

Is Parental Age Related to the Risk of Alzheimer's Disease?

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Advanced maternal and paternal age were investigated as putative risk factors for AD in 198 clinically diagnosed Alzheimer patients and in 198 randomly selected healthy controls. No significant differences in average age of fathers and of mothers at birth of the subject were observed. The risk of AD was not significantly different across categories of maternal and paternal age. The association with parental age was not different for sporadic and familial AD. These findings do not support the view of a maternal or paternal age effect on AD.

Advanced parental age has been suggested as a putative risk factor for Alzheimer's disease (AD) because of its clinical and pathogenetic links with Down's syndrome. However, studies of this subject have yielded equivocal results. In four studies the offspring of old mothers had a higher risk of developing the disease than those of young mothers (e.g. Cohen *et al*, 1982; Amaducci *et al*, 1986) but this was not the case in eight others (e.g. De Braekeleer *et al*, 1988; Jouan-Flahault *et al*, 1989). In the largest study, with 116 clinically diagnosed Alzheimer's patients and 97 population controls, maternal age over 40 years was associated with a nearly five-times increased risk of AD (Amaducci *et al*, 1986). A recent additional analysis of that study showed that the increase in risk was restricted to sporadic Alzheimer patients (those with no family history of AD); in cases with familial AD the relative risk was not elevated (Schoenberg *et al*, 1988). We report a study of the putative association of AD and parental age in 198 Dutch Alzheimer patients who were compared with 198 population controls.

Method

The ages of the mother and father at birth of 198 Alzheimer patients and 198 age- and sex-matched healthy population controls were assessed, as part of a case-control study of Alzheimer's disease in the Netherlands. This study has been described in detail elsewhere (Hofman *et al*, 1989). In the patients the diagnosis of AD was made before the age of 70 years.

Patients

All patients in whom the clinical diagnosis of AD was made in the period of January 1980 to July 1987, who were not yet 70 years at the time of diagnosis, and who lived in the four northern provinces of the Netherlands or in the region of the city of Rotterdam, were eligible for this study. All patients in these areas were seen by three of the authors (WS, TAT and RH). Dementias other than AD were excluded

using the clinical history, a neurological examination, and neuropsychological and laboratory tests (McKhann *et al*, 1984). The diagnosis of AD was made in patients fulfilling the following criteria: (a) slow progressive decline of intellectual function; (b) Clinical Dementia Rating scale score of >0.5 (Hughes *et al*, 1982); (c) Short Portable Mental Status Questionnaire (SPMSQ) score of <20 (Pfeiffer, 1975); (d) Hachinski scale score of ≤ 7 (Hachinski *et al*, 1974); and (e) no evidence for abnormalities other than cerebral atrophy, on a computerised tomography (CT) and no evidence for focal dysfunction on an electroencephalograph (EEG). Of the 278 patients brought to our attention, 201 satisfied these criteria, and in 198, data on putative risk factors for AD were obtained.

Controls

For each patient a reference subject was randomly selected from the municipal population register, matched for age (within 5-year age-groups) and gender, and living in the same municipality as the patient at the time of diagnosis. All controls were apparently healthy, with a normal cognitive function and an SPMSQ score of ≥ 20 .

Data collection and analysis

The age of the parents at birth of the Alzheimer patient and the birth order of the patient and his/her siblings were obtained from the next of kin (in general the wife or husband, or a child), as part of a structured interview on risk factors for AD. The parental age in the control subjects was also obtained in the same way. Reliable information on maternal age and birth order was obtained in 184 patients and controls, and on paternal age in 160 patients and controls. The data were checked either by using the municipal population register or information from a second family member. Full information was collected on dementia in the family. Only those with at least one first-degree relative with dementia were considered to have a familial AD.

The strength of the association of maternal and paternal age and AD was assessed by computation of the relative risk (odds ratio), with 'parents younger than 25 years at birth of the patient or control' as the reference category. The analysis was done for all cases and then separately

TABLE I
Age of parents at subject's birth and relative risk for AD in all patients and those with sporadic AD

Age of parent at subject's birth: years	Mothers				Fathers			
	No. of patients	No. of controls	RR ¹	95% CI ³	No. of patients	No. of controls	RR ¹	95% CI ³
All patients								
≤24	52	46	1.0 ²		27	21	1.0 ²	
25-29	54	52	0.9	0.5-1.6	50	42	0.9	0.5-1.9
30-34	45	45	0.9	0.5-1.6	43	45	0.7	0.4-1.5
35-39	18	29	0.6	0.3-1.1	18	32	0.4	0.2-1.0
40+	15	12	1.1	0.5-2.6	22	20	0.9	0.4-1.8
Total	184	184			160	160		
Patients with sporadic AD								
≤24	28	24	1.0 ²		13	12	1.0 ²	
25-29	25	27	0.8	0.4-1.7	25	22	1.1	0.4-2.8
30-34	24	24	0.9	0.4-1.9	21	20	1.0	0.4-2.6
35-39	10	12	0.7	0.3-1.9	10	13	0.7	0.2-2.2
40+	7	7	0.9	0.3-2.8	9	11	0.8	0.2-2.5
Total	94	94			78	78		

1. Relative risk (RR) adjusted for age, sex and area of residence.
2. Reference category.
3. 95% confidence intervals.

TABLE II
Differences in mean (standard error of mean) age of parents at birth of patients and controls by family history of dementia

Family history of dementia	Mean mothers' age: years				Mean fathers' age: years			
	patients (s.e.m)	controls (s.e.m)	difference (s.e.m)	95% CI	patients (s.e.m)	controls (s.e.m)	difference (s.e.m)	95% CI
Yes	28.4 (0.7)	29.6 (0.6)	1.2 (0.9)	-0.6, 3.0	31.1 (0.9)	32.5 (0.8)	1.4 (1.2)	-1.0, 3.6
No	28.8 (0.7)	29.1 (0.6)	0.3 (0.9)	-1.5, 2.1	30.4 (0.7)	32.0 (0.8)	1.6 (1.1)	-0.6, 3.8
Total	28.6 (0.5)	29.3 (0.5)	0.7 (0.7)	-0.7, 2.1	30.7 (0.5)	32.2 (0.6)	1.5 (0.8)	-0.1, 3.1

for sporadic cases (no first-degree relatives with Alzheimer's disease) only. The relative risk is presented with a 95% confidence interval (95% CI). The matching variables (age, gender and area of residence) were taken into account by entering them into a model for logistic regression (Schlesselman, 1982). The reported relative risks are based on the regression coefficient yielded by this model. A separate matched-pair case-control analysis showed similar results. In an additional analysis, the mean age of the mother and father at birth of the subject was compared for patients and controls.

Results

The risk of AD was not significantly different across categories of maternal and paternal age at birth of the subject (Table I). The relative risk for maternal age of 40 years or over was 1.1 (95% CI 0.5-2.6). In sporadic (non-familial) Alzheimer patients the risk was also not different over strata of parental age (Table I). The relative risk for maternal age of 40 years or over was 0.9 (0.3-2.8). No

significant differences in average ages for mothers and fathers at birth of the subject were observed (Table II). A separate analysis showed no significant differences in birth order between Alzheimer patients and controls. This applied both to those with and those without a family history of AD.

Discussion

There is much evidence to suggest that genetic factors play a part in the aetiology of AD. In epidemiological studies, strong familial aggregation of Alzheimer patients has been observed, and recently, genetic linkage between AD and marker loci on chromosome-21 has been reported (St George-Hyslop *et al*, 1987). There is also evidence for clinical and neuro-pathological links between AD and Down's syndrome (Anonymous, 1987). These observations have led to the hypothesis that advanced parental age may cause abnormalities of chromosome-21, which may lead to AD.

This study fails to confirm previous findings of a maternal age effect on the risk of AD. The average age of the parents at birth of the subjects was, if anything, slightly lower in the patients than in the controls. This study differs from others in that it is considerably larger, and employed randomly selected population controls.

Two methodological issues have to be discussed. Firstly to reduce misclassification of Alzheimer patients as much as possible we applied the diagnostic criteria suggested by McKhann *et al* (1984) rigorously and restricted our study to patients in whom the diagnosis was made before the age of 70 years. However, we cannot rule out that some misclassification has occurred and as in other studies this tends to dilute a true difference in maternal age between the study groups. Secondly, this study was performed in early-onset Alzheimer patients. We do not know to what extent the present findings apply to AD with a later onset.

In conclusion, we suggest that parental age at birth of the subject is not likely to be a risk factor for AD.

Acknowledgement

The authors thank Verona Otten for her contribution to data-collection, and Drs H. A. Valkenburg and H. W. ter Haar for their advice. This study was supported by the SOOM foundation; it is part of the Eurodem EC Concerted Action on the Epidemiology of Dementia.

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British Journal of Psychiatry (1990), **157**, 275-278

The Effects of Chronic Lithium Treatment on Psychomotor Performance Related to Driving

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A group of 16 psychiatric out-patients in remission, who had been taking lithium carbonate as their sole medication for at least three months, were compared with a control group of