MEDICAL GRAND ROUNDS

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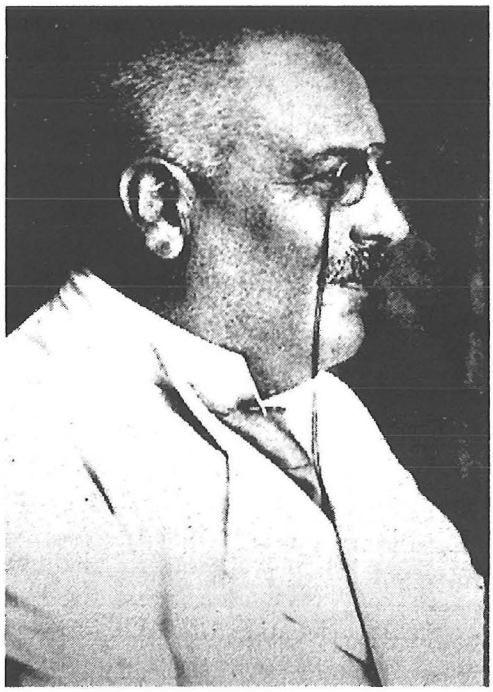
Losing it Part II:

When is Dementia not Alzheimer's



Belinda A. Vicioso, MD, FACP
General Internal Medicine
Geriatrics Section

The University of Texas
Southwestern Medical Center
at Dallas

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GRAND ROUNDS 2001

LOSING IT, PART II: DEMENTIA, WHEN IS IT NOT ALZHEIMER'S?

Introduction

I would like to present my Grand Rounds on cognitive impairment and the dementia syndrome.

In 1907, neuropathologist Alois Alzheimer reported on the progressive clinical features and the senile plaques and neurofibrillary tangles of the devastating illness that today bears his name. In doing so, he exemplified the efforts of other neuroscientists of his time such as Broca and Wernicke to use newly found histological methods to correlate cognitive dysfunction with changes in brain structure. In describing his and the findings of others, he wrote,

"It is clear that there exist many more mental illnesses than our textbooks indicate. In many such cases, a further histological examination must be effected to determine the characteristics of each single case. We must reach the stage in which the vast well-known disease groups must be subdivided into many smaller groups, each with its own clinical and anatomic characteristics."[1]

Today, the advent of symptomatic therapies for Alzheimer's disease has placed increasing emphasis on its early diagnosis. Because of the work begun in Berlin ninety-four years ago, there is also growing recognition that there are other important causes of dementia. In the next 45 minutes, I will review this nosology of dementia with you. In doing so, I will take you through the definition of dementia and its epidemiology; present to you the main causes of dementia focusing on those that are not Alzheimer's disease; and finally, introduce a diagnostic approach that is based on guidelines published last month by the American Academy of Neurology.

Definition

Historically, the term dementia has been used in a variety of ways. Introduced to American medical literature by Benjamin Rush in 1812, it was borrowed from Pinel, the French psychiatrist who had used it to refer to patients with acquired idiocy. Since its introduction, the term has been defined and redefined, each new meaning reflecting the evolution of knowledge concerning the disorders that produce intellectual deterioration.

Today, the most widely used definition of the dementia syndrome is that of the American Psychiatric Association, Diagnostic Statistical Manual (DSM-III R, 1987 and DSM-IV, 1994). (Figure 1)

Figure 1. Definition of Dementia, DSM-IV

Dementia is the development of multiple cognitive deficits manifested by memory impairment and one or more of the following:

- *Aphasia*
- *Apraxia*
- *Agnosia*
- *Disturbance in executive function*

The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning.

Based on the common pattern of cognitive deficits known in 1987, this definition has two limitations. First, in requiring that all demented individuals have **memory impairment** it excludes disorders that spare memory or that present with predominantly behavioral and language disorders. Second, the requirement of social or occupational **disability** renders the definition imprecise and unquantifiable. Thus, patients in minimally demanding circumstances are not considered demented with the same disability that would warrant the diagnosis of dementia in a more demanding situation.

A more updated definition is the one describing dementia as a *syndrome of acquired, persistent intellectual impairment produced by brain dysfunction. This impairment compromises at least three of the following spheres of mental activity: language, memory, visuospatial skills, emotion and cognition (abstraction, calculation, judgment and executive function).*[2]

Like the DSM-IV, this definition is based on evaluation of abilities that are readily testable in the office or that may be quantitated with more extensive neuropsychological testing. The stipulation that intellectual impairment be acquired distinguishes dementia from the congenital mental retardation syndromes and illiteracy. An examiner must be certain that the failed material was previously within the grasp of the patient before considering the diagnosis of dementia. **Persistence** is included to exclude acute

confusional states noted in cases of acute trauma, illness, and metabolic or toxic disorders. Except for a few metabolic or infectious processes that advance rapidly to coma and death, dementing illnesses do not affect all **mental activities** to the same degree. In fact it is the pattern of losses that helps us identify the underlying nature of the dementing disorder.

In common disorders such as AD, both definitions apply equally well. In less common conditions such as the dementia with Lewy bodies and the frontal dementias where memory loss may not be the presenting symptom, the DSM-IV definition loses diagnostic power.

Epidemiology

Dementia is a common disorder in the elderly involving as many as 10% of those over age 65 and 50% of individuals over the age of 85. More specifically, the prevalence of dementia doubles with every five-year increase in age.[3] A public health problem of enormous proportions, the annual cost of managing the most common type, Alzheimer's disease, is estimated to be more than $200 billion in the United States alone.[4, 5]

The incidence and prevalence of the dementia syndrome vary according to the definition of dementia employed. For instance, the age-specific incidence of dementia in the 65 to 69 year age group was reported as 0.07% per year in the Framingham study in which only moderate to severe dementias were included. It was almost ten times higher or .6% per year in the East Boston study which included mild cases and did not require functional impairment to be present. Both in Framingham and in East Boston, the incidence for the age group 85 and older was fourteen times higher than in the younger group.

Types of dementia

Exact determination of the frequency of different types of dementia also varies according to diagnostic criteria and cohort. The diagnostic formulations of dementia that are most widely used are the clinical definitions contained in the Diagnostic and Statistical Manual, 3rd and 4th editions (DSM-IIIR or the DSM-IV) and the clinical criteria contained in the National Institute of Neurologic, Communicative Disorders and Stroke-AD and Related Disorders Association (NINCDS-ADRDA) Work Group. (Figure 2)

Figure 2. Criteria for clinical diagnosis of Alzheimer's disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

- dementia established by clinical examination and documented by Mini-Mental Test,[1] Blessed Dementia Scale,[2] or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- 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 pro-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 perception (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:
  - normal lumbar puncture as evaluated by standard techniques,
  - normal pattern or nonspecific 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:

- plateau in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional or physical outbursts with 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 diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

- sudden, apoplectic onset;
- 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.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

- may be made on the basis of the dementia syndrome in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

- the clinical criteria for probable Alzheimer's disease and
- histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

- familial occurrence;
- onset before age of 65;
- presence of trisomy-21; and
- coexistence of other relevant conditions such as Parkinson's disease.

G McKhann, D Drachman, M Folstein, R Katzman, D Price, and EM Stadlan Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease Neurology 1984 34: 939-944.

First formulated in 1984 to differentiate between AD and vascular dementias, they do not take into account the growing body of knowledge about neurodegenerative disorders and their clinicopathological features.

In 1998 in the New England Journal of Medicine, Mayeux et al[6] reported on the correspondence between the clinical and the pathological diagnoses of patients with dementia who had been evaluated at all 26 Alzheimer's Disease Research Centers.

Mean age of patients at death was 77. Using the NINCDS-ADRDA criteria, of 2188 individuals with the dementia syndrome, 1833 were given a clinical diagnosis of AD. Diagnosis was confirmed pathologically in 1770 patients at autopsy for an overall sensitivity of 93%. Four hundred and eighteen patients out of the 2188 did not have AD, including 190 patients who had been given a pre-mortem diagnosis of AD, for a low specificity of 55%. The specificity of these clinical criteria worsened with age, dropping to 23 percent in those over the age of 79.

If one goes beyond the Alzheimer's expert centers into the community, vascular disease becomes an equally common correlate of the clinical dementia syndrome, especially in older cohorts. Earlier this year in the Lancet, the neuropathology group of the United Kingdom's Medical Research Council Cognitive Function and Aging Study reported on the pathological findings of 209 individuals that had come to necropsy. The median age at death was 85.5 years. They found that cerebrovascular (78%) and Alzheimer-type pathology (70%) were common in all subjects. Clinical dementia was present in 100 (48%) subjects, of whom 64% met clinical criteria for probable AD. However, 33% of the 109 non-demented individuals had equivalent densities of neocortical plaques and tangles. Vascular lesions were equally common in both demented and non-demented groups although the proportion with multiple vascular pathologies was higher in the demented group.[7] Authors concluded that most patients had mixed disease therefore challenging "conventional diagnostic criteria in this setting".

In these and in other studies featuring younger patients, autopsy findings of clinically demented subjects who do not have predominant Alzheimer's disease are distributed primarily among **vascular disease, Lewy body disease and frontotemporal gliosis.**[8] (Figure 3) As a group, today these are known as the non-AD dementias.

Figure 3. Causes of Dementia in Adults by Etiologic Category*

Neurodegenerative Disorders
Alzheimer's disease†
Down syndrome†
Parkinson's disease†
Dementia with Lewy Bodies
Frontotemporal dementias
  Pick's disease†
  Frontal lobe dementia
  Frontal lobe dementia associated with motor neuron disease
  Progressive nonfluent aphasia
  Semantic dementia
Tauopathies‡
  Frontotemporal dementia with parkinsonism linked to chromosome 17†
  Familial progressive subcortical gliosis†
  Familial multiple system tauopathy†
  Corticobasal degeneration
  Progressive supranuclear palsy
Multiple system atrophy
Huntington's disease†
Mesolimbocortical dementia
Amyotrophic lateral sclerosis-parkinsonism-dementia complex
Argyrophilic brain disease

Cerebrovascular Disorders
Vascular dementia
  Multiinfarct dementia
  Subacute arteriosclerotic encephalopathy (Binswanger's disease)
  Amyloid angiopathy
    Hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCWA-D) †
  Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leuko-encephalopathy (CADASIL) †
Hippocampal sclerosis
Vasculitis
Subarachnoid hemorrhage
Neurocognitive disorders associated with cardiac bypass

Prion-Associated Disorders
Creutzfeldt-Jakob disease†
  Variant Creutzfeldt-Jakob disease (linked to bovine spongiform encephalopathy)
Gerstmann-Sträussler-Scheinker disease†
Fatal familial insomnia†

Neurogenetic Disorders†
Spinocerebellar ataxias
Dentatorubral-pallidoluysian atrophy
Hallervorden-Spatz disease
Gangliosidoses
Kufs disease (adult neuronal ceroid lipofuscinosis)

Neurogenetic Disorders (con't.)
Machad-Joseph disease (Azorean disease)
Lafora's disease
Mitochondrial encephalopathies
Myotonic dystrophy
Porphyrias
Hepatolenticular degeneration (Wilson's disease)

Infectious Disorders
Meningitis (e.g., tuberculosis)
Encephalitis (including herpes simplex)
  Human immunodeficiency virus
  Lyme disease
Progressive multifocal leukoencephalopathy
Neurosyphilis
Whipple's disease

Toxic/Metabolic Encephalopathies
Systemic
  Thyroid, parathyroid, pituitary, adrenal, liver, pulmonary, pancreas, kidney, or blood disorders
  Sarcoidosis
  Sjögren's syndrome
  Systemic lupus erythematosus
  Hyperlipidemia
  Nutritional deficiencies (vitamins B_1, B_{12})
  Fluid and electrolyte abnormalities
  Hypoglycemia
  Hypoxic/ischemic disorders
Toxic
  Drugs
  Alcohol
  Industrial agents
  Heavy metals (Pb, Hg, Mn, Ar, Th, Al, Sn, Bi)
  Carbon Monoxide

Miscellaneous
Demyelinating
  Multiple sclerosis
Post-traumatic
  Subdural hematoma
  Dementia pugilistica
Neoplasm
  Paraneoplastic syndromes (limbic encephalitis)
  Direct effects of primary and metastatic tumors
Hydrocephalus
Affective disorders (depression)

**Partial list. Some disorders (e.g., hippocampal sclerosis) are assigned arbitrarily to an etiologic category.*
†Linked to genetic abnormalities.
‡Other disorders, including Pick's disease, also can be considered as tauopathies.

Modified from Friedland. Alzheimer's disease: Clinical features and differential diagnosis. Neurology 42:545-551, 1993.

Vascular Disease

After Alzheimer's disease, cerebrovascular disease is the second most common cause of dementia. In population-based cohorts, some vascular pathology exists in 29-78% of dementia cases coming to autopsy. Pure vascular disease, VD accounts for dementia

in only 10% of cases. As in Alzheimer's disease, incidence and prevalence of vascular disease increases with age. Also increasing with age is the likelihood that both conditions will be present concurrently. Patients with underlying AD are more likely to become demented after a vascular event[9] or in the face of the more chronic changes associated to hypertension[10], coronary artery disease[11], atrial fibrillation and diabetes.[12]

Cognitive function and the prevalence of dementia were determined clinically for participants in the Nun Study who later died. Of the 102 participants, 45 met clinical criteria for dementia. Upon autopsy, 61 met neuropathological criteria for AD, 41 did not. Among subjects meeting criteria for AD, those with a brain infarct were more likely to have a clinical diagnosis of dementia than those without infarcts. The prevalence of dementia was 75% for those with a large infarct in the lobes of the neocortex and 57% for those without infarcts. Among members of the group that did not meet the neuropathological criteria for AD, those with and those without a brain infarct had similar cognitive abilities.[13]

The clinical manifestations of vascular disease or ischemic brain injury of the brain depend to a large degree on location. Focal neurological deficits such as **weakness, visual fields cuts** and **asymmetric reflexes** are frequent but may be absent if the injury occurs entirely within the non-motor-sensory networks. **Extrapyramidal signs** are associated with lesions in the basal ganglia. **Gait disturbance** ("lower body parkinsonism") may be seen with basal ganglia or deep white matter lesions.[14] Because the frontal-subcortical circuit structures are very vulnerable to perfusion changes, individuals with vascular brain injury are more likely to be **apathetic** and **depressed** than agitated or psychotic.[15] In general, **memory impairment** is more variable, less severe and more likely to respond to cueing than in AD.[16] With small artery disease, diminished executive function is characteristic. With involvement of larger arteries, **strokes, aphasia, apraxia,** and **neglect** are seen.

Because of the difficulty in correlating varying clinical and varying pathological findings, research guidelines developed to identify patients with dementia due to vascular disease, have low predictive values even with the inclusion of the results of imaging testing.[17] To date the most useful of all is the Hachinski Ischemic Score (Figure 4), which although lacking imaging criteria, remains the most sensitive way of differentiating patients with dementia due to vascular disease from AD.[18]

Fig. 4. Modified Hachinski Ischemic Score*

	Absent	Present
Abrupt onset	0	2
Stepwise deterioration	0	1
Somatic complaints	0	1
Emotional incontinence	0	1
History or presence of hypertension	0	1
History of strokes	0	2
Focal neurologic signs	0	2
Focal neurologic symptoms	0	2

* A score that is ≥ 4 is suggestive of vascular dementia.
(From Rosen et al, Ann. Neurol. 7:487, 1980)

The focus on the label of "vascular dementia" distracts from the fact that preceding it is an array of subclinical cognitive impairments that may be preventable and perhaps, reversible. Both the Framingham and the Honolulu Heart Study[19] have provided evidence of an association between high mid-life systolic pressures and cognitive decline later in life. In the Framingham study, this association was more apparent in those left untreated. In 2000, a longitudinal study using the Medical Research Council database in Britain[20] found that among hypertensives, reduction in systolic blood pressure could protect against cognitive decline. (Antihypertensives used were beta-blockers and thiazides.) More recently, at the annual meeting of the American Society of Hypertension, UCLA researchers reported on the results of a prospective randomized uncontrolled trial of 66 patients between the ages of 65 and 80 with previously untreated or poorly controlled hypertension. All had multiple white matter infarcts on MRI, cognitive dysfunction defined by neuropsychological testing and absence of stroke. Patients were randomized to felodipine or enalapril. Maximum improvement in cognition lead by executive function occurred at 12 weeks and persisted as long as the study lasted. PET scans done concurrently showed improved glucose metabolism as well.[21]

Dementia with Lewy bodies

In 1817, James Parkinson wrote the original essay describing the disease that today bears his name. Although the clinical description of shaking palsy is today as accurate as it was then, his claim that intellect was spared by the degenerative condition is today, invalid. For, with the advent of relatively effective treatments for the early phases of the disease, the later aspects of the condition are now better understood. We know now that 50% of patients with Parkinson's disease, PD will develop clinical dementia. Recently, the development of new -syncline stains has allowed the detection of PD's pathognomonic Lewy bodies in the cortical neurons of up to 25% of all brains of patients carrying clinical diagnoses of dementia. Patients with this histological presentation of dementia and some Parkinson's-like features are now described as having dementia with Lewy bodies or, DLB.

The clinical syndrome of dementia with Lewy bodies has been defined as *the presence of dementia with relative sparing of memory, gait and balance disorder, prominent hallucinations and delusions, sensitivity to antipsychotics and fluctuations in attention.*

In 1996, a group of experts proposed consensus criteria based on these and other findings. (Figure 5) However, reliability of the diagnoses based on the criteria is low, especially in the very old.[22]

Figure 5. Consensus Criteria for the Clinical Diagnosis of Probable and Possible Dementia with Lewy Bodies

1. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontalsubcortical skills and visuospatial ability may be especially prominent.

2. Two of the following core features are essential for a diagnosis of *probable* DLB, one is essential for *possible* DLB.
   (a) Fluctuating cognition with pronounced variations in attention and alertness
   (b) Recurrent visual hallucinations that are typically well formed and detailed
   (c) Spontaneous motor features of parkinsonism

3. Features supportive of the diagnosis are
   (a) Repeated falls
   (b) Syncope
   (c) Transient loss of consciousness
   (d) Neuroleptic sensitivity
   (e) Systematized delusions
   (f) Hallucinations in other modalities

   (Depression and REM sleep behavior disorder have been suggested as additional supportive features.)

4. A diagnosis of DLB is less likely in the presence of
   (a) Stroke disease, evident as focal neurologic signs or on brain imaging
   (b) Evidence on physical examination and investigation of any physical illness, or other brain disorder, sufficient to account for the clinical picture.

From McKeith IG, Ballard CG, Perry RH, et al: Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology

In DLB, there is **relative sparing of memory function** that is explained by the smaller burden of pathology in the entorrhinal cortex compared to what is seen in early classical AD. DLB patients are more impaired than AD patients on various tests of attention. **Fluctuation in cognitive performance** is present in 58% of cases and is observed at some point in the course of the disease in 75%. This fluctuation is an important feature in the diagnosis. Excessive daytime drowsiness with transient confusion on waking occurs commonly. These episodes may last from a few seconds to several hours and often lead to the diagnosis of a transient ischemic attack.

Neuropsychiatric features other than fluctuating cognitive impairment are common in DLB and patients are therefore more likely to be seen in psychiatric clinics or emergency rooms. **Visual hallucinations occur** in 33% of cases at the time of presentation. Hallucinations are well formed, often detailed and of animated figures, which provoke varying emotional responses from fear to amusement and indifference, usually with some insight into the unreality of the episode once it is over. It is the persistence of visual hallucinations in DLB that helps to distinguish this disorder from the episodic disturbances that occur transiently in dementias of other etiologies or in cases of acute delirium. **Delusions** are present in about 50% of patients. Unlike the

poorly formed, mundane ideas in AD that are based on forgetfulness and confabulation, they are often bizarre, fixed and complex. Also seen are **auditory, olfactory and tactile hallucinations** that can lead to the diagnosis of late-onset psychosis. Depressive symptoms are more common in DLB than in AD and similar to the frequency reported in PD.[23]

Extra pyramidal syndrome features are present in 24% of pathologically confirmed DLB. Because of this, one of the hallmarks of early DLB is **increased sensitivity to antipsychotics**. Findings such as masked fascies, stooped posture and festinant gait are as common in DLB patients as they are in PD. However, there is no resting tremor and to date, authors report equivocal improvement with levodopa. The relative high frequency of postural instability in early DLB in comparison with PD is another distinguishing feature and is likely to represent more extensive brain stem involvement. Contrastingly, there is no motor involvement in the early and middle stages of AD.

By themselves, cognitive tests do not reliably differentiate DLB from AD or VD. Similarly, even though patients with DLB show less temporal lobe atrophy on MRI than do patients with AD, neuroimaging is not helpful in distinguishing among dementia subtypes.[24]

The significant clinical and neuropathological overlap between DLB, PD and Alzheimer's has led some authors to suggest that it may represent common pathogenetic mechanisms.[25] Most cases of AD, PD and DLB are sporadic; 10% or less are inherited. Although age is an important risk factor, the factors that initiate neurodegeneration, causing aberrant protein production and sustaining their accumulation, are unknown.[26]

Frontotemporal dementias

The frontotemporal dementias, FTD comprise a group of disorders with a common, basic degenerative pattern such as that seen in frontal lobe degeneration of the non-Alzheimer type, progressive and semantic aphasia and Pick's disease, which constitutes only minor part of the FTD case material. In a group of individuals with early onset dementia, the FTD's constitute up to 10% of the neuropathological diagnoses.[27]

In all of the FTD's there is mild to moderate frontal lobe atrophy. Microscopically, the degenerative process consists of cortical microvacuolation and increase in astrocytes. Neurons show atrophy and there is a striking loss of synapses.. The histopathological pattern is homogenous varying only in terms of distribution and severity. Pick's intracellular inclusion bodies are rare but another feature of Pick's, the balloon cell, is more common. Alzheimer changes are not seen except in the oldest cases and then to a degree compatible with what is expected for age.

Clinical onset is very insidious. Mean age of onset in one post-mortem series was 56±7.6 years (range 45-70 years) and the estimated duration of the disease is 3-17 years. Patients with pure Pick's disease live longer than patients with predominant AD.[28]

Most patients with pathological confirmation of FTD will fulfill the clinical NINCDS-ADRDA criteria for AD.[29] When compared with AD patients, patients with FTD are less disoriented, and have **more difficulty problem solving**. Memory-wise, patients with FTD have **memory impairment** due to retrieval and **organizational problems** due to frontal lobe deficits. **Short-term memory** seems to be relatively spared. When scrutinized more closely, most patients show **lack of concentration**. Unlike AD patients, patients with FTD have relatively **preserved abilities to negotiate the environment.**[30] Like AD, however, **speech is involved early** with initial unrestrained talking and then use of stereotyped comments and set phrases. Progressive reduction in verbal fluency, which may antedate the onset of any other cognitive features, is often greater that that seen in AD.

The initial stage of frontotemporal dementias is also characterized by **changes of personality and behavior and affective symptoms.** (Figure 6) Often, hypochondriasis, schizophrenia, obsessive-compulsive disorder behavior, and affective changes such as depression, anxiety, excessive sentimentality, and suicidal ideations are so pronounced that patients may end up in a psychiatry ER or treated for depression or psychosis long before a diagnosis of dementia is made. **Signs of disinhibition often appear as restlessness, impulsivity, and irritability** and craving for affection and sexual contacts. **Kluver-Bucy syndrome** may present with hyperorality. All of these signs and symptoms take place in patients who have had normal premorbid personalities.

Figure 6. Clinical Diagnostic Features of Frontotemporal Dementia (Abbreviated). Consensus Statement by the Research Groups in Lund and Manchester

Core Diagnostic Features

Behavioral Disorder

Insidious onset and slow progression
Early loss of personal and social awareness
Early loss of insight
Early signs of disinhibition (such as unrestrained sexuality, violent behavior, inappropriate jocularity, restless pacing)
Mental rigidity and inflexibility
Stereotyped and perseverative behavior (wandering, clapping, singing, as well as hoarding of objects and rituals involving hygiene and dressing)
Hyperorality (oral/dietary changes, overeating, food fads, excessive smoking and alcohol consumption, oral exploration of objects)
Distractibility, impulsivity, and impersistence
Utilization behavior (unrestrained exploration/use of objects in the environment)

Affective Symptoms

Depression, anxiety, excessive sentimentality, suicidal ideation, delusion (early and evanescent)
Hypochondriasis, bizarre somatic preoccupation (early and evanescent)
Emotional unconcern and remoteness, lack of empathy
Amimia (inertia, aspontaneity)

Speech Disorder

Progressive reduction and stereotypy of speech
Echolalia and perseveration
Late mutism

Preserved Spatial Skills and Praxis

(Intact abilities to negotiate the environment)

Physical Signs

Early primitive reflexes
Late akinesia, rigidity, and tremor
Early incontinence
Low and labile blood pressure

Investigations

Normal EEG despite clinically evident dementia
Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality
Neuropsychology: profound failure on "frontal lobe" tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder

Supportive Diagnostic Features

Onset before 65
Positive family history or similar disorder in a first-degree relative
Bulbar palsy, muscular weakness and wasting, fasciculations (motor neuron disease)

From "The Human Frontal Lobes" Miller and Cummings, The Guilford Press: New York. 1999.

Many parallels have been drawn between FTD and AD. As with DLB, intracellular deposition of aggregated proteins with cellular disregulation and death seems to underlie the neurodegenerative process.[31] In addition, there are genetic mutations that seem to be responsible for the less common, familial early onset forms of these conditions.[32] What other genetic, environmental or infectious factors produce brain degeneration in such a large number of individuals remains a major mystery.

Evaluation

The purpose of the clinical evaluation process is to identify individuals with the dementia syndrome and specific dementia subtypes.

Dementia is a very expensive but silent epidemic. Although it affects up to 50% of all individuals over the age of 80, 21% of family members, 22% nurses and 25% doctors fail to recognize dementia in the elderly.[33]

Implications of unrecognized dementia are profound. A study of morbidity and disability in the oldest old found that dementia was the most common disabling condition in both men and women.[34] Only by diagnosing dementia can we address issues of reversibility, delay decline and possibly, enhance remaining function. Only in understanding our patients' true cognitive abilities can we improve compliance, reliability or accuracy of symptom reporting, and address patient safety concerns, avoiding victimization and averting family and patient crises.

Dementia evaluation is best done in the outpatient setting following the resolution of acute illness, delirium and the treatment of depression.

Historical information provided by the patient, family members or third party observers such as home nurses or neighbors is the cornerstone of the diagnosis. Do not expect patients themselves to report their impairment but when they do, listen. A recent meta-analysis[35] showed an association in community based population samples between memory complaints and memory impairment after adjustment for depressive symptomatology.

Other clues that a cognitive evaluation is necessary are: recent delirium, transitional living situation, history of Parkinson's, depression, diabetes, and unexplained loss of function. In addition, because undetected dementia is a risk factor for delirium[36,37], many geriatricians recommend that a cognitive screening test be administered as part of the pre-operative evaluation of all individuals over the age of 75.

Among the younger elderly where dementia is present in only 5-10% of patients, warning signs are the presence of vascular disease or motor findings, new, unintentional weight loss or a change in compliance, mood, behavior or personality. In the younger old, difficulty performing familiar job skills or tasks such as driving often go undetected. (Drivers with even mild cognitive impairment have traffic risk equivalent to that of drivers between ages of 16 and 21 or those driving under the influence at a blood alcohol concentration of <0.08.[38])

Once the diagnosis of the dementia syndrome is made, the evaluation should focus on historical and physical exam in pursuit of its etiology. In my discussion of the non-Alzheimer 's dementias, I have reviewed the diagnostic clinical features distinguishing them from Alzheimer's disease. (Figure 8)

Figure 8. Distinguishing features of early dementias

	Memory	Language	Executive Function	Visuospatial	Behavior	Motor Symptoms
Alzheimer's	Early, short term loss>long term; (-) cueing	Poor word list generation	Preceded by memory loss	Early topographic disorientation	Socially appropriate; late agitation; >misidentification	Late
Vascular	Variable; (+) cueing	Aphasia if cortex involved	Variable	Variable	Apathy or depression	Focal findings; mild bradykinesia if basal ganglia involved
DLB	Fluctuating alertness; memory spared	Slower	Spared	Impaired	Hallucinations, bizarre delusions	Worse with antipsychotics; some EPS 50% cases
FTD	Decreased concentration> short term memory loss; (+) cueing	Unrestrained but empty. Aphasia may antedate dementia	Early	Spared	Early disinhibition, hypochondriasis, affective disorders, mania	Infrequent motor neuron disease

Cognitive function evaluation

Many tools are available for the measurement of cognitive function. Insensitive to small changes, they should be interpreted in the context of information already known about the patient and should not override clinical judgment. If results are suspect, it may be useful to refer patient for further testing or, after excluding cognitive stressors such as drugs, depression or thyroid disorders, to repeat the tests after watchful waiting. Barriers to the use of cognitive assessment tools include the time needed to administer the test, having the test at hand, concern that the patient will be offended and concern that the diagnosis of an incurable impairment will upset the patient and family. When examined, most geriatric patients will find the testing helpful. Despite family member reluctance it distresses only 5% of all patients. Following testing, it is paramount that there be linkage between detection, diagnosis and provision of information and services.

The neurocognitive exam

Attention. Before beginning a mental status exam and using any of the cognitive examination tools described below, it is vital that patients' state of arousal, basic attention span and ability to concentrate be tested. By starting here, an examiner will save time, as patients with poor attention spans cannot be expected to perform well on tests of other domains. Arousal is tested by observation. The spectrum of arousal can vary from hyperarousal to normal alertness, to lethargy and somnolence, stupor or coma. Basic attention is best tested with a forward digit span. An intact patient will be able to repeat 7± 2 random single numbers given to him/her in a steady monotone at the rate of one word per second. Ability to concentrate is best tested by tasks such as asking a patient to spell cat, love and world backwards or to reverse the days/week, months/year or ABC's. Attention systems are exquisitely sensitive to delirium from any source. However, even patients with moderate dementia can repeat 5 digits correctly.

Another easy and impressive screening test is the modified "WORLD" test. In it, patients are asked to spell the word backwards and forwards and then reorder its letters in alphabetical sequence.[39]

Memory. Memory testing is included in the Mini-Mental State Exam, which formally tests registration and recent, short-term working memory (three to five word recall in 5-10 minutes). Failure to recall and retrieve these words with cueing points to hippocampal involvement seen in AD; ability to recall after hearing a categorical cue, is suggestive of a non-AD dementia, depression, strokes or perhaps the normal aging process. Remote memory testing is better assessed with historical or life events.

Language. There are three main screening domains: comprehension, fluency and repetition. To test comprehension, test along a spectrum of difficulty, first by pointing, then pointing by description (point to an exit from this room); then asking yes or no questions (are the lights on in this room? Do you put your socks on before your shoes?) and by asking passive (A lion and tiger were fighting, the lion was killed by a tiger, which animal is dead?) or possessive questions (Is my brother's sister a man or woman?).[40] A good test for fluency is asking a patient to name animals in one minute (18±6 is normal) or to make categorical lists such as ten words starting with letter B.

Visuospatial. Visuospatial skills are easily tested by having patient copy a three-dimensional cube or with the less challenging skill of copying the intersecting pentagons that appear in the MMSE.

Executive function. Executive function associates the capacity to perform the elements of a complex task with the orchestration of the task and its actual execution. Patients with impaired executive function behave like 6 year olds: they can zip their zippers, button their buttons, and tie their shoes but they cannot get dressed by themselves. In serving as a parent or assistant, care providers act as surrogate frontal lobes. Executive dysfunction is present in the very old and in patients with disease involving the frontal lobe and its subcortical circuits including uncontrolled hypertension, HIV and diabetes. It is easily measured by the **clock task**.[41] In this test, which has several interpretations, patients are asked to draw the face of a clock with the numbers in it and place the hands at a specified time (11:10 or 1:45). Strengths of this test are that it is simple, quick to administer and always accessible to the clinician.

Multitask cognitive tests. The most commonly used tests in the United States are the Folstein Mini Mental Status Exam, MMSE, the clock drawing and the time and change test. Hierarchical functional abilities are also a useful indirect measure of cognitive abilities.

Developed in 1975 by Susan and Marshall Folstein, the **MMSE** (Figure 7) is the most universally employed test of cognition. The lingua franca for drug trials and dementia research, it is non-specific and non-diagnostic and its results are colored by patients' previous educational experience and native language. Another important problem in using it is a sole evaluation tool is that it includes no measure of executive function.

Figure 7. Mini-Mental State Exam

I. Orientation (Maximum score 10)

Ask "What is today's date?" Then ask specifically for parts omitted: eg. "Can you also tell me what season it is?	Date (eg. January 21)..	1 ___
	Year	2 ___
	Month	3 ___
	Day (eg. Monday)	4 ___
	Season	5 ___
Ask "Can you tell me the name of this hospital?"	Hospital	6 ___
"What floor are we on?"	Floor	7 ___
"What town (or city) are we in?"	Town/City	8 ___
"What county are we in?"	Country	9 ___
"What state are we in?"	State	10 ___

II. Registration (Maximum score 3)

Ask the subject if you may test his/her memory. Then say "ball." "flag," "tree" clearly and slowly, about one second for each. After you have said all 3 words, ask subject to repeat them. This first repetition determines the score (0-3) but keep saying them (up to 6 trials) until the subject can repeat all 3 words. If (s)he does not eventually learn all three, recall cannot be meaningfully tested.	"ball"	11 ___
	"flag"	12 ___
	"tree"	13 ___
	Record number of trials: ____	

III. Attention and calculation (Maximum score 5)

Ask the subject to begin at 100 and count backward by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). Score one point for each correct number.	"93"	14 ___
OR	"86"	15 ___
	"79"	16 ___
	"72"	17 ___
	"63"	18 ___
If the subject cannot or will not perform this task, ask him/her to spell the word "world" backwards (D,L,R,O,W). The score is one point for each correctly placed letter, eg., DLROW = 5, WLORW = 3. Record how the subject spelled "world" backwards: _____ D L R O W	Number of correctly-placed letters	19 ___

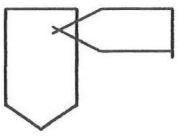
IV. Recall (Maximum score 3)

Ask the subject to recall the three words you previously asked him/her to remember (learned in Registration).	"ball"	20 ___
	"flag"	21 ___
	"tree"	22 ___

V. Language (Maximum score 9)

Naming: Show the subject a wristwatch and ask "What is this?" Repeat for pencil. Score one point for each item named correctly.	Watch	23 ___
	Pencil	24 ___
Repetition: Ask the subject to repeat, "No ifs, ands, or buts." Score one point for correct repetition.	Repetition	25 ___
3-Stage Command: Give the subject a piece of blank paper and say "Take the paper in your right hand, fold it in half and put it on the floor." Score one point for each action performed correctly.	Takes in right hand ..	26 ___
	Folds in half	27 ___
	Puts on floor	28 ___
Reading: On a blank piece of paper, print the sentence, "Close your eyes." in letters large large enough for the subject to see clearly. Ask the subject to read it and do what it says. core correct only if (s)he actually closes his/her eyes.	Closes eyes	29 ___
Writing: Give the subject a blank piece of paper and ask him/her to write a sentence. It is to be written spontaneously. It must contain a subject and verb and make sense. Correct grammar and punctuation are not necessary.	Writes sentence	30 ___

Copying: On a clean piece of paper, draw intersecting pentagons, each side about 1 inch and ask subject to copy it exactly as it is. All 10 angles must be present and two must intersect to score 1 point. Tremor and rotation are ignored, eg.



Score: Add number of correct responses. In section III include items 14-18 or 8tem 19, not both (Maximum total score 30.)

Total Score _____

Indicate subject's level of consciousness: _____ (a) coma, (b) stupor, (c) drowsy, (d) alert

Folstein MR, et al. Mini-Mental State: A practical method of grading the cognitive state of the patient for the clinician. J Psychiatr Res 1975;12:189.

The **Time and Change test** is a simple performance-based measure of the patients' ability to tell time and make change. Validated in both in-patient and out patient settings, it has high specificity (96%) and negative predictive accuracy (93%) and is not

influenced by patients' educational or cultural background. Sensitivity is low in cases of mild dementia.[42] (Figure 9)

Figure 9. Brief description of Time and Change test

***Telling time**: In the telling time task, patients must respond to a clock face set at 11:10. Time to response is measured with a stopwatch. The patient is allowed two tries for a correct response within a 60 second period.*

***Making change task**: In the making change task, three quarters, seven dimes and seven nickels are placed in front of the patient. The patient is cued to give one dollar in change. Response time is measured with a stopwatch. The patient is allowed two tries within a 120 second period.*

Finally, there are **four instrumental activities of daily living** that seem to correlate well with cognitive impairment. They are, in escalating order of skill: ability to independently and correctly use the telephone, ability to transport oneself or use means of transportation independently, ability to take medications independently and ability to handle finances. All of these activities should be carried out entirely without assistance and supervision, a stipulation that is often difficult to ascertain.

Differential diagnosis

What other comorbidities should be screened for in elderly patients undergoing an initial assessment for dementia?

The evaluation of individuals with dementia is often directed toward searching for potentially treatable or remediable causes. In 1988, Clarfield[43] reviewed all cases of reported partially and totally reversed dementias finding that after one year only 3% had totally reversed. Reversible causes were those related to drugs, depression and thyroid disease. Dementias most likely to be reversible were those with shorter duration of symptoms, those where dementia was less severe, those where patients took fewer prescription drugs and those who had less cortical atrophy on CT.

A more recent study reported on results of dementia work ups at Columbia's ADC.[44] In no cases did treatment improve cognition even though some patients were found to have B12 or thyroid abnormalities.

Based on the findings of these and other studies, the American Academy of Neurology recommends the following guidelines for the routine evaluation of the demented patient:

- Complete blood count
- Serum electrolytes
- Glucose, BUN and creatinine
- B12 level
- Liver function tests

- Thyroid function tests
- Depression screening

Vitamin B12. Cyanocobalamin deficiency is common in the elderly.[45] Patients with B12 deficiency have lower cognitive performance scores than non-deficient subjects. Reports on reversal of dementia in patients with B12 deficiency are equivocal at best.

Thyroid function. Hypothyroidism is common in the elderly. Nondemented patients with hypothyroidism have lower mental status test scores than euthyroid individuals. Elevated TSH levels carried an increased risk for dementia in a European population based study.[46] Subclinical hyperthyroidism in the elderly increases the risk for dementia even in those patients with normal T4 levels.[47]

Depression. Prospective studies show that patients with depression and coexistent cognitive impairment are very likely to have an underlying dementia on longitudinal follow-up.[48] Late-life depression also increases the risk for diagnosis of dementia.[49,50] Validated instruments for screening for depression even in the presence of cognitive impairment include the Yesavage Geriatric Depression scale short form.

Tests for syphilis. Within the last twenty years there have been no reported cases of tertiary syphilis as causing dementia in the elderly. Except among high-incidence populations, screening for the disorder in patients with dementia without an increased pretest probability is not indicated.

Biomarkers. There are currently no genetic markers recommended for routine diagnostic purposes. The CSF-14-3-3 protein is useful when CJD is clinically suspected (rapidly progressive dementia, cerebellar ataxia, myoclonus).

Imaging

The American Academy of Neurology has revised its position against recommending neuroimaging for initial diagnostic evaluation of patients with dementia. Structural neuroimaging with a non-contrast CT or MR scan is now deemed appropriate. Despite the recommendation, the evidence for the diagnosis of treatable lesions remains scant.

Patients with the non-AD dementias are more likely to have CT abnormalities. Engel and Gelber[51] found a low rate of CT abnormalities in patients meeting criteria for probable AD. In patients with less common dementia presentations such as onset before age 60, focal signs or symptoms or the presence of gait disturbance, CT abnormalities were found in 52% of patients including infarctions, brains tumors and hydrocephalus.

Neuroimaging is very sensitive to the detection of clinically silent cerebrovascular disease. In one clinicopathological study, ten percent of cerebrovascular findings on imaging were not confirmed on pathology.[52] Although imperfect, structural MRI currently is the most sensitive and specific test for parenchymal brain injury. Both silent and symptomatic complete infarcts are well seen. White matter infarcts are visualized easily; however, incomplete gray matter infarcts often go undetected. When seen, white matter infarcts are a good marker for small artery disease and therefore may identify the brain at risk.[53] Beyond vascular disease and even though they are less specific, findings of brainstem or frontal lobe atrophy may point clinicians to the other non-AD dementias.

Whether CT or MRI should be preferred is an issue that may be settled by practical considerations of cost and accessibility. Computerized tomography is sufficient to rule out reversible causes of dementia[54] and is more specific in the detection of cerebrovascular disease whereas MRI may be more helpful in the differential diagnosis of the types of degenerative dementia. However, direct CT-MR comparisons have not been performed.

Conclusions

- Dementia is a syndrome of acquired persistent intellectual impairment that is part of a cognitive continuum regardless of etiology.

- Its DSM-IV definition and the NINCDS-ADRDA clinical criteria that were developed 17 years ago to distinguish between Alzheimer's and vascular disease favor the diagnosis of AD and do not reflect the current knowledge base.

- Other common causes are vascular disease and the other degenerative dementias: FTD, DLB, and PD. that may share a common etiological pathway with AD.

- Current criteria are specific for diagnosis in younger elderly, but not for the very old. In the very old, the likelihood of overlapping pathology is high.

- At all ages, cognitive changes are aggravated by medication, depression and disease and predict delirium and disability. The goal of evaluation is to identify the individual dementia syndrome and to treat elements of reversibility in the hope of delaying disability and maximizing function.

- There are currently no biomarkers recommended for routine diagnosis of dementia.

- Screening for depression, B12 deficiency and thyroid disease should be performed in all patients with cognitive impairment. Screening for syphilis is not justified unless clinical suspicion for neurosyphilis is present. The CSF-14-3-3

protein is useful for the diagnosis of Creutzfeldt-Jakob disease in patients with a consistent clinical syndrome

- Structural neuroimaging with either a non-contrast CT or MRI in the initial evaluation of dementia is appropriate. Because of insufficient data on validity, no other imaging procedure is recommended.

Finally, the diagnosis of the dementia syndrome regardless of etiology, management and treatment strategy, should not take place in a vacuum. Provision of information and support services for both patients and their beleaguered caregivers should always follow.

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