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Alzheimer Disease and its Growing Epidemic: Risk Factors, Biomarkers and the Urgent Need for Therapeutics

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SYNOPSIS

Alzheimer disease represents one of the greatest medical challenges that face this century; the condition is becoming increasingly prevalent worldwide and as yet, no effective treatments have been developed for this terminal disease. Since the disease manifests at a late stage after a long period of clinically silent neurodegeneration, knowledge of the modifiable risk factors and the implementation of biomarkers is crucial in the primary prevention of the disease and pre-symptomatic detection of AD, respectively. This review discusses the growing epidemic of AD and antecedent risk factors in the disease process. Disease biomarkers are discussed and the implications that this may have for the treatment of this currently incurable disease.

Keywords

Alzheimer disease; risk factors; biomarkers; epidemiology

INTRODUCTION

Alzheimer disease represents one of the greatest medical challenges that face this century; the condition is becoming increasingly prevalent worldwide and as yet, no effective treatments have been developed for this terminal disease. In the United States in 2015, over five million people suffered with AD, costing over 170 billion dollars. Since the disease

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manifests at a late stage after a long period of clinically silent neurodegeneration, knowledge of the modifiable risk factors and the implementation of biomarkers is crucial in the primary prevention of the disease and pre-symptomatic detection of AD, respectively. This review discusses the growing epidemic of AD and antecedent risk factors in the disease process. Disease biomarkers are discussed and the implications that this may have for the treatment of this currently incurable disease.

EPIDEMIOLOGY

Alzheimer disease (AD) is the most common dementia in the elderly and is a growing epidemic across the globe. Although the risks associated with developing AD are multifactorial, the greatest risk factor by far is aging[1]. The age-specific risk of AD dramatically increases as individuals get older; findings from the Framingham study in the early 1990s showed that the incidence doubles every five years up to the ages of 89 years[2]. Age-dependent increases have been seen in other studies[3–5]. Unsurprisingly therefore, with global reductions in fertility and extended life expectancies, the number of patients with AD is expected to increase as populations age[6]. In the United States, it is estimated that approximately 5.3 million people had AD in 2015; 5.1 million people being 65 years and older and approximately 200,000 people under the age of 65 years with early onset AD (EOAD) [7–9]. It is estimated that the number of new cases of AD and other dementias will at least double by 2050 and substantially increase the socioeconomic burden worldwide[7, 10].

In 2010, it was estimated that dementia afflicted 35.6 million people worldwide, many of which will have AD, with the projection that this figure will double every twenty years[11]. The incidence of AD is generally lower in many less economically developed countries than in North America and Europe, however, sharp rises in prevalence have been predicted and seen in China, India and Latin America[12, 13].

The effect of this increasing dementia has obvious socioeconomic consequences for each country affected, through costs of hospital care and also of caregivers. In the USA, the total payments were estimated at $226 billion of which Medicare and Medicaid provided 68% [7, 14], whilst out-of-pocket expenses for patients and their families were expected to be $44 billion[7].

CLASSIFICATION AND STAGING

Revised criteria and guidelines by the National Institute on Aging and the Alzheimer Association published in 2011 (NIA-AA) have recognized three stages of Alzheimer disease: preclinical Alzheimer disease, mild cognitive impairment (MCI) due to Alzheimer disease and dementia due to Alzheimer disease[8, 15]. These are described as follows:

1. Preclinical AD: pre-symptomatic of AD with early AD-related brain changes as detected by neuroimaging or other biomarker studies;
2. Mild cognitive impairment (MCI) due to AD: mild cognitive decline but still able to perform activities of daily living;

3. Dementia due to AD: cognitive decline is more pronounced and interferes with activities of daily living[7].

With this classification in mind, it follows that the actual number of individuals with active disease are gross underestimates because they are based on approximations of diagnosed symptomatic patients and largely ignores the vast number of individuals who are preclinical, in whom the disease process is active but asymptomatic[16]. This long pre-clinical phase of AD is characterized by progressive neuronal loss, the formation of neurofibrillary tangles (NFT) and the deposition of amyloid plaques within the brain[17–20]. Although the exact pathogenesis of AD is debated, the prevailing hypothesis is that the neurodegeneration is the result of the amyloid cascade, in which aberrant digestion and processing of the amyloid precursor protein (APP) results in the accumulation of neurotoxic Aβ oligomeric proteins[21–24]. These proteins aggregate to form the insoluble amyloid plaques that are seen at microscopic examination of autopsy brains of AD patients.

BIOMARKERS

It is widely believed therefore that future therapeutics should be introduced during the preclinical and MCI stages of the disease course so as to preserve the existing functioning neural networks[7, 25]. In order to provide effective recognition of preclinical AD, there will likely need to be widespread implementation of disease biomarkers, such as in national screening programs targeting specific age groups and other high-risk categories. Such screening may prove popular as many patients are keen to know their disease status at an earlier time point[26–28].

Current disease biomarkers focus on indicators of cerebral amyloidosis or synaptic dysfunction. Markers of brain amyloidosis include reduced CSF $A\beta_{42}$ concentrations and increased amyloid tracer uptake on positron emission tomography (PET) [29]. These changes are followed after a period of time with markers of neuronal injury, notably increased CSF tau levels and brain atrophy on magnetic resonance imaging (MRI) [30, 31]. PET tau imaging has great promise as a biomarker and may be able to provide estimates of pathological disease stage[32]. Validation is needed prior to introduction of these tests into the clinical setting, but would certainly be useful in providing a more complete overview of the current number of patients with AD and also in evaluating pre-clinical therapeutic response.

RISK FACTORS

The modifiable and non-modifiable risk factors of AD are important because they provide insight into the predispositions of the disease process prior to onset and also provides stratification of individuals who may be at increased risk. Besides aging, which, as discussed previously, is the most significant risk factor; other determinants of AD include genetic risk factors, and non-genetic, modifiable risk factors.

NON-MODIFIABLE GENETIC RISK FACTORS

Recent genome wide association studies (GWAS) have revealed many new genes that increase the risk of developing AD[33]. This review, however, considers the most commonly

discussed genetic influences on the disease, notably mutations in ApoE, APP and presenilin mutations.

ApoE

Of all of the mutations identified in AD, genome wide association studies have demonstrated that it is the ε4 allele of the *APOE* gene that poses the greatest risk for AD[34–38]. ApoE is a 34 kDa astrocytic protein that is encoded on chromosome 19q13. The apoE gene has three alleles that result in the production of ε2, ε3 and ε4 isoforms. One of its principal functions within the CNS is the delivery of cholesterol to neurons via the ApoE receptor[39]. ApoE3 is the most common variant, present in approximately 60% of the population and is regarded as having no altered risk in AD[7, 35, 36]. However, the next most common allele is the ε4 followed by the ε2 allele. ApoE heterozygosity with ApoE4/E3 or ApoE4 homozygosity confers a significantly risk of developing AD, from three-fold to eight-twelve fold, respectively. In approximately 40% of cases of AD, ApoE4 is identified [40]. Furthermore, patients with ApoE4 have poorer cognitive performance in childhood and tend to develop the disease significantly earlier than those with ApoE3[41]. In a population based study, patients who had suffered a head injury and carried the ApoE4 allele had a ten times increased risk of developing AD, unlike those without the allele who were at two-fold increased risk[42]. The MIRAGE study demonstrated that patients who have suffered head injury are at markedly increased risk of developing AD[43]. Curiously, the ε2 isoform bestows a decreased risk of AD than the ε3 allele[36]. It comes as no surprise therefore that the ε2 allele is over-represented in centenarians[44].

Triggering Receptor on Myeloid Cells 2

Discovery of the triggering receptor on myeloid cells 2 (TREM2) allele as a rare genetic predisposition for AD has sparked interest because of its role in inflammation[45]. TREM2 is a receptor found on microglia that is important in phagocytosis and dampening the CNS immune response[46]. Mutation in TREM2 is rare, however, the most common receptor mutation (R47H) increases the risk of LOAD by approximately twofold. Furthermore, mutations in TREM2 are associated with more severe degrees of atrophy in AD than those without[47]. Mutations in TREM2 that increase the risk and severity of AD may result from derangements in neuroinflammation and amyloid clearance.

APP and Presenilin Mutations

Early onset familial AD (EOAD), which usually begins in patients younger than 65 years of age, represents less than 1% of cases of AD[48]. EOAD is often caused by autosomal dominant mutations such as mutations in amyloid precursor protein (APP), presenilin-1, and presenilin-2 genes[48].

Mutations in proteins that are involved in the synthesis of Aβ result in downstream overproduction of the pathological Aβ. APP is encoded on chromosome 21q21.3 and comprises 3 transcript variants, the most common of which protein within the CNS is 695 amino acids long[49]. Over 30 coding APP mutations have been identified that usually result in an autosomal dominant EOAD because of increased Aβ production, shifts in synthesis of pathologic $A\beta_{1–42}$, or production of Aβ that may have increased susceptibility to

aggregation[50]. Of interest, not all APP mutations result in AD preponderance; actually, one mutation was found to be protective[50]. Presenilin is one of the proteins that constitute the active site of γ-secretase and therefore mutations alter the efficacy of this enzyme increasing the amount of $A\beta_{1-42}$ production. Presenilin mutations account for the majority of cases of familial AD[48].

Down Syndrome

Down syndrome (DS) is the most common chromosomal abnormality with an incidence of 1 per 733 live births and is characterized by trisomy 21[49]. Since APP is encoded on chromosome 21q21.3, this results in three copies of the APP protein. This increased abundance of APP expression, production of Aβ is considered to be one of the mechanisms as to why many of these patients develop EOAD. Given that the lifespan of patients with Down's syndrome is now 55–60 years of age, approximately 70% of patients will suffer from AD[51].

Cardiovascular Health

A large body of evidence suggests that cardiovascular disease increases the risk of dementia. Studies that have investigated patients with clinical and subclinical cardiovascular disease have poorer cognitive function than those without[52, 53]. Cortical ischemic changes can increase the risk of dementia[54]. However, studying the role of cardiovascular disease and AD is complicated by several issues, notably that extensive cardiovascular disease and dementia may preclude from a clinical diagnosis of AD and may instead favor a diagnosis of multi-infarct dementia[55].

Studies have shown mixed results with regard to the influence of hypertension and this is in part due to differences in study design[54, 56–58]. Observational studies however have generally shown that increased hypertension are associated with cognitive decline and an increased likelihood of developing AD, possibly through blood vessel injury, protein extravasation, neuronal injury and subsequent Aβ accumulation[59].

Diabetes Mellitus

Diabetes mellitus (DM) is associated with an increased risk of cognitive decline and AD later in life. Observational studies of type 2 DM (T2DM) have found that T2DM nearly doubles the risk of AD[60–62]. In the Religious Orders Study, 824 individuals who were older than 55 years of age, were evaluated for cognitive decline and AD and found that those with DM had a 65% increased risk of developing AD after a mean 5.5 year period[63]. The cognitive decline was found to be mainly in perceptual speed. Several meta-analyses have further confirmed an increased risk of AD in DM. The biological mechanism for this association may relate to competition of Aβ and insulin for insulin degrading enzyme, thereby reducing Aβ clearance. Alternatively, increased Aβ aggregation has been demonstrated through increased age-related glycation end-products that can occur in DM.

Anti-diabetic therapies in patients with DM and cognitive impairment and also in patients with AD have shown improvement in cognition, which may be related to the anti-inflammatory properties of these drugs.

Traumatic Brain Injury

Traumatic brain injury (TBI) is a growing public health concern worldwide because the incidence is rising and it carries a significant healthcare and socioeconomic burden for society[64–68]. For patients who survive TBI, the average life expectancy is considerably shortened and many cases of TBI suffer chronic neurological and psychological morbidity that reduces quality of life [69–72]. More data is now showing that there are ongoing chronic changes within the brain following TBI and that these ensuing processes may result in further damage with possible neurodegenerative sequelae[73]. The first documentation of a syndrome that directed attention towards a neurodegenerative phenomenon after head injury was ‘punch drunk syndrome’. This syndrome described degenerative changes after repeated episodes of sub-lethal head injuries in professional boxers [74]. This condition is now termed chronic traumatic encephalopathy (CTE) and afflicts a diverse range of people including professional and amateur players of contact sports as well as veterans [75–78]. CTE has pathological features that overlap with AD and TBI is recognized to shorten the time to onset of AD[79]. Furthermore, it is now considered that TBI is the most significant environmental risk factor for AD[76, 80].

Recent data has demonstrated that in both long-standing TBI and AD there is chronic inflammation within the brain parenchyma and this persistent inflammatory milieu within the brain parenchyma could be where the pathophysiology of TBI and AD converge[81, 82].

Following TBI the amyloid levels increase due to several factors. Firstly, APP expression is noticeably increased post-TBI[83, 84]. APP is particularly prominent at the axon terminals where there has been axonal transection and axonal transection is known to occur even in mild cases of TBI [85, 86]. Secondly, β-secretase and γ-secretase, enzymes that both contribute to the digestion of APP and formation of Aβ are also upregulated[87–89]. These increases in both substrate and enzymes, results in increased deposition of amyloid at the axon bulbs and offers one explanation as to how the risk of AD is increased after TBI [90].

The Influence of Neprilysin and TBI

Removal of cerebral amyloid is likely to be multifactorial, involving partly passive diffusion of soluble amyloid, active transport mechanisms and cellular digestion[91, 92]. The degree of amyloid pathology post-TBI and in AD is particularly influenced by neprilysin. Neprilysin is a membrane zinc metalloprotease that is capable of digesting Aβ peptide and thus has the capability of reducing the amyloid load within the brain[93]. Neprilysin knockout mice demonstrate increased amyloid burden in a gene-dose dependent correlation[94]. Johnson and colleagues demonstrated that in post-mortem subjects, the degree of amyloid burden was most in patients who had more than 41 GT repeats in the promoter region of the neprilysin gene, which was considered to be related to defective amyloid clearance [95]. Curiously, neprilysin expression increases post-TBI and this may be a mechanism by which Aβ and amyloid plaques are cleared months after injury, despite increased intra-axonal APP and presenilin-1 expression [96]. With age-related reduction in neprilysin, the balance between formation of amyloid and its breakdown may shift towards accumulation of amyloid and this may be responsible for the preponderance to AD post-TBI[97].

There is also likely to be a contribution to amyloid breakdown from microglial activation. Neprilysin, metalloproteinase-9 and several other factors that are released by healthy microglia, digest Aβ[98]. There is a heightened neuro-inflammatory response following TBI that persists, and the activation of microglia most likely releases factors that will assist in the digestion of Aβ. However, with aging, the efficacy of microglial breakdown is likely to be lost, and may even accentuate the accumulation, thereby causing a gradual shift toward accumulation of amyloid in the dynamic Aβ turnover[99].

Previous Amyloid Exposure

One of the most concerning developments over the past few years has been the accumulation of evidence that suggests infectivity of amyloid in a prion-like fashion. In a recent case series of iatrogenic CJD, a proportion of patients who received homogenized human pituitaries for growth hormone replacement were found to have significant cerebral amyloid angiopathy at autopsy, to an extent that was inconsistent with age[100]. Given that pituitaries may have amyloid deposits, there is the possibility that amyloid could seed through peripheral injection with proteopathic spread over subsequent decades[100, 101]. The proteopathic spread of amyloid in the brain has been demonstrated in numerous animal models and in human AD pathological staging[102].

The main fear that stem from these findings is that iatrogenic infection may occur from re-used surgical instruments, since amyloid is difficult to remove from metal devices[103]. Further research is needed in this area in order to gauge the significance of these findings on amyloid infectivity.

Protective Factors

In general, environmental influences that are anti-inflammatory appear to be beneficial at reducing the likelihood of developing AD. Low calorie diets that are sustained for a protracted period of time are associated with reduced free radical production and increased brain neurogenesis and BDNF concentrations, all of which are recognized to promote healthier brain aging[44, 104]. Data regarding diets that are rich in antioxidants and polyunsaturated fatty acids (PUFA) have proved inconclusive with some studies demonstrating a reduction in the risk of AD, whilst others showing no such association[105–107].

Other protective influences include cognitive stimulation and a high educational achievement, which improves cognitive reserve[108, 109]. Physical exercise does appear to reduce the risk of developing dementia and can show improvements in cognition in patients with dementia[110–114].

Perspectives

While the incidence of AD appears to be increasing worldwide, the age-specific risk of developing AD in high income countries may be decreasing. Improvements in diet, exercise, education and management of chronic conditions, such as DM, appear to be improving the individual age-specific risk of AD within the USA[115]. However, in view of longer life expectancies and worldwide increases in the prevalence of other risk factors, such as obesity

and DM, the incidence of AD is most likely set to increase considerably with significant socioeconomic impact.

Future work on the development and validation of biomarkers and on the introduction of therapeutics into the preclinical phase of AD has the greatest promise in the effective treatment of this otherwise incurable disease.

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KEY POINTS

- Alzheimer disease is increasing in prevalence worldwide
- Many individuals have preclinical AD without symptoms
- Biomarkers are currently in development for detecting preclinical AD that may be amenable to novel therapies
- Addressing modifiable risk factors should also help to reduce the prevalence of AD in the future