ISSN: 2321-8045 Impact Factor : 2.6605(UIF) Volume - 4 | Issue - 40 | 20 aPRIL - 2017

Science Park
International Research Journal

ALZHEIMER'S DISEASE: A CLINICAL AND BASIC SCIENCE REVIEW

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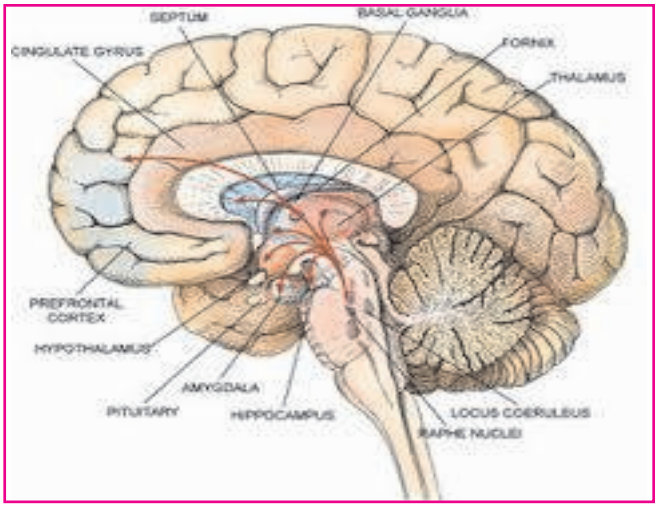
ABSTRACT :

Alois Alzheimer and Auguste D The German psychiatrist and neuropathologist Dr. Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as AD. In his landmark 1906 conference lecture and a subsequent 1907 article, Alzheimer described the case of Auguste D, a 51-year-old woman with a 'peculiar disease of the cerebral cortex,' who had presented with progressive memory and language impairment, disorientation, behavioral symptoms (hallucinations, delusions, paranoia), and psychosocial impairment.13 Remarkably, many of the clinical observations and pathological findings that Alzheimer described more than a century ago continue to remain central to our understanding of AD today.



INTRODUCTION

The world's population is rapidly aging, and the number of people with dementia is expected to grow from 35 million today to 65 million by the year 2030. In the United States alone, 5 million or 1 in 9 people over the age 65 are living with Alzheimer's disease (AD), the most common cause of dementia. For comparison, according to the Centers for Disease Control and Prevention (20092012 estimates), about 3 million older adults in the United States have asthma, 10 million have diabetes, 20 million have arthritis, and 25 million have hypertension. Primary care physicians and specialists alike will encounter older adults with dementia at an increasing frequency during their careers. As dementia carries significant implications for patients, their families, and our society, it is imperative for wellrounded physicians to have a solid understanding of this topic. The purpose of this review article is to provide a brief introduction to AD and the related concept of mild cognitive impairment (MCI). The article emphasizes clinical and neurobiological aspects of AD and MCI with which medical students should be familiar. In addition, the article describes advances in the use of biomarkers for diagnosis of AD and highlights ongoing efforts to develop novel therapies.

DEMENTIA

Dementia is a clinical syndrome (a group of cooccurring signs and symptoms) that involves progressive deterioration of intellectual function.4 Various cognitive abilities can be impaired with dementia, including memory, language, reasoning, decision making, visuospatial function, attention, and orientation. In individuals with dementia, cognitive impairments are often accompanied by changes in personality, emotional regulation, and social behaviors.

EPIDEMIOLOGY OF AD

AD is a critical public health issue in the United States and many other countries around the world, with a significant health, social, and financial burden on society. An estimated 5 million Americans have AD, with a new diagnosis being made every 68 sec.8 In the United States, AD is the fifth leading cause of death among older adults, and about $200 billion are spent annually on direct care of individuals living with dementia. Worldwide, it is estimated that 35 million people have AD or other types of dementia, and about 65 million people are expected to have dementia by 2030 (115 million by 2050).9 AD is a multifactorial disease, with no single cause known, and several modifiable and non-modifiable risk factors are associated with its development and progression. Age is the greatest risk factor for the development of AD. The likelihood of developing AD increases exponentially with age, approximately doubling every 5 years after age 65.10,11 The vast majority of individuals suffering from AD are aged 65 or older and have 'late-onset' or 'sporadic' AD (95% of all cases

NEUROPATHOLOGY OF AD

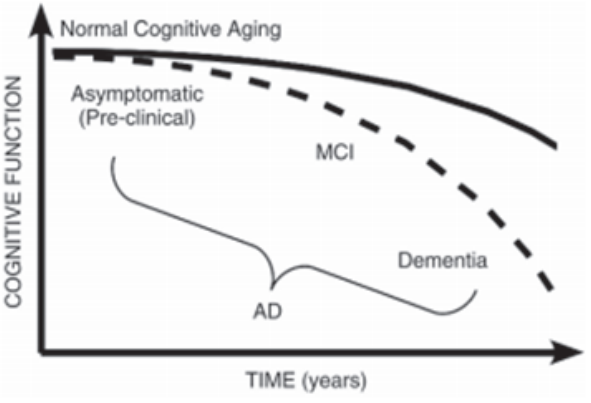
AD is a progressive neurodegenerative brain disorder that causes a significant disruption of normal brain structure and function. At the cellular level, AD is characterized by a progressive loss of cortical neurons, especially pyramidal cells, that mediate higher cognitive functions.17,18 Substantial evidence also suggests that AD causes synaptic dysfunction early in the disease process, disrupting communication within neural circuits important for memory and other cognitive functions.19 AD-related degeneration begins in the medial temporal lobe, specifically in the entorhinal cortex and hippocampus.20 Damage to these brain structures results in memory and learning deficits that are classically observed with early clinical manifestations of AD.

DIAGNOSIS OF AD

The gold standard for the diagnosis of AD is an autopsy-based (post-mortem) pathological evaluation. The presence and distribution of amyloid plaques and NFT in the brain is used to establish the diagnosis of 'definitive' AD and stage the disease.22 In clinical settings, the diagnosis of AD is largely based on medical history, physical and neurological examinations, and neuropsychological evaluation, as well as the exclusion of other etiologies using selective ancillary testing.

TREATMENT OF AD

There is no cure for AD, and drug therapy for the disease is still in its infancy. Approved medications for the treatment of probable AD help control the symptoms of AD but do not slow down the progression or reverse the course of the disease itself.12 At present, the mainstay of AD therapy are drugs that target neurotransmitter systems in the brain. AD primarily damages glutamateand acetylcholine-producing neurons and their associated synapses, and this damage correlates well with early cognitive symptoms of AD.19 Acetylcholinesterase inhibitors help improve memory function and attention in AD patients by interfering with the breakdown of acetylcholine, thereby increasing the levels of the neurotransmitter at the synapse. There are currently three FDA-approved cholinesterase inhibitors:27 rivastigmine and galantamine (for mild to moderate AD), and donepezil (for all stages of AD). Memantine is another FDA-approved medication for use in moderate to severe AD but belongs to a different class of drugs known as NMDA (glutamate) receptor antagonists.27 Both classes of medications are generally well-tolerated, with gastrointestinal upset, dizziness, and headache being the most common adverse effects observed. In recent years, a number of potential disease-modifying AD drugs have been evaluated in clinical trials, and several others are being evaluated in ongoing trials. Drugs that act to decrease the amount of Ab protein in the brain have received the most attention due to the prominent pathogenic role ascribed to Ab in the AD literature.



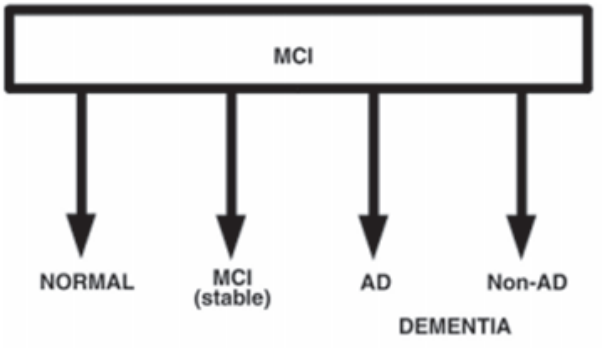
MILD COGNITIVE IMPAIRMENT

The MCI Concept

MCI is a syndrome characterized by memory and/ or other cognitive impairments that exceed the decline in cognition associated with the normal aging process. MCI is often regarded as a precursor to dementia or a transitional state between healthy cognitive aging and dementia (Fig. 1).37 The most widely used clinical criteria for the diagnosis of MCI are those proposed by Petersen and colleagues at the Mayo Clinic (Table 4).38 Researchers have also proposed several subtypes of MCI based on distinct neuropsychological profiles.39 Amnestic MCI involves memory-only impairments, while non-amnestic MCI involves only impairments in cognitive domains other than memory (e.g., executive function/attention, language, and visuospatial function).

BIOMARKERS OF AD AND MCI

Several neuroimaging and other biomarker approaches are being used to study AD and MCI. In the short term, biomarkers of AD are needed to improve the selection of patients in clinical trials, while in the long term biomarkers are needed to identify high-risk patients for early treatment as well as for monitoring disease progression and response to treatment. This section describes some of the widely used biomarker approaches and the related findings in AD and MCI.



MAGNETIC RESONANCE IMAGING

MRI uses a strong magnetic field and radio frequency waves to non-invasively characterize the structure of the brain by measuring the energy released by protons within various tissue components, such as gray matter, white matter, and cerebrospinal fluid (CSF). Volumetric MRI has been used to study regional patterns of brain atrophy in patients with MCI and AD.20,47,48 Medial temporal lobe atrophy, involving the hippocampus and entorhinal cortex in particular, is the earliest and most prominent MRI feature evident in AD and predicts progression from MCI to AD dementia.49 On volumetric MRI, AD patients also show marked enlargement of the lateral ventricles, portions of which are adjacent to the medial temporal lobe.50 Diffusion tensor imaging (DTI) is another MRI-based technique that, by measuring the diffusion of water molecules, is able to delineate the

organization of white matter in the brain and allows researchers to quantitatively assess the integrity of white matter fiber tracts.51

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography utilizing 18F-fluorodeoxyglucose (FDG-PET) as a radioactive tracer is a nuclear imaging technique which measures regional brain metabolism. The earliest sign of AD detectable on an FDG-PET scan is the hypometabolism of the posterior cingulate cortex and precuneus.54 This hypometabolism is also detectable at the MCI stage of the disease.55 FDGPET has also proven to be of value in distinguishing different forms of dementia, especially AD versus frontotemporal dementia.55,56

FLUID BIOMARKERS

CSF-based and blood plasma-based protein biomarkers are also being investigated for diagnosis of AD. Several studies have used immunoassays to measure the levels of various proteins in the CSF, finding that patients with AD show decreased levels of the 42 amino acid isoform of the Ab (Ab-42) peptide and elevated levels of the phosphorylated tau (P-tau) peptide.61,62 A recent longitudinal study showed that baseline Ab-42/ P-tau ratio could accurately predict the progression from MCI to AD.63

CONCLUSION

Since Alois Alzheimer described the first case of AD more than a century ago, much progress has been made in understanding the biology and clinical aspects of the disease. Substantial advances have been made in characterizing pre-dementia stages of AD, such as MCI, and improving the diagnostic and therapeutic options available for managing AD. Our ability to find the 'cure' for AD ultimately depends not only on having an accurate view of the cellular and molecular processes that go awry but also on having optimal biomarkers to enable early diagnosis and timely therapeutic intervention in at-risk individuals. Recognizing the urgent need to develop clinically useful neuroimaging and other biomarkers for the early detection of AD, the NIA sponsored the ongoing Alzheimer's Disease Neuroimaging Initiative (ADNI) beginning in 2004.62 The ADNI, which is akin to the Framingham Heart Study in its ambitions, is a publicprivate partnership and the largest project of its kind that seeks to collect longitudinal neuroimaging data along with clinical data, neuropsychological assessments, and biological specimens (e.g., blood and CSF) from MCI, AD, and healthy older subjects. The ADNI and similar large-scale initiatives are likely to rapidly advance our knowledge on dementia and AD and will catalyze the development of significantly more effective therapies for AD than exist today. To conclude, the reader is left with some important issues that must be resolved in the future as we move toward a 'cure' for AD in the 21st century:

(1) What is the optimal combination of biomarkers for
(a) early detection of AD; and
(b) monitoring disease progression and response to treatment?
(2) What is the optimal therapeutic strategy for
(a) prevention of AD;
(b) treatment of AD; and
(c) sporadic versus familial AD? (i.e., therapeutic targets, role of medications versus lifestyle modification, optimal time to intervene)

ACKNOWLEDGEMENTS:

I would like to thank Andrea Bozoki, MD (Michigan State University, Department of Neurology), for reviewing the material in this article on diagnosis and treatment. I am grateful to my grandmother Khana for inspiring me to conduct research on Alzheimer's disease and to pursue a career in clinical neuroscience.

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