The Clinical Problem of Symptomatic Alzheimer Disease and Mild Cognitive Impairment

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Alzheimer disease (AD) is the most common cause of dementia in the elderly. Clinicopathological studies support the presence of a long preclinical phase of the disease, with the initial deposition of AD pathology estimated to begin approximately 10–15 years prior to the onset of clinical symptoms. The hallmark clinical phenotype of AD is a gradual and progressive decline in two or more cognitive domains, most commonly involving episodic memory and executive functions, that is sufficient to cause social or occupational impairment. Current diagnostic criteria can accurately identify AD in the majority of cases. As disease-modifying therapies are being developed, there is growing interest in the identification of individuals in the earliest symptomatic, as well as presymptomatic, stages of disease, because it is in this population that such therapies may have the greatest chance of success. The use of informant-based methods to establish cognitive and functional decline of an individual from previously attained levels of performance best allows for the identification of individuals in the very mildest stages of cognitive impairment.

Alzheimer disease (AD) is by far the most common cause of dementia in the United States, accounting for over 70% of dementia cases in individuals ≥ 70 years of age (Alzheimer's Association 2011). The incidence of AD increases exponentially with age, and doubles every 5 years after the age of 65 (Kukull et al. 2002).

Estimates from the Alzheimer's Association in 2011 indicate that over 5.4 million people in the United States have AD, including 5.2 million

people 65 years of age or older. With the increasing age of the U.S. population, it is estimated that this number will increase by 50%—with over 7.7 million people in that age range affected by AD—by the year 2030, and will almost triple to 11–16 million by the year 2050. AD is the leading cause of nursing home placement, and a major economic health burden with costs estimated at $140 billion in healthcare, nursing home placement, and lost wages and productivity for family members and caregivers. In the

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absence of effective disease-modifying therapies or prevention strategies for AD, it is likely that the health, social, and economic burdens of AD will increase substantially in the next 10–20 years.

AD is the sixth-highest cause of death across all ages in the United States, and the fifth-highest cause of death for those 65 years of age or older (Alzheimer's Association 2011). Unlike most other major causes of mortality in the elderly, deaths from AD have continued to rise over the last decade; an increase of 66% in deaths owing to AD was reported in the period 2000–2008. As AD is often under-recognized as a cause of death, it is possible that increased mortality rates owing to AD may even be higher than previously reported.

Significant advances in our understanding of the clinical, psychometric, neuropathological, genetic, and biological characteristics of AD have been made since Alois Alzheimer presented the first case of "presenile dementia," later identified by Kraeplin as AD, in 1906 (Alzheimer et al. 1987). This article reviews the clinical presentation, diagnostic criteria, and differential diagnosis of AD with particular focus on its earliest symptomatic stages. Individuals with early stages of AD pathology are the most likely to benefit from disease-modifying therapies should they become available (Tarawneh and Holtzman 2009). Therefore, the ability of clinicians to accurately detect AD in the earliest symptomatic (or even presymptomatic) stages, and to reliably differentiate AD from other causes of dementia, will likely have major therapeutic and prognostic implications in the future.

HEALTHY COGNITIVE AGING

Several cognitive changes are associated with healthy nondemented aging. The speed of mental processing (Birren and Fisher 1995), simple and choice reaction times (Botwinick and Thompson 1968), and perception times (Walsh et al. 1979) are slowed in the elderly compared with their younger counterparts, and may represent the cognitive functions that most clearly decline with age. While these changes may result

in pervasive deficits in neuropsychological testing (Park et al. 1996), in the absence of a dementing illness, they do not appear to be functionally significant.

Short-term memory loss (exemplified by free recall of a list of words or stories; Gilbert and Levee 1971; Crook and West 1990), with relative preservation of immediate (Blum et al. 1970; Drachman and Leavitt 1972) and long-term memory (Luszcz and Bryan 1999) has been reported in healthy elderly as early as the sixth decade. Memory decline in early AD, as opposed to what occurs with normal aging, represents a consistent and progressive change from the individual's prior abilities, and often results in mild impairment in daily functions (Morris 1993). On the other hand, the "benign" forgetfulness of healthy aging is typically mild, inconsistent, and not associated with impairment in daily activities. In contrast to the amnestic-type memory impairment seen in AD, normal aging is associated with a retrieval deficit type of impairment that responds well to clues and multiple-choice questions (Farlow 2007).

Some decline in verbal fluency and difficulty with naming may begin to appear in the seventh or eighth decades, respectively (Albert et al. 1988). However, most language functions such as phonological characteristics, lexical decisions (Howard et al. 1981), and syntactic knowledge (Obler et al. 1985) remain intact with age. Sustained and selective attention is preserved well into the eighth or ninth decade (Albert 1994). Language difficulty beyond mild naming difficulty or marked attention deficits should alert to the possibility of an underlying pathology. A decline in working memory (i.e., the ability to simultaneously store and process information; Babcock and Salthouse 1990) and executive functions (Parkin and Walter 1992; Troyer et al. 1994) may be associated with normal aging. Insight, social engagement, and visuospatial functions are generally retained in healthy elderly (Farlow 2007).

It is a common notion that substantial cognitive changes may occur with healthy aging. However, some of the previous studies attributing cognitive changes to age may have

been inadvertently contaminated by individuals with unrecognized mildly symptomatic or presymptomatic dementia (Howieson et al. 1993). Longitudinal studies of healthy elderly populations who have been carefully assessed to avoid inclusion of those with underlying presymptomatic pathology generally demonstrate a largely flat trajectory with stable cognitive performance well into the ninth decade of life (Howieson et al. 1993; Rubin et al. 1998). The main clinical distinction between cognitive changes of aging and those of underlying dementia is that, in the absence of an underlying pathology, the cognitive changes of aging are benign and relatively static, whereas they are progressive and associated with functional impairment in dementia. Healthy elderly retain the ability to use compensatory strategies (e.g., keeping lists and calendars) and are capable of learning and adaption skills (e.g., as evidenced by practice effects on repeated neuropsychological testing and acclimation to the testing environment), which potentially contribute to their stable cognitive performance over time.

DEFINITION OF DEMENTIA

In general terms, dementia can be described as an acquired syndrome of impaired cognition produced by brain dysfunction. From a practical perspective, dementia is characterized by a decline from a previously established level of cognitive and functional performance of an individual that is sufficient to interfere with daily activities. There are two commonly used sets of criteria for the clinical diagnosis of dementia. The National Institute on Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS/ADRDA) criteria for AD describe a gradual and progressive decline in two or more cognitive domains that is confirmed by abnormalities on clinical and neuropsychological testing, and is associated with impairment in social or occupational functions (Table 1; McKhann et al. 1984). The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for dementia (Table 2; American Psychiatric

Association 1994, 2000) are comparable to those proposed by the NINCDS/ADRDA, and include insidious and progressive decline in memory and at least one more cognitive domain that results in social and occupational impairment.

DETECTION OF DEMENTIA

As described previously, the clinical diagnosis of dementia generally relies on the demonstration of measurable deficits in two or more cognitive domains. These deficits have traditionally been measured by the comparison of an individual's cognitive performance with that of a "norm" of nondemented individuals matched for age, gender, and education. This approach, therefore, represents an interindividual comparison of psychometric performance and does not determine whether the impaired performance represents a decline for that individual from their previously attained level of cognitive performance. Inherent cultural, ethnic, and educational biases in the test measures (Doraiswamy et al. 1995; Manly et al. 1998), and the insensitivity or "ceiling effect" of many measures for mild impairment, may limit the ability of neuropsychological testing to detect very early stages of dementia. Furthermore, because putatively normal samples are likely to be contaminated by individuals with presymptomatic AD (Sliwinski et al. 1996), the cut-points may be too permissive and fail to capture some individuals in the early stages of disease, further blurring the distinction between very mild impairment and healthy aging. By relying on intraindividual cognitive decline rather than interindividual comparisons of psychometric performance, it may be possible to identify individuals at even earlier stages of cognitive impairment.

ALZHEIMER DISEASE

The NINCDS/ADRDA criteria classify AD into "probable," "possible," or "definite" (Table 1; McKhann et al. 1984), and have been widely used in both clinical trials and research settings. The NINCDS/ADRDA criteria for "probable" AD and *DSM-IV* criteria both have acceptable

Table 1. National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for Alzheimer disease

I. Criteria for the clinical diagnosis of *probable* Alzheimer disease
Dementia established by clinical examination and documented by the Mini-Mental State Examination, 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
Absence of systemic disorders or other brain diseases that could account for the dementia

II. A *probable* Alzheimer disease diagnosis 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
Laboratory results of normal lumbar puncture as evaluated by standard techniques
Normal pattern or nonspecific changes in EEG, such as increased slow-wave activity
Evidence of cerebral atrophy on computed tomography (CT) with progression documented by serial observation

III. Other clinical features consistent with the diagnosis of *probable* Alzheimer 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, 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 disorders
Seizures in advanced disease
CT normal for age

IV. Features that make the diagnosis of *probable* Alzheimer 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
Seizures or gait disturbances at the onset or very early in the course of the illness

V. Criteria for *possible* Alzheimer disease may be made with
Dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in onset, in the presentation, or in clinical course
Presence of second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia
A single, gradually progressive severe cognitive deficit identified in the absence of other identifiable causes

VI. Criteria for diagnosis of *definite* Alzheimer disease are
The clinical criteria for probable Alzheimer disease
Histopathologic evidence obtained from a biopsy or autopsy

Clinical Diagnosis of AD: Report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. (Modified from KcKhann et al. 1984; reprinted, with permission, from Lippincott Williams & Wilkins © 1984.)

sensitivity (81%) and specificity (70%) for AD (Knopman et al. 2001), and are associated with neuropathological confirmation rates of 85% or greater (Berg et al. 1998).

As our knowledge of the clinical and biological aspects of AD has grown vastly over the last few decades, revisions to the 1984 criteria were recently proposed (McKhann et al. 2011). The focus of these revisions was to incorporate modern clinical, imaging, and laboratory assessments into the original criteria, with assurance of the flexibility of these criteria for

Table 2. Diagnostic and Statistical Manual of Mental Disorders

Multiple cognitive deficits
Criterion A
A1. Memory impairment
A2. One or more of the following:
    Aphasia (language disturbance)
    Apraxia (impaired motor activity)
    Agnosia (impaired recognition)
    Disturbed executive function
      (planning, organization, etc.)

Criterion B
Cognitive deficits in criteria A1 and A2 each cause
  impairment in social or occupational functioning
Are not due to a CNS disease
Are not due to a medical disorder
Do not occur solely during the course of delirium

Criterion C
Gradual and continued cognitive decline

Criterion D
Other systemic neurologic and psychiatric illnesses
  should be eliminated

Criterion E
Alzheimer disease should not be diagnosed in the
  presence of delirium

Data from the American Psychiatric Association 2000.

use by both general healthcare providers, who may not have access to neuropsychological testing, advanced imaging, or cerebrospinal fluid (CSF) testing, as well as specialized research investigators to whom such measures may be available.

Revisions to the core clinical criteria for "probable" AD include the description of dementia as a decline from an individual's previous level of functioning that is of sufficient degree to interfere with work or usual activities, the recognition of nonamnestic presentations of AD, and the acknowledgment of the distinguishing features of other causes of dementia that may be encountered in the elderly population. Additionally, the revised criteria suggest that, in individuals who meet clinical criteria for "probable" AD, biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is underlying AD pathology (referred to as "probable AD dementia with evidence of the AD pathophysiological

process"). While biomarkers may assist in the diagnosis of AD in clinical trials and investigational studies, biomarker testing is not routinely recommended for the diagnosis of AD in the clinical setting (Knopman et al. 2001). Limitations include the lack of standardization of quantitative analyses across different centers, limited availability in community settings, and the need for further validation of diagnostic algorithms that incorporate biomarkers in the diagnosis of AD (McKhann et al. 2011).

In this context, the diagnosis of AD remains a fundamentally clinical diagnosis. Obtaining a detailed history from the patient *and* from a well-acquainted informant of the onset, course, progression, and characteristics of cognitive and functional decline is of primary importance. Other components of the clinical assessment include the mental state exam, a functional and behavioral assessment, general physical and neurological exam, and (optionally) neuropsychological testing. Risk factors should be determined, including previous vascular disease, hypertension, diabetes mellitus, lipid disorders, head trauma, and/or family history of dementia. Clinical features that distinguish AD from other dementia etiologies should be carefully sought. Concomitant medical, neurological, or psychiatric illness and the use of medications with possible effect on cognitive performance should be documented.

A wide variety of clinical measures are available for the evaluation of cognitive and behavioral performance of individuals with suspected dementia (Table 3). These measures provide useful information to aid in clinical diagnosis and monitoring of disease progression. In general, mental status testing includes level of alertness, attention, orientation, short-term and remote memory, language, visuospatial functioning, calculation, and executive functioning or judgment. The Mini-Mental State Exam (Folstein et al. 1975) and Clock Drawing (Brodaty and Moore 1997) are among the most widely used screening tools in clinical practice. Another brief instrument that may be useful to screen for dementia in the office consists of an informant questionnaire of eight items (Table 4; Galvin et al. 2005); however, its

Table 3. Selected clinical measures in evaluating patients suspected of dementia

Brief cognitive screening tests (bedside mental status examination)

Short Blessed Test (SBT)	Six-item weighted version of the Information–Memory–Concentration Test; usually completed in 5 min; good correlation with AD pathology
Mini-Mental Status Examination (MMSE)	Nineteen items measuring orientation, memory, concentration, language, and praxis; most widely used screening test
Seven-minute screen	Four tests (orientation, memory, clock drawing, and verbal fluency)
General Practitioner Assessment of Cognition (GPCOG)	A six-item screening test similar to the SBT, a clock drawing, and a five-item informant questionnaire
Clock Drawing	Single test measuring multiple cognitive domains; requires minimal training; multiple scoring systems with proven validity

Clinical staging instruments (global measures of dementia severity)

Clinical Dementia Rating (CDR)	Five-point ordinal scale; assesses cognitive ability by a structured informant interview and patient assessment in six domains with descriptors for each level of severity
Global Deterioration Scale (GDS)	Seven-point ordinal scale; has global descriptors for each level of severity
Cambridge Mental Disorders of the Elderly Examination	Five-point ordinal scale; assesses cognitive ability by a structured informant interview and patient testing; includes the Dementia Scale and the Mini-Mental Stage, and has global descriptors for each level of severity

Behavioral scales (noncognitive disturbances, e.g., affective disorders, personality or psychomotor changes, psychoses)

Geriatric Depression Scale (GDS)	Assesses 30 items (either self-rated or observer-rated) of depressive items in older adults
Agitation Inventory	A caregiver questionnaire that assesses the frequency of 29 behaviors in three categories: physically aggressive, physically nonaggressive, and verbally disruptive
Neuropsychiatric Inventory (NPI)	Assesses 10 behavioral disturbances for frequency and severity by an informant interview
Consortium to Establish a Registry for Alzheimer Disease (CERAD) Behavior Rating Scale for Dementia	Combination of items from other instruments; informant-based assessment of behavioral and psychiatric symptoms in patients with dementia

Modified from Morris et al. 2006.

diagnostic utility in clinical settings remains to be fully evaluated. Neuropsychological testing is not routinely required in clinical practice but may be helpful in delineating dementia profiles and monitoring cognitive decline in clinical trials. Most neuropsychological batteries for AD employ tests for episodic memory (e.g., delayed recall tasks) and executive function (e.g., attention-switching) among other cognitive domains.

The practice parameter guidelines of the American Academy of Neurology for the diagnosis of dementia recommend screening for hypothyroidism, vitamin B12 deficiency, and depression in the routine assessment of individuals with suspected dementia, as these comorbidities may potentially contribute to the cognitive impairment of AD (Knopman et al. 2001). Structural neuroimaging with noncontrast computed tomography (CT)

Table 4. AD8: Brief informant interview to differentiate aging and dementia: Report only a change caused by memory and thinking difficulties

Is there repetition of questions, stories, or statements?
Are appointments forgotten?
Is there poor judgment (e.g., buys inappropriate items, poor driving decisions)?
Is there difficulty with financial affairs (e.g., paying bills, balancing checkbook)?
Is there difficulty in learning or operating appliances (e.g., television remote control, microwave oven)?
Is the correct month or year forgotten?
Is there decreased interest in hobbies and usual activities?
Is there overall a problem with thinking and/or memory?

Data adapted from Galvin et al. 2005; reprinted, with permission, from Lippincott Williams & Wilkins © 2005.

or magnetic resonance imaging (MRI) to rule out undetected pathology (such as hydrocephalus, neoplasms, subdural hematoma, or cerebrovascular disease) should also be included in the initial assessment. [18]Fluoro-deoxyglucose–positron emission tomography (FDG-PET) may have promise as an adjunct to the clinical diagnosis of AD (Hoffman et al. 2000); however, further studies are needed to evaluate its diagnostic utility beyond that of a competent clinical diagnosis. In the particular cases when the differentiation between AD and frontotemporal dementia (FTD) on clinical grounds alone is problematic, the detection of bilateral frontal hypoperfusion with relative sparing of the posterior cortex using single-photon emission computed tomography (Tc^{99}-HMPAO-SPECT; Pickut et al. 1997) or hypometabolism of these regions on PET (Ishii et al. 1998) in FTD may assist in making the distinction. It is controversial whether the determination of the Apolipoprotein E (*APOE*) genotype in a patient with dementia improves diagnostic specificity to a sufficient degree to be clinically useful (Mayeux et al. 1998; Farlow 2007). Until disease-modifying treatments are available, there is currently no evidence to support the use of genetic analyses, CSF analyses, or other putative CSF biomarkers in the routine diagnosis of AD (Frank et al. 2003).

CLINICAL PHENOMENOLOGY OF AD

The core clinical features of AD include gradual and progressive decline in memory, executive function, and ability to perform daily activities. However, there is variability among individuals in age of onset, family history, and the appearance of noncognitive symptoms such as behavioral or motor abnormalities. Rates of disease progression and survival also vary considerably among different individuals.

Age is the most important risk factor for AD (Farlow 2007). The onset of clinical symptoms is uncommon before the age of 50, although rare cases in individuals in their twenties or thirties have been reported (Portet et al. 2003). The prevalence of AD increases with age from an estimated prevalence of 1%–2% of the population by the age of 65, to 15% by the age of 75, and 35%–50% by the age of 85 (Hebert et al. 2003). A positive family history is found in approximately 20% of the cases. Several genetic mutations have been identified in early-onset autosomal dominant familial AD, involving genes for amyloid precursor protein (*APP*), presenilin-1 (*PS-1*), and presenilin-2 (*PS-2*) (Waring and Rosenberg 2008). Together, these mutations cause less than 1% of all cases of AD (Blennow et al. 2006), and less than 10% of cases in individuals with a positive family history of AD who are under the age of 65.

Therefore, in most cases, AD is a sporadic, age-dependent, late-onset disease (Hebert et al. 2003). The major genetic risk associated with most cases of sporadic late-onset AD is conferred by a positive family history of dementia (Silverman et al. 1994) and by the *APOE* genotype (Saunders et al. 1993). The *APOE* ε4 allele is carried by 15%–20% of individuals and is associated with a higher risk of AD. Individuals who are homozygotes for *APOE* ε4 have a 50% risk of symptomatic AD in their mid to late 60s, whereas 50% of *APOE* ε4 heterozygotes develop symptomatic AD by their mid to late 70s (Saunders et al. 1993). The *APOE* ε4 genotype, however, does not seem to influence clinical disease progression following the onset of symptoms, and may have a differential effect in the early biological stages of disease.

Mortality is increased by 40% in AD (Ganguli et al. 2005), with cardiovascular, infectious, and respiratory causes of death being the most commonly reported. The median survival following a diagnosis of AD is 4 years for men and 6 years for women (Larson et al. 2004). In older adults, the presence of dementia as a predictor of mortality exceeds the risk of diabetes, heart disease, and other more common life-threatening illnesses by two- to threefold (Tschanz et al. 2004).

Initial Presentation (Very Mild and Mild AD)

Clinicopathological studies suggest the presence of a long preclinical phase of AD, with AD pathology estimated to begin a decade or longer prior to the onset of cognitive symptoms (Price and Morris 1999). Following the initial signs of cognitive impairment, patients progress at variable rates from the mildest to the most severe stages. In most cases, symptoms progress slowly in the very early stages so that several years of cognitive decline might occur before an individual with AD is brought to medical attention.

Significant impairment in short-term memory with inability to retain new information is the outstanding clinical feature on presentation in most individuals with AD. However, aphasic or visuoconstructional deficits may occasionally prevail. Characteristic reports of short-term memory loss by the informant include repetition of questions or statements, frequently misplacing items, and difficulty remembering the names of familiar people.

Working memory, long-term declarative memory, and implicit memory are affected to a much lesser degree than short-term declarative memory in AD (Forstl 2010). Individuals with early AD experience difficulties with executive functions such as planning and organizational skills, judgment and problem solving, and handling complicated tasks. More demanding house chores or financial transactions may be performed poorly or only with assistance.

There may be evidence of slight temporal or spatial disorientation including mild difficulty with time relationships, or the need for additional assistance in arriving at destinations. Spatial disorientation frequently causes problems with driving as individuals are less capable of estimating time and speed. Therefore, individuals with even mild AD should be carefully assessed for driving ability. Language impairment in early AD includes reduced verbal fluency, word-finding difficulty, hesitancy of speech, or circumlocution.

Subtle personality and behavioral changes (e.g., apathy, withdrawal, passivity, and reduced motivation) are seen in 25%–50% of the cases. Significant depressive symptoms and mood changes are reported in 20%–30% of cases with early-stage AD (Zubenko et al. 2003). Agitation, psychosis, and anxiety are not typically seen in these initial stages (Geldmacher 2009), and become increasingly more common with disease progression. Anosognosia, or unawareness of illness, is seen in 50% of individuals with AD. In many cases, this represents a domain-specific deficit in self-monitoring and should not be attributed to psychological denial (Geldmacher 2009).

Individuals with early AD usually appear normal to casual inspection and may be able to function independently outside the home, although they may require assistance with some activities.

Moderate and Severe AD

These stages are marked by progressive decline in cognitive functions resulting in more severe functional impairment and increasing dependence on others in activities of daily living. While some individuals with moderate AD may remain engaged in community affairs, individuals with severe AD have no pretense of independent function at home or in the community, and typically appear too ill to be taken to social functions outside the family home.

Individuals with moderate to severe AD have pronounced difficulty retaining new information. Newly learned material is rapidly lost or only fragments remain; individuals are often described by family as "living in the past." Disorientation becomes more marked and may occur in familiar environments, as individuals may be unable to recognize family members or

close relatives. Individuals with moderate AD may continue to perform simple house chores (often with supervision); however, more complicated tasks are abandoned. Executive functions and logical reasoning significantly deteriorate at this stage.

Behavioral symptoms, when present, are more commonly seen in the advanced stages of AD. These include hallucinations, mostly of visual quality (Lauter 1968), delusions (including the "theft" of misplaced items or "infidelity" of spouse) and illusionary misidentification (Reisberg et al. 1996). Agitation with temper tantrums, verbal or physical aggression, disruption of sleep–wake cycles, anxiety, and aimless or restless activities such as wandering or hoarding are common at this stage (Devanand et al. 1997).

Almost all cognitive functions are lost in the severe stages of disease. Individuals are completely dependent on comprehensive nursing care. Language is reduced to simple phrases or even single words, although emotional receptiveness may be retained. Assistance with simple functions such as eating may be required, as even basic motor functions such as chewing and swallowing can be impaired. Double incontinence is common. Most patients are bedridden at this stage, and die of complications of aspiration, infection, or inanition.

NEUROLOGICAL EXAMINATION

The general physical and neurological exam may often remain normal throughout most of the course of AD. Extrapyramidal signs (e.g., bradykinesia, rigidity, and reduced facial expression) are seen in 30% of cases; however, rest tremor is rare (Scarmeas et al. 2004). Gait disturbances become more prominent with disease progression and are associated with a substantially higher risk for falls. Primitive reflexes, such as snout and grasp reactions, may also appear. Although only a small proportion of individuals with severe AD experience myoclonus and epileptic seizures, their incidence in AD is higher than that in the general population (Romanelli et al. 1990).

DIFFERENTIAL DIAGNOSIS

While AD accounts for the vast majority of dementia cases seen in clinical practice, clinical, psychometric, and neurologic findings that point to other causes should be carefully sought and evaluated. In a pathological study of 382 brains of individuals with dementia who were referred to the State of Florida Brain Bank, the vast majority (77%) had a pathological diagnosis of AD (Barker et al. 2002). Of these, 54% had "pure" AD pathology, whereas concomitant pathologies (e.g., Lewy body or vascular disease) were detected in the remainder. Additionally, AD pathology was present in most cases of dementia with Lewy bodies (DLB) (66%) and vascular dementia (77%) (Barker et al. 2002).

Vascular Dementia

Vascular dementia (VaD) is a heterogeneous phenotype that may result from a large spectrum of underlying vascular pathologies, types of vascular brain injury, and regional distribution of infarcts and hemorrhages (Chui and Nielsen-Brown 2007). No single neuropsychological profile is characteristic of VaD. However, abstraction, mental flexibility, information processing speed, and working memory are the domains most commonly involved (Desmond et al. 2000). Verbal memory, especially retention, tends to be better preserved in VaD than AD (Sachdev et al. 2004). Cognitive decline appears to be slower, whereas mortality rates are higher in VaD compared with AD (Chui and Nielsen-Brown 2007).

While several epidemiological surveys identify VaD as the second most common cause of dementia after AD (Fitzpatrick et al. 2004; Ravaglia et al. 2005; Chui and Nielsen-Brown 2007), VaD is probably overdiagnosed as a cause of dementia. It is estimated that less than 5% of dementia cases in the United States are caused by stroke alone (Barker et al. 2002). It is important, however, to recognize contributions of vascular pathology to dementia in AD; cerebrovascular lesions can precipitate the appearance of dementia in AD, or contribute to the cognitive impairment in the early stages. Vascular

pathology is commonly observed in association with AD pathology (Barker et al. 2002), and cardiovascular risk factors are increasingly linked to a higher risk of AD in epidemiological studies (Casserly and Topol 2004).

Dementia with Lewy Bodies

DLB is perhaps the second most common cause of dementia after AD; as many as 40% of autopsied demented patients have sufficient cortical LBs to be diagnosed with DLB (Galvin et al. 2006; Tarawneh and Galvin 2007). In addition to dementia, DLB is characterized clinically by the presence of at least two of three core features: recurrent well-formed visual hallucinations (42%), spontaneous parkinsonism (55%), and cognitive fluctuations (15%–85%) (McKeith et al. 1996). Core features are usually apparent even when the dementia is mild. In the presence of one core feature, a diagnosis of "probable" DLB can be made if at least one suggestive feature, such as rapid eye movement (REM) sleep behavior disorder or neuroleptic sensitivity (McKeith et al. 1996), is also present.

Other features that may support the clinical diagnosis of DLB include repeated falls and syncope, transient (unexplained) loss of consciousness, autonomic dysfunction, depression, systematized delusions, and hallucinations in other modalities (McKeith et al. 1996). While these criteria have high diagnostic specificity for DLB, their diagnostic sensitivity is variable, and often low, even in specialized centers (Knopman et al. 2001). These criteria appear to be less useful in distinguishing the pure form of DLB (which is rare) from the more common form in which concomitant AD pathology is also present.

Compared with individuals with AD, individuals with DLB are more likely to be impaired on tests of psychomotor, executive, and visuoconstructive or visuoperceptual functions, and less likely to be impaired in verbal recall (Salmon et al. 1996), at the time of their initial evaluation (Stavitsky et al. 2006). Individuals with DLB are more likely to exhibit early psychiatric symptoms (e.g., hallucinations and delusions;

Weiner et al. 2003) and passive personality traits (diminished emotional responsiveness, apathy, and purposeless hyperactivity; Galvin et al. 2007) compared with individuals with AD.

Cognitive fluctuations (waxing and waning of arousal and cognition) may be difficult to reliably identify in DLB. Daytime drowsiness or lethargy, daytime sleep of 2 or more hours, staring episodes, and episodes of disorganized speech may help distinguish the fluctuations of DLB from AD (where patients may have "good" and "bad" days) and from nondemented aging (Ferman et al. 2004). REM behavior disorder is characterized by loss of normal muscle atonia during REM sleep associated with excessive activity while dreaming, and when present, may further help distinguish DLB from AD (Boeve et al. 2003).

Frontotemporal Lobar Degeneration

Frontotemporal lobar degeneration (FTLD) is a heterogeneous group of disorders characterized by progressive neurodegeneration in the frontal and anterior temporal regions (Brun 1987). FTLD typically presents between 45 and 65 years of age, and in this age group, has comparable prevalence to that of AD (Ratnavalli et al. 2002). FTLD accounts for up to 20% of all patients with degenerative dementias (Neary et al. 2000), and is associated with a positive family history in 40% of the cases (Viskontas and Miller 2007).

FTLD encompasses three subtypes: frontotemporal dementia, semantic dementia, and nonfluent aphasia (Neary et al. 1998). Different clinical, genetic, and neuropathologic features are seen among these subtypes (Viskontas and Miller 2007). In FTD (often referred to as "the behavioral variant of FTLD"), there is predominant involvement of the right frontal lobe, resulting in progressive behavioral and personality changes that disturb social conduct. Features include disinhibition, apathy, emotional blunting, lack of insight, disordered eating patterns, and executive dysfunction. Individuals with nonfluent aphasia have selective involvement of the left frontoinsular region, and present predominantly with hesitant nonfluent speech, agrammatism, phonological errors, and

speech apraxia. Semantic dementia predominantly involves the anterior temporal lobe; individuals with predominant left temporal lobe involvement present with profound anomia and impaired word comprehension associated with progressive loss of conceptual knowledge of language, whereas individuals with predominantly right temporal lobe involvement present with deficits in empathy and knowledge about people's emotions, and may later progress to prosopagnosia and multimodality agnosia for objects.

While the clinical distinction between AD and fully expressed FTLD may not be difficult, this can be challenging in the mild stages of disease. Hypometabolism in the frontal lobes on PET (Ishii et al. 1998) and amyloid imaging using PET with Pittsburgh Compound B (PET-PIB) (Engler et al. 2008) may assist in the differentiation between FTLD and AD in these cases.

Medical and Psychiatric Disorders

Depression is a common diagnosis among elderly with cognitive complaints. In contrast to individuals with AD who often deny significant impairment, depression generally results in subjective, sometime pronounced, memory complaints with minor cognitive deficits in nondemented individuals (Powlishta et al. 2004). Deficits in attention and concentration are frequently reported (Gouras 2008). However, focal cognitive deficits such as aphasia or apraxia are not characteristic of depression, and should alert the clinician to an alternative diagnosis as the cause of the cognitive impairment.

The clinical distinction between depression and AD may sometimes be difficult. Some symptoms used to diagnose depression in the elderly (such as apathy, reduced motivation, loss of interest, and decreased energy) can be seen in AD. Moreover, AD and depression may overlap; depression was present in approximately 20% of individuals with early-stage AD in one study (Powlishta et al. 2004). There is no evidence that depression significantly worsens cognitive impairment beyond the effect of AD, or that depression alone can cause

dementia (Powlishta et al. 2004). Prospective studies suggest that individuals with depression and coexistent cognitive impairment are in fact highly likely to have an underlying dementia on follow-up (Alexopoulos et al. 1993; Visser et al. 2000).

Treatable medical conditions such as vitamin B12 deficiency and hypothyroidism are relatively common in the elderly; however, they are rarely the sole cause of dementia (Knopman et al. 2001). While these disorders may contribute to cognitive impairment in individuals with AD, treatment of the medical problem is unlikely to result in a significant cognitive benefit once AD is clinically established.

MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) has been proposed as a condition of impairment intermediate between what is considered "normal for aging" and that which is sufficient for a diagnosis of dementia or AD. The original criteria for MCI require the presence of a subjective memory complaint (preferably confirmed by a reliable collateral source) with objective evidence of memory impairment by cognitive testing in the setting of generally preserved activities of daily living. Impairment in memory is determined based on an individual's performance in reference to standardized neuropsychological data from age- and education-matched controls; performance below 1–1.5 standard deviations from "normal" is typically considered significant.

The utility of MCI criteria in identifying individuals as high risk for further cognitive decline and progression to AD (annual rate of 10%–15% in MCI compared with 1%–2% for nondemented elderly 80 years of age or less) was adopted by the American Academy of Neurology practice parameters for early detection of dementia and MCI in 2001. The concept of MCI has, however, evolved considerably over the years, leading to revisions to the diagnostic criteria (Petersen et al. 2009).

The original MCI criteria were designed to characterize the early stages of AD, and therefore focused on memory impairment (Petersen

et al. 2001). However, our current knowledge indicates that not all MCI subjects progress to AD; some remain stable and others progress to non-AD dementias. Revisions to the criteria recognize impairment in nonmemory domains (e.g., attention, visuospatial function, executive function, and language) in the diagnosis of MCI (Winblad et al. 2004), resulting in the emergence of amnestic (including memory impairment) and nonamnestic (including nonmemory cognitive domains) MCI subtypes (Petersen 2004). Since recent studies indicate that individuals with MCI may experience some changes in everyday activities (e.g., financial capacity; Griffith et al. 2003), revisions to the criteria allow for some difficulty in performing daily functions that is not of a sufficient degree to impair these functions.

MCI criteria do not require the determination of an etiological basis for cognitive impairment. Some individuals who meet MCI criteria may be impaired because of incipient AD, incipient non-AD dementia, a potentially reversible disorder (e.g., depression or medication-induced cognitive dysfunction), or simply be at the lower end of normal (but stable) cognitive performance. While many individuals with MCI eventually progress to AD, others remain stable or progress to other forms of dementia, and a small proportion may actually improve. Thus, there is a considerable degree of heterogeneity in the MCI population. New research criteria for MCI that incorporate CSF biomarkers in the diagnostic algorithm may be particularly useful in the evaluation of the likelihood of a future diagnosis of AD versus non-AD dementia in individuals with nonamnestic MCI (McKhann et al. 2011).

There may be conceptual and practical limitations to the application of MCI criteria in clinical practice. For example, the diagnosis of amnestic MCI can be based solely on subjective memory complaints in the absence of collateral information. Studies suggest that self-reports of memory impairment are more likely to be associated with a diagnosis of depression than with a future diagnosis of dementia, and that verification of cognitive impairment by a collateral source improves the predictive ability

for progression to dementia (Carr et al. 2000). The distinction between "some difficulty" versus "impairment" in performing daily functions is arbitrary, and often depends on the judgment of the clinician and the availability and reliability of collateral information.

MCI criteria focus on objective testing of an individual's performance in reference to standardized norms derived from age- and education-matched controls to establish cognitive impairment (i.e., interindividual decline). However, based on our experience, the detection of cognitive decline from the premorbid level of functioning (i.e., intraindividual decline), through clinical evaluation and reports by a reliable collateral source, often allows an accurate diagnosis of AD to be made in individuals who meet criteria for MCI, or even in individuals who are insufficiently impaired to meet MCI criteria and often referred to as "preMCI." In one series, the clinical diagnosis of AD in individuals who met criteria for amnestic MCI, and who underwent autopsy, was confirmed by a neuropathological diagnosis of AD in 84% of the cases (Morris et al. 2001). Furthermore, amnestic MCI closely resembles the neurobiological phenotype of clinically diagnosed AD, although at a milder stage. Individuals with amnestic MCI and those clinically diagnosed with AD share several common features, including cognitive, behavioral, and psychometric performance (Feldman et al. 2004), as well as genetic (Dik et al. 2000), neuroimaging (Jack et al. 2004), and CSF (Pratico et al. 2002) biomarker characteristics. In the authors' opinion, informant-based methods that focus on intraindividual decline can accurately identify AD in a subset of individuals who meet criteria for amnestic MCI.

The ability of physicians to identify the earliest symptomatic stage of AD may have implications in counseling, prognosis, and therapeutic decision-making. Early detection may allow time for counseling regarding safety issues (e.g., driving), financial planning, advance directives, and home arrangements. Since disease-modifying therapies are most likely to be effective if administered in the early stages of disease, this population is the most likely to

benefit from such therapies should they become available in the future.

CONCLUDING REMARKS

AD is the most common cause of dementia, and a leading cause of mortality and morbidity in the elderly. The identification of individuals in the earliest symptomatic (and presymptomatic) stages of the disease is important, because it is in this population that disease-modifying therapies may have the greatest chance of success. The NINCDS/ADRDA and *DSM-IV* criteria have good diagnostic accuracy for AD, and are widely used for the diagnosis of AD in clinical settings. Informant-based interviews that focus on establishing a decline in an individual's cognitive performance from previously attained levels of performance may allow for the identification of individuals with even very mild degrees of cognitive impairment.

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