Educational History Is an Independent Predictor of Cognitive Deficits and Long-Term Survival in Postacute Patients With Mild to Moderate Ischemic Stroke

Johanna Ojala-Oksala, MSc; Hanna Jokinen, PhD; Valtteri Kopsi, BM; Kalevi Lehtonen, BM; Liisa Luukkonen, BM; Antti Paukkunen, BM; Lotte Seeck, BM; Susanna Melkas, MD, PhD; Tarja Pohjasvaara, MD, PhD; Pekka Karhunen, MD, PhD; Marja Hietanen, PhD; Timo Erkinjuntti, MD, PhD; Niku Oksala, MD, PhD, DSc

**Background and Purpose**—Poststroke cognitive decline and white matter lesions (WML) are related to poor poststroke survival. Whether cognitive reserve as reflected by educational history associates with cognitive decline, recurrent strokes, and poststroke mortality independent of WML is not known.

**Methods**—A total of 486 consecutive acute mild/moderate ischemic stroke patients subjected to comprehensive neuropsychological assessment (n=409) and magnetic resonance imaging (n=395) 3 months poststroke were included in the study and followed-up for up to 12 years. Odds ratios (OR) for logistic and hazard ratios for Cox regression analyses are reported (OR and hazard ratio ≤ 1 indicates a beneficial effect).

**Results**—Long educational history (per tertile) was associated with lower frequency of executive dysfunction in models adjusted for age, sex, marital status, and stroke severity (OR, 0.75; P<0.05) but not when adding WML as a covariate. In contrast, educational history was independently associated with less memory impairment (OR, 0.67; P<0.01), aphasia (OR, 0.69; P<0.05), visuospatial and constructive deficits (OR, 0.70; P<0.05), Mini-Mental State Examination score <25 (OR, 0.53; P<0.0001), and dementia (OR, 0.66; P<0.01). In Cox regression analysis, educational history was not associated with recurrent strokes, but it associated independently with favorable poststroke survival (hazard ratio, 0.86; P<0.05)

**Conclusions**—Long educational history associates with less poststroke cognitive deficits, dementia, and favorable long-term survival independent of age, gender, marital status, stroke severity, and WML in patients with mild/moderate ischemic stroke. This supports the hypothesis that educational history as a proxy indicator of cognitive reserve protects against deficits induced by acute stroke. *(Stroke. 2012;43:2931-2935.)*

Key Words: education ■ stroke ■ survival

Cognitive impairment and dementia predict poor long-term survival after stroke.1,4 Poststroke cognitive impairment is associated with cerebral small vessel disease characterized by white matter lesions (WML).5,6 In patients with acute stroke, WML are associated with poststroke depression,7 dementia,8 disability and disturbances in activities of daily living,9 recurrent strokes,10 and poor cardiovascular survival.10,11 In addition to these, marital status in the elderly12 and social support in stroke patients13,14 are important factors predicting survival.

Long history of education has been shown to associate with poststroke cognitive function measured within 1 year15 and decreased frequency of aphasia immediately after stroke.16 Interestingly, in elderly subjects without a history of clinical stroke, long history of education is also associated with decreased frequency of WML-associated cognitive impairment.17 History of education has been hypothesized to protect from brain injury by brain reserve capacity, either via actual brain reserve estimated by histology and imaging18 or via cognitive reserve estimated by behavioral methodology.19 Cognitive reserve hypothesis states that high premorbid intelligence and education provide the subject with reserve capacity, which buffers or compensates the brain against the effects of aging and disease.19 In neurologically healthy older

Received June 15, 2012; accepted July 18, 2012.

From the School of Medicine (J.O., V.K., K.L., L.L., A.P., L.S., N.O.), Surgery, University of Tampere, Tampere, Finland; Institute of Behavioural Sciences (H.J.), University of Helsinki, Helsinki, Finland; Department of Neurology (H.J., S.M. T.P., M.H., T.E.), Helsinki University Central Hospital and Department of Neurological Sciences, University of Helsinki, Helsinki, Finland; School of Medicine (P.K., N.O.), Forensic Medicine, University of Tampere and Fimlab Laboratories, Tampere University Hospital, Tampere, Finland; Department of Vascular Surgery (N.O.), Department of Surgery, Tampere University and Tampere University Hospital, Tampere, Finland.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.112.667618/-/DC1.

Correspondence to Niku Oksala, Docent, MD, PhD, DSc, Consultant Vascular Surgeon, Department of Surgery and Forensic Medicine, Medical School, University of Tampere and Tampere University Hospital, 33014 University of Tampere, Tampere, Finland. E-mail nikuuoksala@gmail.com

© 2012 American Heart Association, Inc.
adults, those with higher reserve as indicated by cognitive performance tolerate higher WML severity than those with lower reserve. Cognitive reserve hypotheses can be used to explain the observations that an ischemic stroke of a given magnitude can produce severe impairment in one patient while leaving another intact.

Socioeconomic factors have been shown to associate with stroke mortality independent of stroke severity in short-term follow-up. Educational attainment has been shown to associate with less cognitive decline after stroke. However, direct evidence about the effect of cognitive brain reserve, a surrogate of which is educational history, on stroke outcome in the long-term is lacking. Moreover, it is not known whether WML modify the effect of education on stroke outcome. In the present study, we hypothesized that cognitive reserve as reflected by long educational history associates with less poststroke cognitive deficits, dementia, stroke recurrence, and favorable poststroke survival independent of age, sex, marital status, stroke severity, and WML.

Materials and Methods
The Helsinki Stroke Aging Memory (SAM) cohort comprised a consecutive series of all Finnish patients with suspected stroke admitted to Helsinki University Central Hospital (n=1622) between December 1, 1993 and March 30, 1995, as described in detail previously. A total of 642 patients fulfilled the inclusion criteria (ischemic stroke, age 55–85 years, living in Helsinki, speaking Finnish language) and were invited to a follow-up visit 3 months later. Of these, 71 died (11.1%) before the 3-month follow-up, 82 refused (12.8%), and 3 were lost (0.5%) because of undefined causes. Finally, 486 of the living patients were included in the cohort. A detailed medical and neurological history was performed (online-only Data Supplement 1).

Standard Protocol Approvals
The study was approved by the Ethics Committee of the Department of Clinical Neurosciences, Helsinki University Central Hospital, Finland. The study was explained to the patients and informed consent was obtained.

Neuropsychological Assessment
A comprehensive neuropsychological assessment was administered to 409 (84.2%) patients 3 months after the index stroke as detailed before. The median and interquartile range (IQR) of National Institutes of Health Stroke Scale (NIHSS) scores were 2.0 (IQR, 8.5) vs 1.0 (IQR, 4.0; P<0.004, Mann-Whitney U test), and median history of education was 8.0 (IQR, 5.0) vs 8.0 (IQR, 4.; P=0.095) years in those not tested (n=77) vs tested subjects (n=486), respectively. The following domains were assessed: global cognitive function, executive functions, memory functions, language, and visuospatial and constructional abilities. Abnormality (impaired vs not impaired) in each domain was judged with the use of normative data from a random healthy Finnish population (2 standard deviations or, if >1 test was used, 1 standard deviation below the level of the norm on several tests indicated abnormality). The normal values were evaluated in different age groups (online-only Data Supplement 2).

Magnetic Resonance Imaging Analysis
Patients were subjected to magnetic resonance imaging at 3 months as detailed before and constituted the final study population (n=395, 81.3%). The reasons for not performing magnetic resonance imaging in 90 patients were as follows: contraindication (27 patients); refusals (33 patients); claustrophobia (2 patients); severe illness (27 patients); and obesity (1 patient). There were no statistically significant differences in gender, age, NIHSS score, white matter lesions, educational history, or marital status between these and the original 486 subjects. WML were rated according to the modified Fazekas rating scale as no to mild, moderate, and severe degree (online-only Data Supplement 3).

Survival
Long-term survival data and causes of death at September 21, 2006, were obtained from Statistics Finland for all the patients. The median follow-up time was 7.4 years (IQR, 7.9) with a range between 0.3 and 12.8 years. The outcome events were recurrent stroke/death attributable to stroke and death from any cause.

Statistical Analysis
Patients were divided into tertiles according to their total educational history consisting of basic education and occupational education (tertile 1, n=151: 0–6 years; tertile 2, n=152: 7–9 years; tertile 3, n=172: ≥10 years). Division into tertiles was considered appropriate because it resulted in an adequate number of patients in each group, allowing sufficient statistical power. All the analyses also were performed including patients with first-ever stroke only (n=379, 78.0%). Because the results were identical in both analyses, all the stroke cases were included in the study. Statistical significance was set at: P<0.05; P<0.01; and P<0.0001 (online-only Data Supplement 4).

Results
Patient Characteristics
Long educational history was associated with younger age (P<0.05), lower prevalence of female sex (P<0.0001), and decreasing NIHSS score (P<0.05). Those with the highest education were more often married or cohabitated, more seldom separated/divorced, and were more seldom widows (P<0.01) No association was seen between education and prevalence of severe WML. Educational history was not associated with cardiovascular risk factors or comorbidities (Table 1).

Neuropsychological Deficits Associating With Educational History
Education was associated with lower frequency of executive dysfunction in models adjusted with age, sex, and marital status (model 1: odds ratio OR, 0.75; P<0.05), age, sex, marital status, and NIHSS score (model 2; OR, 0.77; P<0.05) but was no longer associated when adjusting for age, sex, marital status, NIHSS score, and WML (model 3; Table 2). In contrast, educational history remained independently associated with less memory deficit (model 1: OR, 0.66; P<0.01; model 2–3: OR, 0.67; P<0.01), aphasia (model 1: OR, 0.63; P<0.01; model 2: OR, 0.67; P<0.01; model 3: OR, 0.69; P<0.05), impairment in visuospatial and constructive abilities (model 1: OR, 0.65; P<0.01; model 2: OR, 0.67; P<0.01; model 3: OR, 0.70; P<0.05), Mini-Mental States Examination score <25 (model 1: OR, 0.49; P<0.0001; model 2: OR, 0.51; P<0.0001; model 3: OR, 0.53; P<0.0001), and dementia (model 1: OR, 0.62; P<0.01; model 2: OR, 0.64; P<0.01; model 3: OR, 0.66; P<0.01; Table 2).

Association of Educational History With Recurrent Strokes
Educational history did not show any association with recurrent strokes (online-only Data Supplement 5).
Association of Educational History With Long-Term Survival

Educational history was independently associated with favorable poststroke survival in all the models (model 1: HR, 0.86; P<0.05; model 2: HR, 0.89; P<0.05; model 3: HR, 0.86; P<0.05; Table 3). Addition of any of the neuropsychological deficits into model 3 resulted in disappearance of the effect of educational history on survival.

Discussion

We showed that short educational history is associated with poststroke neuropsychological deficits and dementia, and that it is a predictor of poor long-term survival independent of age, sex, marital status, stroke severity, and WML in patients with mild/moderate ischemic stroke. Interestingly, the total burden of cardiovascular risk factors and comorbidities was not dependent on educational history. This supports the hypothesis that the adverse clinical effects and outcome after ischemic stroke are mediated via cognitive reserve.

Our present findings of strong association of educational history with neuropsychological deficits are in line and extend the results of the previous studies with a follow-up ranging from 24 hours to 1 year. Whether this is attributable to increased resistance or improved recovery from injury is not known. Our findings were, in majority, independent of WML, which indicates that the protective effect of education is not attributable to protection against development of WML. The strong interference of WML with executive function is supported by present findings.

Our findings of no association of educational history with recurrent strokes are indirectly supported by a previous study in which socioeconomic status was not associated with stroke recurrence in long-term follow-up for up to 10 years. Contrary to these findings, socioeconomic status associated with recurrent stroke in men of low socioeconomic status.
the potential confounding effect. Addition of any of the neuropsychological deficits into survival models resulted in disappearance of the effect of educational history on survival. This indicates that educational history is strongly associated with postacute neuropsychological deficits, which override the effect of education to long-term survival.

As a strength, our unit is responsible for primary stroke management of all inhabitants living in the Helsinki area and the long-term survival data are comprehensive, with few unresolved deaths and including a detailed neuropsychological examination. It is also the only consecutive study controlling for main confounder, including severity of stroke. It must be emphasized, however, that a significant proportion of patients had low NIHSS score, which indicates that the majority of patients had mild/moderate ischemic strokes. There is also a possibility of selection bias because of formation of the cohort 3 months after the index stroke and drop-out of 156 patients (11.1%) before that. Most probably, the majority of these patients are those with severe stroke, which may contribute to low overall NIHSS score. Independent data from the same district during the collection of the cohort (Statistics Finland) showed that up to 64% of stroke related deaths occurred in women. The proportion of women (49.9%) in the present study suggests that there is selection bias, especially because of the fact that women have more severe strokes and substantially greater 1-month mortality rates; therefore, the mortality rates may be underestimated. It should be noted that the number of patients with hypertension is underestimated because the current criteria for hypertension are significantly lower than those used in the present study (≥160/95 mm Hg).

Because patients with the most severe disability could not be assessed with comprehensive neuropsychological examination, there is a possibility for survival bias because these patients are prone to impaired survival. In addition, we could not recover data on occupation, occupational status, or income, which are used in the literature to reflect the socioeconomic status. We consider history of education as a reasonable surrogate of cognitive reserve because it is easily ascertained and an objective measure. However, the relationships between different proxies and cognitive brain reserve are complex. It is also possible that educational history and components of socioeconomic status, such as occupational attainment, leisure activity, literacy, and number of spoken languages, exert synergistic or ultimately separate effects on cognitive brain reserve. In contrast to socioeconomic factors such as occupational class and income, educational history can be applied equally to both genders and different age groups, and it is more comparable between different countries and is more stable over time. Moreover, it is a more reliable indicator of socioeconomic status in the elderly because it includes a large proportion of economically inactive subjects otherwise excluded. We emphasize that educational data may be subject to geographical variation; therefore, the results must be interpreted with caution.

**Conclusions**

Educational history is a predictor of poststroke cognitive deficits and long-term survival independent of age, sex,
marital status, stroke severity, and white matter lesions in patients with mild/moderate ischemic stroke. No association between educational history and cardiovascular risk factors and comorbidity burden was found. This supports the hypothesis that the adverse clinical effects and outcome after ischemic stroke are mediated via cognitive reserve.

Acknowledgments
The authors thank Statistics Finland for their expert assistance in the data collection.

Sources of Funding
This study was supported by grants from the Maira Tapanen Foundation; the Paavo Nurmi Foundation; The Finnish Angiologic Association; the Medical Council of the Academy of Finland (Helsinki); the Clinical Research Institute, Helsinki University Central Hospital; the Yrjö Jahnsson Foundation (Helsinki); the Finnish Cultural Foundation and the Elli and Elvi Oksanen Fund of the Pirkanmaa Fund under the auspices of the Finnish Cultural Foundation (Tampere); the Medical Research Fund of Tampere University Hospital; the Finnish Medical Foundation; and the Finnish Foundation for Cardiovascular Research (Helsinki).

Disclosures
None.

References
Educational History Is an Independent Predictor of Cognitive Deficits and Long-Term Survival in Postacute Patients With Mild to Moderate Ischemic Stroke
Johanna Ojala-Oksala, Hanna Jokinen, Valtteri Kopsi, Kalevi Lehtonen, Liisa Luukkanen, Antti Paukkunen, Lotte Seeck, Susanna Melkas, Tarja Pohjasvaara, Pekka Karhunen, Marja Hietanen, Timo Erkinjuntti and Niku Oksala

Stroke. 2012;43:2931-2935; originally published online August 30, 2012; doi: 10.1161/STROKEAHA.112.667618

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/43/11/2931

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/10/25/STROKEAHA.112.667618.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL

DATA SUPPLEMENT 1

Hypertension was defined as blood pressure ≥160/95 recorded twice. Diagnosis of atrial fibrillation (AF) was based on electrocardiographic (ECG) findings. Diagnosis of myocardial infarction (MI) was based on ECG (ST-elevation ≥ 2 mm in at least two chest leads, ≥ 1 mm elevation in limb leads, and relevant Q- and T-wave alterations) findings and laboratory injury markers. Diagnosis of cardiac failure (CF) was based on clinical, thoracic X-ray and ECG findings. Diabetes (DM) was defined as previously documented diagnosis, current use of insulin or oral hypoglycemic medication, or fasting blood glucose >7.0 mmol/l. Peripheral arterial disease (PAD) was considered if the patient had claudication, 2 peripheral pulses missing, history of amputation or peripheral arterial surgery due to atherosclerosis. Smoking habits were scored at admission as non-smokers and smokers (current or former). Laboratory analyses included total cholesterol, HDL-cholesterol and triglycerides. Stroke severity was assessed using National Institutes of Health Stroke Score (NIHSS). Dementia was determined according to DSM-4 criteria. Marital status was graded as: married/cohabitation, single, separation/divorced, widow.
DATA SUPPLEMENT 2

Global cognitive function was measured with the Mini-Mental State Examination and available for all the patients. Executive functions including attention were evaluated with the Trail making test, the Stroop color naming test and the Digit span subtest of the Wechsler Memory Scale, the modified Wisconsin Card Sorting Test and the verbal fluency test. Data was available in 365 and missing in 44 subjects (10.8%). The assessment of memory functions included the Logical memory and Visual reproduction subtests of the Wechsler Memory Scale-revised as well as the Fuld Object Memory Evaluation. Data was available in 379 and was missing in 30 subjects (7.3%). Language was evaluated with the short version of the Token test the Boston naming test and the verbal fluency test as described previously. Moreover, overall evaluation of speech functions was based on the Boston Diagnostic Aphasia Examination. Data was available in 395 and missing in 14 subjects (3.4%). Visuospatial and constructional abilities were assessed with the Block design subtest of the Wechsler Adult Intelligence Scale-revised, the clock test (recognizing and setting time), and by copying a triangle, a flag, and a 3-dimentional cube and a cross. Data was available in 391 and missing in 18 subjects (4.4%).
DATA SUPPLEMENT 3

MRI was performed with a 1.0 T imaging equipment (Siemens Magnetom). The protocol included transaxial T2, PD-and T1-weighted 5 mm-thick slices (conventional spin echo- technique) and a three-dimensional gradient-echo-sequence yielding 64 3 mm-thick coronal sections. WMLs were rated on T2 and PD-weighted images in accordance to the modified Fazekas rating scale to no to mild, moderate and severe degree. In no to mild degree of WMLs periventricular lesions included no more than a small cap or thin lining and in other WM (white matter) areas no more than large focal lesions. In moderate degree of WMLs the periventricular lesions included no more than a large cap and a smooth halo, and the other WM areas no more than focal confluent lesions. The severe degree of WMLs included cases with extending caps or irregular halo in the periventricular area and diffusely confluent lesions or extensive WM change in other WM areas. Of the patients, 111 (28.0%) had mild, 71 (17.9%) had moderate and 214 (54.0%) had severe WMLs. Since there were no differences in survival analyses between moderate and mild WML categories, these categories were combined.
Chi-square test was used to test dichotomous variables and Kruskall-Wallis-test for independent samples to test continuous variables due to non-normal distribution. Binary logistic regression analysis was used to study the association of educational history (dummy variable coded according to tertiles of years of education) with neuropsychological deficits per tertile of educational history. Three models were constructed, the first (Model 1) adjusting with age and sex and marital status, the second (Model 2) adjusting with age, sex, marital status and stroke severity as assessed by NIHSS, the third (Model 3) adjusting with age, sex, marital status NIHSS and WMLs. Since cardiovascular risk factors and co-morbidities showed no association with educational history in univariate analyses, they were not included in the models. To analyze the association of educational history with recurrent strokes and survival Cox proportional hazards survival analysis per tertile of educational history was performed utilizing the same models described above.
DATA SUPPLEMENT 5

Cox regression analysis on the association of educational history (per tertile: 0-6 years, 7-9 years and ≥10 years) on recurrent strokes in long-term follow up in Stroke Aging Memory (SAM) cohort. Model 1: age (per year), sex, marital status; Model 2: age, sex, marital status, NIHSS (per point); Model 3: age, sex, marital status, NIHSS, WML.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 HR (95% CI)</th>
<th>Model 2 HR (95% CI)</th>
<th>Model 3 HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06 (1.04-1.08)***</td>
<td>1.06 (1.04-1.08)***</td>
<td>1.06 (1.03-1.08)***</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.85 (0.62-1.16)</td>
<td>0.86 (0.63-1.18)</td>
<td>0.92 (0.65-1.31)</td>
</tr>
<tr>
<td>Marital status</td>
<td>0.99 (0.88-1.12)</td>
<td>1.00 (0.89-1.13)</td>
<td>0.99 (0.86-1.13)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>not included</td>
<td>1.04 (1.02-1.07)***</td>
<td>1.05 (1.02-1.08)***</td>
</tr>
<tr>
<td>Severe WML</td>
<td>not included</td>
<td>not included</td>
<td>1.20 (0.86-1.68)</td>
</tr>
<tr>
<td>Education</td>
<td>0.91 (0.77-1.08)</td>
<td>0.96 (0.81-1.15)</td>
<td>0.95 (0.78-1.16)</td>
</tr>
</tbody>
</table>

WML, white matter lesion, NIHSS, National Institutes of Health Stroke Scale. Statistical significance: * p<.05, * p<0.01, *** p<0.0001.