

OVERVIEW OF AD FROM A CLINICAL PERSPECTIVE

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Alzheimer's disease (AD) largely is a disorder of older adults. Only 7% of all individuals with symptomatic AD are younger than 75 years of age.¹ However, because as the population ages, the overall prevalence of AD is increasing rapidly, there are hundreds of thousands of individuals with "early-onset" AD in the United States. The term, "early-onset AD", has been defined variously based on the age at onset of symptoms but often refers to age 60 years or younger. The younger the age at onset, the more likely that the individual is a member of a family with dominantly inherited AD. Much of what has been learned about AD has come from studies of early-onset individuals. In fact, the original Alzheimer patient was 51 years of age when diagnosed by Professor Alzheimer in 1901.

The clinical picture of early-onset AD is not fundamentally different than the more common late-onset AD, and thus the information in this testimony largely applies both to early-onset and late-onset AD. Some reports, however, indicate that early-onset AD is more likely to have associated disorders, such as myoclonus, seizures, and language disturbances, and follow a more aggressive course of deterioration. Although the development of AD is tragic at any time in the lifespan, it brings considerable added difficulties when it comes in the prime of life. Early-onset individuals often are undiagnosed for years after symptoms begin because many doctors think that AD occurs only in late life. Moreover, onset of dementia in middle age rather than older adulthood magnifies the typical disruption caused by AD because of responsibilities that no longer are shared by most older adults: parenthood and child-rearing, financial burdens such as mortgages, and work. Early-onset individuals leave their families in financial hardship because they lose their jobs and still must wait years before qualifying for disability or social security. The diagnosis of AD also precludes eligibility for long-term health care insurance and other programs.

AD is an irreversible brain disorder that is characterized by progressive neuronal deterioration causing loss of brain cells and their connections (synapses) with other brain cells. Its pathological hallmarks, amyloid plaques and neurofibrillary tangles, are detected in the cerebral cortex by microscopic examination of brain tissue. AD is relentlessly progressive and inevitably fatal. It is among the most-feared of all illnesses because it progressively robs the individual of his or her most human attributes: memory, reasoning, insight, language, personality, and self-awareness. In doing so, the individual gradually loses the ability to conduct activities of daily living and becomes increasingly disabled and dependent on others. The advanced symptomatic stages leave the individual uncomprehending, mute, nonambulatory, and unable to eat, swallow, or

maintain sphincter control. Death occurs from complications of the illness on average 7 to 8 years after onset of symptoms.

As a chronic illness marked by steadily increasing disability and dependence, AD is enormously expensive because of the amount of supervision and care that must be provided to affected individuals. It is estimated that the current annual cost of AD in the United States is \$140 billion. The world population is aging at an unprecedented rate and coupled with age-associated illnesses, most notably AD, will have dramatic effects on existing health, pension, and social insurance systems.² Much of the care for individuals with AD is provided by family members on a 24 hour, 7 days a week basis with resulting physical, psychological, and financial distress for the caregiver. The devastating emotional toll on caregivers of individuals with AD encompasses rage, denial, fear, isolation, and anguish as the person who was their loved one inexorably erodes away.^{3,4}

The initial stage of AD begins with pathological brain changes that gradually accumulate in the absence of symptoms. This preclinical stage may last many years or even decades before sufficient neuronal and synaptic damage occur to cause loss of function. For reasons yet unknown, AD begins in the most phylogenetically advanced brain regions so that initial symptoms involve uniquely human cognitive abilities. Neurodegeneration caused by AD progresses gradually so that the appearance of symptoms is insidious, making it impossible to precisely date the transition from cognitive normality to impairment. The transitional stage has several names, including prodromal AD, incipient AD, and mild cognitive impairment. With further progression of symptoms, it is evident that the individual has declined relative to his or her previous cognitive abilities such that they no longer can conduct accustomed activities at their usual level. This symptomatic phase of AD typically is referred to as dementia of the Alzheimer type (DAT).⁵ The DAT stage of AD progresses through different levels of symptomatic severity, from very mild, mild, moderate, and severe.⁶

Diagnosing AD remains in the hands of the clinician. No test is yet available that replaces an assessment by an experienced clinician. Unfortunately, many practicing physicians fail to detect or diagnose DAT, which is unrecognized in over half of all individuals with the illness.⁷ Factors that may contribute to underdiagnosis by physicians include lack of knowledge about AD (particularly for early-onset forms), therapeutic nihilism regarding currently approved therapies, and insufficient time, resources and reimbursement for appropriate diagnosis and management.

Diagnosis is accomplished by obtaining a history of the onset, presenting features, and course of the cognitive and functional impairment. The history is obtained from an informant (generally the spouse or an adult child) as the majority of individuals with DAT lack insight into their impairment. The emphasis is on capturing a history of intraindividual decline from previously attained levels in the patient's cognitive ability to perform everyday tasks adequately.⁸ The degree of cognitive impairment is quantitated by mental status tests and, in some instances, by neuropsychological testing. The behavioral status of the patient is evaluated and a general and neurological examination, combined with a minimal laboratory evaluation (including neuroimaging with computed

tomography or magnetic resonance imaging [MRI], are performed to exclude other potentially dementing disorders.⁹ The diagnostic accuracy of experienced clinicians for symptomatic AD, as confirmed by neuropathological examination, is as high as 93%.¹⁰

There is much promise that the accurate diagnosis of AD, regardless of its clinical status, will be enhanced by the use of imaging and fluid biomarkers. Although these potential “tests” still lack the necessary validation in clinical settings to be incorporated into practice, research studies provide strong evidence that structural brain changes (both whole brain volume and regional volumetry) as detected by MRI, metabolic brain changes (altered glucose or oxygen metabolism, visualization of amyloid plaques in the living brain) as detected by positron emission tomography (PET), and assays in the cerebrospinal fluid (CSF) of critical proteins, including amyloid-beta (A β) and tau, can identify individuals with the disease. Although biomarker research still is in the early phase, emerging evidence suggests that the sequence of AD abnormalities may be detected first by CSF changes, followed by PET imaging for amyloid plaques and then by regional hypometabolism, and then by loss of brain volume. Altered levels of CSF tau and A β have already been demonstrated in one study to predict which cognitively normal older adults will develop DAT in 3-4 years.¹¹ Biomarkers are likely to be incorporated into revised sets of diagnostic criteria for AD.¹²

Although there are many putative risk factors for AD, by far the two most well-established are increasing age and a family history of the disorder. The genetics of AD is complex. In rare families (constituting <1% of all individuals with AD), AD is inherited as an autosomal dominant trait. Mutations in one of 3 genes (amyloid precursor protein, presenilin 1, presenilin 2) are found in these families. Each child of a parent with one of these gene mutations has a 50/50 chance of inheriting that mutation; if they do, they will develop AD, often at a very early age (as early as 30-40 years). Genetic testing for these mutations is available but should always first involve genetic counseling, as there are no effective treatment options at present for persons who discover that they are mutation carriers. A more common genetic factor for AD is the polymorphism, apolipoprotein E ϵ 4 (APOE4), which confers increased susceptibility to developing AD but is not itself a cause of the disorder. The risk associated with the APOE4 allele cause increased A β deposition in the brain and an earlier age of onset of the symptoms of AD. Genetic testing for APOE status is not recommended at present because APOE4 is not always associated with the disease.

Truly effective therapies for AD likely are years from becoming reality. There is great optimism, however, that eventually drugs will be available that arrest or considerably retard the Alzheimer pathological process. Many candidate agents currently being evaluated in clinical trials target A β metabolism or deposition, but many compounds address other, non-A β pathogenic mechanisms.¹³ There is consensus that the earlier in the disease course that safe and effective therapies can be administered, the greater the likelihood for success. Indeed, the greatest window for therapeutic intervention success may be in the preclinical stage of AD, prior to the appearance of DAT. Biomarkers already are able to characterize preclinical AD in research settings, suggesting that it may be possible to identify cognitively normal persons who are at great

risk for becoming demented. If so, then the interventional paradigm may shift from treatment to prevention of AD.¹⁴

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