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On the Way to Alzheimer's Disease

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On the Way to Alzheimer's Disease

Current research indicates that the onset of Alzheimer's disease is preceded by a stage termed "mild cognitive impairment." By recognizing the characteristics of this preclinical phase and administering the proper treatments, physicians may be able to stop the progression toward AD.

By M. Saleem Ismail

The search for treatment of Alzheimer's disease (AD) has taken a front seat during the past decade. Demographics and staggering resource utilization[1] have added urgency to our efforts in preventing, diagnosing, and treating this debilitating illness.

As research in the field of aging and dementia move forward, researchers have employed a two-pronged approach: We not only need to devise means to identify individuals who may develop AD, but we also need to investigate novel treatment strategies. Many exciting pharmacological interventions have been identified, although we have still not found a valid diagnostic test to reliably distinguish AD from other dementias.

Mild Cognitive Impairment

Recently, a great deal of attention has been focused on the concept of a boundary or transitional state between normal aging and AD, or less specifically, dementia. It is now believed that the onset of AD is commonly preceded by an interim phase known as "mild cognitive impairment" (MCI).[2] Several descriptors, such as *incipient dementia, isolated memory impairment,* and *questionable dementia* have been coined, reflecting an attempt by investigators to characterize a "preclinical phase"—a transitional state between normal aging and the earliest stage of cognitive impairment.[3] MCI appears to be a signal of disease onset that can help target individuals for early interventions. Researchers and clinicians are pinning their hopes on the chance that identifying and treating this preclinical phase can halt the progression toward AD.

"Normal" Forgetfulness Versus MCI

The boundaries between the cognitive changes of aging and MCI—as well as MCI and mild AD—are not very well delineated. The primary distinction between normal adults/control subjects and subjects with MCI is in the

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area of memory without impairment of other cognitive functions such as language, perception, motor skills, and judgment. In clinic, I often come across older adults and their families who believe that memory impairment is part of aging, and I am sure some of you may ask, "Where does normality end and abnormality begin?" Since there is no firm demarcation, the concept of a transitional phase becomes even more important.

Most studies have found that cognition does not decline in most older adults. Cognitive deficits are often a consequence of a clinical or subclinical disease process. There is association among disease, functional impairment, social disengagement, and cognitive impairment. There is age-related mild slowing in the speed of thought processing, particularly in processing parallel thoughts. A mild and benign difficulty in remembering names of individuals on meeting them, misplacing keys and spectacles, or difficulty in remembering infrequently used phone numbers may represent an age-related change. Such a change does not represent a sharp, severe, or persistent decline from a previous level and does not interfere with an individual's day-to-day functioning.

Several factors need to be kept in mind when assessing an individual's memory and learning. These include hearing or visual deficits, general medical conditions, use of medications, motor deficits, educational background, living arrangements, and cultural concepts of aging. In addition, depression, being common in old age, is associated with social isolation and can be an underlying cause of cognitive decline.

Despite controversies regarding how to clearly characterize those who have normal age-related forgetfulness and those with MCI, most experts recognize the importance of making this distinction. Subjects with MCI in contrast to normal individuals show impairment in a test of memory called "delayed recall." (An individual is provided some information and is asked to recall it after five minutes.) There is vast agreement that a significant decline in "verbal episodic memory" (memory of specific events such as phone messages and appointments) is the earliest and most sensitive sign of incipient AD at the preclinical stage.

As mentioned earlier, other cognitive abilities, such as language, motor skills, and executive functions, are spared. Having the ability to perform activities of daily living such as driving a car or balancing a checkbook—and not having other cognitive deficits—may make it difficult for an individual with MCI to be identified. The memory loss that distinguishes healthy adults from those thought to have MCI or preclinical AD is abnormal for the individual's age and level of education.

Transition from MCI To Dementia

Dementias are described as cognitive disorders involving impairment of memory with deficits in language, abstract thinking, attention, orientation, and judgment. AD is the most common form of dementia,[4] which increases in prevalence thirty to fifty percent by age eighty-five. AD, like MCI, is characterized by memory impairment. However, unlike MCI, memory impairment is not sufficient to make a diagnosis of probable AD. According to American Psychiatric Association's classification,[5] probable AD is characterized by a progressive memory impairment that is not from a psychiatric, general medical, or substance use disorder. Such deterioration is accompanied by deficits in at least one other mental function such as perception (agnosia), language (aphasia), or a motor skill (apraxia). In addition, these deficits are severe enough to interfere with an individual's social and occupational functioning.

Let's think of it this way: Some of us, at some point, will develop mild cognitive impairment, which will be characterized by significant memory impairment for our age and educational level. Some—but not all—of those individuals will progress towards AD. An encouraging finding for those who see the glass as half full: MCI, or a preclinical phase, is detectable up to seven years before someone meets established criteria for AD.[6] We also know that an average delay in diagnosis of AD is about two years, which allows us a window of opportunity if we could develop reliable markers/methods to identify susceptible individuals and nip progression in the bud.

My review of literature suggests that not all individuals diagnosed with MCI develop AD, as one study in particular showed that a small number of patients remained cognitively stable even after four years of observation. In any case, it is true that people with MCI have an increased risk of progressing to AD approximately at a rate of ten to twelve percent per year, in contrast to normal

adults, who convert at a rate of one to two percent per year. Effective interventions are urgently needed, considering that thirty-eight percent of the middle- and older-aged adults fulfill criteria for MCI.[7] It is heartening to know that many pharmacological agents aimed at delaying cognitive decline are readily available. In addition, numerous clinical trials by the National Institute of Health and the pharmaceutical industry are underway.

Why Break Bad News Early?

Some experts have questioned the view that older individuals with some susceptibility (e.g. family history) should be screened regularly, even before they have demonstrated any symptoms. Another concern is whether to break bad news early when we are not able to stop the decline. Certainly, at this juncture, medical science has not had an unlimited success in its effort to prevent or treat the decline once it has started. But we do have a window of opportunity—lasting several years—to attempt to intervene in order to improve quality of life for patient and caregivers.

Those of us who argue in favor of identifying susceptible individuals at the earliest possible stage insist that even at the milder stages of the disease, patients retain significant functions and can play an active role in planning and preparing for their future needs. Decisions such as healthcare proxy, power of attorney, and advance directives can be made—preferably while an individual is fully involved. A timely diagnosis removes the uncertainty about the cause of cognitive decline, which allows family to avoid enormous stress and strained relationships resulting from blame and denial. An early diagnosis allows education of caregivers in a timely manner regarding patient safety and handling. Caregivers also need to plan their lives as they anticipate increased physical and emotional demands.

From a clinical point of view, an early assessment allows evaluation for other reversible and treatable causes of memory impairment. In addition, families and their caregivers may elect to have certain experimental and investigational treatments available to retard progression of MCI, although conclusive evidence regarding these treatments must await results of clinical trials in progress.

Clinical Evaluation for MCI

A diagnostic test or marker that would distinguish patients with MCI from normal older adults, and those with early AD, is not available at this time. Clinicians often find themselves confronted by patients in this "no man's land" between normal aging and dementia. In the absence of a diagnostic test, we use criteria and guidelines that have been developed for research and clinical evaluations. A commonly used set of criteria, developed by researchers at Mayo Clinic, includes...

(a) complaint of memory problems either by patient, family, or referring physician;
(b) memory deficit abnormal for age and education;
(c) no evidence of difficulty in carrying out activities of daily living and other cognitive functions; and
(d) these individuals do not meet criteria for AD.[8]

Most adults who suspect some memory problems would generally seek help from their primary-care physicians, who may elect to do preliminary assessment and then obtain a consultation with colleagues who are trained in diagnosing such disorders. In either event, the involvement of a knowledgeable informant is crucial and worth the effort. Spouses and other adults in the family sometimes make very important observations regarding patients' memory changes and resultant impact on functioning providing a sensitive indicator of illness.

An assessment for MCI includes a detailed personal and family history, a physical examination, and a review of daily self-maintenance functions. These include such daily tasks as dressing, eating, toileting, housekeeping, shopping, accounting, food preparation, and transportation. A diagnostic evaluation also includes laboratory tests such as a blood picture to look for anemia or infection; tests for liver and thyroid functions; levels of vitamin B12 and folic acid; and tests for diseases such as syphilis or HIV. In suspected cases where no other cause could be found, a CAT scan or MRI of the head is recommended, which helps to exclude certain neurological illness and to identify the severity of brain shrinkage (atrophy). Specialized tests such as SPECT scan and APOE genetic typing are performed at few research centers, and are not part of routine evaluations.

Available Treatments

The first step in treatment is always to provide education and support to affected individuals and caregivers regarding available options. By "treatment," we often mean pharmacological interventions—but these are only part of the treatment plan. As many of you may know or may have read, several pharmacological agents that enhance memory and slow cognitive decline are being used in treatment of mild to moderate AD. Most widely used agents are called cholinesterase inhibitors, as they increase the level of the neurotransmitter acetylcholine by inhibiting its destruction. These agents include donepezil, rivastigmine, and galantamine. I must point out that these medications have not yet been approved by the Food and Drug Administration for treatment of MCI. Several large-scale trials are underway to assess the efficacy of these agents in this particular disorder. At the same time, many physicians consider it a standard of care to offer these agents, in combination with vitamin E, to their patients with MCI. Other interventions that are being used or tested include melatonin, gingko biloba, and anti-inflammatory agents such as rofecoxib and celecoxib.

Summary

Memory is an integral part of our survival; it allows us to learn and respond to our environment. Diagnosis and prevention of predictors of dementia, or specifically Alzheimer's disease, has become a focus of geriatric research. Mild cognitive impairment is one of those potential predictors, and we hope that by instituting effective strategies at this early stage, we would lessen the tremendous toll on affected individuals, their families, and our society.

Endnotes

1. *See* Richard L. Ernst, et al., *The U.S. Economic and Social Costs of Alzheimer's Disease Revisited,* 84 AM. J. PUB. HEALTH 1261 (1994).

2. *See* C. Flicker, et al., *Mild Cognitive Impairment in the Elderly: Predictors of Dementia,* 41 NEUROLOGY 1006 (1991).

3. John C. Morris, *The Challenge of Characterizing Normal Brain Aging in Relation to Alzheimer's Disease,* 18 NEUROBIOLOGY AGING 388 (1997). *See also,* Ronald C. Petersen, *"Normal Aging, Mild Cognitive Impairment and Early Alzheimer's Disease,* 1 NEUROLOGIST 326 (1995).

4. ADVISORY PANEL ON ALZHEIMER'S DISEASE, FOURTH REPORT OF THE ADVISORY ON ALZHEIMER'S DISEASE, 1992, (NAT'L INST. OF HEALTH, 1993).

5. AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FOURTH EDITION (DSMD-IV).

6. *See* Richard T. Linn, et al., *The 'Pre-Clinical' Phase of Probable Alzheimer's Disease: A 13-Year Prospective Study of Framingham Cohort,* 5 ARCH. OF NEUROLOGY 485 (1995).

7. Barbara B. Sherwin, *Mild Cognitive Impairment: Potential pharmacological treatment options,* 48 J. AM. GERIATRIC SOC'Y 431 (2000).

8. Ronald C. Petersen, et al., *Mild Cognitive Impairment; Clinical Characterization and Outcome,* 56 ARCH. OF NEUROLOGY 303 (1999).