Educational Attainment and Socioeconomic Status of Patients With Autopsy-Confirmed Alzheimer Disease

David G. Munoz, MD, FRCPC; G. R. Ganapathy, MD, FRCPC; Michael Eliasziw, PhD; Vladimir Hachinski, MD, FRCPC, DSc

Objective: To determine whether patients with autopsy-confirmed Alzheimer disease (AD) have different educational attainment and socioeconomic status than subjects without neurodegenerative disease.

Design: Comparison of 2 groups of autopsied patients. Information on education and occupation was obtained by telephone interview of relatives conducted post mortem.

Patients: One hundred fifteen patients enrolled in the University of Western Ontario Dementia Study with dementia and fulfilling diagnostic criteria of AD at autopsy were compared with 142 patients 65 years or older without dementia who died in the hospital and in whom autopsy did not show neurodegenerative disease.

Main Outcome Measures: Highest education level attained, years of education, occupation, and socioeconomic and income levels. All results were adjusted for sex, age at time of death, and year of birth.

Results: There were no statistically significant differences in education, occupation, or socioeconomic and income levels between the groups.

Conclusions: There is no evidence that educational attainment is different in patients with AD than in subjects who die in the hospital from other diseases. These results indicate that education does not protect against advanced AD.

Arch Neurol. 2000;57:85-89

FAMILY early-onset varieties of Alzheimer disease (AD) can be explained by mutations in the β-amyloid protein precursor gene, the presenilin genes, and other, undiscovered genes. The common sporadic late-onset variety is more complex. The ε4 allele of apolipoprotein E is undoubtedly a strong risk factor, and other genetic polymorphisms have been proposed as additional contributors to the risk of developing the disease. However, environmental factors must also play a role, as indicated by the common discrepancy in expression of the disease among identical twins. Currently, the only nongenetic factors to be upheld by replication in epidemiological studies are head trauma and education. The latter is the subject of the present report.

Higher education attainment has been reported to reduce the risk of dementia, as determined by population-based prevalence studies. The type of dementia is often but not always identified as AD. The weakness of these studies is the diagnosis of dementia, which is at times determined following brief cognitive tests and the application of rating scales without assessment by a physician, the use of imaging, or long-term follow-up. Education can artifically distort performance on these tests, leading to incorrect classification of subjects. Moreover, several well-conducted studies some with follow-up, found no association of education with the prevalence of dementia. Studies investigating the incidence of dementia are also divided among those finding and not finding an association between education and the risk of dementia.

Assuming that an inverse relationship exists between educational attainment and the risk of dementia, 2 types of mechanisms could mediate this phenomenon. The brain reserve hypothesis postulates that individuals possess a cognitive reserve above the threshold for dementia; that education promotes the development of more efficient cerebral activity, possibly through the formation of more abundant or proficient synapses; and that the onset and progression of the degenerative process may be unrelated to education, but its manifestation as dementia is delayed in subjects who are better educated because of their greater cognitive reserve. Alternatively, the brain-
METHODS

Data on patients with AD were obtained from the University of Western Ontario Dementia Study, a prospective longitudinal study of AD that began in 1977. Patients were recruited following referral from family practitioners, internists, neurologists and psychiatrists working in southwestern Ontario under the standard Canadian universal coverage rules. One of the authors (V.H.) joined the study in 1982 and made a clinical diagnosis of dementia in all cases included in this report. The autopsy rate of patients in the University of Western Ontario Dementia Study was 70%; there was no difference in reported age of onset, rate of progression, and age at time of death between patients with or without autopsy. Prior to the end of 1994, 199 autopsies had been performed, of which 143 received a pathological diagnosis of AD according to criteria of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD); this constitutes the population base of this study. Although the original pathological report had been issued prior to the publication of the CERAD criteria, another of the authors (D.G.M.) reviewed all cases in the University of Western Ontario Dementia Study to ensure that diagnoses conformed to current criteria. Of the 143 autopsies with an AD diagnosis, 25 carried an additional diagnosis of dementia with Lewy bodies, and 39 had cerebral infarcts. In 12 cases, these were considered severe enough to contribute to the dementia, and a diagnosis of mixed dementia was considered. The 56 excluded cases had miscellaneous pathological diagnoses. This group consisted of 15 cases with pure dementia with Lewy bodies, 5 with multi-infarct dementia; 7 with Pick complex (including Pick body dementia, corticobasal degeneration, and dementia lacking distinctive histopathological characteristics); 3 with hippocampal sclerosis; 2 with progressive supranuclear palsy; 2 with Hallervorden-Spatz disease; 3 with Creutzfeldt-Jakob disease; 4 with alcoholic dementia; 10 with no structural abnormality sufficient to explain the dementia; and 1 each with glioma, metastases, old trauma, hydrocephalus, and dementia with argyrophilic grains. Although data on educational attainment and SES had been obtained in many cases as part of the University of Western Ontario Dementia Study, this information was not used to ensure comparability with controls without dementia. Instead, one of the authors (G.R.G.), blinded to the University of Western Ontario Dementia Study data, interviewed relatives as indicated below. Relatives were able to provide the information sought in 115 cases.

The autopsy-proven control group consisted of individuals 65 years or older who died and had an autopsy performed at University Hospital, London, Ontario, with or without a history of neurological disease but with no history of dementia and in whom the brain either was considered normal or showed abnormalities other than neurodegenerative lesions upon histological examination. The presence of a few neurofibrillary tangles in the hippocampus and parahippocampal gyrus and of neuritic senile plaques (<5nm² in these regions and the neocortex) was considered within normal limits. The presence of any number of senile plaques of the diffuse type did not change the diagnosis. In practice, the cases that were excluded on the basis of histological examination were limited to 2 cases fulfilling the CERAD histological criteria for AD, with Parkinson disease and 1 with multiple-system atrophy. Starting in reverse order from December 31, 1994, we identified 200 consecutive patients who fulfilled the pathological criteria. Among those who fulfilled the age requirement, information on education and occupation was obtained (n = 142).

The request for a hospital autopsy originated from the attending physician for diagnostic purposes, and consent was granted by the next of kin of the deceased.

battering hypothesis (del Ser et al) postulates that the apparent effect of education is a result of its association with socioeconomic status (SES). Socioeconomic status is a major determinant of exposure to industrial and non-industrial toxins; habits, such as smoking or drinking; diet; and access to medical care. Any of these factors could conceivably alter the risk of AD.

The ideal approach to proving or disproving these hypotheses would be to subject a random sample of the population to clinical and psychometric assessments and then examine their brains after death to obtain a reliable diagnosis of the disease process responsible for the dementia. Since such a sample is not available, the present study ascertained educational attainment and SES for individuals in whom the status of the brain had been unequivocally established at autopsy.

RESULTS

The distribution of sex, age at time of death, and year of birth were all significantly different in the 2 groups (Table 1); thus, adjustments to the percentages and means were essential to compare them. Highest educational level attained was not statistically different in the 2 groups (Table 2). Although occupation level was statistically nonsignificant in the logistic regression analysis, it is still noteworthy that patients with AD were 2.4 times more likely (15.6% vs 6.4%) to be in a low-income occupation than control patients, and control patients were 2.3 times more likely (38.0% vs 16.8%) to be homemakers than patients with AD (Table 2). Neither the estimated socioeconomic nor income levels were significant. Similar results were observed among the occupation variables when the analyses were repeated for the subgroup of patients in the workforce (Table 3).

COMMENT

Interpretation of the results of the current study is limited by the fact that neither the AD nor the control group represents a random sample of their respective reference populations. With regard to the AD group, it is likely that subjects who consent to participate in a research project are better educated than individuals who refuse. The high autopsy rate (70%) and the lack of difference for a number of demographic and clinical measures for subjects who had an autopsy and those who did not suggest that the impact of additional bias is limited. With respect to the control group, the Canadian
The procedure used to obtain information on education and occupation of the deceased was identical in the control and AD groups. The telephone number of the next of kin was obtained from the patient’s hospital chart. Once contacted, relatives were told that the purpose of the project was to assess possible risk factors for brain diseases and that we sought information concerning the education (years of education and highest degree obtained) and occupation of the deceased. In cases with multiple or sequential occupations, relatives were asked to choose the main occupation based on the number of hours worked during a year (for multiple occupations) and number of years worked (for sequential occupations). They were told that participation was strictly voluntary. Not a single relative refused to provide the information, although in some cases we were referred to another relative. The same author (G.R.G.) interviewed relatives of control patients and patients with dementia. We obtained 2 measures of education: the number of years of education and highest attainment level (none, public school only, high school, and any college or university education).

Occupation was also scored in 2 ways. First, we classified subjects as either a homemaker or 1 of 3 levels as follows:

- High income: major profession, higher executive, proprietor of a large concern, business manager, other lesser profession and medium-size business, or farmer with more than 200 acres.
- Medium income: minor profession, administrative staff, small business owner, or clerical/sales staff.
- Low income: machine operator, semiskilled employee, or unskilled employee.

Second, each subject’s main occupation was classified into 1 of 514 categories listed in the Canadian Classification and Dictionary of Occupations. The average income data for the occupation were obtained from the tables of Blishen et al,28 which are derived from the 1981 Census of Canada and supplementary tabulations obtained from Statistics Canada. The Blishen SES score was derived from occupation alone. This index is not a measure of occupational prestige but a composite index of the prevailing income and education levels for each occupation. Any individuals who were reported to be homemakers were assigned a Blishen code of 6142 (housekeepers, servants, and related occupations) rather than classified as having had the SES of spouse. Because of the uncertainty of the appropriateness of this classification, we also performed the analysis restricted to those individuals in the workforce, that is, those listing an occupation other than homemaker. Ethnicity was not recorded, although almost all subjects were white, as is the general population of this age in southwestern Ontario.

Differences between the AD and control groups in regard to education and occupation levels were first assessed in a univariate (unadjusted) analysis using a \( \chi^2 \) test. Logistic regression was then used to adjust for the imbalance of sex, age at time of death, and year of birth. For this analysis, membership in the AD or control group was the dependent variable, whereas education and occupation level were the independent variables. Adjusted percentages were computed by exponentiating the logit.29 The mean number of years of education and the mean socioeconomic and income levels were first compared using an independent 2-sample \( t \) test (unadjusted analysis). Analysis of covariation was then used to adjust for sex, age at time of death, and year of birth, yielding adjusted means.

universal health care coverage system substantially reduces hospital admission bias in comparison with other countries. However, the population attending a university hospital may be better educated than the Canadian average, and education may influence consent to autopsy. These caveats, which apply to virtually any autopsy-based study, should be considered in interpreting the results obtained, which simply reflect the comparison of outpatient and inpatient subgroups attending the same hospital.

Our data indicate that the educational attainment for patients with autopsy-confirmed AD is no different from that of a sample of individuals who underwent autopsies at the same hospital. These results are not incompatible with some aspects of the brain reserve hypothesis, since most patients with AD who underwent autopsies were in the terminal stages of the disease, whereas the expected effect of education would be manifested during the early stage of mild dementia. However, our results are inconsistent with a persistent protective effect of education in advanced AD. The only other study to examine the effect of education on the development of AD in an autopsy-confirmed series was likewise unable to confirm the predictions of the brain reserve hypothesis.30

In previous articles, in which we have examined the age of onset and time course of AD in University of Western Ontario Dementia Study patients, we have shown that low educational attainment was associated with a delayed onset of the disease.25,31 This effect decreased but persisted after correction for year of birth23 and might be explained by the association of cerebral infarcts with both low education and advanced age. The unconfirmed results of the Nun Study suggest that the presence of cerebral infarcts, even minor ones, markedly increases the clinical manifestations of AD-type brain lesions.33 The brain-battering hypothesis (del Ser et al34) proposes that the protective effect of education is mediated indirectly

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alzheimer Disease Group (N = 115)</th>
<th>Control Group (N = 142)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, %</td>
<td>40.0</td>
<td>58.4</td>
<td>.003</td>
</tr>
<tr>
<td>Age at time of death, y*</td>
<td>77.8 (8.5)</td>
<td>75.3 (6.5)</td>
<td>.008</td>
</tr>
<tr>
<td>Year of birth*</td>
<td>1909 (8)</td>
<td>1916 (7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Values are mean (SD).
through SES by reducing physical assault on the brain in the form of toxins and infarcts. The observation that patients with AD are between 2 and 3 times more likely to have worked in low-income occupations raises the possibility that factors associated with SES play a role in the development of the disease. However, the difference does not reach the level of statistical significance, and at this point the conservative view must be that no effect of SES has been demonstrated. However, if expanded studies were to demonstrate the role of SES in the development of AD, the fact that homemakers do not participate in the increased risk of low-income occupations but the opposite suggests that the causes of AD should be sought in the differences in lifestyle and level of exposure to injurious agents or substances, rather than in the use of the brain for intellectual activities traditionally associated with formal education.

Accepted for publication June 10, 1999.

This study was supported by grant MT-12707 from the Medical Research Council of Canada, Ottawa, Ontario (Dr Munoz), and by grant 98/3157 from the Fondo de Investigación del Sistema Nacional de Salud of Spain.

Corresponding author: David G. Munoz, MD, Department of Pathology, The University of Western Ontario, London, Ontario, Canada N6A 5C1 (e-mail: dmunoz@julian.uwo.ca).

REFERENCES