EPIDEMIOLOGY AND RISK FACTORS OF ALZHEIMER'S DISEASE

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ABSTRACT

Background: Alzheimer's disease (AD) is a devastating, irreversible, neurodegenerative disease with a high prevalence in our ageing society. Up to 50% of people over 85 years are believed to be affected, and this number only increases with age. Understanding the risk factors associated with such an impactful illness is of utmost importance, as is the investigation of factors which could prevent or at least slow its progression.

Objective of this paper is to discuss the epidemiology and risk factors associated with Alzheimer's disease as well as the potential protective factors and biomarkers available for its early diagnosis.

Risk factors: There are both genetic and non-genetic risk factors associated with AD. The mutated genes associated with hereditary early-onset AD are presenilin 1 (PSEN1), presenilin 2 (PSEN2) and the amyloid precursor protein (APP). For sporadic AD, the e4 allelic variant of apolipoprotein E (APOE) is a well-known risk factor. Having one e4 allele increases the risk of sporadic AD three-fold , having two copies increases this risk up to fifteen times. Between 40 and 80% of all individuals with AD are carriers of at least one apoE4 allele. Of non-genetic risk factors, the most harmful ones include the presence of other underlying diseases such as cardiovascular disease, hypertension, obesity, and traumatic head injury. The most protective factors for preventing AD include education, physical activity and a healthy diet.

Conclusion: Since the main risk factor for developing AD is age, there is little that can be done in terms of stopping ones ageing. However, implementing lifestyle choices that are preventative and decreasing those that are harmful, may at least slow down the progression of AD. Finding reliable biomarkers of the disease would be hugely beneficial in screening individuals at risk, and is currently an area of great interest in AD research, with potential

plasma biomarkers including increased Neurofilament Light (NFL), decreased Aβ42/40 ratios, and increased T- and P-Tau.

KEY WORDS: Epidemiology of Alzheimer's disease, amyloid-beta, biomarkers, risk factors, ageing

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ABBREVIATIONS:

Ab - Amyloid-beta,
AD - Alzheimer's disease,
AML - Amyotrophic lateral sclerosis,
APOE apolipoprotein E,
APP - amyloid precursor protein ,
CSF - cerebrospinal fluid,
FDA - Food and Drug Administration,
HD - Huntington's disease,
MAPT - microtubule-associated protein tau,
ND - Neurodegenerative diseases,
NFL - Neurofilament Light
NINCDS–ADRDA - National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,
PD - Parkinson's disease,
PET -Positron Emission Tomography,
PSEN - presilinin ,

INTRODUCTION

Neurodegenerative diseases (ND) is an umbrella term used to describe diseases which alter, or destroy the function of neurons, especially those in the brain, leading to neuro-degeneration, i.e. destruction and eventual death of neurons. The most common and widely distributed ND includes Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic lateral sclerosis (AML). AD alone was thought to affect 40 million people worldwide in 2015, with this number estimated to rise to 135 million in 2050 (Alzheimer's

Association, 2015). This suggests one third to one half of people over 85 years are predicted to be affected by AD by 2050 (Alzheimer's Association, 2015). *Figure 1* shows the predicted rise in AD cases, including data from 2000 through to 2030 (Hebert et al, 2001).

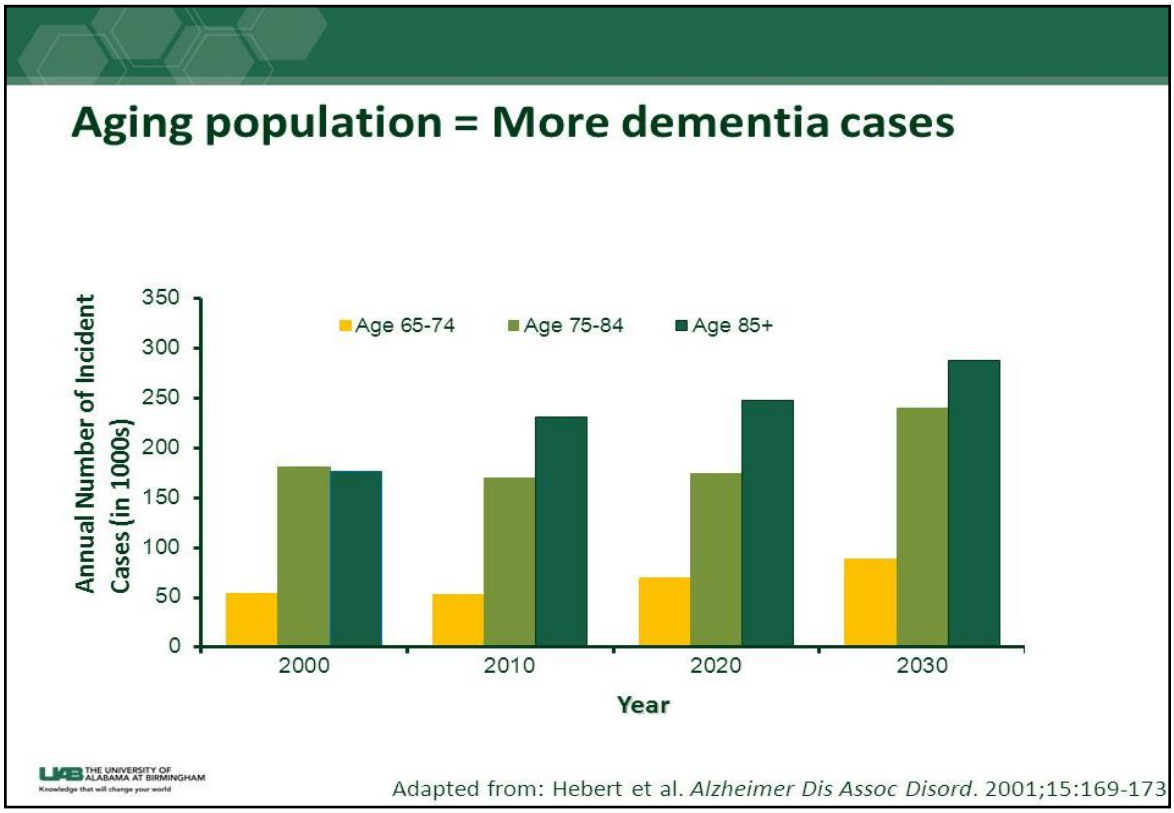

Figure 1. The predicted rise in AD and the incidence of AD related to age (Hebert et al, 2001)

There is a direct link between age and the probability of developing AD, as can be seen from *Figure 1*. For this reason, age is considered the most important risk factor. However, unlike smoking or exercise, growing older is not something we have the ability to alter. On the contrary, our modern-day Third World society is proud of its ability to prolong people's lives beyond what we once may have thought possible. Yet, with this prolongation of life, comes also the burden of diseases of old age, specifically neurodegenerative diseases such as AD and its accompanying disorder - dementia. In a study published in 2006, the worldwide costs

of dementia were calculated to be approximately $160 billion, and since our ageing population is only growing, we can expect these costs to continue increasing (Wimo et al, 2006). So where do we go from here?

PATHOPHYSIOLOGY OF AD

Alzheimer's disease, sometimes referred to as Alzheimer's dementia, is based on the finding of two observable neuropathological changes in the human brain (Erkkinen at al., 2018). The first one is the accumulation of extracellular neuritic plaques, made up primarily of 42-amino-acid amyloid-beta (Ab42). Ab42 is created upon the cleavage of amyloid precursor protein (APP) and assembles in the form of plaques in the brain of AD patients. The second pathological finding is that of intracellular neurofibrillary tangles of the hyperphosphorylated form of microtubule-associated protein tau (MAPT). The presence of these two alterations is responsible for the outwardly visible symptoms of AD, which usually starts as mild cognitive impairment and eventually leads to a diagnosis of dementia.

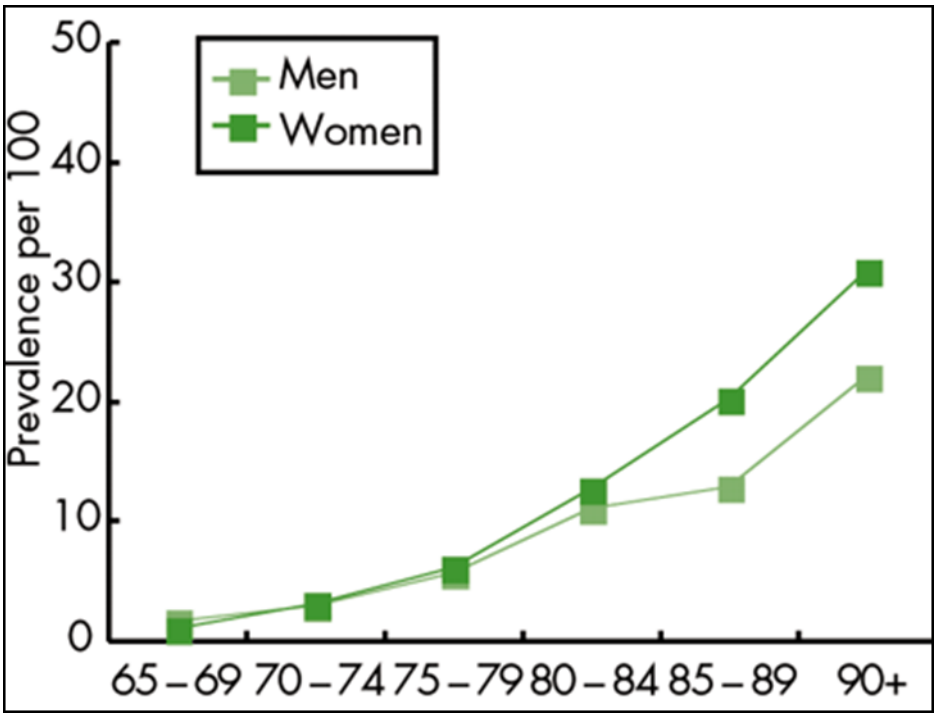

Figure 2. Prevalence of dementia across 10 European population based studies (Lobo A et al., 2000)

Indeed, AD is the reason behind between 60 and 80% of all dementia cases worldwide (Reitz et al., 2011; Mayeux and Stern, 2012; Sosa-Ortiz et al., 2012). The most common risk factor for developing dementia is age, and there is an estimated 15-fold increase in its prevalence from ages of 65 to 85 (Mayeux and Stern, 2012). This can also be observed from the graph in *Figure 2*, which shows that by the age of 90, over 30% of all women can be expected to be diagnosed with dementia.

It is speculated that the incidence rate of AD doubles every five years, therefore it is very important to understand the risk as well as the protective factors influencing this disease (Mayeux and Stern, 2012; Erkkinen et al., 2018). Since ageing is a risk factor over which we have no control, let us look at other factors that may be promising in at least off-putting the start of this debilitating disease.

RISK FACTORS

There is currently no known cure or even an effective disease-modifying drug to treat AD and therefore its diagnosis is almost synonymous with a troubling, terminal illness that has no light at the end of the tunnel. There are at present five medications approved of by the Food and Drug Administration (FDA) to treat AD dementia, but these can only address symptoms and cannot change the course of this disease (Hsu and Marshall, 2017). For this reason, identifying those with the highest risk of developing AD and taking preventative measures to postpone disease onset is of utmost importance.

Currently, a definitive diagnosis of AD can only be made once a post-mortem brain biopsy has been performed (Zvěřová, 2018; 2019). If the presence of Ab42 plaques and MAPT tangles in the brain is found, it is confirmed that the patient, indeed, suffered from AD. A post-mortem diagnosis, however, is of little use to clinicians and scientists working to combat the disease in its early stages. The issue of using various biomarker levels as potential predictors of AD severity will be discussed further on in this article.

Genetics

In terms of genetics, having a first-degree relative with AD can increase the risk by up to 3.5-fold, and this risk intensifies when additional family members are affected (van Duijn et al., 1991). Early-onset AD, which is classified as AD that occurs before 65 years of age, may sometimes present with an autosomal dominant inheritance pattern, however this account for less than 1% of all AD cases (Ryman et al., 2014). The mutated genes responsible for these

inherited early-onset patterns are most commonly presenilin 1 (PSEN1), presenilin 2 (PSEN2) and amyloid precursor protein (APP) and may be responsible for up to 13% of cases of early-onset AD (Campion et al., 1999). Interestingly, the APP gene is found on chromosome 21, explaining why patients with Down's syndrome can present high rates of early-onset AD (Margallo-Lana et al., 2004).

In terms of sporadic AD cases, the most well-known genetic risk factor is the presence of the e4 allelic variant of apolipoprotein E (APOE). The protein can have 3 variants - e2, e3 and e4 and of these e4 is associated with the most negative outcomes. Having one e4 allele increases the risk of sporadic AD three-fold, having two copies increases this risk up to fifteen times (Blennow et al., 2006). Between 40 and 80% of all individuals with AD are carriers of at least one apoE4 allele (Mahley et al., 2006), however e3 is still the most common variant both in the general population (72% – 87%) and in those with AD (Myers et al., 1996). The frequency of the different alleles varies across populations of people with the disease - affecting 9% of patients in Japan, compared to 20% of African-Americans (Erkkinen et al., 2018). However, some populations seem not to be affected by this allele at all. Two studies on Nigerian populations did not find the same association between the APOE e4 allele and AD, that have been recorded in numerous other papers (Gureje et al., 2006; Hall et al., 2006). Therefore, there must be other factors at play than merely allelic variation.

Non-genetic risk factors

In their 2012 study, Mayeux and Stern (2012) investigated the factors that modified the risk of being diagnosed with AD. These factors, both protective and harmful are summarized in *Table I*. As can be seen from *Table I*, the factors with the most harmful effects include the presence of other underlying diseases such as cardiovascular disease, hypertension, obesity - linked to diabetes mellitus type two, and traumatic head injury. On the contrary, the most protective factors were education, physical activity and a healthy diet.

These protective factors have also been confirmed in other studies. Both young and old individuals alike, partaking in cognitively stimulating activities like learning, reading or playing games, are much less likely to be diagnosed with dementia later on in life (Fratiglioni et al., 2004; Carlson et al., 2008). Physical activity is known to improve the symptoms of various diseases including depression, hypertension and indeed AD. A systematic review conducted by Farina et al. showed that exercise may have a positive effect on the rate of cognitive dec-

line in patients already diagnosed with AD (Farina et al., 2014). Another review found that physical activity, especially aerobic exercise, is associated with less age-related white and grey matter loss and also with less neurotoxic factors (Cheng, 2016).

Table I

Factors modifying the risk of Alzheimer's disease

Antecedent	Direction	Possible mechanisms
Cardiovascular disease	Increased	Parenchymal destruction Strategic location ↑ Aβ deposition
Smoking	Increased	Cerebrovascular effects Oxidative stress
Hypertension	Increased / decreased	Microvascular disease
Type II diabetes	Increased	Cerebrovascular effect Insulin and Aβ compete for clearance
Obesity	Increased	Increased risk of type II diabetes inflammatory
Traumatic head injury	Increased	↑Aβ and amyloid precursor protein deposition
Education	Decreased	Provides cognitive reserve
Leisure activity	Decreased	Improves lipid metabolism, mental stimulation
Mediterranean diet	Decreased	Antioxidant, anti-inflammatory
Physical activity	Decreased	Activates brain plasticity, promotes brain vascularization

Source: Mayeux and Stern, 2012

A Mediterranean diet is the one composed mainly of fish, plant foods, olive oil, moderate levels of wine consumption and low levels of poultry and red meat. Studies have shown that

such a diet, which is high in antioxidants and polyunsaturated fatty acids, is linked to reduced levels of AD (Gu et al., 2010). These micronutrients seem to have the ability to decrease the risk of cerebrovascular disease as well as to reduce oxidative stress and have favourable effects on neuronal and vascular functions and inflammatory processes (Yehuda et al., 2002; Vokó et al., 2003). A review published by Hagan et al. (2016) supports these dietary suggestions. They found a strong association between greater intake of total flavonoids and anthocyanins and slower rates of cognitive decline. This may be due to the fact that anthocyanins cross the blood-brain barrier and localize in the hippocampus - the part of the brain which is involved in learning and memory (Devore et al., 2012). There is also some evidence that caffeine may be a protective factor for the development of AD, as well as other foods high in flavonoids such as tea, red wine and cacao (Nehling, 2013).

Nuts are high in monounsaturated and polyunsaturated fats and their intake is connected to improved lipid profile and lower risk of cardiovascular disease, a known risk factor for developing AD (Grosso and Estruch, 2016). It comes as no surprise, that Hagen et al. reported an association between higher nut intake and better cognitive function (O'Brien et al., 2014; Hagen et al., 2016).

DISCUSSION

As stated at the beginning of this paper, age is a risk factor that we have no control over. Therefore any interventions and preventative measures must be focused on decreasing the modifiable risk factors and increasing the protective ones associated with the development of AD. Since AD is considered "the costliest disease in the world, amounting to $200 billion annually in the United States alone", there is indeed a great incentive for preventative programmes to be put into place (Hsu and Marshall, 2017). Especially since it is estimated that measures to prevent, or at least delay, the onset of AD by five years could decrease Medicare costs of AD by half (Alzehiemer's Association, 2010).

Finding new, reliable, specific and sensitive ways of testing for AD should be at the forefront not only of medical research, but of governmental politics and policies in general. Already six years ago, AD was one of the main themes discussed at the G8 summit in London in 2013, and this year the topic of the world's ageing population was talked about at length at the G20 summit in Osaka 2019. Since the only way to currently definitively diagnose AD is post-mortem, an interest in finding blood-based or cerebrospinal fluid-based (CSF) biomarkers has

grown exponentially during the last few decades. Biochemical markers including neuroimaging could facilitate diagnosis, predict AD progression from a pre-AD state of mild cognitive impairment, and be used to detect the efficacies of disease-modifying therapies (Zvěřová, 2018). There are a few key players that are being investigated as the basis for standardised biochemical-based diagnostic tests. As of 2007, the NINCDS–ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) has accepted Positron Emission Tomography (PET) scan combined with a volumetric magnetic resonance imaging (MRI) scan, and an invasive cerebrospinal fluid protein analysis of Aβ, total-Tau, and Phospho-Tau as a suitable procedure for the diagnosis of AD (Zvěřová, 2019).

The problem with obtaining CSF samples is that lumbar punctures may be seen as time-consuming, complicated and invasive, whereas PET scans are only available at specialised hospitals, and are rather expensive. If these were to be used as screening tests for large proportions of the population, they could be seen as neither cost- nor time-effective. Therefore the search for blood or plasma based AD biomarkers continues, with a few promising players at hand. These include increased plasma/serum Neurofilament Light (NFL), decreased plasma Aβ42/40 ratios, and increased T- and P-Tau (Zetterberg, 2019). The hope is that research into this area will continue, with the possibility of developing an accurate non-invasive AD test that will help diagnose the disease before its devastating symptoms have already set in and irreversible brain damage has occurred.

This paper has discussed the genetic risk factors as well as the non-genetic ones that influence a person’s possibility of being diagnosed with AD. Of the non-genetic risk factors mentioned above, all of them are lifestyle related. Therefore lifestyle changes supporting healthy habits such as a cleaner diet high in healthy fats and antioxidants, and increased cognitive and physical activity may lead to a decrease, or at least a delayed onset, of AD. This is partly due to the fact, that the aforementioned healthy habits also decrease the development of the non-genetic risk factors of AD such as obesity, hypertension and cardiovascular disease. All these are considered so called “civilization/lifestyle diseases” and implementing simple habits such as a short walk every day, or more conscious food consumption can lead to decreased prevalence of the above mentioned diseases, and this may then be reflected in a decreased prevalence of AD, as well. Since these are lifestyle changes, it is up to the individuals themselves to implement them.

CONCLUSION

Neurodegenerative diseases are a worldwide problem of our ageing society, with the most prevalent one, Alzheimer's disease, estimated to cost $200 billion annually in the United States alone. Since our population is only getting older, and the greatest risk factor for developing Alzheimer's disease is age, it is important to implement preventative measures that will at least delay the onset of this devastating disease. These preventative measures should take into account protective factors in the development of the disease, such as a healthy diet and increased physical as well as cognitive activity. It is the responsibility of health care providers to provide this information to individuals at risk, but it is the individuals' responsibility to implement these lifestyle changes, if they wish to decrease their chances of being diagnosed with Alzheimer's disease. Furthering research into developing reliable and affordable AD diagnostic tools is also of utmost importance. This could help identify individuals at risk of developing, or in the early stages of the disease, before devastating irreversible brain damage has already occurred.

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