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Research Article

ALZHEIMER DEMENTIA: CAN BE PREVENTED BEFORE SYMPTOMS START?

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Abbreviations
Aβ =Beta-amyloid protein; AD= Alzheimer disease; ApoE= Apolipoprotein E; APP=Amyloid precursor protein ; CSF= Cerebrospinal fluid; MCI= Mild cognitive impairment; MID= Mediterranean diet; NFT= Neurofibrillary Tangles; NIA=National Institute on Aging; PET=positron emission tomography

A B S T R A C T

Alzheimer disease (AD) is a neurodegenerative disease. It is the most common cause of dementia. Its symptoms start to appear after many years of asymptomatic pathophysiology of the brain's neural cells. In 2012, the National Institute on Aging (NIA) and the Alzheimer's Association established a new guideline that classified Alzheimer disease AD into three stages, which are pre-clinical stage, mild cognitive impairment (MCI) stage and lastly dementia due to AD. Since that time until 2017, most of the Alzheimer's researches were focusing on how the disease can be diagnosed in pre-clinical stage. There are many benefits behind the early diagnosis of AD, especially if we know there is no cure for the disease until now. Early diagnosis can be decelerating the progression of the disease, through early intervention with medication and applying the protective value. As many neurosciences' physicians believed, future planning to deal with AD depended mostly on early diagnosis to preserve brain function.

INTRODUCTION

Dementia is a progressive decline in the cognitive function of the brain, in which cerebral cortex can be entirely or partially affected (Kumar and Clark's, 2009). It is a collection of symptoms rather than a disease, that resulted from damaging neurons in the brain. It is characterized by cognitive and memory loss without any alertness or consciousness deterioration (Chapman, Williams, Strine, Anda, & Moore, 2006). The cognitive impairment include many symptoms (memory loss, difficulty in understanding words and failure to recognize people or objects) (Chapman *et al*., 2006). Moreover, patients with dementia usually experience social and occupational behavior issues. In 2015, over 46 million people were living with dementia worldwide (Prince, 2015). This number thought to be doubled every 20 years, as published on (world Alzheimer report, 2015), reaching to 74.7 million in 2030 and 131.5 million in 2050. Dementia has many causes as listed in Table 1(Barker *et al*., 2002). The most common cause of dementia is Alzheimer's disease AD, which is account for 60 to 80% of all causes of dementia (Yiannopoulou & Papageorgiou, 2013).

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AD and Dementia

AD is a 6th leading cause of death in US (Xu, Kochanek, Murphy, & Tejada-Vera, 2016). From 1984 to 2011, international guidelines for AD diagnosis was based on clinical symptoms of dementia (G. McKhann *et al*., 1984). On 2011, the National Institute of Aging and the Alzheimer's Association established new guidelines that classified AD into three stages, pre-clinical stage, Mild cognitive impairment (MCI) stage, and lastly dementia due to AD. Moreover, AD diagnostic criteria have been modified based on starting of MCI associated with positive biomarkers (cerebrospinal fluid analysis and positron-emission tomography imaging) (G. M. McKhann *et al*., 2011)**.**

Table 1 Causes of dementia

Degenerative causes	Alzheimer's disease Dementia with Lewy bodies Front temporal lobar degeneration Parkinson's disease
Vascular	Vascular dementia
Metabolic	Uremia and Liver failure
Toxic	Alcohol
Vitamin deficiency	B12 thiamin
traumatic	Brain injury
Intracranial lesion	Subdural hematoma tumors
infection	HIV
endocrine	Hypothyroidism hypoparathyroidism
Psychiatric	pseudodementia

Source :(Terry & Davies, 1980)

Alzheimer Disease

AD is a neurodegenerative slowly progressive brain disease (Alzheimer's Association report, 2017). It has been discovered since 1906 (Lage, 2006). From that time until now, no obvious therapeutic intervention is produced for complete cure of the disease. The first AD drug AD was approved in 1993, known as Cognex (anticholinesterase drug) (Miller, 2000). Up to date, all drugs that approved to treat AD are only symptomatic therapies, therefore no intervention is known to prevent, slow or stop the progression of the disease. That raises so many questions and controversies and this field became the focus of interest for the neuroscience researcher.

Risk Factors

The main cause of AD still unknown, but there are many risk factors contributed to develop the disease. Some of them are modifiable risk factors and others are not as summarized in Table 2. Age and genetic are both considered as the most important risk factors (Roses, 1996).

Table 2 Risk factors of AD

Modifiable Risk Factor	Unmodified Risk Factor
• Depression (Green *et al*., 2003). • Low thyroid stimulating hormonelevel (Van Osch, Hogervorst, Combrinck, & Smith, 2004). • Lack of physical activity (Scarmeas *et al*., 2009). • Obesity at midlife (Kivipelto *et al*., 2005)	• Age (Folch *et al*., 2016; Lindsay *et al*., 2002). • Genetic factors e.g. apolipoprotein E gene (Tsai *et al*., 1994). • Female Sex after menopause mostly due to estrogen deficiency (Paganini-Hill & Henderson, 1994).

Pathophysiology

The main pathological changes in AD are accumulation of amyloid protein plaques outside the neurons (Aβ),accumulation of neurofibrillary tangles (NFT) inside the neurons and exaggerated inflammatory response (Dá Mesquita *et al*., 2016). These abnormal proteins are found to be accumulated primary in the brain region that are essential for memory such as entorhinal cortex and hippocampus (Du *et al*., 2004). Laterally, cerebral cortex that responsible for language, cognitive, and social behavior will be also affected. At late stage of the disease, many areas of the brain like cerebral cortex, ventricles and hippocamps can be severely damaged(Du *et al*., 2004).

Amyloid Beta Protein Plaques (Aβ)

Aβ peptide is 40–42 amino acids substance (Kim N Green, 2010). It has a major role in pathophysiology of AD. Brain Aβ pathology is thought to occur as a result of genetic mutation in either APP (amyloid precursor protein) gene , presenlin1 (PS1) or presenlin2 (Dá Mesquita *et al*., 2016). The proteolytic APP cleavage by action of α-, β- or γ- secretase is a main different in physiological and pathological condition. In physiological condition, APP is cleaved by α-secretase (Kim N Green, 2010) into soluble non-amyloidogenic substance (sAPPα) which acts as neuroprotective substance. In amyloidogenic pathological condition, β secretase enzyme cleaved APP on another cleavage sites, and then γ-secretase did another cleavage, which create $A\beta_{40}$ and $A\beta_{42}$.$A\beta_{40}$ and $A\beta_{42}$are a serious end products for Aβ peptide aggregation (F Lichtenthaler, 2012), which are deposited in extracellular space as senile plaques (Korczyn, 2008). It has been found that, $A\beta_{42}$ is the major component of plaque (Gu & Guo, 2013). This deposition found to be occurred between the neurons leading to synaptic dysfunction and neural death.

Neurofibrillary Tangles (NFT)

NFT is a toxic aggregation insoluble fiber forming abnormally within brain's cells, composed of hyper-phosphorylated tau. Tau protein is normally found in microtubules and plays an important role in microtubule stabilization. It can indirectly regulates synaptic construction and function (Brion *et al*., 2001). When tau protein is hyper-phosphorylated abnormally (either by Cyclin-dependent protein kinase 5 or glycogen synthase kinase-3β), it separates from the microtubular system and produces intraneuronal aggregated NET, which block transport system in neural cell, espicaly in memory area leading to cognitive impirments (Du *et al*., 2004).However, the cause and mechanism of tau hyperphosphorylation still not fully known.

Chronic Inflammation

Inflammation and immune disturbance are another hallmark of AD. Microglia is a brain phagocytic cell, has a major role to clean debris, waste and foreign particles. Normally, it presents in inactive state. (Meraz-Ríos, Toral-Rios, Franco-Bocanegra, Villeda-Hernández, & Campos-Peña, 2013). In AD, when Aβ plaques accumulate and aggregate outside neuron, the microglia is activated, producing acute and chronic response against this aggregation. This activation leads to production of nitric oxide, reactive oxygen species, pro inflammatory cytokines (interleukin-1 ,interleukin-6, tumor necrosis factor α) and Prostaglandin E2 (Lue *et al*., 2001). These mediators stimulate astrocyte, which all producing local inflammation and increasing the proinflammatory signals, leading to neural injury (Meraz-Ríos *et al*., 2013).

These pathological changes gradually appear over years and cause undetectable changes in memory and mental status. During this slowly building up the patient looks almost healthy (Karlawish, Jack, Rocca, Snyder, & Carrillo, 2017). It has been found that, brain changes that associated with AD began around 20 years before the clinical symptoms start to appear on the patient (Beason-Held *et al*., 2013). Attractively, Heiko Braak suggested that in AD, pathological aggregation in the brain may started as early as 50 years before appearing of clinical symptoms (Braak & Braak, 1995).

Recently, it has been found that diagnosis of AD in the first 2 stages may be more effective in reducing manifestation of AD dementia (Rajan, Wilson, Weuve, Barnes, & Evans, 2015). According to that finding, all new researches in AD in last year's were focused on the diagnosis of AD before dementia start (Dubois, Padovani, Scheltens, Rossi, & Dell'Agnello, 2016; Forlenza *et al*., 2015; Herukka *et al*., 2017; Sevigny *et al*., 2016).

Future plane to decrease incidence of alzheimerdementia

The principles, that are now suggested to decrease the incidence of Alzheimer associated dementia, are combined between improvement of education level (Dartigues, Foubert-Samier, & Helmer, 2013), protective factors (healthy diet and regular exercise) and early diagnosis of pathological changes of the disease.

Education and AD

It has been found that, low education level is associated with increased incidence of AD (Dartigues *et al*., 2013). Improvement of educational level has been strongly associated with decrease the incidence of AD (Dartigues *et al*., 2013). One study done on 2000, divided the people into three study level groups to identify the association between education level and incidence of AD, and the result has been shown that the risk of AD is increased with decreasing years of education (Letenneur *et al*., 2000). However, most but not all studies reach to this conclusion (Sharp & Gatz, 2011).

Exercise and AD

Moderate intensity exercise associated with increase cerebral neural activity, brain metabolism and cerebral blood flow to supply skeletal muscle (Barnes, 2015; Ogoh & Ainslie, 2009). In 2006, one study was done over 1740 individuals older than 65 years. All of them were have normal cognitive behavior at the time of study. After 6 years following up, it has been found that, those who were exercised 3 or more times per week were had 32% reducing risk to development of cognitive impairment in compared with individual who were unexercised or exercised less than 3 times per week (Tiukinhoy & Rochester, 2006). Another study done on 299 old individuals with mean age of 78 years, suggested strong relation between regular walking (more than 72 blokes per week) and volume of gray matter in frontal, entorhinal, occipital and hippocampus regions, and therefore reducing risk of cognitive impairment (Erickson *et al*., 2010). From these two studies and many others, regular exercise is one of the important factor to protect the brain against neurodegenerative disease (Barnes, 2015).

Healthy Diet and AD

There were many studies that assessed the beneficial effects of certain types of food to slower the progression of AD (Lista, Dubois, & Hampel, 2015). Mediterranean diet (MID) refers to diet composed mainly on high amount of vegetables, fruits, beans, cereals, unsaturated fatty acids (olive oil), moderate amount of milk products, and low amount of meat and saturated fatty acids (Singh *et al*., 2014). It has been found that MID associated with 33% reducing risk of MCI as well as reducing the progression of MCI to AD (Singh *et al*., 2014). MID is found to be associated with low levels of C reactive protein and anti-inflammatory cytokines (Fung *et al*., 2005), therefore it can reduce inflammation and oxidative stress during AD pathophysiology (Steele, Stuchbury, & Münch, 2007). MID is also associated with reduced risk of cardiovascular disease and insulin resistance which are both risk factors for AD (Singh *et al*., 2014).

Another type of food that had been studied and showed its effectiveness in reducing AD is *Docosahexaenoic acid (DHA)*, which is omega 3 fatty acid. It is active component of fatty fish (Horrocks & Yeo, 1999). In multi animal model studies, protective effect of DHA against Aβ accumulation and hyperphosphorylation of tau were confirmed (Calon & Cole, 2007). On humans, it has been found that decrease level of DHA in the brain associated with cognitive decline and onset of AD,(Horrocks & Yeo, 1999) due to its ability to reduce Aβ generation and deposition in the brain (Grimm *et al*., 2011). However, the exact mechanism behind that still not fully clear. Interestedly,caffeine is another component that can protects the brain from AD due to its anti-oxidant property (Arendash & Cao, 2010). It has been found that, drinking of 3 to 5 cups of coffee per day can decrease the risk of dementia and AD in late life by 65% (Eskelinen & Kivipelto, 2010). Some studies were done to find a beneficial effect of specific type of fruits against cognitive decline**.** Citrus fruits, blueberries and strawberries have anti-oxidant and anti-inflammatory properties, and therefore having a role in brain health and reducing the risk of cognitive decline (Devore, Kang, Breteler, & Grodstein, 2012). Besides, cherry juices are rich in melatonin, and significantly associated with enhance sleep quality and therefore protect from cognitive impartment (Howatson *et al*., 2012; McCune, Kubota, Stendell-Hollis, & Thomson, 2010).

Social Activity and AD

Different activities (reading, writing, dancing, traveling and games) were found to protect the person against cognitive decline, MCI and therefore AD (Akbaraly *et al*., 2009). Many studies have been found that marital status is associated with AD. The risk of AD in person who lives alone (either separated, divorced, widowed or never married) is increased,(van Gelder *et al*., 2006) as cognitive stimulation with others may protect the brain from decline function (Wang, Karp, Winblad, & Fratiglioni, 2002). Moreover, losing partner after age of 65 can lead to cognitive decline, this is seen more observably in men who lose his partner (Lee, DeMaris, Bavin, & Sullivan, 2001).

Sleep and AD

Association between sleep and AD has been found strongly in many studies (Ju, Lucey, & Holtzman, 2014). Sleep disturbance can lead to AD (Ju *et al*., 2014; Lim, Gerstner, & Holtzman, 2014). It has been found that more accumulation of Aβ is associated with sleep disturbance (Ju *et al*., 2014; Nesse, Finch, & Nunn, 2017). One reason behind that, glymphatic system, which is drains interstitial fluid from the brain and has its importance to removing Aβ out from the brain to peripheral lymphatic system (Xie *et al*., 2013), found to be acting twice during sleep (Ju *et al*., 2014). Another reason behind protective effect of sleep in AD resulted from anti properties effect of melatonin against AD (Nesse *et al*., 2017). Melatonin is hormone that is produced by the pineal gland under regulation of suprachiasmatic nuclei of anterior hypothalamus (Lim *et al*., 2014). Melatonin formation and secretion is closely related to sleep rhythm and night-time sleep (Nesse *et al*., 2017). It has been found that melatonin is secreted at night, mostly during sleep at dark area with maximum secretion from 2 to 4 A.M (Pandi-Perumal, Zisapel, Srinivasan, & Cardinali, 2005). Melatonin has anti-oxidant property that acts against Aβ toxicity (Pandi-Perumal *et al*., 2005). Besides, Aβ plaque is accumulated in the regions that regulate sleep-weak cycle (hypothalamus and brain steam) and therefore, leading to sleep disturbance (Nesse *et al*., 2017; Rothman & Mattson, 2012). As a protective value, adults need to sleep at night, in the dark area, 7 hours per day to get beneficial effect of the sleep against cognitive impairment (Eugene & Masiak, 2015; Nesse *et al*., 2017; Pandi-Perumal *et al*., 2005; Spurgeon, 2002).

Early diagnosis is a new suggestion kay

2017 Alzheimer's Disease Facts and Figures (Association, 2017) reported that the prevalence of AD in U.S is estimated to be 10 % (one in every 10 peoples with age of 65 years or

older has Alzheimer's dementia). So, this is considered a high percentage especially if it is known that there is no cure for AD. Because of that, early detection of AD become now one of the important goals for Alzheimer research. It has been found that early intervention with medications in MCI stage of AD become one of the very important roles to control and slow the disease progression (Rajan *et al*., 2015). Since 2012, Alzheimer association and NIC advise researchers to focus on AD biomarkers that confirmed Alzheimer's-pathological changes in pre-clinical stage. Until now, the biomarkers, that can be used for AD diagnosis at MCI or even before any symptoms appear, are analyses of Aβ and hyper-phosphorylated tau in cerebrospinal fluid (CSF), which is specific and sensitive diagnostic value for AD,(Mantzavinosa, Alexiou, Greig, & Kamal, 2017) and abnormalities shown in amyloid positron emission tomography (PET) imaging (Gillette-Guyonnet *et al*., 2008). Hippocampus atrophy seen by *magnetic resonance imaging* is a good biomarker to evaluate AD in late stage (Tateno *et al*., 2015). Many studies suggested routine clinical use of CSF analysis (Forlenza *et al*., 2015) to detect pathological changes of AD in person who started to has MCI with normal abilities for doing daily activities (Herukka *et al*., 2016; Herukka *et al*., 2017). It has been found that the chance of AD is increased when the result of Aβ and tau hyperphosphorylated proteins in CSF are positive (Mantzavinosa *et al*., 2017). Florbetapir-PET imaging is another diagnostic test for AD that shown its importance in an early stage of the pathological changes (Sevigny *et al*., 2016). However, using of these biomarkers in pre-clinical stage of AD still not recommended internationally as it is invasive.

CONCLUSION

AD is a most common cause of dementia. In most cases the disease is diagnosed in late stage and the medications that are prescribed for the patient have only beneficial effects to relief the symptoms. Early intervention with medications and educates the patient about life style protective value of AD (during preclinical and IMC stages) were suggested to decrease the incidence of Alzheimer dementia. Now a day, many advices were rising to put a new guideline that can help to diagnose AD in preclinical stage by screening tests like CSF analysis or PET imaging in those individuals with high risk factors. So, the progression of the pathological changes of the AD can be slowed down, and therefore the incidence of Alzheimer dementiacan be prevented. (Karlawish *et al*., 2017).

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