Epidemiological of and risk factors for Alzheimer's disease: A review

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Background. Alzheimer's disease (AD) is the most common form of dementia. It is a degenerative, incurable and terminal disease. The increasing prevalence of AD is, among other reasons, due to population aging, which is, to a certain extent, seen worldwide. Continuous advances in health care keep increasing life expectancy. Official statistics are likely to significantly underestimate the actual prevalence of AD. Alzheimer's disease represents an important public health problem. Its aetiology is still unknown and for this reason, it is necessary to study all potential risk factors which may contribute to the development of this disease.

Methods. We searched original and review articles addressing Alzheimer´s disease using key words Alzheimer's disease, epidemiology, risk factors and prevention. We found and used one hundred and four references.

Conclusions. Based on epidemiological studies, genetic studies, neuroimaging methods and neuropathology research, three basic etiological hypotheses of the development of AD have been formulated: genetic, vascular and psychosocial. At present, the level of evidence is insufficient for the etiological role of other factors, such as nutrition, occupational exposure to various substances and inflammation. From the point of view of early diagnosis and application of primary or secondary prevention principles, genetic factors are the most important.

Key words: Alzheimer's disease, epidemiology, risk factors, prevention

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia. It is a degenerative, incurable and terminal disease. Although it is mostly diagnosed in people over 65 years, a less prevalent early-onset form may develop much earlier.

Alzheimer's disease affects most (up to 75%) of the more than 35 million people suffering from dementia worldwide. The prevalence is believed to double every 20 years. Thus, it is estimated that approximately 115 million people may be affected by AD in 2050. The disease has a major impact not only on the sufferers but also on persons caring for them as well as the entire society.

The etiological factors are mostly unknown. There is increasing evidence of the role that certain risk factors play in the development of the disease, such as genetic and vascular factors or disorders. Also known are psychosocial factors which may positively influence the pathogenesis and clinical manifestation of the disease. Therefore, intervention in these areas may lower the risk of its development or at least delay the clinical manifestation.

The increasing prevalence of AD is, among other reasons, due to population aging, which is, to a certain extent, seen worldwide.

OCCURRENCE

Prevalence

Aggregate data from studies on the prevalence of AD in Europe reported the age-standardized prevalence of AD in people aged 65 or more to be 4.4% (ref.[1]). A US study performed in a representative sample of persons over 70 years of age reported AD prevalence of 9.7% (ref.[2]). The global prevalence of AD is estimated at 3.9% in people older than 60 years, with regional variations in individual continents[3].

In developed countries, approximately 1 in 10 persons over 65 years of age suffers from a form of dementia compared with more than one third of those older than 85 years[4,5].

Incidence

Two US studies of persons aged 65 or more reported an AD incidence of 15.0 per 1,000 person-years. The incidence rates for males and females were 13.0 and 16.9 per 1,000 person-years, respectively[6,7].

In a 3 year follow-up, a Swedish prospective study involving 987 persons aged 75 years or older found the incidence rates of dementia in the age group of 75-79 years to be 19.6 and 12.4 per 1,000 person-years in females and males, respectively. In those aged 90 or more, the incidence rates of dementia were 86.7 per 1,000 person-years in females and 15.0 per 1,000 person-years in males.

A similar distribution by age and gender was seen in AD. The risk of the development of any form of dementia is reported to be approximately twice as high in females as in males and the risk of Alzheimer's disease is as much as three times higher in females[8].

Numerous other studies report the incidence rates of dementia and AD as the number of persons per year.

For example, in a British prospective cohort study of 1,070 persons aged 65 or more and followed for 3 years, the incidence of all types of dementia was 9.2 per 1,000 population and year, of which the AD incidence was 6.3 per 1,000 population and year[9].

Koukolík reported approximately 35,000 AD patients aged 65 years or more in former Czechoslovakia in 1983 (ref.[10]).

According to the Czech Alzheimer Society, approximately 130,000 people in the Czech Republic currently suffer from dementia, two thirds of which have AD.

RISK FACTORS

Hypotheses

Based on epidemiological studies, neuroimaging methods and neuropathology research, three etiological hypotheses of the development have been reported, with moderate or strong evidence[11]:

- genetic,
- vascular, and
- psychosocial.

At present, the level of evidence is insufficient for the etiological role of other factors, such as nutrition, occupational exposure to various substances and inflammation.

Genetic hypothesis

Early-onset familial AD is usually caused by autosomal dominant mutations in the genes for amyloid precursor protein (APP), presenilin 1 and presenilin 2. This form of AD accounts for approximately 2–5% of all AD cases[12].

First-degree relatives of patients with AD are at higher lifetime risk of developing the disease than the rest of the population[13]. Both genetic and other factors contribute to the increased risk and familial aggregation of AD cases. As far as genetic factors are concerned, this risk may be partly due to the presence of the apolipoprotein E (APOE) apoE4 allele. Other genes also contribute to the pathogenesis of this mental disorder[14]. The apoE4 allele is the only proven genetic factor so far identified in the development of both the early- and late-onset forms of AD. This factor increases susceptibility to AD but it is neither necessary nor sufficient for the development of this disease. The higher the number of the apoE4 alleles, the higher the risk of AD and the lower the age of onset. The risk effect of the presence of the apoE4 allele decreases with age. Generally, approximately 15-20% of AD cases may be attributed to this risk[15].

Tens of other candidate genes with polymorphisms affecting the risk of the development of AD have been studied. Predominantly, these are secretase genes – e.g. BACE1 (beta-site amyloid precursor protein-cleaving enzyme 1), presenilin 1, peptidase genes – e.g. ECE1 (endothelin-converting enzyme), IDE (insulin-degrading enzyme), microtubule and cytoskeletal genes – e.g. MAPT (microtubule-associated protein tau), synaptic genes – e.g. ABCA1 (ATP-binding cassette A1 transporter), anti-apoptotic genes – e.g. IL-1 (interleukin 1), protease genes -e.g. ACE (angiotensin-converting enzyme) and other genes such as the gene for APP.

Vascular hypothesis

Vascular risk factors, such as smoking, obesity and high total cholesterol levels, together with vascular morbidity, such as hypertension, diabetes mellitus and asymptomatic cerebral infarction, are associated with a higher risk of dementia including Alzheimer's disease.

Smoking

Earlier cross-sectional studies often reported a lower prevalence of AD among smokers compared with non-smokers[16]. This seemingly protective effect was probably due to survivor bias since the proportion of smokers among the prevalent cases was smaller.

When incident cases of AD were studied, however, the situation was completely reversed[17-19]. That is, numerous analytical studies found a significantly increased risk of AD associated with cigarette smoking, especially in apoE4 allele non-carriers[20-22]. Meta-analyses of these analytical studies concluded that current smoking was associated with an increased risk of the development of AD, with RR=1.79; 95% CI 1.43–2.23 (ref.[23,24]).

Alcohol

It is well recognized that alcohol abuse causes alcohol dementia. Moreover, middle-aged heavy drinkers, especially apoE4 allele carriers, were found to have a more than 3-fold higher risk of dementia and AD later in their lives[25]. On the other hand, the risk of developing dementia and AD was reduced in light and moderate alcohol consumers[26,27].

In heavy consumers, alcohol clearly damages the brain. Even light to moderate alcohol consumption was found to be related to brain atrophy and volume loss[28,29].

Overweight and obesity

Higher BMI in middle age is a risk factor for AD and other dementias. Higher BMI or obesity (in particular abdominal obesity) at around the age of 50 years means an increased risk of dementia 20-25 years later[30-33]. Several analytical studies in the elderly suggested that a significant decrease in BMI was associated with a higher risk of AD in the following 5-6 years[37,38].

Blood pressure and management of hypertension

Increased blood pressure in middle age, especially if uncontrolled, was associated with a higher risk of the later development of AD in several observational studies[39,40].

Findings from analytical studies of the association between blood pressure and the risk of dementia are not

consistent. Studies with a relatively short follow-up (less than 3 years) found no or even an inverse association between blood pressure values and the risk of dementia and AD (ref.[41]). Since dementia has a long latent period and blood pressure may drop in its pre-clinical stage, an absent or inverse association may be interpreted as a result of the process[42,43].

However, analytical studies with a longer follow-up (e.g. more than 6 years) reported an inverse association[44-46], suggesting that low blood pressure later in the life may contribute to the development or clinical manifestation of dementia including AD (ref.[41,47]).

Longitudinal studies have repeatedly shown a protective effect of antihypertensive drugs against the development of dementia and AD (ref.[41,48,49]). Recent analytical studies have suggested that the protective effect of antihypertensive therapy may depend on its duration and the patient's age. Greater protective effects were found in the younger elderly (e.g. under 75 years of age) and in those with long-term treatment[50,51]. Antihypertensive therapy may protect against dementia and AD by delaying the atherosclerotic process, decreasing the number of atherosclerotic lesions and improving cerebral perfusion[41].

Hypercholesterolemia and statin therapy

High total serum cholesterol levels in middle age were found to be a risk factor for the development of AD at a later age[52,53]. High total cholesterol in middle age is a risk factor for the development of AD and other dementias 20 years later but decreasing serum cholesterol levels in late middle age may be due to ongoing disease processes and may represent a marker for later AD and other dementias[54].

According to several cross-sectional and case-control studies, the use of statins significantly decreases the prevalence of AD (ref.[55,56]). Whereas an analytical study (the Rotterdam Study) showed that the use of statins was associated with a lower risk of AD (ref.[57]), other prospective studies found either no beneficial effect or only a slightly decreased risk of AD related to the use of statins[58,59]. Experimental studies have suggested that statins may decrease the production of beta amyloid both *in vitro* and *in vivo*. Statins also have various other effects that may be beneficial for the CNS and thus may lower the risk of AD.

Nutritional factors

Several analytical studies showed a decreased risk of AD associated with higher intake of antioxidants such as vitamins E and C (ref.[60,61]), either in the diet or in dietary supplements. However, some studies found a negative effect[62]. Yet other studies showed that the Mediterranean diet (high intake of fish, fruit and vegetables rich in antioxidants) was associated with a lower risk of AD, independent of vascular risk factors[63,64]. A Cochrane systematic review concluded that supplementation with folic acid and vitamin B12 had no beneficial effect on cognitive functions despite the fact that folic acid and vitamin B12 effectively decrease serum homocysteine levels[65].

It was also reported that a diet rich in saturated fats and cholesterol increased the risk of AD (ref.[66]) whereas polyunsaturated fatty acids and fish may be protective against dementia[67,68].

Diabetes mellitus

Many longitudinal studies found an increased risk of not only neurodegenerative but also vascular dementia in people with diabetes[69–71]. This risk was confirmed by a systematic review[72]. The presence of diabetes in middle age or a longer duration of diabetes may play a key role in the development of AD and other dementias[73,74]. Moreover, borderline conditions, prediabetes or impaired glucose tolerance are also related to an increased risk of AD and other dementias in very old people[75]. This relationship may be partly explained by diabetic comorbidities such as hypertension and dyslipidaemia[76–78].

A relationship was also found between a higher prevalence of AD in an elderly population in Finland[79], although an analytical study of a multiethnic cohort of the elderly in the USA found no association between the metabolic syndrome and either the prevalence or incidence of AD, despite the fact that two components of the syndrome, i.e. diabetes and hyperinsulinaemia, were associated with increased risk of incident AD (ref.[80]).

Cardiovascular and cerebrovascular diseases

A significantly increased risk of dementia and AD was found in patients who had suffered a stroke as well as clinically silent cerebral infarction confirmed by magnetic resonance imaging[81,82].

Also cardiovascular diseases are associated with an increased incidence of dementia and AD, with the highest risk of dementia in persons with peripheral artery disease, suggesting that extensive peripheral atherosclerosis is a risk factor for AD (ref.[83,84]).

Neuropathological studies have suggested that cerebrovascular lesions, atherosclerosis and neurodegenerative changes often coexist with each other in the brain, producing a clinical manifestation of the dementia syndrome[85,86].

Psychosocial hypothesis

A systematic review found that psychosocial factors and an active lifestyle throughout life may decrease the risk of dementias including AD (ref.[87]).

Education and socioeconomic status

Lower education is tied to increased risk of dementia and AD. This link has been confirmed by many cross-sectional and longitudinal studies[88,89]. Although education and socioeconomic status are highly correlated with each other, when studied separately, an independent association was only found for education[90].

Social network and social engagement

Longitudinal observational studies suggest that a poor social network or a lack of social engagement are associated with decreased cognitive functions and dementia[87,91]. The risk of dementia was also higher in elderly persons with increased social isolation and less frequent and unsatisfactory contacts with relatives and friends. Persons with low neuroticism combined with high extraversion

had a lower risk of dementia[92]. Low levels of social engagement in late life and decreased social engagement from middle to late life were associated with a two-fold increase in the risk of the development of dementia and AD later in life[93,94].

Physical activity

Regular physical exercise is associated with a delay in onset of dementia and AD in the elderly without cognitive impairment[95]. Physical activity in the form of various leisure activities rather than sports or specific physical exercise led to a decrease in the risk of dementia[96]. Even low-intensity physical activity such as walking may lower the risk of dementia and cognitive impairment[97]. A significant protective effect of regular physical activity in middle age, with respect to the development of dementia and AD later in the life, was found especially in persons with the apoE4 allele[98].

Mental activity

Various activities requiring a mental effort, such as reading, social and cultural activities, knitting, gardening, dancing, tabletop games, playing musical instruments, watching specific TV programmes, showed a protective effect against dementia and AD (ref.[99,72]). A study of Swedish twins showed that complexity of work, in particular more complex work with people, may reduce the risk of AD (ref.[100]). A recent neuroimaging study suggested that a high level of complex mental activity across the lifespan was correlated with reduced hippocampal atrophy[101].

PREVENTION

Primary prevention

Although the mechanisms of action of vascular and psychosocial factors participating in the pathogenesis and clinical manifestation of AD have not been fully understood, primary prevention is possible since most vascular and psychosocial factors including lifestyle factors are modifiable[11,102].

Primary prevention strategies addressing the vascular pathway in the development of AD include:
- measures against hypertension, obesity, increased glucose levels and diabetes mellitus in middle age,
- measures against cardiac failure and preventing very low blood pressure and thus maintaining sufficient cerebral perfusion.

Primary prevention strategies focused on maintaining an active and socially integrated lifestyle:
- ensuring an extensive social network,
- frequent participation in social physical and intellectual stimulating activities[11,87].

Secondary prevention

AD is characterized by a pre-clinical stage lasting several years during which progressive neurodegenerative changes occur in the brain, even before the onset of typical clinical signs[103]. However, this pre-clinical stage is difficult to identify although some clinical markers, neuroimaging biomarkers and biochemical markers are available[104]:
- mild cognitive impairment (isolated memory loss),
- biochemical markers in the serum and cerebrospinal fluid (beta amyloid and tau protein),
- neuroimaging methods are considered an effective tool for diagnosing AD in the pre-clinical stage (amyloid positron emission tomography is able to measure beta amyloid in the brain *in vivo*),
- volumetric magnetic resonance imaging detecting medial temporal lobe atrophy.

Tertiary prevention

The goal of tertiary prevention of AD is to rule out functional disability and, if possible, improve the quality of life:
- cognitive training,
- treatment with cholinesterase inhibitors (donepezil, rivastigmine, galantamine),
- treatment with N-methyl D-aspartate receptor antagonists (memantine).

CONCLUSION

Alzheimer's disease represents an important public health problem. Its aetiology is still unknown and for this reason, it is necessary to study all potential risk factors which may contribute to its development.

From the point of view of early diagnosis and potential application of primary or secondary prevention, genetic factors are the most important.

ABBREVIATIONS

AD, Alzheimer's disease.

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CONFLICT OF INTEREST STATEMENT

Author's conflict of interest diclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

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