensus criteria, neuropsychological profile, and neuroanatomical profile give credit toward the validity of this diagnosis. A criticism of the criteria for the frontotemporal dementias is that there may be more overlap among the three subtypes of dementia than the subtypes suggest.

Sensitivity and Specificity:

Not found specifically for progressive non-fluent aphasia.

Prevalence:

Between 3 and 10% of community sample of dementia have some form of FTD (cited in Gislason et al., 2003). Data indicating the prevalence of progressive non-fluent aphasia specifically were not found.

Neuropsychological Profile:

Neary et al. (1998) describe the profile as typically presenting with nonfluent aphasia without memory or perceptual difficulties, although difficulty in the ability to express verbally may interfere with performance on verbal memory tests. Thus, the authors state that it is important to look for normal memory and rates of forgetting on *visual* memory tests. To determine normal perceptual performance, recognition of line drawings would indicate intact perception. Individuals with FTD-pnf show phonemic paraphasias, word finding difficulty, picture naming problems and decreased word list generation (more pronounced on phonemic than semantic fluency) according to the CCCDTD3.

Smici et al. (2006) describe FTD-pnf as being characterized by agrammatic speech and anomia with relative sparing of single word comprehension. Sentence comprehension is impaired for more difficult morphosyntactic constructions. Confrontational naming and calculation are also spared, although FTD-pnf patients exhibit decreased fluency and working memory.

Neuroanatomical Profile:

McKhann et al. (2001) found that FTD patients (identified using overarching criteria) had atrophy of anterior temporal lobes and frontal lobes on CT and MRI scans. Scans using SPECT, PET and perfusion MRI found decreased perfusion of the temporal and frontal lobes. McKhann et al. (2001) note that "striking asymmetry" between the hemispheres itself is common. The authors also noted that FTD is more specific than AD, as AD typically has more widespread atrophy and perfusion deficits, which, for example, often involve the parietal lobes or temporoparietal areas.

Pasquier et al. (2003) reviewed imaging in FTD and Primary Progressive Aphasia and found that FTD tends to affect frontal areas bilaterally whereas PPA tends to affect the left temporal area asymmetrically.

Kertesz et al. (2003) found that significant left frontotemporal atrophy occurred in most Primary Progressive Aphasia patients, and that MRI provided the most useful information as compared to CT or SPECT. The authors note that patients in the very early stages may not have neuroimaging signs, and patients in the late stage may have bilateral atrophy. The authors did not differentiate semantic PPA from non-fluent PPA.

Semantic Dementia

Neary et al. (1998). International consensus criteria.

Semantic disorder (impaired understanding of word meaning and/or object identity) is the dominant feature initially and throughout the disease course. Other aspects of cognition, including autobiographical memory, are intact or relatively well preserved.

I. Core diagnostic features
- Insidious onset and gradual progression
- Language Disorder characterized by
  - Progressive, fluent, empty spontaneous speech
  - Loss of word meaning, manifested by impaired naming *and* comprehension
  - Semantic paraphrasias *and/or*
- Perceptual disorder characterized by
  - Prosopagnosia; impaired recognition of identity of familiar faces *and/or*
  - Associative agnosia: impaired recognition of object identity
- Preserved perceptual matching and drawing reproduction
- Preserved single-word repetition
- Preserved ability to read aloud and write dictation orthographically regular words

II. Supportive diagnostic features
- Speech and language
  - Press of speech
  - Idiosyncratic word usage
  - Absence of phonemic paraphrasias
  - Surface dyslexia and dysgraphia
  - Preserved calculation
- Behavior
  - Loss of sympathy and empathy
  - Narrowed preoccupation
  - Parsimony
- Physical Signs
  - Absent or late primitive reflexes
  - Akinesia, rigidity, and tremor

Investigations
Neuropsychology: Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition; Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memory for autobiographical events
EEG: normal
Brain imaging (structural and/or functional): Predominant anterior temporal abnormality (symmetric or asymmetric).

III. Supportive Features

Onset before age 65; positive family history of similar disorder in a first degree relative; Bulbar palsy muscular weakness and wasting, fasciculations (associated motor neuron disease present in minority of patients)

IV. Diagnostic exclusion features
Historical and Clinical
- Abrupt onset with ictal events
- Head trauma related to onset
- Early, severe amnesia
- Spatial disorientation
- Logoclonic, festinant speech with loss of train of thought
- myoclonus
- Corticospinal weakness
- Cerebellar ataxia
- choreoathetosis

Investigations (exclusionary)
Brainimaging: predominant postcentral structural or functional deficits; multifocal lesions on CT or MRI
Laboratory tests indicating brain involvement of metabolic or inflammatory disorder such as MS, syphilis, AIDS and herpes simplex encephalitis

V. Relative diagnostic exclusion features
- Typical history of chronic alcoholism
- Sustained hypertension
- History of vascular disease (e.g., angina, claudication)

Related Research on Semantic Dementia

Criteria Sources:

There are no DSM-IV-TR criteria for semantic dementia (SD). DSM-IV-TR simply states that frontotemporal dementia not due to Pick's disease warrants further research. As described in the fv FTD section, the consensus criteria are generally accepted in the literature. Semantic dementia is sometimes referred to as a "semantic subtype" or "fluent subtype" of "primary progressive aphasia" (see previous section for a description of PPA).

Validity:

Validity studies were not found specifically for semantic aphasia but consensus criteria, neuropsychological profile, and neuroanatomical profile give credit toward the validity of this diagnosis. A criticism of the criteria is that there may be more overlap among the three subtypes of dementia than the subtypes suggest.

Sensitivity and Specificity:

None reported specifically for semantic dementia.

Prevalence:

Between 3 and 10% of community sample of dementia patients have some form of FTD (cited in Gislason et al., 2003). Although data were not found for specific SD prevalence numbers, Kertesz (2003) suggests that SD is less common than progressive non-fluent aphasia.

Neuropsychological Profile:

Neary et al. (1998) describe semantic dementia patients as having profound semantic loss (difficulty in word comprehension and naming, or face and object recognition). However, phonology and syntax, basic perceptual processing, spatial skills, and day to day memory remain intact. The authors state that word comprehension, naming, and famous face recognition or object recognition tasks should be impaired in patients with SD. The authors recommend that the clinician should ensure that the problems in testing are due to semantic difficulties rather than visual or verbal processing (i.e., make sure the patient can copy, match stimuli, and repeat words). Neary et al. also state that the patient with semantic dementia should have normal performance on at least 2 spatial tests. As memory tests are likely compromised by semantic disorder, the patient should be able to remember day to day autobiographical events.

According to the CCCDTD3, SD patients show decreased speech content and impaired performance on semantic measures including deficits in category fluency, noun definitions and comprehension, picture naming, reading irregular words and semantic associations.

Neuroanatomical Profile:

There are no studies that specifically report neuroimaging details of semantic dementia. As stated in earlier sections, McKhann et al. (2001) found that FTD patients (identified using overarching criteria) had atrophy of anterior temporal lobes and frontal lobes on CT and MRI scans. Scans using SPECT, PET and perfusion MRI revealed decreased perfusion of the temporal and frontal lobes. McKhann et al. (2001) note that “striking asymmetry” is common. The authors also noted that AD typically has more widespread atrophy and perfusion deficits, which, for example, often involve the parietal lobes or temporoparietal areas.

Frontotemporal dementia and Movement Disorders

There is increased recognition of the similarities (both in terms of symptoms and underlying neuropathology) between corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), amyotrophic lateral schlerosis (ALS) and frontotemporal dementia (FTD). Although these disorders/syndromes remain distinct, they can co-occur and the overlapping of symptoms implies understanding of the diagnostic criteria is important for differential diagnosis purposes.

Corticobasal Degeneration (CBD)

CBD is a multi-system disorder resulting in asymmetrical parkinsonian features, apraxia, alien limb phenomena, sensory loss of dysphasia. Approximately 30%-50% of patients eventually show signs of depression and frontal-lobe behavioural changes including apathy, disinhibition, impulsive and irritability. Although there has been an increase in research on CBD, there are currently no consensus criteria for this disorder, nor are there data available on incidence and prevalence rates.

Core Characteristics: progressive asymmetric rigidity and apraxia

- Limb apraxia
- Alien limb behaviour
- Strictly asymmetric parkinsonism (unilateral rigidity)
- Jerky dystonia of the limbs
- Gaze Palsy

Neuropsychological profile:

The cognitive symptoms of CBD and FTD overlap considerably. Nonfluent aphasia, frontal executive deficits, oral and limb apraxia, apathy and depression are prominent.

Neuroanatomical profile:

CBD impacts the mesial frontal lobe, the frontal opercular region as well as the parietal lobe and basal ganglia. The parietofrontal cortex is often involved in a focal or asymmetric manner. White matter deficits are observed. Particularly the substantia nigra tends to degenerate in the maximally affected side of the brain.

Progressive supranuclear palsy (PSP)

Initial symptoms of PSP often include loss of balance and falls as well as changes in personality, motor slowing and visual difficulties. In the late stage of PSP patients are wheelchair bound. These individuals develop a characteristic growling and groaning speech and become immobile with akinesia, rigidity and dystonia.

The NINDS-SPSP (National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy) criteria were developed through examination of previously published criteria by a panel of neurologists using retrospective clinical information from patients with autopsy

confirmed cases of dementia or parkinsonism. Modified criteria were proposed based on this investigation and revised by a consensus of experts in movement disorders.

Mandatory inclusion criteria:

Possible PSP:
- Gradually progressive disorder
- Onset at age 40 or later
- Either vertical (upward or downward gaze) supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of disease onset
- No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria

Probable PSP:
- Gradually progressive disorder
- Onset at age 40 or later
- Vertical (upward or downward gaze) supranuclear palsy and prominent postural instability with falls in the first year of disease onset
- No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria

Definite PSP:
- Clinically probable or possible PSP and histopatholgic evidence of typical PSP

Mandatory exclusion criteria:
- Recent history of encephalitis
- Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy
- Hallucinations or delusions unrelated to dopaminergic therapy
- Cortical dementia of Alzheimer's type (severe amnesia and aphasia or agnosia, according to NINCDS-ADRA criteria)
- Prominent, early unexplained dysautonomia (marked hypotension and urinary disturbances)
- Severe, asymmetric parkinsonian signs (i.e., bradykinesia)
- Neuroradiologic evidence of relevant structural abnormality (i.e. basal ganglia or brainstem infarcts, lobar atrophy)
- Whipple's disease, confirmed by polymerase chain reaction, if indicated

Supportive criteria:
- Symmetric akinesia or rigidity, proximal more than distal
- Abnormal neck posture, expecially retrocollis
- Poor or absent response of parkinsonism to levodopa therapy
- Early dysphagia and dysarthria
- Early onset of cognitive impairment including at least two of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs

Neuropsychological Profile:

PSP is a clinical syndrome of axial dystonia, bradykinesia, falls, dysphagia, vertical gaze palsy with behavioral symptoms and aphasia (Steele et al.). This syndrome is considered a prototype of subcortical dementia in later descriptions of disorder with the associated neuropsychological pattern of a subcortical dementia (i.e., poor learning but relatively intact recall, particularly with recognition, psychomotor slowing, poor cognitive set-shifting; nonfluent aphasia, apathy). PSP often begins as a cognitive disorder affecting executive function or language or as a neuropsychiatric disorder with apathy or other behavioural symptoms. Some studies have found no neuropsychological differences between PSP and CBD and the pathological features tend to overlap.

Neuroanatomical Profile:

Progressive supranuclear palsy syndrome (PSPS) reflects that some cases can have different underlying pathologies but still be considered suspected PSP. Individuals diagnosed with PSP show neuroimaging changes in the frontosubcortical grey and white matter, subthalamic nucleus and substantia nigra. As well, the pathology of this syndrome includes tau 4R neurofibril tangles and globose neurons.

Motor Neuron Disease (MND)

The motor neuron diseases are a heterogeneous group of disorders with a common progressive degeneration of the motor neurons resulting motor symptoms including weakness associated with muscle atrophy. These diseases can involve the upper motor neurons (UMN), lower motor neurons (LMN) or a combination of both. Specific disease phenotypes include ALS, primary lateral sclerosis (PLS), progressive muscular atrophy 9PMA), spinal muscular atrophy (SMA), spinal bulbar muscular atrophy (Kennedy's disease), progressive bulbar palsy, bibrachial amyotrophy, and monomelic amyotrophy. The most common adult-onset motor neuron disease is ALS, however cognitive impairment similar to frontotemporal dementia can occur in any motor neuron disease.

The clinical standard for diagnosis of ALS is the Revised El Escorial World Federation of Neurology Criteria.

Clinically definite ALS:
> Clinical evidence of the presence of LMN (lower motor neuron) as well as UMN (upper motor neuron) signs in the bulbar region and at least two spinal regions, or the presence of UMN and LMN signs in at least three spinal regions

Clinically definite familial ALS:
> Laboratory supported: may be applied when ALS presents with progressive UMN and/or LMN signs in at least one region (in the absence of another cause for the abnormal neurological signs)

Clinically probably ALS:
> Clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to the LMN signs

Clinically probable familial ALS

Laboratory supported: clinical signs of UMN and LMN dysfunction alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes

Clinically possible ALS:

Clinical signs of UMN and LMN dysfunction are found together in only one region, or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of clinically probably ALS – laboratory supported cannot be proven

Clinically suspected ALS:

LMN only in at least 1 region or UMN only in at least 1 region

UMN and LMN findings:

Bulbar
UMN symptoms: dysphagia, spastic dysarthria, laryngospasm, pseudobulbar affect, cheek biting
UMN signs: poor palate movement, slow tongue movement, jaw jerk, palmomental sign, active facial reflex
LMN symptoms: difficulty chewing, sialorrhea, dysphagia, slurred speech, hoarseness
LMN signs: facial weakness, tongue weakness, tongue atrophy, facial/tongue fasciculations

Limb
UMN symptoms: stiff, slow movement, clonus triggered by movement
UMN signs: spasticity, hyperreflexia, spastic gait, pathologic reflexes (Babinski, Hoffman's)
LMN symptoms: weakness, cramps
LMN signs: weakness, muscle atrophy, fasciculations, hyporeflexia

Prevalence:

Motor neuron diseases are progressive leading to death from respiratory paralysis after an average of 3-5 years. Incidence rates of 1-3 per 100 000, and prevalence of 3-5 per 100 000 have been estimated.

Neuropsychological Profile:

Cognitive and behavioral impairments are observed in as high as 50% of cases of ALS. ALS is conceptualized as a multisystem disorder in which motor system deficits are prominent but also non-motor manifestations can be observed including cognitive and behavioral impairments. A subgroup of ALS cases develops a frontotemporal dementia.

Neuroanatomical Profile:

MND is characterized by death of lower motor neurons (anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (originating in layer five of the motor cortex and descending via the pyramidal tract to

synapse with lower motor neurons either directly or indirectly via interneurons). When lower motor neuron dysfunction occurs first, the first evidence of these disorders is asymmetric weakness, usually first evident distally in one of the limbs as well as the recent development of cramping with volitional movements in early morning. When the initial denervation involves the bulbar rather than limb muscles difficulty chewing, swallowing and face and tongue movements are evident. With prominent corticospinal involvement there is hyperactivity of muscle-stretch reflexes (tendon jerks) and spastic resistance to passive movements of the affected limbs.

Cortical Cerebellar Atrophy (CCA)

CCA is associated with impaired executive functioning (i.e. planning, set shifting, verbal fluency, abstract reasoning, working memory), spatial cognition (i.e. problems with visuospatial organization and memory), personality changes (i.e. blunting of affect or disinhibited behavior) and language deficits (i.e. agrammatism and dysprosodia). These deficits appear to be over and above cerebellar atrophy associated motor difficulties. Neurotransmitter studies suggest cerebellar atrophy is associated with a degeneration of afferent cholinergic projections to the cerebellum and lower choline levels in cereberospinal fluid as compared to healthy individuals.

Alcohol-Related Dementia

Alcohol-Related Dementia (ARD)

This set of diagnostic criteria is taken from Oslin, Atkinson, and Smith (1998) and is consensus-based criteria modeled after criteria for NINCDS criteria for AD and vascular dementia.

I. Dementia

Dementia is defined as a significant deterioration of cognitive function sufficient to interfere in social or occupational functioning. As defined by DSM IV this requires deterioration in memory and at least one other area of intellectual functioning. Moreover, the cognitive changes are not attributable to the presence of delirium or substance induced intoxication or withdrawal.

II. *Definite* ARD

At the current time there are no acceptable criteria to definitively define ARD.

III. *Probable* ARD

Criteria for clinical diagnosis of "probable ARD" include the following:

1. A clinical diagnosis of dementia at least 60 days after the last exposure to alcohol.
2. Significant alcohol use, as defined by a minimum average of 35 standard drinks per week for men, and 28 for women, for a period of greater than 5 years. The period of significant alcohol use must occur within 3 years of the initial onset of cognitive deficits.

The diagnosis of ARD is supported by the presence of any of the following:

1. Alcohol-related hepatic, pancreatic, gastrointestinal, cardiovascular, or renal disease, that is, other end organ damage.
2. Ataxia or peripheral sensory polyneuropathy (not attributable to other specific causes)
3. Beyond 60 days of abstinence, the cognitive impairment stabilizes or improves.
4. After 60 days of abstinence, any neuroimaging evidence of ventricular or sulcal dilatation improves
5. Neuroimaging evidence of cerebellar atrophy, especially the vermis

The following clinical features cast doubt upon the diagnosis of ARD:

1. The presence of language impairment, especially dysnomia or anomia
2. The presence of focal neurologic signs or symptoms (except ataxia or peripheral sensory polyneuropathy)
3. Neuroimaging evidence for cortical or subcorticol infarction, subdural hematoma, or other focal brain pathology
4. Elevated Hachinski Ischema Scale score

Clinical features that are neither supportive nor cast doubt upon the diagnosis of ARD:

1. Neuroimaging evidence of cortical atrophy
2. The presence of periventricular or deep white-matter lesions on neuroimaging, in the absence of focal infarct(s)

3. The presence of Apolipoprotein delta 4 allele

IV. *Possible* ARD

1. A clinical diagnosis of dementia at least 60 days after the last exposure to alcohol.
2. Either: Significant alcohol use as defined by a minimum average of 35 standard drinks per week for men (28 for women) for 5 or more years. However, the period of significant alcohol use occurred more than 3 years but less than 10 years prior to the initial onset of cognitive deficits.

Or

Possibly significant alcohol use as defined by a maximum average of 21 standard drinks per week for men (14 for women) but no more than 34 drinks per week for men (27 for women) for 5 years. The period of significant alcohol use must have occurred within 3 years of the onset of cognitive deficits.

V. *Mixed* Dementia

A diagnosis of mixed dementia is reserved for clinical cases that appear to have more than one cause for dementia. The classification of probable or possible should continue to be used to convey the certainty of the diagnosis of ARD. The classification of mixed dementia should not be used to convey uncertainty of the diagnosis or to imply differential diagnosis.

VI. *Alcohol as a contributing factor* in the development or course of dementia.

The designation of alcohol as a contributing factor is used for the situation in which alcohol is used, but not to the degree required or within the time required to meet the classification of probable or possible ARD. The designation should not preclude the use of Probable Vascular Dementia or Probable Dementia of the Alzheimer's Type.

Substance-Induced Persisting Dementia

The following criteria are taken from DSM-IV-TR (APA, 2000).

A. The development of multiple cognitive deficits manifested by both:
(1) memory impairment (impaired ability to learn new information or to recall previously learned information)
(2) one (or more) of the following cognitive disturbances:
(a) aphasia (language disturbance)
(b) apraxia (impairment in skilled motor performance despite intact motoric functions)
(c) agnosia (failure to recognize or identify objects despite intact sensory functions)
(d) disturbance in executive functioning (planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The deficits do not occur exclusively during the course of a delirium and persist beyond the usual duration of Substance Intoxication or Withdrawal.
D. There is evidence from the history, physical examination, or laboratory findings that the deficits are etiologically related to the persisting effects of substance use (e.g., a drug of abuse, a medication).
Code [Specific Substance]-Induced Persisting Dementia: (291.2 Alcohol; 292.82 Inhalant; 292.82 Sedative, Hypnotic, or Anxiolytic; 292.82 Other [or Unknown] Substance)

Related Research on ARD

Criteria Sources:

DSM-IV-TR and Oslin et al. (1998) are the main sources of criteria for alcohol related dementia. Oslin et al. (1998) suggest that DSM-IV criteria for ARD relies too heavily on clinician interpretation of use (i.e., "how much is too much?"). Oslin and colleagues' criteria specify the amount and timing of alcohol necessary to meet criteria. Saxton, Munro, Butters et al. (2000) applied Oslin's criteria to their patients diagnosed with DSM-IV's alcohol-induced persisting dementia and found that 6/10 met criteria for probable ARD and 2/10 met criteria for possible ARD.

Validity:

The existence of ARD is controversial. Clinicians who disagree with this concept propose that ARD is actually AD, vascular dementia, or a mild form of Wernike Korsakoff, whereas some clinicians hypothesize that there are no long term effects of alcohol consumption for the central nervous system (Saxton, Munro, Butters et al., 2000).

There have been no studies validating DSM-IV criteria (Oslin et al., 1998). Olsin and Cary (2003) performed a validation study using their criteria and found that patients who met criteria for possible ARD showed a particular pattern of neuropsychological deficits (see below), and had a more stable course of decline. Saxton et al. (2000) also reported a distinct neuropsychological profile for ARD as compared to AD or normals (see below), which provides support for the validity of the diagnosis.

Greenberg & Lee (2001) describe the different types of psychosis that can occur with alcohol use and withdrawal (e.g., perceptual disturbance) and discuss some of the long term effects of alcohol use (e.g., alcohol dementia, hepatic encephalopathy, etc.).
Moriyama et al. (2006) describe limitations of the DSM-IV criteria including ambiguous terms to describe abnormal alcohol use, duration of abstinence may impact cognitive functions but are unclear in the diagnosis, and the qualitative differences between ARD and AD or VaD are unclear.

Specificity and Sensitivity: None reported.

Prevalence:

ARD may be more common than previously thought. Carlen, McAndrews, Weiss, et al. (1994) found that 24% of nursing home patients met criteria for ARD; however, only 25% of that group had actually been given a diagnosis of ARD. Saxton et al. (2000) cite studies that suggest 22-29% of dementia cases might have been alcohol related.

Furthermore, Salazer Thomas and Rockwood (2001) used the CSHA to demonstrate that 8.9% had definite alcohol abuse and 3.7% had probable alcohol abuse, which suggests that in general, alcohol abuse among the older adults is much more common than previously given credit, and thus the potential for ARD is increased.

Neuropsychological Profile:

Oslin and Cary (2003) found that cognitive (as measured by the MMSE) and physical functioning (as measured by Activities of Daily Living) in ARD do not deteriorate as they do in patients with AD.

Saxton et al. (2000) found distinct neuropsychological profiles among patients with AD and alcohol-induced persisting dementia (as determined by DSM-IV criteria). Patients diagnosed with AD had more pronounced deficits in confrontational naming (BNT), recognition memory (CLT and Recognition Memory Test for Words), animal fluency, and orientation compared to ARD patients. Patients diagnosed with ARD had more pronounced deficits in fine motor control (Grooved Pegboard) than alcoholics without dementia. Patients with ARD had worse performance than normal controls on measures of initial letter fluency (FAS), fine motor control (Grooved pegboard), and free recall than alcoholics without dementia.

Krabbendam, Visser, Derix et al. (2000) compared patients with Korsakoff's syndrome, chronic alcoholics, and healthy controls on neuropsychological measures and structural MRI and found normal performance in chronic alcoholics. Note that the authors recruited alcoholics rather than ARD, and administered an incomplete neuropsychological battery (Verbal Learning Test, Stroop, Concept Shifting, Letter Digit Substitution Test, and Word Fluency).

Munro, Saxton & Butters (2001) found neuropsychological performance for patients with alcohol dementia was neither typical of a cortical dementia, like Alzheimer Disease, nor a subcortical dementia, like dementia due to Parkinson Disease. The authors based there conclusions on the finding that peformance on procedural and declarative memory are doubly dissociated (i.e., procedural is intact in cortical but not subcortical dementias, whereas declarative is intact in subcortical but not cortical dementia); although patients with AD performed worse on declarative memory as compared to alcohol dementia and normals, procedural memory did not differentiate the groups.

Differential Diagnosis:

As described above, Saxton et al. (2000) found that patients diagnosed with AD had more pronounced deficits in confrontational naming (BNT), recognition memory (CVLT and Recognition Memory Test for Words), animal fluency, and orientation compared to ARD patients.

Neuroanatomical Profile:

Oslin and colleagues' criteria state, "after 60 days of abstinence, any neuroimaging evidence of ventricular or sulcal dilatation improves" and "neuroimaging evidence of cerebellar atrophy, especially the vermis". They also state that "cerebral atrophy neither supports nor refutes diagnosis".

Brun and Anderson (2000) performed an autopsy study of alcoholics and found that all subjects had atrophy of the superior vermis (cerebellum) and Purkinje cell loss. Most also had changes in the walls of the third ventricle. Mesencephalic changes were not observed. The authors also noted that there was a consistent pattern of synapse loss in the superior laminae of the frontal cortical area (BA 10) (not related to liver disease or mental illness). The authors suggest that the cortical changes are similar to those found in FTD.

Krabbendam, Visser, Derix et al. (2000) compared patients with Korsakoff's syndrome, chronic alcoholics, and healthy controls on neuropsychological measures and structural MRI. The authors found although patients with Korsakoff's had decreased brain volume, chronic alcoholics were normal.

Note on amount of alcohol: Review indicates that less than 20 drinks per week is not associated with cognitive deficit (Oslin et al., 1998).

Normal Pressure Hydrocephalus

The following consensus guidelines were published by Relkin et al. (2005) and are recommended by the CCCDTD3 for diagnosing idiopathic normal-pressure hydrocephalus.

Probable INPH

I. History (reported symptoms should be corroborated by an informant and must include):
   a) insidious onset
   b) origin after age 40
   c) a minimum duration of at least 3-6 months
   d) no evidence of an antecedent event such as head trauma, intracerebral hemorrhage, meningitis or other known cause of secondary hydrocephalus
   e) progression over time
   f) no other neurological, psychiatric, or general medical conditions that are sufficient to explain the presenting symptoms

II. Brain imaging (performed after onset of symptoms must show evidence of:
   a) ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement
   b) no macroscopic obstruction to CSF flow
   c) at least one of the following supportive features:
      i. enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy
      ii. callosal angle of 40 degrees or more
      iii. evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination
      iv. an aqueductal or fourth ventricular flow void on MRI

Other brain imaging findings may be supportive of an INPH diagnosis but are not required for a Probable designation:
   a) a brain imaging study performed before onset of symptoms showing smaller ventricular size or without evidence of hydrocephalus
   b) radionuclide cisternogram showing delayed clearance of radiotracer over the cerebral convexities after 48-72 hours
   c) cine MRI study or other technique showing increased ventricular flow rate
   d) a SPECT-acetazolamide challenge showing decreased periventricular perfusion that is not altered by acetazolamide

III. Clinical (findings of gait/balance disturbance must be present plus at least one other area of impairment in cognition, urinary symptoms, or both)

With respect to gait/balance, at least two of the following should be present and not be entirely attributable to other conditions
   a) decreased step height

b) decreased step length
c) decreased cadence (speed of walking)
d) increased trunk sway during walking
e) widened standing base
f) toes turned outward on walking
g) retropulsion (spontaneous or provoked)
h) En bloc turning (turning requiring three or more steps for 180 degrees)
i) Impaired walking balance, as evidenced by two or more corrections out of eight steps on tandem gait testing

With respect to cognition, there must be documented impairment (adjusted for age and educational attainment) and/or decrease in performance on a cognitive screening instrument, or evidence of at least two of the following on examination that is not fully attributable to other conditions:

a) psychomotor slowing (increased response latency)
b) decreased fine motor speed
c) decreased fine motor accuracy
d) difficulty dividing or maintaining attention
e) impaired recall, especially for recent events
f) executive dysfunction, such as impairment in multistep procedures, working memory, formulation of abstractions/similarities, insight
g) behavioural or personality changes

To document symptoms in the domain of urinary incontinence, either one of the following should be present:

a) episodic or persistent urinary incontinence not attributable to primary urological disorders
b) persistent urinary incontinence
c) urinary and fecal incontinence

Or any two of the following should be present:

a) urinary urgency as defined by frequent perception of a pressing need to void
b) urinary frequency as defined by more than six voiding episodes in an average 12-hour period despite normal fluid intake
c) nocturia as defined by the need to urinate more than two times in an average night

IV. physiological (CSF opening pressure in the range of 5-18 mm Hg as determined by a lumbar puncture or a comparable procedure. Appropriately measured pressures that are significantly higher or lower than this range are not consistent with a probable NPH diagnosis)

Possible INPH

I. History: reported symptoms may:
a) have a subacute or indeterminate mode of onset
b) begin at any age after childhood

c) may have less than 3 months or indeterminate duration
d) may follow events such as mild head trauma, remote history of intracerebral hemorrhage, or childhood and adolescent meningitis or other conditions that in the judgment of the clinician are not likely to be causally related
e) coexist with other neurological, psychiatric, or general medical disorders but in the judgment of the clinician not be entirely attributable to these conditions
f) be nonprogressive or not clearly progressive

II. Brain imaging – ventricular enlargement consistent with hydrocephalus but associated with any of the following:
a) evidence of cerebral atrophy of sufficient severity to potentially explain ventricular size
b) structural lesions that may influence ventricular size

III. Clinical
Symptoms of either:
a) incontinence and/or cognitive impairment in the absence of an observable gait or balance disturbance
b) gait disturbance or dementia alone

IV. Physiological
Opening pressure measurement not available or pressure outside the range required for probable INPH

Unlikely INPH

I. no evidence of ventriculomegaly
II. signs of increased intracranial pressure such as papilledema
III. no component of the clinical triad of INPH is present
IV. symptoms explained by other causes (e.g., spinal stenosis)

Related Research on NPH

Criteria Sources:

The consensus criteria proposed by Relkin et al. (2005) and supported by the CCCDTD3 are evidence-based guidelines for the clinical diagnosis of INPH. These guidelines were developed through evidence in medical literature from 1966 to 2003 and were supplemented by expert opinion.

Validity:

It has been suggested that the only way to reliably validate a diagnosis of INPH is through a documented positive response to shunt placement. Relkin et al. (2005) argue however this criteria is limited and would result in a high rate of false-negatives due to individuals who do not respond well to a shunt due to coexisting conditions such as AD.

Prevalence:

NPH is believed to account for as much as 5% of cases of dementia. Incidence rates of 1.8 out of 100 000 people have been reported (Chaudhry et al., 2007).

Neuropsychological Profile:

The primary cognitive deficits seen in INPH suggest a subcortical process including slowing of thought, inattentiveness and apathy as well as encoding and recall difficulties. Speech output may be disturbed secondary to dysexecutive or motivational problems. Individuals with INPH tend to score higher than those with AD on measures of orientation and delayed recall. As well, individuals with INPH tend to score lower than those with AD on measures of attention and concentration, digit span and other frontal executive measures (Ogino et al., 2005). Compared to healthy controls, individuals with NPH tend to show a gradual decline in active retrieval from memory (both immediate and delayed) with relatively preserved memory storage (recognition) (Chaudhry et al., 2007).

Neuroimaging Profile:

Individuals diagnosed with INPH show ventricular enlargement as documented by an Evan's index of 0.3 or greater or an equivalent measure reflecting an increased ratio of ventricular size to cranial diameter.

Differential Diagnosis:

The CCCDTD3 recommends a typically differential of obstructive hydrocephalus, multiple systems atrophy (associated with ataxia and incontinence), vascular gait impairment, and AD with gait impairment.

Dementia Due to Other Medical Condition (294.1x)

This set of criteria is taken from DSM-IV-TR (APA, 2000).

A. The development of multiple cognitive deficits manifested by both
(1) memory impairment (impaired ability to learn new information or to recall previously learned information)
(2) one (or more) of the following cognitive disturbances:

a) aphasia (language disturbance)
b) apraxia (impaired ability to carry out motor activities despite intact motor function)
c) agnosia (failure to recognize or identify objects despite intact sensory function)
d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition other than Alzheimer's disease or cerebrovascular disease (e.g., HIV infection, traumatic brain injury, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jacob disease, normal pressure hydrocephalus, hypothyroidism, brain tumor, or vitamin B12 deficiency).

D. The deficits do not occur exclusively during the course of a delirium.

Code based on presence or absence of a clinically significant behavioral disturbance:
294.10 Without Behavioral Disturbance: if the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.
294.11 With Behavioral Disturbance: if the cognitive disturbance is accompanied by a clinically significant behavioral disturbance. (e.g., wandering, agitation)

Coding note: Also code the general medical condition on Axis III (in this case, 332.0 Parkinson's disease).

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