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REVIEW

Differentiating Age-Related Memory Loss From Early Dementia

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Memory loss occurs in more than 40% of individuals older than age 60.[1] Alzheimer's disease (AD) or another type of dementia develops in some of these people, but others remain healthy. There is currently no reliable way to distinguish between these 2 outcomes.

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Dementia is characterized by impairment in short- and long-term memory, associated with impairment in abstract thinking, impaired judgment, other disturbances of higher cortical function, or personality changes. The disturbance is severe enough to significantly interfere with work, usual social activities, or relationships with others.[1] Alzheimer's disease (AD) is the most common cause of dementia, followed by vascular dementia. AD and vascular dementia often occur in the same patient.[1]

Clinical dementia is easily detectable: patients forget important information such as the names of children and the spouse, they may be disheveled, the house may be unkempt, judgment deteriorates, and financial affairs are in disarray.[4] The exact date of onset of clinical dementia is almost never known because symptoms develop gradually.

Preclinical dementia refers to the time between disease onset and clinically recognizable symptoms, which lead to the diagnosis of dementia. This period is usually measured in years. For example, preclinical AD may exist for 5 to 10 years prior to the clinical diagnosis of AD. Preclinical dementia is characterized by (1) abnormal episodic memory (the ability to encode, store, and retrieve new information),[5,6] and (2) preservation of other cognitive abilities, such as semantic memory (recall of previously acquired knowledge), executive functioning (planning, organizing, sequencing, abstracting), and visuospatial function.[4,7] The difficulty from a diagnostic perspective is that impairment of episodic memory in preclinical dementia may be comparable to what is often found in healthy older people. Indeed, complaints of memory impairment are so common in the elderly that they have been considered a ''normal'' feature of the aging process.

Complicating the distinction between preclinical dementia and memory changes that accompany normal aging is the relationship between self-reported memory loss and actual performance. In general, self-assessment of memory corresponds to actual performance on cognitive measures. However, there is a great deal of variation, and the presence

of non-neurologic disease,[8] depression, or functional impairment can affect the accuracy of reported memory skills. For example, nondepressed people who function well on activities of daily living (ADL) tend to minimize actual memory decline, perhaps because of concerns that others may impose restrictions on their independent functioning. On the other hand, people who are depressed or disabled tend to report memory decline even if actual memory is intact.[5,9] The distinction is further complicated because depression is common in AD and can be an early manifestation of the disease.[4,10]

Identification of preclinical dementia is assuming greater importance from a medical and a public health perspective because of the expectation that future treatments will prevent or slow the progression of AD.[11,12] Preclinical dementia is also important to companies that sell long term care insurance to older applicants since AD is one of the most common causes of large-amount and long-duration claims for long term care insurance.[13] The presence of preclinical dementia would also affect risk in applicants for life insurance.

"BENIGN" MEMORY IMPAIRMENT

A number of clinical labels have been proposed to describe nonprogressive memory deficits that fall within the limits of normal aging. One of the first attempts—benign senescent forgetfulness—was made in 1962,[14] followed by age-associated memory impairment, age-related cognitive decline, and other designations. Table 1 lists some of the clinical labels used to identify ''benign'' memory impairment in the elderly.[15,16,17,18] As discussed later, none of these classifications can consistently distinguish between patients with a benign, age-related disorder and those who progress to clinical dementia.

Age-Associated Memory Impairment

Age-associated memory impairment (AAMI) was defined in 1986 by a working group of the U.S. National Institute of Mental Health.[19] AAMI criteria include:

- Subjective memory decline
- Objective evidence of memory loss (in a well standardized memory test, a score of at least 1 standard deviation below the mean for younger adults)
- Adequate intellectual function
- Absence of dementia or any other disease that affects memory (eg, stroke, depression) in a person aged 50 years or older
- No medical disorders that could produce cognitive deterioration (eg, serious cardiac disease, poorly controlled diabetes mellitus, and cancer not in remission for 2 years or longer)

A diagnosis of AAMI theoretically identifies individuals with benign, age-related memory loss. But problems with this definition quickly appeared. One difficulty was that the memory tests used to define AAMI did not consider a person's original level of cognitive functioning when defining decline.[21] The result was that AAMI partially reflected intellectual level, such that people with higher intelligence were less likely to fulfill AAMI criteria.[21] A more significant concern was that studies reported markedly different AAMI prevalence rates depending on whether all of the above diagnostic criteria were used and/or whether exclusion criteria were properly applied. Table 2 displays AAMI prevalence rates in different studies.[23] Only the British and Finnish studies carefully

Table 1. Clinical Labels for What is Thought to be ''Benign'' Memory Impairment

Designation	Acronym
Age-associated memory impairment	AAMI
Age-consistent memory impairment	ACMI
Age-related cognitive disease	ARCD
Aging-associated cognitive decline	AACD
Benign senescent forgetfulness	BSF
Circumscribed memory impairment	—
Isolated memory impairment	—
Late-life forgetfulness	LLF

Table 2. Prevalence of AAMI, By Country

Country	Prevalence (%)	Age (years)
Spain (Coria, 1993)‡	7	≥65
Italy (Di Carlo, 2000)	8	65–84
Canada (Ebly, 1995)*	17–31	≥65
Britain (Barker, 1995)†	24	65–79
Australia (Lane, 1989)	35	≥65
Finland (Koivisto, 1995)†	39	60–78

‡ Low sensitivity screening test used primarily to identify dementia.

* Prevalence varied with the study center.

† Studies that carefully applied AAMI criteria.

applied all of the AAMI criteria,[19] and the prevalence rates of 24% and 39%, respectively, might be considered the most accurate estimates at this time. As a further indication of the inaccuracy of prevalence estimates, Larrabee and Crook[23] found that the prevalence of AAMI in older populations varied from 35% to 98% depending on the age of the population and which diagnostic criteria were used.

One of the best AAMI prevalence studies was done by Barker et al.[20] The prevalence of AAMI among 125 British patients increased and later decreased with advancing age: 50 to 64 years, 24%; 65 to 79 years, 31%; and 80 to 94 years, 16%. This apparently contradictory finding—one would have expected the prevalence of AAMI to continue to increase with age—was due to the increasing incidence of diseases that were AAMI exclusionary criteria. Thus, the stated prevalence of AAMI at older ages (16% at ages 80 to 94 years) may underestimate the actual prevalence because exclusion criteria eliminate many people who might otherwise be diagnosed with AAMI.

Most epidemiologic studies indicate that AAMI is usually nonprogressive and more likely to be a phenomenon of normal aging rather than part of the continuum from normal aging to a pathological state such as AD. However, patients with AAMI are still a heterogeneous group with a variable prognosis. Hänninen et al[24] observed 176 Finnish patients (mean age 77 years) with AAMI to determine the clinical course. After average follow-up of 3.6 years, subjects were re-classified into 6 subgroups:

1. Persistent AAMI, 59.1%
2. Clinical dementia, 9.1%
3. Mild cognitive decline that did not meet criteria for AAMI or dementia, 7.4%
4. Improved memory that was superior to AAMI criteria, 9.7%
5. Development of a disease that served as an AAMI exclusion criteria, 8.5%
6. Subjects who no longer reported subjective memory loss in everyday life (and hence no longer satisfied AAMI criteria), 5.1%

In this study the incidence of dementia in subjects with AAMI varied from 1.5% to 3.6% per year. These data agree with other estimates that people with AAMI develop dementia at a rate of 2.5% to 2.9% per year, which is approximately 1.5 to 2 times higher than the incidence of dementia in the general population (1% to 2% per year).[25] Thus, there is a subset of patients with AAMI who already have preclinical dementia. In the future many of these individuals will be identified clinically with a combination of neuropsychological tests, neuroimaging and genetic testing.[26,27]

In summary, there are difficulties with the definition of AAMI that limit its use for clinical or insurance purposes. Depending on the population and the specific memory tests that are administered, the majority of apparently normal older people could be diagnosed with AAMI,[28] and conservative estimates of AAMI prevalence range from 24% to 39%.[24] Of more practical importance is the observation that many patients with AAMI no longer satisfy the diagnostic criteria when retested several years later. Some improve, others progress to mild cognitive impairment or clinical dementia, and some develop an unrelated impairment that excludes the diagnosis of AAMI.

Table 3. Prevalence of Age-Related Cognitive Decline, By Age and Gender

	Age-Related Cognitive Decline (%)		
Age	Males	Females	Total
65–69	3.0	5.2	4.2
70–74	3.7	7.9	5.8
75–79	8.4	12.7	11.0
80–84	11.9	14.3	13.2

Age-Related Cognitive Decline

Age-related cognitive decline (ARCD) is defined in DSM-IV[29] as ''an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age.'' Di Carlo et al[16] estimated the prevalence of ARCD in 3425 elderly people selected from 8 municipalities throughout Italy. Some study participants were living in an institution, and thus these data would not be totally applicable to an insured lives population. ARCD was diagnosed in 7.5% of subjects. The prevalence of ARCD increased with older age and was always higher in females (Table 3).

Comparison of Classifications

Schröder et al[17] determined the prevalence of cognitive abnormalities in a community-dwelling cohort of 202 healthy German subjects (105 males, 97 females) age 60 to 64 years according to 4 diagnostic classifications. Overall, 47% of the cohort showed reduced performance on one or more of the tests. Table 4 displays the prevalence of dementia according to different classifications. For example (top data row), cognitive impairment was present in 13.5% of subjects according to AAMI criteria alone, in 3.0% according to both AAMI and ACMI, in 1.5% according to both AAMI and LLF, and in 8.5% according to both AAMI and AACD criteria. The highest prevalence was found with the AACD classification (23.5%), and the lowest prevalence with the LLF classification (1.5%). These prevalence rates were generally comparable to those in other series. Thus, the prevalence of ''benign'' cognitive abnormalities varied greatly with the diagnostic criteria, and patients diagnosed with benign cognitive impairment according to one classification were often normal per another classification.

Table 4. Comparison of Prevalence Rates (%) of Cognitive Impairment According to 4 Different Diagnostic Classifications

Classification	AAMI	ACMI	LLF	AACD
AAMI	13.5	3.0	1.5	8.5
ACMI	—	6.5	0.0	0.0
LLF	—	—	1.5	1.5
AACD	—	—	—	23.5

AAMI = age-associated memory impairment, ACMI = age-consistent memory impairment, LLF = late-life forgetfulness, AACD = aging-associated cognitive decline.

MILD COGNITIVE IMPAIRMENT

Some people with apparently ''benign'' memory loss are at greater risk for clinical dementia. This observation generated another set of clinical labels to identify the subset of patients with memory impairment suggestive of early dementia.[30] The most common label is ''mild cognitive impairment.'' Others include ''mild cognitive disorder'' and ''subclinical cognitive impairment.''

Mild cognitive impairment (MCI) is characterized by memory loss that is beyond what would be expected for age or educational background. It is generally thought to represent a transitional stage between normal aging and early AD. The prevalence of MCI in the general population is uncertain since it has only recently been characterized in the literature and uniform diagnostic parameters have not been determined. Petersen et al[18,31] suggested the following criteria: (1) subjective (self-reported) memory complaint; (2) objective evidence of abnormal memory for age (scores of more than 1.5 standard deviations below age-appropriate normal values on tests of episodic memory);[32] (3) preserved general

Table 5. Annual Incidence Rate (%) of Dementia (All Causes) and Alzheimer's Disease in Healthy People (Data Based on 12 Studies)

Age	Dementia	Alzheimer's Disease
60–64	0.11%	0.06%
65–69	0.33	0.19
70–74	0.84	0.51
75–79	1.82	1.17
80–84	3.36	2.31
85–89	5.33	3.86
90–94	7.29	5.49
95+	8.68	6.68

intellectual functioning (tests of non-memory cognitive functions are normal); (4) intact ADLs; and (5) absence of a clinical diagnosis of dementia.

There are physiologic similarities between MCI and AD, which suggest that MCI often represents preclinical AD. For example, neuroimaging indicates significant abnormalities of the hippocampus in some patients with MCI and in all patients with AD,[33] and there is over-representation of the ϵ4 allele of the apolipoprotein E gene in both MCI and AD.[28,34] Data from 6 studies on 476 patients with MCI indicated that the rate of progression from MCI to dementia or AD was between 6% and 25% per year,[18] with an average of 12% per year.[35] In contrast, healthy elderly people develop dementia at a much lower rate (Table 5).[35]

People with MCI function fairly well in the community and their symptoms are not apparent to those with whom they have casual contact. Family and friends become aware of the problem as the memory loss progresses.[36] Certain patterns of forgetfulness are more serious. For example, occasional forgetfulness (eg, losing one's car keys) is probably normal, whereas forgetting important events—despite a conscious effort to remember them—is not. When such incidents become chronic and progressive, they are strongly suggestive of MCI. Likewise, memory complaints are more likely to be valid if accompanied by memory-related problems in daily functioning, eg, if people forget the names of relatives and close friends, or where they left things, and whether they have ever lost their way on familiar streets.[8]

The Clinical Dementia Rating Scale (CDR) was initially designed as a staging instrument for AD, but it is frequently used now to help identify MCI. This clinical scale rates the severity of dementia as absent (0), questionable (0.5), mild (1), moderate (2), or severe (3).[37] The typical patient with MCI would score 0.5. However, there is some heterogeneity in the classification of a CDR score of 0.5, as some patients with this score could be described as having MCI, while others would warrant a diagnosis of AD or incipient AD.[32] The distinction between these diagnoses is that patients with MCI have memory loss that is beyond what would be expected for age or educational background, but other cognitive functions are normal or only slightly abnormal.[34] Those who are diagnosed with AD or incipient AD (and have a CDR of only 0.5) have memory impairment plus abnormalities of other cognitive functions. Morris et al[32] observed 277 American patients with a CDR score of 0.5. During follow-up of up to 9.5 years, all subjects progressed to clinical dementia (AD in almost all cases), with a rate of progression that correlated with the degree of baseline cognitive impairment. The authors concluded, ''individuals considered by current criteria to have only MCI, in fact, have very mild AD.''

Bozoki et al[38] reported that it was possible to predict which patients with AAMI would develop AD. Study subjects included 17 subjects with memory deficits but no other cognitive abnormalities (Group I), and 31 patients with memory deficits plus impairment of language, attention, visuospatial function, or verbal fluency (Group II). After mean follow-up of 4±2 years, 24% of Group I patients progressed to AD compared with 77% of subjects in Group II. This study confirmed that the predictive ability of neuropsychological tests in patients with memory complaints can be significantly improved by considering cognitive domains other than memory.

Ritchie et al[30] examined the ability of MCI and AACD (decline of more than one standard deviation in any area of cognitive functioning in comparison with age-matched controls) to predict dementia in a cohort of 397 elderly French patients. They identified 3 problems that limited the usefulness of MCI as a predictive tool. First, a diagnosis of MCI did not clearly differentiate patients with cognitive impairment from normal subjects. Second, subjects with MCI were an unstable group, with many patients moving from MCI to normal cognition or AACD during 3-year follow-up, and a smaller number progressing to dementia. Third, AACD was a *better* predictor of dementia than was MCI; during 3-year follow-up, 11% of subjects with MCI developed dementia compared to 29% of subjects initially classified as AACD. This latter finding contradicted the tenet that ''age-associated'' cognitive decline is a benign disorder.

CLINICAL DEMENTIA

Table 6 lists symptoms that are suggestive of dementia.[3] Progressive memory impairment is usually the first indication of disease, followed by other cognitive changes, psychiatric symptoms, problem behaviors, changes in drives, and impairment of instrumental activities of daily living (IADL). ADLs are maintained until late in the course of the disease. Detection of early clinical dementia is facilitated by questioning friends and family members; these caregivers may have adapted coping strategies (eg, shopping or financial management) to help the patient with dementia or to conceal the level of impairment.

Undetected Clinical Dementia

Undetected clinical dementia refers to persons who meet standard diagnostic criteria for dementia but who have not come to medical attention for evaluation of their symptoms.[11] Among community-dwelling older people with clinical dementia who are seen by general practitioners, the prevalence of undetected dementia ranges from 33% to 97%, with most cases representing mild dementia.[11,39] Dementia may not be reported to the physician because of embarrassment, symptoms are not recognized by the patient or are accepted as a normal part of aging, or the patient may feel that an extensive work-up is unnecessary.[11,40] Likewise, family members often do not detect dementia in older relatives, with one study finding that more than 60% of people with dementia were not recognized by family members as having memory problems.[41] Knopman et al[42] reported that a median of 1.6 years elapsed between the caregiver's first recognition of a symptom of dementia and the first physician visit to evaluate the problem. Another explanation for undetected dementia is that physicians may not screen for early dementia.

Even moderate to severe dementia may not be recorded in medical records, either because it was not detected or because the physician decided not to enter the diagnosis.[43] Sternberg et al[11] observed that the ''potential harm of early identification of dementia relates to the repercussions of carrying the label of cognitive impairment, including the inability to obtain life insurance or health insurance.'' This comment suggests that some physicians believe patients should be able to obtain insurance coverage *after* a diagnosis of mild dementia has already been made, without regard to the higher-risk status attendant to this diagnosis.

DETECTION OF PRECLINICAL ALZHEIMER'S DISEASE

Extensive neuropathological damage occurs during the long preclinical period prior to the diagnosis of AD.[44] During this time when the only manifestation may be mild memory impairment, it will often be possible for clinicians to make a preclinical diagnosis of AD via neuropsychological tests, neuroimaging and genetic testing.[18,27,44,45]

Neuropsychological Tests

Neuropsychological tests are useful for identification of early cognitive impairment

Table 6. Symptoms Suggestive of Dementia

Cognitive Changes	Psychiatric Symptoms		Problem Behaviors	Changes in Drives	IADL/ADL Function
Attention	Acute confusion	Fearful	Catastrophic	Excessive appetite	Bathing, grooming
Calculating	Anhedonic	Hallucinations	Demands interaction	Excessive sleep	Continence
Concentration	Anxiety	Illusions	Getting lost	Hypersexuality	Cooking
Executing	Apathetic	Irritable	Hoarding, rummaging	Hyposexuality	Dressing
Forgetfulness	Crying spells	Labile	Intrusive	Out of bed at night	Driving
Language	Death, suicidal	Low energy level	Noisy	Poor appetite	Feeding
Memory	Delusions	Panic	Outbursts	Sleeping poorly	Finances
Orientation†	Depression	Paranoid	Physically aggressive	Weight loss	Hearing and sight
Personality change	Disinterested	Rapid speech	Restless		Hobbies
Planning, organizing	Diurnal variation	Self-deprecating	''Sundowning''*		Housekeeping
Recognizing	Easy frustration	Somatic complaint	Sexual aggression		Mistakes at work
Social rules	Euphoria	Withdrawn	Uncooperative		Mobility (falls)
Writing, reading	Fatigues easily		Verbal abuse		Shopping
			Wandering		

† Date, time, place, common facts (eg, current President or Prime Minister).
* ''Sundowning'' refers to confused behavior that begins after sunset.

Table 7. Median Scores on the Mini-Mental State Examination, By Age and Educational Level

Age	4th Grade	8th Grade	High School	College
50 to 64	23	27	28	29
60 to 64	23	26	28	29
70 to 74	22	25	27	28
80 to 84	20	25	25	27
>84	19	23	26	27

in situations where conversational skills are well preserved. One of the more common tests is the Mini-Mental State Examination (MMSE). The MMSE is not diagnostic of dementia nor does it accurately distinguish among the various causes of dementia. A score of 24 or higher is generally considered normal, although performance varies with age and education (Table 7).[45] In general, the more poorly older individuals perform on tests of cognitive function, the more likely they are to progress to frank dementia, even if the MMSE score is within the lower bounds of the normal range. For example, individuals with MMSE scores of 25 or 26 are now accepted into many of the current trials of new medications for AD.[27] The MMSE was originally designed as a bedside screening tool for the clinician, and it has limitations as a screening tool in the general population. Test sensitivity can be as low as 49%, ie, the result would be considered normal in half the patients with dementia.

The 10-word Delayed Word Recall Test is another common test. It has a high sensitivity (89%) and specificity (98%) for identifying patients with mild dementia in a clinical setting, but performance is lower in individuals with early cognitive impairment.

New screening tests are being developed to identify people who might benefit from treatment of early dementia.[40] Grober et al[6] tested the ability of the Free and Cued Selective Reminding Test to identify patients at high risk for dementia in a cohort of 264 initially nondemented, elderly U.S. community volunteers in the Einstein Aging Study. During 5-year follow-up, dementia developed at dramatical-

ly higher rates among patients who performed poorly on baseline memory tests. Solomon et al[46] reported data on a ''7 minute neurocognitive screening battery'' used to detect AD. The screening battery consisted of 4 tests: enhanced cued recall, temporal orientation, verbal fluency, and clock drawing. There was a high degree of sensitivity and specificity for detection of very mild, mild, and moderate AD, and a high degree of test-retest reliability and interrater reliability.

Knopman et al[47] developed the Minnesota Cognitive Acuity Screen (MCAS) to assess cognitive function. The test consists of 9 subsections—orientation, attention, delayed-word recall, comprehension, repetition, naming, computation, judgment and verbal fluency—that are used to determine a composite score. Research indicates that MCAS can accurately identify an individual's cognitive state in 98% of cases, with a sensitivity and specificity of 97.5% and 98.5%, respectively. This proprietary test was developed by Nation's CareLink.[48] It is used by some companies in the United States to evaluate cognitive status in older insurance applicants. MCAS can be administered in approximately 15 minutes as a face-to-face assessment or via a telephone interview.

The diagnostic criteria for AD require the gradual onset and progression of memory impairment plus abnormalities of at least 3 other cognitive or functional domains. For this reason, clinicians look for additional cognitive problems during the evaluation of memory loss, such as:

- Aphasia (language disturbance)—Ask the patient to name body parts or objects in the room. Frequent use of vague terms such as ''thing'' and ''it'' may signify deterioration of language function.
- Apraxia (inability to carry out motor activities despite intact motor function)—Ask the patient to show how one uses a common object, such as a hammer or a toothbrush.
- Agnosia (failure to recognize objects despite intact sensory function)—Ask the patient to close his/her eyes, place a common object (eg, a key or a coin) in his/her hand, and ask the patient identify the object without looking at it.
- Executive functioning (planning, organizing, sequencing, abstracting)—Ask the patient to put a piece of paper in his/her right hand, fold it in half and put it on the floor; perform serial subtraction of 7s; spell the word ''world'' backward; and produce verbal word lists such as names of animals or items in a grocery store.

Neuroimaging

Neuroimaging can detect abnormalities associated with AD during the multi-year period that characterizes preclinical dementia.[15,26] Structural magnetic resonance imaging (MRI) can detect atrophy of the hippocampus (an early predictor of subsequent decline) and also differentiate normal subjects from those with MCI.[36] Memory-activation imaging compares brain activity at rest and during active memory tasks, using either functional MRI imaging or positron-emission tomography (PET). Both tests measure signal intensity associated with relative cerebral blood flow during tasks requiring memory or other cognitive skills. Studies suggest that functional imaging tests correlate with future risk of AD, even in people who had normal results on tests of memory and normal functional MRI scans during periods of mental rest.[49] Most official dementia diagnostic guidelines do not recommend neuroimaging as part of the routine assessment. However, decreasing costs and increasing availability of neuroimaging will likely lead to greater use in the future.[50]

Genetic Testing

AD is associated with 3 causal genes: APP, PS1, and PS2. Together these genes are responsible for less than 10% of AD cases (familial AD).

Approximately half of the cases of late-onset (after age 60 years) AD are associated

with apolipoprotein E (APOE). APOE is a susceptibility gene, ie, inheritance of certain forms of APOE increases or decreases the likelihood of AD. There are 3 allelic variants of APOE: ϵ2, ϵ3 and ϵ4. The ϵ4 allele is associated with a greater risk of AD and development of AD at an earlier age, ϵ2 confers a decreased risk and older age at onset, and ϵ3 conveys an average risk. Genotypes vary with race and ethnicity:

- The ϵ3 allele is the most common in Caucasian people. With a 50% incidence of AD by age 70, ϵ4/ϵ4 homozygotes (2% of the population) have the greatest risk. ϵ2/ϵ3 heterozygotes (12% to 14% of the population) have a median age of onset of AD that is over age 90. The risk and age at onset of AD for the ϵ3/ϵ3 heterozygotes (the most common genotype) lies between these 2 extremes.[49,51]
- In Japan, where the ϵ4 allele frequency is about half that in the United States, most people with the ϵ4 allele who develop AD have the ϵ3/ϵ4 genotype.[51] Consequently, there are fewer Japanese with disease onset before age 70, and more with onset in the mid to late 70s.
- In Finland, the prevalence of the ϵ4 allele is high at 22% of the population, but AD prevalence is not comparably elevated. It is thought that the high incidence of myocardial infarction (APOE also conveys a greater risk of coronary heart disease) may result in death in many ϵ4 carriers before they could develop AD.
- The association of the ϵ4 allele and AD remains controversial in African Americans and Hispanics.[51] An analysis of 5930 patients with AD concluded that the ϵ4 allele was a risk factor in all ethnic groups studied: Caucasian, African American, Hispanic, and Japanese, and equally in men and women.[52]
- The APOE ϵ4 allele was the most important genetic risk factor for sporadic AD among Chinese in Taiwan.[53] However, the prevalence of the ϵ4 allele was still low, which may partially account for the lower prevalence of AD among the Chinese. The authors of this study postulated that other risk factors may be associated with AD in Chinese populations.

There are currently 2 clinical uses for APOE tests: (1) detection of preclinical AD, and (2) prediction of AD in asymptomatic people. Studies have reported a modest increase in risk (1.13 to 4 times higher)[54,55] of AD among asymptomatic carriers of the ϵ4 allele, and a slight decrease in AD risk in ϵ2 carriers. Screening of asymptomatic people is still limited to research settings. It is not known how APOE increases the risk of AD. The protein produced by APOE may play a role in amyloid plaque deposition or clearance, but other mechanisms are being investigated.[51] Once AD develops, prognosis is not affected by the APOE genotype.[52]

TREATMENT

Located within the temporal lobe is the hippocampus, a structure that plays a significant role in learning and memory. The hippocampus contains a nucleus (the nucleus basalis of Meynert) responsible for production of acetylcholine, a neurotransmitter required for memory. Atrophy of these cells leads to low concentrations of acetylcholine and memory impairment. The rationale for administering acetylcholine esterase inhibitors (AChEI) to patients with early AD is to slow the enzymatic breakdown of acetylcholine and thereby lessen the degree of cognitive impairment. Tacrine was the first AchEI developed for treatment of AD, but its use was limited by side effects. Later treatments were better tolerated because they caused more selective inhibition of AchE. Donepezil was introduced next, followed by Rivastigmine and Galantamine.[56] Only 15% to 40% of patients benefit from AchEI, and the effects are symptomatic without altering the overall progression of AD.

SUMMARY

General

- Mild memory loss can be caused by normal aging, depression, physical illness, and the early stages of AD and other progressive cognitive disorders.
- Elderly insurance applicants often admit to a decline in memory. Sometimes the problem is benign in nature and related to normal aging; at other times, it is a manifestation of MCI, the onset of which commonly precedes AD.
- Preclinical dementia may exist for 5 to 10 years prior to the clinical diagnosis of AD. Impairment of episodic memory in these cases may be comparable to what is often found in healthy older people.
- The combination of self-reported memory loss and lack of objective evidence of impaired memory suggests the possibility of subclinical depression.

"Benign" Memory Impairment

- Many clinical labels (AAMI, ACMI, etc.) have been created to describe nonprogressive memory deficits that fall within the limits of normal aging. None of these classifications can consistently distinguish between patients with a benign, age-related disorder and those who progress to clinical dementia.
- Difficulties with labels for ''benign'' memory loss include failure to consider the original level of cognitive function; prevalence rates that vary greatly with the study, the country, and/or the specific memory test; conservative estimates of prevalence rates that include 24% to 39% of the elderly population; lack of a single standardized memory test for diagnostic purposes; and heterogeneity of people with the diagnosis.
- ''Benign'' memory loss is often an unstable diagnosis, with frequent transitions to normal (no memory deficits), mild cognitive impairment, clinical dementia, and intermediate states. Truly benign, age-related memory impairment should be stable over time.[32]
- As a group, people with ''benign'' memory loss develop dementia at a rate that is approximately 1.5 to 2 times higher than the general population incidence. The reason is because some people with ''benign'' memory loss have preclinical dementia due to AD or another cognitive disorder.

Mild Cognitive Impairment

- MCI means mild memory loss beyond what is expected for age or educational background. This condition generally represents preclinical AD.
- People with MCI have memory loss, but other cognitive functions are normal or only slightly abnormal. In contrast, those with early AD have memory impairment plus abnormalities of other cognitive functions.
- The average conversion rate from MCI to AD is 12% per year, compared to an AD incidence rate of 1% to 2% per year in healthy elderly people.
- People with MCI function fairly well in the community and their symptoms are not apparent to those with whom they have casual contact.
- Occasional forgetfulness (eg, losing one's car keys) is probably normal, whereas forgetting important events—despite a conscious effort to remember them—is not. When such incidents become chronic and progressive, they are strongly suggestive of MCI.
- Memory complaints are more likely to be valid if accompanied by memory-related problems in daily functioning, eg, if people forget the names of relatives and close friends, or whether they have ever lost their way on familiar streets.
- MCI has deficiencies as a predictor of future cognitive impairment. There is no agreement regarding which neuropsychological tests should be used to make the diagnosis. Some authors have reported that MCI is an unstable diagnosis and that it

does not clearly differentiate patients with progressive cognitive impairment from normal subjects.

Clinical Dementia

- Many cases of mild clinical dementia are not detected by family, friends, or physicians.
- AD or another cognitive disorder is more likely if memory loss is accompanied by other cognitive changes, psychiatric symptoms, problem behaviors, changes in drives, and impairment of IADL or ADL function.
- A diagnosis of dementia is supported by the presence of aphasia, apraxia, agnosia, and abnormalities of executive functioning.
- Assistance with IADLs by families and friends may indicate early dementia.

Detection of Preclinical Alzheimer's Disease

- In patients with mild memory loss, clinicians may be able to diagnos preclinical AD via neuropsychological tests, neuroimaging, and genetic testing.
- ''Low normal'' scores on neuropsychological testing may indicate incipient clinical dementia.
- The APOE ϵ4 allele is associated with a greater risk of AD and development of AD at an earlier age, ϵ2 confers a decreased risk and older age at onset, and ϵ3 conveys an average risk.
- Some of the differences in AD prevalence worldwide are related to racial and ethnic differences in APOE genotype.

Treatment

- Identification of preclinical AD is assuming greater importance because of the expectation that future treatments will prevent or slow the progression of AD.
- Only 15% to 40% of patients benefit from treatment with acetylcholine esterase inhibitors. The effects are symptomatic and do not alter the overall progression of AD.

UNDERWRITING CONSIDERATIONS

Applicants with "Benign" Memory Impairment

- There are 2 fundamental problems. First, the diagnosis is often unstable, with frequent transitions to normal (no memory deficits), mild cognitive impairment, clinical dementia, and intermediate states. Second, it is uncertain if all pertinent information is known by the insurer, eg, should the diagnosis really be MCI or early AD, does the applicant know that memory loss is progressive, and has the attending physician shared the results of tests done during the medical evaluation.
- Some insurers consider other factors that might assume greater importance given the known history of memory loss, eg, other cognitive changes, psychiatric symptoms, problem behaviors, changes in drives, and impairment of IADL or ADL function.
- Risk increases if memory tests are in the ''low normal'' range and if the diagnosis is recent.
- Some insurers ask the attending physician specific questions regarding duration of memory loss, likelihood of preclinical dementia, results of tests done during the medical evaluation, and whether he/she believes that the applicant is at higher risk (specify product) for a claim due to cognitive impairment compared to other patients of the same age.
- The average ''best case'' scenario (assuming no antiselection or misrepresentation) is an incidence of AD that is 1.5 to 2 times higher than the general population incidence.
- If the diagnosis was made recently, some insurers would choose to re-evaluate the risk (including an updated physician's statement) at a later date.
- Risk varies with the product, degree of memory loss, duration of stability, life expectancy, and overall likelihood of disability based on functional status and comorbid impairments.
- For long term care insurance, some insur-

ers are more conservative if the product provides home care benefits because of concern that lengthening the waiting period may not provide significant protection since cognitive claims are generally of long duration.

Applicants with Mild Cognitive Impairment

- There is a high rate of progression to AD or other types of clinical dementia.
- Many insurers decline applications for long term care insurance if MCI is present.
- Some insurers decline applications for life insurance for one or more of the following reasons:
  - Shortened life expectancy due to AD and/or multiple co-morbid impairments, such as cardiovascular disease, arthritis, frailty, etc.
  - Moral hazard of naming a beneficiary who is the caregiver
  - Legal risk incurred by entering a contract with a party that is mentally impaired

Underwriting Requirements

- The protective value of a physician's statement is limited with regard to detecting memory loss and early cognitive impairment. A large percentage of community-dwelling people with mild dementia have not been detected, and some physicians do not enter a diagnosis of dementia in the medical records or do not share this information with insurers.
- Depending on the product, some insurers obtain a cognitive test on all older insurance applicants, eg, ages 70 and older.
- If cognitive testing is done by the insurer on applicants with known ''benign'' memory loss, a ''face-to-face'' test would generally provide a more accurate estimate of risk compared to a telephone interview.

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