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Epidemiology and Genetics of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common form of dementia. It is a degenerative and incurable terminal disease. AD accounts for 75% of all forms of dementia all over the world. Its etiology is still unknown. Numerous risk factors of AD have already been discovered. In this paper, some preliminary results are presented.

The results suggested that persons with AD often had cardiovascular disease in their history. Conversely, they did not have diabetes mellitus, hypertension and cerebrovascular disease. A relationship between the ApoE4 allele and a higher risk of AD was found (OR 2.52). Among ACE genotypes, the I allele increases the risk of AD, and in this pilot sample, the II genotype showed the OR on the borderline of significance (OR 1.43;95% CI 0.97-2.12).

Keywords: Epidemiology; Alzheimer's disease; Risk factors; Genetics

Introduction

It is generally accepted that Alzheimer's disease (AD) is the most frequent form of dementia. The etiology of AD is still unknown and three risk factors are hypothesized to be involved indevelopment of the disease (a) vascular risk factors, (b) genetic risk factors and (c) behavioral risk factors [1].

For various reasons, no exact data on the incidence and prevalence of AD are available. There is no compulsory notification, it is difficult to distinguish between different forms of dementia and there is no exact diagnostic test.

Mostly, there are only estimates of the actual incidence or prevalence. Worldwide, there are about 38 million persons with dementia, with 75% of them having AD. In Europe, there are more than 7 million people with dementia, and in the Czech Republic, 120,000 cases of AD are notified [2-4].

Material and Methods

Since 2010, an epidemiological study assessing the importance of selected vascular and genetic risk factors has been underway. The aim was to recruit 800 AD cases and 800 controls. In this paper, some preliminary results from analyses of 394 cases and 287 controls are presented.

The diagnostic criteria for selection of subjects were (a) Mini Mental State Examination (MMSE) test score below 24 points (b) slow development of cognitive impairment and (c) other forms of dementia excluded by a CT scan in the group of cases, and (e) MMSE score above 28 and (f) matched gender and age (± 5 years) in the group of controls [5].

Results

Data from questionnaires obtained from 394 cases and 130 controls were analyzed. The questionnaires contained demographic data and information concerning different risk factors.Vascular and genetic risk factors were used in this preliminary evaluation.

There were almost 80 % of females in both groups. The mean age was 79 years in cases and 73 in controls. A total of 96.7 % of cases had the late-onset form of AD (after 65 years of age). The clinical course was slow in 85%.

The results suggested that persons with AD often had cardiovascular disease (CVD) in their history (OR 1.44;95% CI 0.94-2.19). Conversely, they did not have diabetes mellitus, hypertension and cerebrovascular disease (OR<1.0) (Table1).

When assessing genetic risk factors, we focused on the genes for apolipoprotein E (ApoE) and angiotensin-converting enzyme (ACE).

The gene for ApoE is found on chromosome 19q13.2 and has 3 major alleles, E2, E3 and E4. There are 6 genotypes depending on combination of these three alleles. The ApoE4 allele is the only confirmed genetic factor contributing to both early- and late-onset AD (Tables 2 and 3) [6].

Risk factor	Cases	controls	OR	95% CI	p-value
CVD	52%	43%	1.44	0.94–2.19	0.089
Diabetes	29%	38%	0.67	0.44–1.02	0.062
Hypertension	69%	79%	0.57	0.36–0.92	0.022
Stroke	15%	22%	0.63	0.38–1.04	0.069

Table 1. Selected vascular risk factors.

	E2	E3	E4
patients (n=373)	5.23	70.64	**24.13**
controls (n=286)	10.49	78.32	**11.19**
OR	0.47	0.66	**2.52**

Table 2. Frequency of apolipoprotein E alleles (%).

	E2/E2	E2/E3	E3/E3	E2/E4	E3/E4	E4/E4
patients (n=373)	0.27	6.97	47.45	**2.95**	**39.41**	**2.95**
controls (n=286)	0.70	17.48	59.80	**2.09**	**19.58**	**0.35**
OR	X	X	X	**1.41**	**2.67**	**8.66**
95% CI	X	X	X	**0.51–3.88**	**1.86–3.82**	**1.11–67.48**
p-value	X	X	X	**0.62**	**0.0000**	**0.01**

Table 3. Frequency of apolipoprotein E genotypes (%).

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	I	D
patients (n=384)	47.14	52.86
controls (n=287)	45.12	54.88
OR	1.08	0.92
95% CI	0.87–1.34	0.74–1.14
p-value	0.472	0.472

Table 4. Frequency of angiotensin-converting enzyme alleles (%).

	II	ID	DD
patients (n=384)	22.39	49.48	28.13
controls (n=287)	16.72	56.79	26.49
OR	1.43	0.75	1.09
95% CI	0.97–2.12	0.54–1.01	0.77–1.53

Table 5. Frequency of angiotensin-converting enzyme genotypes (%).

Among ACE genotypes, the I allele increased the risk of AD (OR 1.08; 95% CI 0.87–1.34) but so far, the difference is not significant (Tables 4 and 5). In both groups, the ID genotype was most frequent, accounting for 49% of cases and 57% of controls. The II genotype was observed in 22% of cases and in 17% of controls (marginal significant difference – OR 1.43; 95% CI 0.97-2.12).

Discussion

Lower education is associated with a higher risk of dementia [7,8]. Current research confirms that vascular diseases have strong association with the development of AD.

Cardiovascular and cerebrovascular diseases increase production and aggregation of pathological amyloid-β protein40-42 [9]. Patients suffering from clinically manifested stroke as well as silent brain infarction are at a significantly increased risk of AD [10,11]. In the presented pilot study, a higher incidence of CVD in the history of patients with AD was detected but the result was not statistically significant in comparison with controls.

As far as diabetes mellitus is concerned, no positive association was found in the presented study. Surprisingly, an inverse association was observed. In a Canadian study from Dalhousie University, the relationship between diabetes and AD was also not found [12]

Similar to CVD, hypertension is a frequent condition of the elderly. A higher risk of AD was found in subjects having systolic blood pressure over 160 mmHg [13].

Some observational studies stated that increased blood pressure in middle-aged persons may lead to the development of AD in old age [14,15].

Some studies with a shorter follow-up (less than 3 years) found no or an inverse association between hypertension and development of AD [16]. This was actually the case of the presented study. Some studies even state hypotension as a risk factor for AD [17].

It is known that the ApoE4 allele is the only confirmed genetic factor contributing to both early- and late-onset AD. This strong association between the ApoE4 allele and AD was also confirmed in the presented study, making it a possible diagnostic marker of AD before full clinical development of the disease.

Some studies showedan association between I/D ACE polymorphism and AD [18].

In the presented study only marginal statistical significance was found. When the final results are evaluated based on the complete group of 800 cases and 800 controls, the situation will be much clearer.

Conclusions

More patients with AD had CVD in their history than controls but the difference was not significant. Diabetes, stroke and hypertension were inversely related to AD; this is in contrast with some other published results. In case of hypertension, the inverse association was statistically significant. The same finding was published by some other researchers [16].

Relationship between the ApoE4 allele and AD was confirmed in the presented paper with high statistical significance which makes it a potential diagnostic marker for AD. In the ACE gene, there was only a marginal association between the I allele presence and a higher risk of AD development.

AD is a serious problem all over the world. It is necessary to study all possible risk factors as their knowledge and detection may contribute to prevention of this condition.

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