Recent Advances in Alzheimer Dementia Biomarkers

A review submitted for partial fulfillment of requirements for master degree of Neurology and Psychiatry

By

Michael Elnemais Fawzy

M.B., B.Ch

Supervised by

Prof. Dr. Nevine Medhat El Nahas

Professor of Neuropsychiatry

Faculty of Medicine- Ain Shams University

Prof.Dr. Yousry Abo-Elnagaa Abd-Elhamid

Assistant Professor of Neurology

Faculty of Medicine-Ain Shams University

Dr. Doaa Abd Allah Elaidy

Lecturer of Neurology

Faculty of Medicine-Ain Shams University

Faculty of Medicine

Ain Shams University

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Aβ:	Amyloid β-peptide.
Ach:	Acetylcholine.
AD:	Alzheimer's disease.
ADAS:	Alzheimer Disease Assessment Scale.
ADCS-ADL:	Alzheimer's Disease Cooperative Study Activities of Daily Living.
APP:	Amyloid precursor proteins.
BACE:	β-site APP-cleaving enzyme.
BDNF:	Brain-derived neurotrophic factor.
BRSD:	Behavioral Rating Scale for Dementia.
CDR:	Clinical Dementia Rating.
CGIC:	Clinical Global Impression of Change.
CSF:	Cerebo spinal fluid.
DAD:	Disability Assessment for Dementia.
DLB:	Dementia with Lewy body.
DTI:	Diffusion tensor imaging.

FGF:	Fibroblast growth factor.
^{18}FDG:	^{18}Fluorodeoxyglucose.
FTD:	Frontotemporal dementia.
GAS:	Goal Attainment Scaling.
GDS:	Global Deterioration Scale.
MCI:	Mild cognitive impairment.
MMSE:	Mini mental state examination.
MSAD:	Mild to Severe Alzheimer's Disease
MRI:	Magnetic resonance imaging.
MRS:	Magnetic resonance spectroscopy.
NFTs:	Neurofibrillary tangles.
NPS:	Neuropsychiatric symptoms.
NPI:	Neuropsychiatric Inventory.
NT:	Neurotrophin.
NINCDS-ADRDA:	National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's disease and Related Disorders Association.
PET:	Positron emission tomography.

PIB: Pittsburgh Compound B.

p-tau: Hyperphosphorylated tau protein.

SPECT: Single photon emitting tracer.

t-tau: Total tau protein.

VaD: Vascular dementia.

VBM: Voxel-based volumetry.

VDCC: Voltage-dependent chloride channel.

α-sec: α-secretase.

β-sec: β-secretase.

γ-sec: γ-secretase.

Alzheimer's disease is an irreversible degeneration of the brain that causes disruptions in memory, cognition, personality, and other functions that eventually leads to death from complete brain failure. Alzheimer's disease usually begins after age 60 and risk increases with age. Younger people in their 30s, 40s and 50s may get Alzheimer's disease, but it is rare. Approximately 5 percent of all cases of Alzheimer's disease are believed to be familial (hereditary). In familial cases, often called early-onset Alzheimer's disease, symptoms typically appear within the age range of 30 - 60 years. Alzheimer's disease represents around 70% of all cases of dementia. Making it the most common cause of dementia and Death from Alzheimer's disease is often underreported or misdiagnosed ***(Wilkinson and Roughan, 2007).***

Common symptoms of Alzheimer disease include: disturbances in memory, attention, and orientation, changes in personality, language difficulties, and impairments in gait and movement. Mood and behavioral symptoms are prevalent in the early stages of AD and their occurrence may precede a diagnosis by up to 3 years. Once present, these symptoms tend to worsen, becoming more prominent and recurrent manifestations of the disease. The most frequently reported mood and behavioral symptoms are apathy (exhibited by 70% of patients), agitation (occurring in 60% of patients) and anxiety (48% of patients). Irritability, dysphoria, aberrant motor behavior, disinhibition, delusions and hallucinations are also common manifestations ***(Gauthier, et al., 2007).***

On average, patients with Alzheimer's disease live for 8 to 10 years after diagnosis, but this fatal disease can last as long as 20 years, or as little as 3 to 4 years if the patient is over 80 years old when diagnosed ***(Roy and Jody, 2007).***

The lifetime risk of Alzheimer's disease among those who reached the age of 65 is approximately 1 in 5 for women and 1 in 10 among men. In the absence of disease, the human brain often can function well up to the 10th decade of life ***(Roy and Jody, 2007).***

The neuropathologic hallmarks of AD are neuritic plaques and neurofibrillary tangles that forms insoluble clumps in the brain and initiate a cascade of events leading to neuronal dysfunction and death. The identification of these mechanisms has helped to understand the pathology of the disease and will aid in the development of therapeutic strategies ***(Yaari and Corey, 2007).***

Neuro imaging and brain mapping techniques offer extraordinary power to understand AD, providing spatially detailed information on the extent of the disease as it spreads in the living brain. Computational anatomy techniques, applied to large databases of brain MRI scans, reveal the dynamic sequence of cortical and hippocampal changes with disease progression and how these relate to cognitive decline and future clinical outcomes **(*Liana and Paul, 2007).*** Cerebrospinal fluid concentrations of amyloid $ß_{42}$ ($Aß_{42}$) peptides and tau proteins may serve as biomarkers for AD (***Thierry, et al., 2007).***

Alzheimer's disease is the 6th leading cause of death in the United States. Worldwide, nearly 36 million people are believed to be living with Alzheimer's disease or dementia. That number is projected to increase to 65.7 million by 2030 and 115.4 million by 2050. Among those who do not personally have Alzheimer's disease, one third worries about getting Alzheimer's. Those who have a parent or parents in law with the disease are even more concerned (***Thierry, et al.,* 2007).**

Normal Aging

It is important to distinguish the normal aging processes from the consequences of particular diseases. Although the likelihood of poor health increases in later life, poor health is not the same as aging.

Normal aging, or senescence, refers to a gradual, time-related biological process that take place as degenerative processes overtake regenerative or growth processes. All individual, if they live long enough, will experience senescence. In contrast, diseases associated with later life, such as Alzheimer's disease, arthritis, or cardiovascular disease, affect some individuals and not others. The biological declines associated with normal aging are relatively mild and gradual compared with the severity and swiftness of the impairments associated with disease.

Primary and Secondary Aging

A conceptual distinction is made between the concept of primary aging and secondary aging. Primary aging, which the same as senescence, refers to the changes that are gradual, inevitable, universal, and insidious. These changes occur in representative individuals living under representative conditions; changes associated with primary aging are not consequences of disease. Secondary aging refers to the processes that affect the rate at which primary aging occurs. Intense work-related stress, prolonged exposure to environmental toxins, and the consequences of disease are examples of secondary factors that accelerate the rate of primary aging processes ***(Hoyer and Roodin, 2003).***

The concept of age

The concept of age is multidimensional. Time since birth (chronological age) is not always a good measure of developmental function. Given the fact that chronological age is not always a proper predictor of functional age, researchers found it increasingly important to develop valid and reliable measures of person's functional abilities ***(Birren and Schroots, 2001)?***

Chronological age

It refers to the number of years that have elapsed since a person's birth. Chronological age per se is often not an accurate index of psychological development. Age is merely a rough marker for processes that influence behavior over time ***(Birren and Schroots, 2001).***

Biological age

It has been defined as an estimate of the individual's position with respect to his or her potential life span. This concept of age involves measures of the capacities of an individual's vital organ system. From this perspective, age is an index of biological health. An individual's biological capacities may differ from those of other persons of the same chronological age ***(Birren and Schroots, 2001).***

Psychological age

It refers to the individual's adaptive capacities; his ability to adapt to changing environmental demands. Individuals adapt to their environments by drawing on various psychological characteristics: learning, memory, intelligence, emotional control, motivational strengths, and coping styles. Therefore, adults who posses such psychological

characteristics to a greater degree than their chronological age-mates are considered "psychologically young", compared with those who possess such traits to a lesser degree ***(Birren and Schroots, 2001).***

Social age

It refers to the social role and expectations people hold for themselves as well as those others impose on them. Considering the role of mother and the behaviors that accompany that role; it is probably more useful in predicting these behaviors to know that a woman is the mother of a 3-year-old child than to know whether she was born 20 or 30 years ago.

The concept of successful aging

There is a current need to increase or improve opportunities for optimal development across life span ***(Lerner, 2001).*** Measures of biological age, psychological age, and social age are relevant to healthy development or successful aging. Successful aging refers to the combination of three components:

1) The avoidance of disease and disability

2) The maintenance of high physical and cognitive capacity in the later years of life.

3) Continued active engagement with life.

In many countries, aging is associated with disability, cognitive and deficits. But substantial and growing evidence indicates that the risk factors for some diseases, such as cardiovascular diseases, can be modified .Research also shows that cognitive deficits and social

disengagement are not inevitable consequences of growing older ***(Vaillant and Mukamal, 2001, Freund and Baltes, 2002).***

Brain aging

Age-related changes in the nervous system may have dramatic effects on the behavioral, cognitive, and personality functioning of the aging individual.

Brain Structure

In an evolutionary sense, the brain stem is the oldest part of the brain. It controls basic biological functions such as breathing and heart rate. The ascending reticular activation system (ARAS), a structure that originates within the brain stem and extends to the other portions of the brain, regulates an individual's state of consciousness and level of arousal. Attached to the brain stem is the cerebellum. This structure helps maintain balance and posture and coordinate body movements. Also, memories for simple learned responses seem to be stored here ***(Woodruff-Pak, 1997).***

The limbic system is a border area between the older parts of the brain (the brain stem and cerebellum) and the newer part of the brain (the cerebral cortex). One part of the limbic system is the hypothalamus that controls eating, drinking, body temperature, and sexual activity. Another component of the limbic system is the hippocampus. A great deal of evidence suggests that the hippocampus plays a major role in memory.

Patients who suffer from amnesia and other disorders characterized by memory failure, display significant damage to the hippocampus. Furthermore, biological changes in the hippocampus that accompany

normal aging may be responsible, in part, for decline in memory abilities with advancing age ***(Raz, 2000, Schacter, 2000).***

The cerebrum is the largest, and evolutionarily the most recent, part of the brain. It totally covers the limbic system as well as significant portions of the brain stem and cerebellum. The cerebrum can be divided into the two hemispheres—the right and the left, and a tract of nerve fibers called the corpus callosum connects the hemispheres. The top covering of the cerebrum is called the cerebral cortex. The cortex may be the most important part of the brain. In fact, it is the cortex which makes us "human"; it serves as the source of personality, cognition, perception, communication, and creativity. The cortex may be divided into four different regions called lobes, where various psychological functions are housed. The frontal lobe is responsible for basic aspects of personality and social behaviors, planning and execution of complex behavioral sequences, and control of motor movements. In the temporal lobe authors find structures involved in the consolidation of long-term memories, in the assigning of emotional properties to incoming experiences, and in simple auditory sensation. The parietal lobe influences the construction of a spatial representation of one's body. Finally, the occipital lobe controls basic visual processing ***(Hoyer and Roodin, 2003).***

As individuals age, they become more likely to suffer from damage or injury to the cortex. Also with aging, the brain becomes less plastic. This means that uninjured parts of the cortex are less likely to take over the functions of injured cortical areas. Damage to the elderly brain usually results from a stroke or a brain tumor. Strokes occur when brain tissue is deprived of oxygen, often when a blood vessel in the brain becomes clogged, plugged, or broken ***(Hoyer and Roodin, 2003).***