INTRODUCTION

Aging is an inevitable and undeniable process that impacts all aspects of our lives. It is associated with a broad range of physiological and psychological changes, including a decline in cognition which contributes to loss of independence and a lower quality of life ***(De Carli, 2003).***

This dementia is slowly progressive with prominent memory disturbance appearing early in the clinical presentation. As the disease progresses, other cognitive domains become involved and behavioral alterations also arise ***(Lyketsos et al., 2000).***

Alzheimer's disease (AD) is the most common cause of the dementia syndrome in later life and has reached epidemic proportion with the explosive growth of the number of the elderly ***(Lyketsos et al., 2000).*** The Prevalence of dementia in Egypt was estimated to be 2% in the urban community and 3.5% in rural community. In the urban community 57% of Egyptians with dementia had AD ***(El-Okl et al., 2002).***

Mild cognitive impairment (MCI), a transitional condition between normal aging and dementia, is characterized by the presence of cognitive dysfunctions in the absence of significant functional loss ***(Petersen et al., 2001).***

Patients with MCI are at higher risk for developing Alzheimer disease (AD) with an estimated conversion rate of 10 to 15% per year. Nonetheless, MCI is a heterogeneous entity characterized by differences in cognitive profile and clinical progression, possibly due to the interplay of genetic, physiologic, and environmental factors ***(Luis et al., 2003).***

Inflammatory mechanisms are associated with AD and they could have a role in contributing to the pathogenesis of this disease. The evidence is based on histopathological brain studies, laboratory studies of peripheral inflammation and the fact that certain anti-inflammatory drugs could modify the course of AD ***(Gupta and Pansari, 2003).***

Activated microglia and astrocytes that accumulate in amyloid beta (Aβ) plaques express pro-inflammatory cytokines, such as acute phase proteins C-reactive protein (CRP) and 1-antichymotrypsin (ACT), and this precedes the neurodegenerative changes in AD neocortex ***(Veerhuis et al., 2003).***

Alpha-1-antichymotrypsin (ACT) is an acute phase protein and a protease inhibitor produced by the liver and brain. ACT is involved in the pathogenesis of Alzheimer's disease (AD), since elevated ACT concentration was found in cerebrospinal fluid (CSF) and brain from AD. ACT has also been shown to influence amyloid deposition in vitro and in animal models of AD ***(Porcellini et al., 2008).***

C-reactive protein has been found in and around Aβ plaques in the brains of patients with dementia. High-sensitivity C-reactive protein (hs-CRP) is a sensitive marker of systemic low-grade inflammation, and increased serum concentrations of hs-CRP has been associated with impaired cognition and an increased risk of vascular dementia and Alzheimer's disease in some follow-up studies ***(Pirjo et al., 2007).***

Apolipoprotein E (ApoE), a major component of lipoproteins, is synthesized primarily in the liver. Also It is produced in the brain, and has significant functions in central nervous system integrity and remodeling ***(Mahley and Rall, 2001).***

ApoE is a polymorphic protein encoded by a gene on chromosome 19. There are three common alleles; ApoE-e_2, ApoE-e_3, ApoE-e_4, which differ only on the basis of one or twoamino acids on positions 112 and 158. The three alleles, e2, e3, and e4, determine the polymorphism leading to the occurrence of six phenotypes, e2/2, e3/3, and e4/4 in homozygotes and e2/3, e2/4, and e3/4 in heterozygotes ***(Dietschy and Turley, 2001).***

APOE4 allele is the most common susceptibility gene for AD. It influences the course of disease by increasing the risk for developing AD and lowering the age at disease onset ***(Corder et al., 1993).***

Recent work in a variety of populations shows that the Apolipoprotein APOE4 allele, a major risk factor for dementia, Alzheimer's and vascular dementia, may modify CRP such that it is lower among carriers of the '4' allele than in non carriers ***(van Oijen et al., 2007).***

AIM OF THE WORK

To assess the relation between inflammatory markers [C-reactive protein (CRP), alpha 1-antichymotrypsin], APOE4 gene and cognitive functions among elderly patients with AD and MCI compared to elderly with normal cognitive function.

AGING AND COGNITION

Aging is an inevitable and undeniable process that impacts all aspects of our lives. It is associated with a broad range of physiological and psychological changes, including a decline in cognition which contributes to loss of independence and a lower quality of life ***(De Carli, 2003).***

Cognitive aging is defined as a pattern of mild age-related decline in cognitive functions. This includes decline in general cognitive function as well as a domain-specific decline in fluid reasoning, mental speed, episodic memory and spatial ability ***(Deary et al., 2000).***

Normal expected age-related memory functions

- Memory functions that remain relatively stable with increasing age:
    - Semantic memory: Facts and general knowledge about the world; remains stable with age, especially if the information is used frequently (However, retrieval of highly specific information, such as names, typically declines).
    - Procedural memory: Acquisition and later performance of cognitive and motor skills.

(Luo and Craik, 2008)

- Memory functions that decrease with age
    - Working memory - Holding and manipulating information in the mind such as reorganizing a short list of words into alphabetical order; verbal and visuospatial working speed, memory, and learning, with visuospatial cognition more affected by aging than verbal cognition.

(Jenkins et al., 2000)

    - Episodic memory: Personal events and experiences
    - Processing speed
    - Prospective memory: The ability to remember to perform an action in the future such as remembering an appointment or to take a medication.
    - Age-related decline in the ability to remember new text information, to make inferences about new text information, to access prior knowledge in long-term memory, and to integrate prior knowledge with new text information.
    - Declines in recollection.

(Head et al., 2008; Luo and Craik, 2008)

Brain Pathology of Cognitive Aging

In humans, the number and length of dendritic segments in specific layers of dorsolateral prefrontal cortex decreases with age, together with a decrease in dendritic spine and synaptic density ***(Uylings and de Brabander, 2002).***

In the non-demented elderly population, the entorhinal cortex and the basal forebrain display diffuse plaques as well as neurofibrillary tangles or pre-tangle tau pathology. It is possible that these lesions also contribute to cognitive aging ***(Mesulam et al., 2004).***

In vivo Structural and Functional Imaging

Recent technical advances permit the investigation of age related brain changes in humans during lifetime.

- In a large cross sectional structural magnetic resonance imaging (MRI) study, medial temporal structures such as the hippocampus or the entorhinal cortex did not show measurable diminution of volume ***(Good et al., 2001).***

- A second in vivo brain imaging technique, positron emission tomography (PET), showed that aging is associated with a decline in glucose metabolism in specific brain regions, such as the anterior cingulate and perisylvian cortex and with changes in neurotransmitter systems, such as a decrease in

D2 dopamine receptors and presynaptic dopamine transporters This dopaminergic decrease may be related to the decrease in mental flexibility that occurs with aging ***(Herholzet al., 2002).***

Aging as a Risk Factor for Neurodegenerative Disease

The strongest risk factor for probable Alzheimer's Disease (AD) is age. Over our lifespan the consequences risk of neurodegenerative disease (indirect consequence of aging). Alternatively, the aging process by itself may be associated with changes that increase the risk of AD (direct effect of aging) ***(Vandenberghe and Tournoy, 2005).***

Indirect consequences of aging

Epidemiological studies provide evidence for an association between probable AD and mid-life hypertension, diabetes mellitus, and hyperhomocysteinaemia ***(Knopman et al.,2001a).***

Clinical stroke is also an important risk factor for the development of AD. In the absence of clinical stroke, the presence of white matter hyperintensities on T2 MRI also increases the risk of dementia ***(Vermeer et al., 2003).***

Direct consequences of aging

Aging and the amyloid cascade hypothesis

In humans, monkeys, and transgenic mice, Amyloid beta (Aβ) levels increase with age. Logically, this could happen through major mechanisms:

1. Increased production of total Aβ or Aβ 42:

Total amyloid precursor protein (APP) mRNA or protein brain levels do not increase with age but there is a significant relative increase in mRNA for two APP isoforms as a result of alternative splicing comparatively increase the production of Aβ ***(Vandenberghe and Tournoy, 2005).***

Activity of b-secretase, a necessary enzymatic step in the production of Aβ, also increases with age in the cortices of both humans and monkeys because of age related post-translational changes ***(Fukumoto et al., 2004).***

2. Reduced Aβ clearance

Neprilysin and insulin degrading enzyme (IDE) are two important Aβ degrading enzymes. The age related changes in these enzymes differ between regions and no clear picture has emerged until now. A genetic polymorphism of apolipoprotein E (APOE) (e4-e4 and e4-e3) is associated with an earlier onset

of the AD in a dose dependent manner. APOE binds to the very low density lipoprotein (VLDL) related protein receptor and also to amyloid plaques. One possible explanation for the association between AD and the APOE polymorphism is that the e 4 polymorphism is associated with a reduced clearance of Aβ 42.

Not only does Aβ 42 increase with age, the toxicity of Aβ may also augment with age. The gradual load of toxic Aβ species can further induce tauopathy, inflammatory changes, and oxidative stress, events that are already setting off in normal aged brains and could intensify Aβ induced pathology ***(Vandenberghe and Tournoy, 2005).***

Mild Cognitive Impairment (MCI)

Definition

MCI is a syndrome defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life **(*Gauthier et al., 2006).***

Current definition

- Subjective memory or cognitive deficit

Objective memory or cognitive deficit

- (assessed via performance on cognitive tests)
- Unimpaired activities of daily living
- Absence of a clinically diagnosable dementia

(Frank and Petersen, 2008)

Epidemiology

Its estimated prevalence in the general population is 19% among individuals age <75, and 29%inthoseage >85.Prevalence of the MCI amnesic-type was 6% and of the MCI multiple cognitive deficits-type was 16% ***(Lopez et al.,2003).***

Types of MCI

Discrepancies between the different definitions of the MCI concept mainly consist of the number and type of the impaired cognitive domains. Primarily, the MCI concept only

requires impairment in memory with preserved general cognitive functioningat the same time ***(Petersen et al., 1999).***

Today, MCI can be divided into 4 subtypes:

- **Amnestic MCI (aMCI) single domain:** objective impairment in memory but not in another cognitive domain.
- **Amnestic MCI (aMCI) multiple domain:** objective impairment in memory and in at least 1 other cognitive domain.
- **Non-amnestic MCI (naMCI) single domain:** objective impairment in a single cognitive domain other than memory.
- **Non-amnestic MCI (naMCI) multiple domain:** objective impairment in at least 2 cognitive domains other than memory.

(Petersen, 2004; Winblad et al., 2004)

Criteria for amnestic mild cognitive impairment (a-MCI)

1. Memory complaint usually corroborated by an informant.
2. Objective memory impairment for age.
3. Essentially preserved general cognitive function.
4. Largely intact functional activities.
5. Not sufficiently impaired, cognitively and functionally, to meet clinical criteria for dementia according to Diagnostic and Statistical Manual of mental disorders, fourth edition (DSM-IV), as judged by an experienced research clinician ***(Petersen,2004).***

- ***Causes of MCI:***

A. Disorders that have a strong relationship with mild cognitive impairment and that can often be easily recognized by clinical examination and/or ancillary tests are:

Parkinson's disease, Huntington's disease, severe brain trauma, brain infections, large intracerebral tumors, cerebral bleeding, large cerebral infarcts, extensive white matter pathology, severe depression, psychotic disorders, longstanding and severe alcohol intoxication, drug intoxication (i.e.prolonged use of high doses of benzodiazepines), severe thiamine or vitamin B12 deficiency, unregulated diabetes mellitus, Hypertension or thyroid disorders ***(Visser, 2003).***

B. Disorders that have a strong relationship with mild cognitive impairment, but that are difficult to recognize by clinical assessment and/or ancillary tests are:

Predementia or prodromal stage of Alzheimer's disease, Lewy body disease, frontotemporal dementia, vascular dementia, Parkinson's disease, multiple system atrophy, or Huntington's disease ***(Visser, 2003).***

C. Disorders that have a weak relationship with mild cognitive impairment:

Mild brain trauma, transient ischemic attack, epilepsy, disorders that chronically or temporarily impaired brain perfusion (hyper/hypotension, stenosis of the carotid artery, generalized atherosclerosis, cardiac surgery), mild depression, bipolar disorders, anxiety disorders, regulated diabetes mellitus or thyroid disorders, vitamin deficiency, heart failure, obstructive sleep apnea syndrome, chronic obstructive pulmonary diseases (COPD), anemia, severe liver or kidney disorders, hearing loss ***(Visser, 2003)***.

- **Concomitant pathogenic factors in MCI**

Several clinical pathological studies have reported that some patients with aMCI had other concomitant neuropathologic features, which may contribute to the clinical presentation of the subjects. For example, aMCI cases also display argyrophilic grain disease, hippocampal sclerosis and vascular disease ***(Petersen et al., 2006).***

Macroscopic cerebral infarcts without a pathologic diagnosis of AD, were found to be more common in naMCI (18.6%) compared to aMCI (13.3%) ***(Schneider et al., 2009).*** Certain vascular dementia subtypes, particularly those related to subcortical microvascular disease, may be preceded by MCI,