Parental Age and Birth Order in Alzheimer's disease: A Case-Control Study in the Saguenay-Lac-St-Jean Area (Quebec, Canada)

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ABSTRACT: Parental age at the time of birth of 133 clinically diagnosed Alzheimer patients from the Saguenay-Lac-St-Jean area (Quebec, Canada) were compared with those of 6 control groups formed out a population registry. The birth order of the Alzheimer patients was also analyzed. The results did not show any parental age or birth order effect, which is in agreement with previous reports. The importance of control selection in such studies is stressed.

RÉSUMÉ: L'âge des parents, le rang de naissance et la maladie d'Alzheimer: une étude faite dans la region du Saguenay-Lac-St-Jean (Québec, Canada) On a calculé l'âge des parents au moment de la naissance de 133 patients atteints de la maladie d'Alzheimer et diagnostiqués cliniquement dans la région du Saguenay-Lac-St-Jean (Québec, Canada) en utilisant un régistre de population. Le rang de naissance des patients a aussi été déterminé. Les résultats ont montré qu'il n'y avait pas de relation entre l'âge des parents et le rang de naissance et la maladie d'Alzheimer, ce qui est en accord avec les résultats obtenus par d'autres chercheurs. L'importance de la sélection des groupes controllés dans de telles études est soulignée.

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Alzheimer's disease (AD) is a progressive dementing illness that manifests itself in mid or late adulthood. It is the most common form of dementing disorder in the elderly.[1]

Previous pathological and epidemiological findings have established an association between Alzheimer's disease and Down's syndrome (DS).[2,3] In particular, Heston et al[3] found an increased prevalence of DS among relative of AD patients as compared to the one expected in the general population. More recently, the B amyloid gene, which is an important component of the plaques in AD and DS, was mapped on chromosome 21.[4-6]

Because parental age, and more particularly maternal age, and birth order are well-known risk factors in Down's syndrome,[7,9] these findings lead a number of researchers to investigate a possible relationship between AD and parental age or birth order.[10-17] No paternal effect was found but analyses of the maternal age and birth order showed conflicting results.

The present study was undertaken to determine whether parental age and birth order were risk factors in a population of 133 clinically diagnosed Alzheimer patients from the Saguenay-Lac-St-Jean (SLSJ) area (Quebec, Canada).

MATERIALS AND METHODS

The Saguenay-Lac-St-Jean area is a quite isolated region located 125 miles North-East of Quebec City. The region was opened to white settlement in the 1840s. The population rose quickly by immigration but mainly by natural increase. At the present time, some 300,000 people live in the SLSJ area.

Since 1972, a population registry has been constructed. It contains over 700,000 birth, marriage, and death certificates and is completed till 1971.[18] Several parameters are recorded for each individual, notably dates and places of birth, marriage and death, socioeconomic status, successive residences. All the families are reconstructed and genealogies can be automatically generated.[19]

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A registry of over 400 presumptive cases of senile dementia of the Alzheimer type from the SLSJ region is now being screened for Alzheimer's disease (IMAGE project). So far, 133 cases have been classified as definite, probable or possible AD following the recommendations of the NINCDS-ADRDA work group.[20]

A method devised by Haldane and Smith[21] was used to decide whether, in our 133 sibships, AD patients tended to be born later. The Haldane-Smith test is based on the sum of the birth ranks of all affected members in all sibships. Hence, this test uses only the affected sibships and no controls. In situations where there is no information on some sibs, the method proposes to eliminate these "unspecified" members. For the present analysis, the deceased sibs and those younger than 40 years of age were considered "unspecified" as their disease status was in fact unknown.

Maternal age was known in 120 cases and paternal age in 122 cases. The mean parental age for the normal sibs of the Alzheimer patients was calculated using the population registry. Parental age at the time of birth of the AD patients' spouses was also determined. Six control groups were created, using the population registry. Controls 1-2-3 were matched on the date of marriage of the parents of the Alzheimer patients (+ or −5 days), their socioeconomic status as defined by the father's profession, the parents' residence and the birth rank of the AD patients. Controls 4-5-6 were randomly selected births matched on sex and year of birth of the Alzheimer patients as well as the socioeconomic status of the parents. The statistical analysis was performed using the Student's paired t test, two-tailed.

RESULTS

The Haldane-Smith test was applied for testing no birth order effect against a later born alternative. No significant result was found (test statistic = −3.075, p > 0.99).

Table 1 shows the parental age at time of birth for Alzheimer patients, normal siblings, spouses, and controls. Both maternal and paternal mean ages at the time of birth of the Alzheimer patients were found to be significantly lower than their ages at the time of birth of the normal siblings (respectively F = 2.64, p < 0.001 and F = 2.25, P = 0.001). No significant difference was found between parental age at the time of birth of the Alzheimer patients and their spouses, or any of the 6 control groups (P > 0.10).

Table 1: Parental age at time of birth for Alzheimer patients, normal siblings, spouses and controls.

	Mother's age		Father's age	
	Mean (years)	S.D. (years)	Mean (years)	S.D. (years)
Alzheimer patients	29.4	6.7	32.6	7.5
Normal siblings	31.5*	4.1	34.9*	5.0
Spouses	29.5	6.1	33.4	6.7
Controls 1	29.7	4.2	33.3	4.7
Controls 2	30.1	4.3	33.5	4.3
Controls 3	29.2	4.3	33.4	5.6
Controls 4	30.2	4.5	33.2	7.0
Controls 5	30.0	4.2	32.5	5.1
Controls 6	29.1	5.7	32.2	6.8

* p < 0.05

DISCUSSION

Previous analyses of the relationship between birth order and Alzheimer's disease has led to negative or indefinite conclusions. Larson et al[10] found that 199 of the 408 patients with senile dementia belonged to the first half of the birth series and the remaining 209 to the second half of the birth series. Using the method of Carothers et al,[22] Whalley et al[11] did not find any significant birth order effect. Amaducci et al[16] found a borderline significant relation between a high birth rank and AD. White et al[17] showed that the average birth order of the 126 autopsy-proven Alzheimer patients was significantly less than the average birth order of the controls selected among the births recorded in the Anoka county (Minnesota). However, the average birth order for the Alzheimer patients was not significantly different from the expected average computed assuming random distribution of the AD cases throughout the sibship.

Our results did not show any evidence of a relationship between a high birth order and AD. In fact, it was noted that testing no birth order effect against an early-born alternative would have given highly significant results (P < 0.001). White et al[17] suggested that their result was probably due to the control families being larger than the AD families. However, the present analysis was based only on the affected sibships and, therefore, there is no possible bias due to the choice of the control families. An early-born effect may sometimes be explained by the lack of ascertainment of younger cases (secondary cases) who have not yet developed the disease or been screened. The use of the Haldane-Smith method that allowed us to eliminate the very young ones in the computing (less than 40 years old) helped reduce this problem.

A younger maternal age at the time of birth of the Alzheimer patients than of the normal siblings (29.4 versus 31.5 years) was found. The direction of this difference is opposite to what would have to be expected if there was a maternal age effect on AD. The difference in the mean maternal age at the time of birth of the Alzheimer patients compared with that of the spouses and controls was not statistically significant. Similar results were already reported by Heyman et al[13] who compared maternal age at the time of birth of 36 clinically diagnosed and patients with their spouses and by Corkin et al[14] who compared the maternal age at the time of birth of 37 clinically diagnosed Alzheimer patients with the age at birth of 34 controls of comparable age and socioeconomic status. A similar conclusion was reached by English and Cohen[15] who compared 64 clinically diagnosed AD cases with their spouses and spouses of 87 patients with Parkinson disease. White et al[17] did not find any significant difference in maternal age at the time of birth of 112 AD patients, most of them autopsy-proven, their normal siblings, and 200 randomly selected births in Anoka county (Minnesota). Cohen et al[12] found an association between maternal age and AD but their controls were not matched on factors such as socioeconomic status. Amaducci et al[16] found a maternal age effect for AD but their controls were not matched on the AD patients' characteristics.

A younger paternal age at the time of birth of the Alzheimer patients than of the normal siblings (32.6 versus 34.9 years) was found. The mean age of fathers at the time of birth of AD cases was not significantly different from the mean age of the spouses or the controls. Such findings were already reported by several workers.[13,14,16,17]

Whalley et al[11] compared 69 autopsy-proven AD cases with 207 unrelated controls matched for year of birth, sex and paternal occupation. They found a significant increase in maternal and paternal ages for the AD cases. However, they did not find any significant parental age effect when using the method of Carothers et al[22] which estimates a relation risk as a function of parental age and birth order and, therefore, used the siblings as controls.

In conclusion, the controversial results described in the literature seem to be a consequence of control selection. The studies that used the siblings or the spouses as controls or matched the controls on socioeconomics status did not show any parental age or birth order effects for Alzheimer's disease. Our results, which are based on six different control groups, are in agreement with these conclusions.

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