An autopsy-verified study of the effect of education on degenerative dementia

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Summary

A longitudinal study of the relationship between education and age of onset, rate of progression and cerebral lesion burden in a series of autopsy-confirmed demented patients with clinical and 6-monthly psychometric follow-up and autopsy was carried out. The study was conducted at the London Health Sciences Centre University Campus of the University of Western Ontario on 87 patients with pathologically confirmed Alzheimer’s disease (60), dementia with Lewy bodies (11) or dementia with Lewy bodies plus Alzheimer’s disease (16). Their educational attainment was classified as below high school, high school or above high school, and was similar to that of the age-adjusted general Ontario population. The age of onset of dementia, age at death, progression of cognitive decline, amount of neurodegenerative changes (senile plaques, neurofibrillary tangles and Lewy bodies) and cerebrovascular lesions (infarcts, lacunar state and white matter rarefaction) were assessed. Less educated patients became demented later and died later, but cognitive function declined at the same rate in all educational groups and there was no difference in the burden of neurodegenerative lesions between them. However, the less educated patients had more cerebrovascular lesions. It can be concluded that higher education does not modify the course of Alzheimer’s disease, but lower education relates to the occurrence of cerebral infarcts. Our results suggest that a ‘brain battering’ model related to the higher prevalence of small vascular lesions in less educated individuals may explain their increased risk of dementia described by epidemiological studies better than the prevalent ‘brain reserve’ hypothesis.

Keywords: education; dementia; vascular lesions; Alzheimer’s disease; cerebral infarcts

Abbreviation: ESD = Extended Scale for Dementia

Introduction

The inverse association between previous education and dementia is one of the most fascinating and debated findings in the field of neurodegenerative diseases (Katzman, 1993). Several epidemiological studies, from different cultural settings, have shown that the prevalence of dementia is higher in poorly educated individuals (Rocca et al., 1990; Zhang et al., 1990; Dartigues et al., 1991; Canadian Study of Health and Aging, 1994; Stern et al., 1994; Ott et al., 1995; Callahan et al., 1996; Evans et al., 1997; Obadia et al., 1997), although other reliable investigators found no evidence (O’Connor et al., 1991; Beard et al., 1992; Bonaituo et al., 1995; Cobb et al., 1995) or only partial evidence (Ott et al., 1999) of this association.

The inverse relationship between previous formal education and dementia could be due to educational skills raising scores on the diagnostic tools (O’Connor et al., 1991), but some studies have suggested that this is not the case (Katzman, 1993; Stern et al., 1994; Callahan et al., 1996). A real association of education and reduced risk of dementia could be explained in two ways (Mortimer and Graves, 1993). The ‘brain reserve’ hypothesis states that education has a protective effect because it enhances the cognitive assets above the threshold for dementia, possibly by increasing synaptic density or efficiency (Fratiglioni et al., 1991; Stern et al., 1992, 1994, 1995a, b; Katzman, 1993) or by acquired skills (Snowdon et al., 1989a, b; Fratiglioni et al., 1991; Katzman, 1993; Stern et al., 1995). The neurodegenerative process assumed to affect individuals, regardless of their educational level, would take longer to bring down a larger reserve to the critical threshold. The alternative, which we may call the ‘brain battering’ hypothesis, assumes that individuals with greater educational attainment and associated...
higher socio-economic status would be exposed to fewer toxins, enjoy a healthier lifestyle and have greater access to quality health care, all of which would tend to spare their brains from lesions contributing to dementing illnesses (Fratiglioni et al., 1991; Hill et al., 1993; Katzman, 1993). Cerebral infarcts may be one of these lesions, whose association with low socio-economic status is well documented (Rocca et al., 1990; Fratiglioni et al., 1991; Ott et al., 1995).

The structural basis of dementia affected by education is controversial. In a Swedish epidemiological study, only alcoholic, unspecified and vascular dementia were influenced by education (Fratiglioni et al., 1991). In a study performed in Shanghai (Zhang et al., 1990) an effect of education was predominant in Alzheimer’s disease, but in two population surveys in Appignano (Rocca et al., 1990) and Rotterdam (Ott et al., 1995) it was observed both in Alzheimer’s disease and vascular dementia. However, the diagnosis in all these studies was based on clinical impression alone using a clinicopathological series of demented patients. The biological basis of the effect of education on the incidence or prevalence of dementia cannot be addressed. It can, however, be used to examine the dose–response effect of educational level on the age of onset and the rate of progression of the disease, especially the burden of different types of brain lesions and the relationship with the degree of cognitive impairment.

We have examined in a cohort of demented patients followed to autopsy, the effect of educational attainment on: (i) the age of onset of mental impairment and death, (ii) the rate of cognitive decline, and (iii) the type and amount of lesions and their relationship to the degree of dementia.

Methods
Setting
The Dementia Study Project of the University of Western Ontario (Merskey et al., 1985) is a 17-year-old prospective clinicopathological study of dementia, based in the memory clinic of a tertiary hospital with a catchment area of 1 500 000 people. The cohort was recruited through referrals from general practitioners, psychiatrists and neurologists working under the universal coverage rules of the Canadian Health Care System. There is no parallel medical system in this area. Participation in the study was voluntary and implied no costs to the patients or their relatives. Consent for autopsy was requested from patient or relative as appropriate; granting consent was not a condition for participation in the study. The autopsy rate of patients in the Dementia Study was 64% but there were no significant differences in the sex distribution, the age of onset of dementia and the age at death between autopsied and non-autopsied patients, as described elsewhere (Bowler et al., 1998).

Patients
The current study was based on all 95 cases in the Dementia Study Project who had died and were autopsied during the period 1986–93. Our clinicopathological research was focused on Alzheimer’s disease and dementia with Lewy bodies; consequently, we excluded six cases with miscellaneous diagnoses (Pick, neuroaxonal dystrophy, Creutzfeldt–Jakob disease, progressive supranuclear palsy and two cases of dementia lacking distinctive histology). No autopsy diagnosis of pure vascular dementia was reached during this period. Two cases for whom information about the level of formal education was missing were also excluded, leaving 87 cases in the analysis.

All patients were Caucasian (38 men, 49 women) and had joined the Dementia Study after informed consent from themselves or their caregivers. The racial distribution is representative of the population of this age in south-western Ontario. On each patient’s entry to the study one neurologist (V.H.) reviewed demographic and clinical data, applied a neurological and mental state examination, and performed a routine complementary work-up (haemogram, serum biochemistry, thyroid hormones, luetic serology, EEG and CT). A cognitive examination with the Extended Scale for Dementia (ESD) (Hersch, 1979) in 80 cases and a functional assessment with the London Psychogeriatric Rating Scale (LPRS) (Hersch et al., 1978) in 85 cases were also done. Patients were followed with regular applications of the ESD and LPRS every 6–12 months. All cases were diagnosed as having dementia according to DSM-III criteria (American Psychiatric Association, 1987) and this diagnosis was confirmed during a follow-up of 1–12 years until death. The length of the follow-up was distributed normally with mean of 5.5 ± 2.4 years (SD), median 5 years.

Clinical data
The following data were obtained from the prospectively recorded Dementia Study Project forms: (i) age at the onset of dementia, according to the caregiver’s information about the first notice of relevant signs of memory or behaviour disturbances, age at death and duration of disease; this information was available in all cases; (ii) ESD cognitive scores recorded in 80 cases when they joined the Dementia Study (4.4 ± 2.3 years after the onset of dementia) and in many cases also during the last few years before death, as presented in Fig. 1. In all patients who reached the state of severe cognitive decline the score in the ESD was considered to be 0 until death; (iii) severe cognitive decline, defined as the point at which the ESD was no longer applicable. This point was accurately identified in 61 cases. The last recorded ESD in 19 cases was above this level. In the remaining 7 cases ESD data was missing and this point could not be established, although they were not severely demented at entry to the study; and (iv) onset of regular bladder incontinence, determined as described previously (Del Ser et al., 1996). This information was available in 79 cases; three patients did not become incontinent during their life span.
The effect of education on degenerative dementia

Previous formal education
Previous education was graded in three levels: 28 cases below high school education (less than grade 9), 32 cases with high school education (grades 9–13) and 27 cases above high school education (20 cases with non-university further education and seven cases with a university degree). Students normally attend high school from 14 to 18 years of age. The number of years of formal education had been recorded in all but 6 cases, all of whom were professionals, and the number of years was estimated from the ordinary length of education required for graduation in their field. Thirty-one cases had been manual workers, 21 cases specialized manual workers, 9 cases white collar workers, 13 cases technical workers and 13 cases professionals.

Pathological study and diagnostic groups
All pathological procedures were performed at the Division of Neuropathology, Department of Pathology, University Hospital of London, Ontario. All pathological measurements were done by the same researcher (T.D.S.) blinded to the clinical and educational information.

The brain was removed at the autopsy, fixed in formalin and cut into 1 cm thick coronal slices. All macroscopic vascular lesions were mapped on a sheet with 18 diagrams of consecutive brain coronal sections. The brain weight and the approximate volume of macroscopic brain infarcts were recorded.

Histological sections from 10 regions (frontal, parietal, occipital and temporal lobes, hippocampus, amygdala, basal ganglia, thalamus, midbrain and cerebellum) were stained with haematoxylin and eosin, Bielschowsky’s method and Congo red. Additional sections were immunolabelled as previously described (Manlow and Munoz, 1992) with an antibody to ubiquitin (Sigma Immunochemicals, Oakville, Ontario, Canada) to facilitate the recognition of cortical Lewy bodies (Dickson et al., 1989) and abnormal neurites in the CA2 sector of the hippocampus (Dickson et al., 1991).

The following pathological variables were assessed in every case.

Semiquantitative variables
Ischaemic lacunar lesions were assessed in the basal ganglia and thalamus and graded in two levels: (i) absent or scarce microscopic, (ii) abundant microscopic or grossly visible. White matter lesions were assessed with a four-point scale in all available histological sections of the centrum semiovale. The average was dichotomized as <2, absent/mild; ≥2, moderate/severe. Amyloid angiopathy was rated as absent or present on the basis of Congo red stain.

Quantitative variables
The following lesions were counted in a Bielschowsky’s stained hippocampal section (side selected at random): the number of intracellular neurofibrillary tangles and ghost tangles in a 1 mm sector of hippocampal pyramidal layer in CA1, adjacent to CA2, and the number of diffuse plaques, neuritic plaques and neurofibrillary tangles in a 0.5-mm wide strip of neocortex located in the depth of the external lip of the collateral sulcus.

In a parallel section stained with haematoxylin and eosin the number of Lewy bodies was counted in a 1-mm wide strip of paleocortex located in the middle of the parahippocampal gyrus. The number of Lewy bodies was also counted on both sides of the substantia nigra in a section of the mesencephalon stained with haematoxylin and eosin, and averaged.

These quantitative measures were done using a reticule of 0.5 × 0.5 mm and counting all lesions which were

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Fig. 1 ESD scores at the time of inclusion and in the 5 years prior to death by educational level. The number of cases assessed at every time point is indicated in parentheses. There were no significant statistical differences between groups at any point. Level of education: triangles = below high school; diamonds = high school; circles = above high school.
partially or totally included in it. Measures were repeated in 20 cases with a test–retest reliability (Pearson’s correlation) of 0.91 for plaques in the cortex, 0.94 for tangles in the hippocampus and 0.95 for Lewy bodies in the substantia nigra.

**Diagnostic groups**

On the basis of histological examination patients were sorted into diagnostic groups defined by the following criteria:

**Alzheimer’s disease (60 cases).** Abundant neocortical neuritic senile plaques and neurofibrillary tangles (eight or more in 1 mm² of the temporal neocortex), as described and illustrated by Mirra and colleagues (Mirra et al., 1993), and no cortical Lewy bodies or abnormal ubiquitinated neurites in CA2. There were also some vascular lesions in 29 cases: moderate microscopic lacunes (10 cases) or macroscopic lacunes (1–6 ml in volume, 12 cases) in subcortical regions, moderate infarcts in the left frontotemporal region (30, 27, 20, 20, 10 and 9 ml in volume, 6 cases), marked white matter hypodensities (13 cases) or hippocampal sclerosis, probably of ischaemic cause (5 cases).

**Pure dementia with Lewy bodies (11 cases).** Numerous cortical (five or more in 2 mm² of the parahippocampal cortex) and subcortical Lewy bodies, abnormal ubiquitinated neurites in CA2 and cortical diffuse plaques, with less than one neurofibrillary tangle or four neuritic plaques per mm² of temporal neocortex. In two cases there were also moderate macroscopic infarcts (6 and 10 ml in volume).

**Dementia with Lewy bodies plus Alzheimer’s disease (16 cases).** Both numerous neuritic plaques, neurofibrillary tangles (eight or more in 1 mm² of the temporal neocortex) and Lewy bodies (one or more in 2 mm² of the parahippocampal cortex) present in the cortex. In four cases there were also moderate microscopic (1 case) or macroscopic infarcts (two cases 3 ml and one case 11 ml in volume).

The whole sample was also divided into two main groups according to the presence or absence of vascular lesions: (i) 52 cases (31 Alzheimer’s disease, 9 pure dementia with Lewy bodies, 12 dementia with Lewy bodies plus Alzheimer’s disease) with pure degenerative lesions, and (ii) 35 cases (29 Alzheimer’s disease, 2 pure dementia with Lewy bodies, 4 dementia with Lewy bodies plus Alzheimer’s disease) with degenerative plus vascular lesions. There was no case with pure vascular dementia.

**Statistical analysis**

All analyses were pre-planned to answer the questions posed in the introduction relating to the dose–response effects of education on dementia. The demographic data, the scores on the ESD (at the time of inclusion in the Dementia Study and every year before death) and the quantitative pathological data were compared with a one-way ANOVA (analysis of variance) between the three educational groups. In order to exclude a confounding cohort effect (Moritz and Petitti, 1993; Cobb et al., 1995; Peterson, 1996) the age of dementia onset and at death were also submitted to another two-way ANOVA, using education and birth cohort as factors. For the study of the relationship of degenerative lesion burden and educational attainment, the effects of age at death, duration of disease and cognitive performance were controlled through the use of ANCOVA (analysis of covariance).

The relationships of the main pathological diagnoses with educational level and with the years of education were analysed with the χ² test and with a one-way ANOVA, respectively.

The relationships of the presence of vascular lesions (lacunar or white matter lesions, macroscopic infarcts, amyloid angiopathy) with educational level were analysed with the χ² test for linear trend.

Finally, the presence of vascular lesions was introduced together with education in a two-way ANOVA in order to separate the influence of each factor on every demographic and pathological dependent variable. Although adjusting for date of birth would seem desirable, it was not possible to do so because all demographic variables were highly correlated with it (age of onset, \( r = -0.89 \); age at death, \( r = -0.95 \); age at severe cognitive decline, \( r = -0.92 \)) No corrections for multiple tests were introduced.

**Results**

The frequency of cases in every educational level was very similar in this sample (below high school, 32.1%; high school, 36.7%; above high school, 31%) to that of the general population of Ontario aged 65 years and over, according to the 1986 Census of Canada [below high school, 36.1%; high school, 34.3%; above high school, 29.4%; \( \chi^2(2) = 0.423, \) n.s.] (Statistics Canada, 1989).

There were no differences between the sexes in the age of onset of dementia (men: 68.4 ± 7.5, women: 68.6 ± 8.3; \( t = 0.118, \) n.s.), years of education (men: 11.7 ± 4, women: 10.7 ± 3.7; \( t = 1.150, \) n.s.) or level of education (men/women: below high school, 31.5/38.6%; high school, 37/36.7%; above high school, 31.5/30.6%; \( \chi^2(2) = 0.992, \) n.s.). Pathological data, other than brain weight, did not show significant differences and therefore sex was not controlled for in the following analyses.

**Demographic data**

Less educated patients were significantly older at the onset of dementia and at death (Table 1). When the sample was divided into three subgroups by date of birth, the significant effect of education on age of onset (education effect, \( F = 4.620, P = 0.01 \); cohort effect, \( F = 66.4, P < 0.001 \)) and age at death (education effect: \( F = 4.3115, P = 0.01 \), cohort
The effect of education on degenerative dementia

Fig. 2 Age at the onset of dementia (A) and at death (B) in three birth cohorts. The two-way ANOVA shows, in addition to a cohort effect, a significant effect of educational level without any interaction effect. Error bars indicate standard deviations. Age of onset: education effect, $F = 4.620$, $P = 0.01$; cohort effect, $F = 66.400$, $P < 0.001$. Age at death: education effect, $F = 4.313$, $P = 0.01$; cohort effect, $F = 95.893$, $P < 0.001$.

Table 1 Demographic data for dementia by education

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Below high school</th>
<th>High school</th>
<th>Above high school</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (years)</td>
<td>$n$</td>
<td>Mean</td>
<td>SD</td>
<td>$n$</td>
</tr>
<tr>
<td>Age at death (years)</td>
<td>28</td>
<td>71.7</td>
<td>7.6</td>
<td>32</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>28</td>
<td>9.2</td>
<td>3.3</td>
<td>32</td>
</tr>
<tr>
<td>Age of severe cognitive decline (years)</td>
<td>21</td>
<td>78.3</td>
<td>8.8</td>
<td>24</td>
</tr>
<tr>
<td>Age of onset of incontinence (years)</td>
<td>26</td>
<td>75.5</td>
<td>8.2</td>
<td>30</td>
</tr>
</tbody>
</table>

*Age of onset of dementia and at death in cases below high school education was significantly later than in cases with high school education ($P < 0.05$). A cohort effect was controlled for in a two-way ANOVA (see text and Fig. 2). †This difference disappeared after controlling for the age of onset (ANCOVA: $F_β = 1.120$, n.s.; $F_μ = 1.079$, n.s.).

effect $F = 95.893$, $P < 0.001$) persisted without significant interaction between cohort and education (Fig. 2). Education had no significant effect on the duration of dementia or the age of onset of urinary incontinence (Table 1). Less educated cases were significantly older when cognition became untestable with the ESD (Table 1), but this difference disappeared after controlling for the effect of age of onset (ANCOVA: $F_β = 1.120$, n.s., indicating a similar effect of the covariable ‘age of onset’ on the independent variable in each group; $F_μ = 1.079$, n.s., indicating absence of difference between group means corrected for the effects of the covariable ‘age of onset’).
Table 2 Pathological data for dementia by education

<table>
<thead>
<tr>
<th>Pathological data</th>
<th>Below high school</th>
<th>High school</th>
<th>Above high school</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n MEAN SD</td>
<td>n MEAN SD</td>
<td>n MEAN SD</td>
<td></td>
</tr>
<tr>
<td>Brain weight (g)‡</td>
<td>28 1085.0 148</td>
<td>30 1124.0 146</td>
<td>27 1154.0 163</td>
<td>0.25</td>
</tr>
<tr>
<td>Temporal neocortex‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuritic plaques‡</td>
<td>26 14.50 11.50</td>
<td>29 18.10 13.80</td>
<td>27 13.20 11.20</td>
<td>0.31</td>
</tr>
<tr>
<td>Diffuse plaques‡</td>
<td>26 20.50 13.50</td>
<td>29 27.40 17.70</td>
<td>27 24.30 14.70</td>
<td>0.26</td>
</tr>
<tr>
<td>Tangles‡</td>
<td>26 19.00 16.30</td>
<td>29 23.20 17.20</td>
<td>27 24.00 18.70</td>
<td>0.99</td>
</tr>
<tr>
<td>Hippocampus‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tangles</td>
<td>26 27.30 21.30</td>
<td>27 32.90 27.00</td>
<td>27 37.10 27.00</td>
<td>0.99</td>
</tr>
<tr>
<td>Ghost tangles‡</td>
<td>26 7.10 12.00</td>
<td>27 5.10 10.30</td>
<td>27 10.30 19.80</td>
<td>0.99</td>
</tr>
<tr>
<td>Lewy bodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parahippocampus§</td>
<td>27 2.70 6.20</td>
<td>30 2.40 5.00</td>
<td>27 2.90 5.40</td>
<td>0.99</td>
</tr>
<tr>
<td>Substantia nigra¶</td>
<td>27 3.70 6.70</td>
<td>28 3.60 5.90</td>
<td>27 3.20 5.40</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*P values were also non-significant after adjustment for the age at death, the duration of the disease and the cognitive performance previous to death; †number of plaques and tangles in a 0.5-mm-wide strip of neocortex located in the depth of the external lip of the collateral sulcus; ‡number of tangles in 1-mm sector of hippocampal pyramidal layer in CA1, adjacent to CA2; §number of Lewy bodies in a 1-mm-wide strip of parahippocampal gyrus; ¶number of Lewy bodies on one side of the substantia nigra.

Cognitive data

The first cognitive scores in the ESD, recorded at an average of 4.4 ± 2.3 years after the onset of dementia, and the scores recorded 5, 4, 3, 2, 1 years or several months before death had a minor tendency to be greater in more educated patients, but the difference did not reach statistical significance at any of these points (Fig. 1). Adjusting for the initial scores did not alter these results.

Neurodegenerative pathology

There was no significant effect of educational level on the quantitative pathological findings (Table 2). More educated patients showed a slight trend to have greater amounts of neurofibrillary tangles, but the density of neurodegenerative lesions (plaques, tangles and Lewy bodies) was highly variable and the level of statistical significance was not reached. These negative results persisted when the age at death, the duration of the disease and the cognitive performance previous to death were controlled for in the ANCOVAs (data not shown but available on request). These tests have an 80% statistical power to detect an effect size (f) of 0.35. Effect size for an ANOVA test is defined as the standard deviation between groups divided by the standard deviation within groups; unlike the F statistic, f is independent of sample size.

Vascular pathology

When the pathological diagnoses were grouped in the standard manner, i.e. by the degenerative condition, disregarding minor vascular lesions, their distribution did not vary between the three educational levels [\( \chi^2(4) = 0.741 \), n.s.; Fig. 3]. There were no differences in the mean number of years of formal education between groups defined by neurodegenerative pathology (Alzheimer’s disease, 10.9 ± 3.5; pure dementia with Lewy bodies, 12.2 ± 3.6; dementia with Lewy bodies plus Alzheimer’s disease, 11.4 ± 5.1; ANOVA: \( F(3) = 0.427, \) n.s.). However, when patients with and without vascular lesions were compared, significant differences were found. Cases with both degenerative and vascular lesions had lower educational attainment (below high school, 51.4%; high school, 20%; above high school, 28.5%; Fig. 3) and less years of formal education (10.9 ± 3.5) than those with pure degenerative lesions (below high school: 19.2%, high school: 48%, above high school: 32.6%; \( \chi^2(2) = 11.336, P = 0.003, 12 \pm 3.4 \) years; Student’s t(85) = 2.428, \( P = 0.01 \)).

Subcortical lacunar and white matter lesions had a tendency to be more frequent in less educated people, almost reaching the significance level (Table 3). Macroscopic infarcts and the presence of any vascular lesion were significantly related to low education (Table 3). This statistical trend towards greater vascular pathology in less educated cases was not due to amyloid angiopathy which showed no correlation with education (Table 3).

When the education and the presence of vascular lesions were simultaneously analysed in a two-way ANOVA, the former had no effect on any of the demographic variables (Table 4). Conversely, the presence of vascular lesions was significantly associated with a later age of onset of dementia, incontinence and severe cognitive decline. The most definite parameter, age at death, was delayed by 6.1 years in patients with additional vascular lesions compared with those with degenerative pathology only (\( P < 0.0001 \)) (Table 4).

Cases with Alzheimer-type lesions

All statistical analyses were also done in the subgroup of 76 cases with Alzheimer-type lesions (60 Alzheimer’s disease and 16 dementia with Lewy bodies plus Alzheimer’s disease). The results were very similar to those of the whole sample and we do not present them in detail. The number of cases
The effect of education on degenerative dementia

Figure 3: Distribution of educational attainment by pathological diagnosis (upper half of the graph) and presence/absence of vascular lesions (lower part of the graph). There is no difference in the distribution of educational attainment between pathological diagnostic groups, but cases with vascular lesions are significantly less educated \( (P = 0.003) \). AD = Alzheimer’s disease; pDLB = pure dementia with Lewy bodies; DLB + AD = dementia with Lewy bodies plus Alzheimer’s disease. Level of education: light stipple = below high school; medium stipple = high school; dark stipple = above high school.

Table 3: Vascular lesions by education

<table>
<thead>
<tr>
<th></th>
<th>Below high school ((n = 28))</th>
<th>High school ((n = 32))</th>
<th>Above high school ((n = 27))</th>
<th>(\chi^2)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcortical lacunar lesions</td>
<td>7</td>
<td>25</td>
<td>1</td>
<td>3.1</td>
<td>3</td>
</tr>
<tr>
<td>Moderate-severe white matter lesion</td>
<td>15</td>
<td>53.5</td>
<td>13</td>
<td>40.6</td>
<td>8</td>
</tr>
<tr>
<td>Macroscopic infarct</td>
<td>14</td>
<td>50</td>
<td>4</td>
<td>12.5</td>
<td>5</td>
</tr>
<tr>
<td>Vascular lesions†</td>
<td>18</td>
<td>64</td>
<td>7</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Amyloid angiopathy</td>
<td>9</td>
<td>32.1</td>
<td>15</td>
<td>46.8</td>
<td>11</td>
</tr>
</tbody>
</table>

*The \(\chi^2\) for linear trend was used; †cases with vascular lesions had moderate or severe lacunes in basal regions (11 cases), marked white matter hypodensities (15 cases) and/or macroscopic infarcts (3–30 ml, 23 cases).

Table 4: Demographic data for dementia by type of lesions

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>Degenerative</th>
<th>Degenerative ± vascular</th>
<th>Lesion</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>Mean</td>
<td>SD</td>
<td>(n)</td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>52</td>
<td>66.4</td>
<td>7.9</td>
<td>35</td>
</tr>
<tr>
<td>Age at death (years)</td>
<td>52</td>
<td>75.7</td>
<td>7.5</td>
<td>35</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>52</td>
<td>9.2</td>
<td>3.1</td>
<td>35</td>
</tr>
<tr>
<td>Age of severe cognitive decline (years)</td>
<td>38</td>
<td>72.6</td>
<td>7.9</td>
<td>23</td>
</tr>
<tr>
<td>Age at the onset of incontinence (years)</td>
<td>49</td>
<td>72.1</td>
<td>7.8</td>
<td>30</td>
</tr>
</tbody>
</table>

*Education had no effect on any of the demographic variables after controlling for the presence of vascular lesions, and the data by level of education are not presented. In all the two-way ANOVAs the interactions between factors were not significant and are also omitted.

Discussion

Our study has examined the association of educational attainment with demographic, progression and lesion burden variables. With regard to age of onset, less educated patients became demented significantly later. This finding has been described previously in cross-sectional studies (Filley et al., 1985; Moritz and Petitti, 1993; Duara et al., 1996; Peterson, 1996) and tentatively attributed to the longer time required by the relatives to become aware of the cognitive decline in a poor social and work environment (Moritz and Petitti,
On the other side of the argument, Stern and colleagues, in a longitudinal study of a referral-based cohort of Alzheimer’s disease patients, found an increased risk of death in cases with higher educational and occupational attainment (Stern et al., 1995b), although a replication study based on a community cross-sectional survey did not corroborate these findings (Geerlings et al., 1997). Our data on age at death (younger in the more educated group) are congruent with those of Stern and colleagues (Stern et al., 1995b). However, they interpreted their findings as due to delayed manifestation of dementia in these patients (when the underlying pathology is well advanced), but they analysed neither the time of evolution, nor pathological data. Had the onset of dementia been overlooked and artefactually delayed in less educated patients (4 years in our series), or alternatively, retarded in more educated individuals, we would expect a shorter span of the clinically detected illness in the corresponding group, assuming no effect of education on the rate of progression. In our series of patients followed until death, we were able to determine that the duration of dementing illness was the same in the three educational groups. Moreover, the observed cognitive scores in the ESD showed the same trend and took the same time to become severe in all groups. Some short longitudinal studies have found that education influences the rate of cognitive decline in Alzheimer’s disease, by using the Mini Mental State Examination (Rasmussen et al., 1996; Christensen et al., 1997) or other tests of crystallized intelligence (Christensen et al., 1997), but more extensive studies (Filley et al., 1985; Mortimer et al., 1992; Bowler et al., 1998) have not detected such an effect. Therefore, our demographic and progression data are consistent with what others have reported, but not with some explanations offered in the literature.

The recruitment rules of clinic-based studies of dementia give rise to a negative correlation between birth year and age of onset of the disease (the sliding window of opportunity effect), as we have reported elsewhere (Bowler et al., 1998). This, in combination with the well-known secular improvement in the spread of education, explains in part the inverse relationship between the age of onset and educational level which we found. However, the persistence of the association after stratification for birth year indicates that this cohort artefact is not the only relevant factor.

The pathogenetic mechanisms underlying the temporal patterns of onset and progression of the illness are best explored by examination of the causative lesions (Kazee et al., 1993). We found that the load of neurodegenerative lesions was unrelated to educational attainment, even after controlling for age at death, duration of dementia and cognitive deterioration. Snowdon and colleagues found a similar lack of inverse association between early linguistic ability (a potential indicator of cultural level) and neurofibrillary tangles and senile plaques (Snowdon et al., 1996).

Conversely, we found that the presence of cerebrovascular lesions is associated with lower education attainment, as well as later ages of onset and death. Our finding that patients with mixed degenerative and vascular lesions were less educated and older is in accordance with population based studies, showing that cerebrovascular lesions and incident stroke (Ferrucci et al., 1996) are more common in the lower socio-economic classes (Rocca et al., 1990; Fratiglioni et al., 1991; Ott et al., 1995) and in late life (Crystal et al., 1993; Skoog et al., 1993; Breteler et al., 1994), and can contribute to the symptomatic onset of dementia (Skoog et al., 1993; Eby et al., 1994). A recent clinicopathological study by Snowdon and colleagues suggests that small cerebrovascular lesions strongly potentiate the dementing effects of degenerative lesions (Snowdon et al., 1994). It should be remarked that these vascular lesions are usually small and they can remain undetected if the diagnosis is based on clinical data only (Kokmen et al., 1996b), as in many epidemiological surveys lacking neuroimaging (Zhang et al., 1990; Canadian Study of Health and Aging, 1994; Stern et al., 1994; Callahan et al., 1996). These difficulties in diagnosis could be the reason why, in some epidemiological studies, the effect of low education on the prevalence of dementia appears only in vascular dementia (Folstein et al., 1991; Bonaiuto et al., 1995; Cobb et al., 1995), whereas in others it appears also in Alzheimer’s disease (Rocca et al., 1990; Zhang et al., 1990; Ott et al., 1995). Several epidemiological studies have considered cerebrovascular lesions as a possible determinant of the higher prevalence of dementia in individuals with low educational attainment (Rocca et al., 1990; Fratiglioni et al., 1991; Cobb et al., 1995; Ott et al., 1995), but they lacked pathological data to confirm their suspicions.

It might seem surprising that the higher prevalence of vascular lesions in less educated individuals would manifest as a delayed onset of dementia and age of death. This is, however, the expected result in a series of demented individuals if we assume that the syndrome of dementia can result from the combined effect of neurodegenerative and vascular lesions (Snowdon et al., 1997; Consortium to Establish a Registry for Alzheimer’s Disease, 1998) and that this association is more frequent in older (Consortium to Establish a Registry for Alzheimer’s Disease, 1998) and less educated subjects. In fact, any factor increasing the risk of dementia and predominantly affecting older individuals would have contrasting effects on population-based epidemiological studies versus clinicopathological series of demented patients, because the rules of selection are different. On a population basis, patients with the factor will show a greater prevalence of dementia than those without it. In a clinical series, demented patients with the factor will be older than those without it, and thus its presence will appear to delay the onset of dementia. We presume that small cerebrovascular lesions are one such factor. Our study also shows that the onset of urinary incontinence is not related to educational attainment, but rather to the type of pathology, confirming a previous report to this effect (Del Ser et al., 1996).

Our results (particularly the independence of education
The effect of education on degenerative dementia

and neurodegenerative lesion load) do not support the hypothesis that the protective effect of education observed in population-based prevalence studies is due to the greater resistance of better educated individuals to the dementia effect of neurodegenerative lesions, as proposed by the ‘brain reserve hypothesis’. Rather, it may be that the lower prevalence of vascular lesions among the better educated could explain this observation. This would be supportive, although by no means demonstrative of the ‘brain battering’ hypothesis.

However, several caveats have to be considered. First, the pathological study probes the state of the brain at the terminal stages of disease (≥9 years after onset in our series). We cannot address a possible, and plausible, protective effect of education limited to the early stages of disease. Secondly, Mortimer suggested that psychosocial risk factors would have their strongest associations with dementia in late onset Alzheimer’s disease (Mortimer, 1988), as was observed in the Shanghai study (Zhang et al., 1990). The average age at death in our sample (78.4 ± 7.2 years) is lower than the average age of living Canadian demented patients (Canadian Study of Health and Aging, 1994), a problem common to many clinicopathological series (Brayne, 1993; Jost and Grossberg, 1995). Perhaps in a series more weighted towards older patients, some effect of education might be found. However, since our study shows that low education, advanced age and cerebral infarcts are associated in demented patients, relationships between education and dementia in the ninth decade may also be determined by the presence of small cerebral vascular lesions. Thirdly, some epidemiological studies have focused on very low education (less than 6 years of schooling) as the risk factor for dementia (Katzman and Kawas, 1994). In fact, a recent study (De Ronchi et al., 1998) which claimed a protective effect for education after controlling for smoking, alcohol consumption and history of hypertension, found no difference between those who had completed 3 years of schooling and those with more lengthy formal education. Since our study included only two cases with no formal education, we cannot comment on this variable. Our results cannot be generalized beyond the conditions associated with westernized, industrialized societies. Vascular risk factors are also associated with early death, including sudden death, and may therefore affect the probability of being included in this sample as well as the length of follow-up, and consequently the risk of progressing to severe cognitive decline.

Furthermore, the relatively small size of our sample raises the risk of a type II error in some of our negative findings. Although the statistical power of the ANOVA in our sample (80%) is appropriate to detect large ($f = 0.35$) effect sizes (Cohen, 1988), it would be less so for smaller effects. Therefore, we cannot rule out that a small effect of education has been undetected. However, this hypothetical effect would be less than the effects of cerebrovascular lesions, which have been easily identified in this study.

Although the distribution of the educational attainment in our sample was very close to that of elderly people, 65 years and over, in Ontario (Statistics Canada, 1989) we are well aware that a selection bias cannot be excluded (Kokmen et al., 1996b), because a clinicopathological series from a university hospital cannot be representative of the general population (Brayne, 1993). The absence of financial restrictions on access to specialized health care in Canada should reduce referral bias in comparison with other settings. We hope our clinicopathological series will encourage population-based studies to test the hypothesis suggested by our results, i.e that the higher prevalence of dementia among less educated individuals in epidemiological surveys reflects the higher prevalence of small cerebrovascular lesions in this group.

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References


The effect of education on degenerative dementia


