SHORT REPORT

Environmental differences in twin pairs discordant for Alzheimer's disease

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Abstract

The aim of this study was to examine the contribution of environmental factors to the pathogenesis of Alzheimer's disease by comparing environmental differences in twin pairs discordant for Alzheimer's disease. Seventy four twin pairs discordant for Alzheimer's disease were found by linking the Finnish twin cohort and the Hospital Discharge Register from years 1972–91. In 50 pairs (25 monozygotic and 25 dizygotic pairs), both co-twins had responded to a questionnaire survey in 1975. Exposure differences were compared between these pairs. A reduced risk of Alzheimer's disease was significantly associated with a higher level of schooling (relative risk 0.3; 95% confidence interval 0.1–0.9, $p=0.029$). In addition, a reduced risk was suggestively associated with ambidextrousness or left handedness ($p=0.083$) and an increased risk with marriage ($p=0.052$), widowhood ($p=0.074$), and a history of cholelithiasis ($p=0.071$). In conclusion, a reduced risk of Alzheimer's disease was associated with a higher level of schooling.

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Although there is a genetic effect on the pathogenesis of Alzheimer's disease related to gene mutations^{1,2} and the apolipoprotein E polymorphism,³ most cases of Alzheimer's disease are sporadic. In epidemiological studies, Alzheimer's disease has been found to be associated with advanced maternal age, head trauma, history of depression, manual work, and low level of education.^{4,5} Environmental determinants of the risk of Alzheimer's disease can be investigated using the co-twin control design, which improves the power of the conventional case-control study. When monozygotic co-twins are discordant for Alzheimer's disease, differences in environmental exposure mostly determine the expression of the disease. Only one co-twin control study on Alzheimer's disease has been published, finding an inverse association between anti-inflammatory treatments and the disease.⁶ In this study, we exam-

ined the exposure differences in 50 twin pairs discordant for Alzheimer's disease.

Subjects and methods

FINNISH TWIN COHORT

The Finnish twin cohort was compiled from the Central Population Registry of Finland using selection procedures described in detail elsewhere.⁷ Briefly, all sets of persons with the same birth date, same sex, same surname at birth, and same local community of birth were identified from the Central Population Registry of Finland. This yielded all the pairs ($n=17\,357$) of same sex adult twins born in Finland before 1958 with both co-twins alive in 1967, as well as a few subjects who satisfied these criteria but who were not biological twins. A baseline questionnaire, administered in 1975, asked whether the subjects were twins and included questions for zygosity classification. The questionnaire also contained medical and psychosocial questions (97 items). The overall response rate was 89%. Further inquiries from local parish records were made on all non-respondents and conflicting responses to determine twinship. The validity of zygosity questions was confirmed by blood typing a subsample of 104 twin pairs living in the Helsinki area.⁸ About 93% of all responding pairs were classified as monozygotic or dizygotic with only 1.7% probability of misclassification. A total of 2489 pairs was left unclassified by zygosity. These consisted of pairs with an unknown address or with non-response to the 1975 questionnaire. The algorithm for classifying zygosity left 7% of respondent pairs unclassified because of conflicting responses to the items.⁸ A total of 13 888 (4307 monozygotic and 9581 dizygotic) twin pairs, who were 18 years of age or older at baseline were identified.

COLLECTION OF TWINS WITH ALZHEIMER'S DISEASE

The collection of twin pairs with Alzheimer's disease is also described in detail elsewhere.⁹ The linkage of a national registry of hospital discharges from the period 1972 to 1991 with the Finnish Twin Cohort yielded 285 twin subjects who had dementia as a discharge diagnosis. The medical records of these twin individuals and their co-twins were reviewed to confirm and classify dementia. The diagnosis

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Distribution of twin pairs discordant for Alzheimer's disease (n=50) according to their discordance for the risk factors

Risk factor	Case with trait/control without	Control with trait/case without	Relative risk (95% CI)	χ^2 p Value
Social factors:				
Ever or never married	10	3	3.33 (0.86–18.9)	0.052
Widowed or not	14	6	2.33 (0.84–7.41)	0.074
Schooling (more or less)	4	13	0.31 (0.073–0.996)	0.029
Lifestyle:				
Ever or never smoker	2	5	0.40 (0.038–2.44)	0.25
Heavy drinker	1	5	0.20 (0.004–1.79)	0.10
Abstainer	9	7	1.29 (0.43–4.06)	0.62
Medical and biological:				
Ambidextrous or left or right handed	3	9	0.33 (0.58–1.34)	0.083
Analgesics (more or less use)	8	14	0.57 (0.21–1.46)	0.20
Analgesics (any or none)	3	8	0.38 (0.06–1.56)	0.13
Antacid (any or none)	6	5	1.20 (0.31–4.97)	0.76
History of hypertension	5	5	1.00 (0.23–4.35)	1.00
History of urticaria	3	3	1.00 (0.13–7.47)	1.00
History of allergic eczema	7	7	1.00 (0.30–3.34)	1.00
History of cholelithiasis	11	4	2.75 (0.82–11.9)	0.071

of dementia was based on the DSM-III-R criteria, which were not fulfilled in either member of 55 pairs. Medical records were not found in 39 probands. Alzheimer's disease was diagnosed in accordance with the NINCDS-ADRDA criteria.¹⁰ Dementia of 94 subjects (51 monozygotic, 43 dizygotic) could be confirmed and classified as Alzheimer's disease. Eight monozygotic pairs and two dizygotic pairs were concordant. Out of 74 discordant pairs, Alzheimer's disease was diagnosed before the questionnaire survey in one monozygotic and in four dizygotic individuals.

QUESTIONNAIRE SURVEY

The questionnaire survey carried out in 1975 contained demographic, medical, and psychosocial questions. Sixteen items from the 96 item questionnaire were selected for the analysis on the basis of their relevance as putative exposure factors. The level of completed education was asked in a question with eight response categories. Each category was assigned an average number of years of schooling, and the number of schooling years was used as a continuous variable in the analyses.

There were 50 discordant pairs (25 monozygotic and 25 dizygotic pairs; 11 male pairs and 39 female pairs), in which both co-twins had responded to the questionnaire. These pairs were included in the study to examine whether patients with Alzheimer's disease differed from their age matched co-twins. The mean age in 1975 was 67.6 (SD 8.8) years for the pairs with Alzheimer's disease and 67.0 (SD 8.1) years for those without Alzheimer's disease ($p=0.69$). The mean age at onset of Alzheimer's disease was 75.9 (SD 7.6)(range 56–89) years.

STATISTICAL ANALYSIS

The informative nature of the study comes from the disease discordant pairs that are also discordant for the putative risk factors. An estimate of relative risk comes from the ratio of the number of pairs in which the diseased twin has reported the risk factor of interest, but not the healthy co-twin, to the number of pairs in which the opposite has occurred. For continuously distributed variables, the mean difference

between the diseased twin and the non-diseased co-twin was computed, and compared with a null hypothesis value of zero.

Results

The table shows the distribution of twin pairs according to their discordance for the categorical risk factors included in the analysis. Longer schooling, when categories of more or less were used, was associated with a reduced risk of nearly 70% ($p=0.029$), which was similar both in monozygotic and dizygotic twins. The mean education level of the twins with Alzheimer's disease (mean 6.1 (SD 1.9) years) was significantly less than that of their co-twins without Alzheimer's disease (mean 6.8 (SD 2.5) years) (paired t test: $t=2.35$, $p=0.023$). The mean difference was equally large among monozygotic (0.6 years) and dizygotic (0.8 years) pairs. In addition to the significant association between schooling and Alzheimer's disease, there were several suggestive associations between putative exposure factors and Alzheimer's disease, in which the level of the significance was >0.05 but <0.1 (an inverse association for ambidextrousness or left handedness and positive associations for marriage, widowhood, and a history of cholelithiasis). The occurrence of other disease histories and putative risk factors were similar among the affected and unaffected co-twins. Of the continuous variables, neuroticism ($p=0.48$), extroversion ($p=0.63$), body mass index ($p=0.94$), and alcohol consumption (g/month; $p=0.53$) were not associated with Alzheimer's disease.

Discussion

Several studies have found an association between limited educational attainment and Alzheimer's disease.^{5–11} In addition, in the American Nun study,¹² low linguistic ability in early life was a strong predictor of poor cognitive function and Alzheimer's disease in late life. Our study provides more evidence for the relation between low educational attainment and increased risk of Alzheimer's disease. The similar risk in monozygotic and dizygotic twins suggests that the association was unrelated to genetic factors. It has been proposed in the threshold model of dementia that neurocognitive capacity, when reduced below a specific threshold, accelerates the development of neuropathological lesions and cognitive impairment. A higher educational level may reflect a higher neurocognitive reserve developed in early life and may thus provide a protective effect against Alzheimer's disease. The important question to be answered is whether education increases neocortical synaptic density. On the other hand, there has been concern that the screening instruments used to identify subjects for cognitive decline may be subject to educational bias.¹³ In the present study, the effect of education on diagnosing Alzheimer's disease may be less significant, because, due to the linkage method, dementia was already clinically evident and mostly moderate or severe at the ascertainment of disease. In addition to the theory of premorbid vulnerability of the brain, lifestyle differences associated with a

low level of low education, such as nutrition, alcohol consumption, and occupational exposure, may explain the higher risk of Alzheimer's disease. Low educational level is related to manual work, which has been found to be a predictor for Alzheimer's disease. Manual workers are at greater risk of exposure to toxic agents than other workers. Occupational solvents have been found to be associated with impaired cognition.¹⁴ In our study, data on possible occupational exposure were not systematically available.

In addition to the association between the level of schooling and Alzheimer's disease, there were associations which did not quite reach the level of significance. The suggestive inverse association between ambidextrousness or left handedness is potentially interesting, because lateralised abnormalities have been found to be an important feature of dementia of the Alzheimer's type. A selective vulnerability of the left hemisphere has been found in dementia of the Alzheimer's type. In a study by Seltzer *et al*,¹⁵ left handedness was underrepresented in late onset Alzheimer's disease compared with the general population. However, further studies are needed to confirm whether right hemispheric dominance might provide protective traits against Alzheimer's disease.

The co-twin control design is a sensitive method, and it may achieve up to twice the power of conventional case-control studies. The advantage of the record linkage method, in addition to the nationwide cohort of twins, is the long follow up time of the twin pairs. The long follow up is essential to exclude the concordance for Alzheimer's disease, as a variation in the disease expression between co-twins may be up to 15 years.⁹ As the questionnaire exposure data were collected with few

exceptions before the manifestation of Alzheimer's disease, recall bias or other effects of dementia on reporting of exposures are unlikely to account for the differences between cases and their co-twins.

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