White Matter Lesions Are Associated With Hospital Admissions Because of Hip-Fractures and Trauma After Ischemic Stroke

Gerli Sibolt, MD; Sami Curtze, MD, PhD; Susanna Melkas, MD, PhD; Tarja Pohjasvaara, MD, PhD; Markku Kaste, MD, PhD; Pekka J. Karhunen, MD, PhD; Niku K.J. Oksala, MD, PhD, DSc; Timo Strandberg, MD, PhD; Timo Erkinjuntti, MD, PhD

Background and Purpose—Cerebral white matter lesions (WMLs), a surrogate for cerebral small-vessel disease, have been shown to be associated with decreasing mobility, gait instability, and falls. The aim of this study was to investigate whether WMLs of the brain are associated with increased incidence of hospital admissions because of any trauma and hip-fractures in a cohort of patients with stroke.

Methods—We included 383 consecutive patients aged 55 to 85 years with ischemic stroke admitted to the Helsinki University Central Hospital (The Stroke Aging Memory cohort) with a 12-year follow-up. National register data were reviewed for hip-fractures, other traumatic injuries, survival data, and causes of death. WMLs were rated using MRI and dichotomized as none to mild and moderate to severe. The data were analyzed using Kaplan–Meier plots (log-rank) and a complex Cox multivariable hazards models for multiple cases per subject to assess hazard ratios with their 95% confidence intervals.

Results—During the 12-year follow-up, there were more hip-fractures (13.5% versus 6.5%; log-rank, \(P=0.01\)) and more hospital admissions because of traumatic injury (22.2% versus 16.7%; log-rank, \(P=0.04\)) in the moderate-to-severe than in the none-to-mild WMLs group. In the complex samples, Cox multivariable model adjusting for age, sex, National Institutes of Health Stroke Scale, infarct size, and poststroke dementia, moderate-to-severe WMLs were associated with increased incidences of hospital admissions because of hip-fractures (hazard ratio, 3.98; 95% confidence interval, 1.55–10.21) and traumatic injuries including hip-fractures (hazard ratio, 1.72; 95% confidence interval, 1.03–2.87).

Conclusions—Patients with ischemic stroke and moderate-to-severe WMLs are at high risk, who experience serious traumatic injuries and especially hip-fractures requiring hospital treatment. (Stroke. 2014;45:00-00.)

Key Words: cerebral small-vessel disease ■ hip fractures ■ trauma

Falls are one of the most common medical complications after stroke.\(^1\)\(^2\) From 55% to 73% of patients with stroke have ≥1 fall within the first year after stroke.\(^3\)\(^4\) Falls are the leading cause of injury-related deaths among the elderly.\(^5\)

Consequently, falls are a threat to older adults’ lives, health, and independence, and additionally cause remarkable direct medical costs.\(^2\) For the development of strategies to prevent falls, associated factors and risk factors of traumatic injuries are of interest.

White matter lesions (WMLs) of the brain are a common finding in aging people and are found in brain MRI by chance or after having a stroke or a transient ischemic attack. WMLs are associated with cardiovascular risk factors and they are considered to be a surrogate for cerebral small-vessel disease.\(^4\)

WMLs of the brain are associated with decreasing mobility, gait instability, and falls.\(^2\)\(^-\)\(^10\) However, the association of the presence of WMLs in long-term follow-up with clinically relevant incidences, as traumatic injuries requiring hospitalization, remains unclear.

The aim of this study was to explore the association of WMLs of the brain with hospital admissions because of any trauma and especially hip-fractures in a cohort of patients with ischemic stroke aged 55 to 85 years followed up for 12 years.

Methods

Patients

The Helsinki Stroke Aging Memory (SAM) cohort consists of 1622 consecutive patients with suspected stroke (all Finnish, white) admitted to the Helsinki University Central Hospital between December 1, 1993 and March 30, 1995. Patients without ischemic stroke (n=175), intracerebral (n=229), or subarachnoid (n=69) hemorrhage were...
excluded. We further excluded patients <55 years (n=258) or >85 years (n=88), those not living in Helsinki (n=158), and those not speaking the Finnish language (n=3).

Of the 642 patients initially meeting the inclusion criteria and invited to a follow-up visit 3 months after stroke, 71 (11.1%) had died before the visit, 82 (12.8%) refused, and 3 patients were lost to follow-up because of unknown cause. The SAM cohort thus consisted of 486 patients of which 388 had their first-ever stroke.

All patients underwent brain computed tomographic scanning at the acute phase, and 396 patients (81.5%) underwent MRI at 3 months. The 90 patients with no MRI data available were excluded from this study. WMLs were rated in accordance with the Leukoaraiosis and Disability in the Elderly rating as none to mild or moderate to severe.12

In addition, we excluded 10 patients for having a modified Rankin Scale of 5 at 3 months after stroke. By definition, patients with modified Rankin Scale 5 are not able to walk and, therefore, do not usually fall. Furthermore, their probability to recover to score 4 or better is low. Of the remaining 386 patients, follow-up data were missing for 3 patients and thus a cohort of 383 patients were included to the present study.

The study was approved by the ethics committee of the Department of Clinical Neurosciences, Helsinki University Central Hospital, Helsinki, Finland. Informed consent was obtained from all patients.

Clinical Evaluation
Medical and neurological history were taken as described before.13 Smoking habits were categorized on admission as nonsmokers and smokers (current or former). History of myocardial infarction, cardiac failure, atrial fibrillation, arterial hypertension, peripheral arterial disease, and diabetes mellitus was established by reviewing all available hospital charts, in addition to a structured interview of the subject and a knowledgeable informant. History of hypertension was defined as systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥95 mmHg. Diabetes mellitus was defined as previously documented diagnosis, current use of insulin or oral antidiabetic medication, or fasting blood glucose >7.0 mmol/L.

Poststroke dementia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders 3rd edition criteria.14 Patients were followed up till September 21, 2006, using extensive national registers kept by the National Institute for Health and Welfare. The national care register contains International Classification of Diseases-Ninth Revision (ICD-9) and ICD-10 diagnosis codes of all hospital treatment periods. ICD-9 codes 820 and 821 and ICD-10 codes S20.0 to S27.9 were considered as hip-fracture. ICD-9 codes 800 to 957 and ICD-10 codes S00.0 to T14.9 were considered as traumatic injuries. Survival data and causes of death were obtained from Statistics Finland.

Data Analysis and Statistics
Pearson χ2 test or Mantel–Haenszel test where appropriate (dichotomous variables), 1-way ANOVA (continuous variables), and binary logistic regression function were used to analyze association among grade of WMLs, hip-fractures, traumatic injuries, demographics, and risk factors. Kaplan–Meier log-rank analysis was used to evaluate the effect of WMLs on the time to first hip-fracture or admission to hospital because of traumatic injuries. The cumulative recurrence risks and their 95% confidence intervals were calculated using life-table function. Patients who died from other cause than hip-fracture or traumatic injuries were considered censored. The cumulative hazard function was plotted and checked that the proportional hazards assumption was met for each parameter included in further models.

WMLs were dichotomized as none to mild versus moderate to severe because of their association with small-vessel disease.15 The association of known risk factors (age, sex, atrial fibrillation, hypertension, diabetes mellitus, smoking status, and low education) with moderate-to-severe WMLs on MRI was analyzed using a binary multivariable model with forced entry.

For the association between WMLs on MRI and traumatic injuries or hip-fractures, a complex multivariate Cox regression proportional hazards analysis for multiple cases per subject with forced entry was used to calculate hazard ratios with their 95% confidence limits adjusted for sex and age. Statistical significance was set at P<0.05. All statistical analyses were performed with SPSS Statistics 22 for Linux (IBM Corp, Armonk, NY).

Results
Baseline characteristics and selected clinical parameters are shown in Table 1. There were 44 patients with first-ever hip-fractures after the index stroke. Of those, 8 had a second and 1 had a third hip-fracture during the 12-year follow-up. There were 50 additional hospital admissions because of trauma other than hip-fracture during the follow-up.

Mean length of hospital stay because of hip-fracture was 63 days for patients with moderate-to-severe WMLs and only 21 days for patients with none-to-mild WMLs.

First hip-fractures occurred in 6.5% (7/108) of the none-to-mild WML group and in 13.5% (37/275) of the moderate-to-severe WMLs group (P=0.05).

During the 12-year follow-up more first-ever hip-fractures after ischemic stroke occurred in the moderate-to-severe WMLs group when compared with that in the none-to-mild WMLs group (Figure 1; log-rank, P=0.013).

In addition, more hospital admissions because of traumatic injury, including hip-fractures, occurred in the moderate-to-severe WML group when compared with that in the none-to-mild WMLs group (Figure 2; log-rank, P=0.041).

In the complex samples, Cox multivariable model adjusting for age, sex, the National Institutes of Health Stroke Scale, infarct size >60 mm, and poststroke dementia (Table 2), moderate-to-severe WMLs were associated with increased incidences of hospital admissions because of hip-fractures (hazard ratio, 3.98; 95% confidence interval, 1.55–10.21) and

<p>| Table 1. Baseline Characteristics and Selected Clinical Parameters Grouped for None-to-Mild and Moderate-to-Severe WML on MRI of 383 Consecutive Patients With Ischemic Stroke in the Helsinki Stroke Aging Memory Study Cohort Followed Up for 12 Years |
|---------------------------------|----------|---------|-----------------|---------|</p>
<table>
<thead>
<tr>
<th>WML</th>
<th>All</th>
<th>None to Mild</th>
<th>Moderate to Severe</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>383</td>
<td>108 (28.2%)</td>
<td>275 (71.8%)</td>
<td>...</td>
</tr>
<tr>
<td>Age at initial stroke, y</td>
<td>71 (65–77)</td>
<td>68 (61–73)</td>
<td>73 (67–78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male sex</td>
<td>186 (48.6%)</td>
<td>60 (55.6%)</td>
<td>126 (45.8%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>72 (18.8%)</td>
<td>23 (21.5%)</td>
<td>49 (17.8%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Hypertension</td>
<td>184 (48.0%)</td>
<td>42 (38.9%)</td>
<td>142 (51.6%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>90 (23.5%)</td>
<td>31 (28.7%)</td>
<td>59 (21.5%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>191 (49.9%)</td>
<td>60 (55.6%)</td>
<td>131 (48.0%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>46 (12.0%)</td>
<td>18 (16.7%)</td>
<td>28 (10.2%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Infarct size &gt;60 mm</td>
<td>230 (56.1%)</td>
<td>65 (22.8%)</td>
<td>164 (71.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1 (0-3)</td>
<td>1 (0-3)</td>
<td>1 (0-3)</td>
<td>0.40</td>
</tr>
<tr>
<td>Poststroke dementia</td>
<td>92 (23.6%)</td>
<td>22 (23.9%)</td>
<td>70 (76.1%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospitalization because of hip-fracture, d</td>
<td>2492</td>
<td>148</td>
<td>2344</td>
<td>...</td>
</tr>
<tr>
<td>Hospitalization because of trauma, d</td>
<td>3537</td>
<td>518</td>
<td>3019</td>
<td>...</td>
</tr>
</tbody>
</table>

Age is median (interquartile range), other values are n (%). LADIS indicates Leukoaraiosis and Disability in the Elderly; NIHSS, National Institutes of Health Stroke Scale; and WML, white matter lesion.
traumatic injuries, including hip-fractures (hazard ratio, 1.72; 95% confidence interval, 1.03–2.87).

**Discussion**

In the present 12-year follow-up study of patients with ischemic stroke, moderate-to-severe WMLs compared with none-to-mild WMLs on MRI were associated with increased incidences of traumatic injuries and especially hip-fractures. To our best knowledge, similar data from a comparable settings have not been published before.

In a prospective community sample study of a population aged 65 to 80 years, hip-fractures occurred more frequently in those with diffuse WMLs when compared with those without. According to the Leukoaraiosis and Disability in the Elderly study, patients with severe WMLs have impaired balance and typically have a history of twice as many falls when compared with mild WMLs. In the study population of the present study, the rates of hip-fractures were even 4.0-fold in patients with moderate-to-severe WMLs when compared with patients with none-to-mild WMLs, whereas rates of trauma leading to hospital admission rates were 1.7-fold.
Patients with moderate-to-severe WMLs had longer stays at hospitals for their first hip-fracture after stroke when compared with patients with none-to-mild WMLs. This might indicate higher complication rates or slower rehabilitation in patients with moderate-to-severe WMLs.

The survival analyses of the present study indicate a higher rate of hip-fractures and hospital admissions because of traumatic injury in the whole poststroke cohort for patients with moderate-to-severe WMLs when compared with those with none-to-mild WMLs. After adjusting for confounders, female sex and age were, in addition to WMLs, independent factors associated with hospital admission because of traumatic injuries. However, age is a well-known risk for impaired gait, falls, and hip fractures. The sex difference might, therefore, be partially confounded by the higher life-expectancy of women. The effect of WMLs may even be underestimated in our study setting because age is such a strong predictor of falls. Increasing morbidity and age in the 12-year study period might also make the population less mobile and more bedridden, which would decrease the risk of falls and, therefore, hip-fractures and injuries.

A major strength of our study is the long 12-year follow-up. In addition, the follow-up diagnoses can be considered reliable because stroke diagnoses in the Finnish Hospital Discharge Registries have been validated against a population-based stroke registry with fairly good positive predictive values (85%–92%). In contrast, data about falls are usually gathered by means of not only self-report by patient or caregiver especially in retrospective settings but also often in follow-up studies although fall-diaries are used in some settings. Possible limitations should be borne in mind when our results are evaluated. We included patients at 3 months after ischemic stroke, which may lead to a selection bias, because the more severely affected or mortally ill patients were excluded. Also the fact that patients with severe gait disturbance tend to be bedridden may affect our results.

**Conclusions**

Patients with ischemic poststroke and more than mild WMLs are at high risk of traumatic injuries, especially hip-fractures, and this is probably because of gait disturbance and instability related to WMLs. Long-term prevention of WMLs may be an important way to prevent traumatic injuries, such as hip-fractures, in aging societies.

**Sources of Funding**

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**Disclosures**

None.

**References**

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백질병변은 허혈뇌졸중 이후 엉덩이 골절 및 외상으로 인한 병원 입원과 관련이 있다

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(Stroke. 2014;45:2948-2951.)

Key Words: cerebral small vessel diseases ■ hip fractures ■ trauma

배경과 목적
대뇌 백질병변(white matter lesions, WMLs)은 대뇌 소혈관질환에 대한 대리(surrogate)로서 움직임 감소, 보행 불안정, 넘어짐 등과 관련이 있음을 보여왔다. 이 연구의 목적은 뇌의 WMLs이 뇌졸중 환자 코호트에서 외상 및 엉덩이 골절로 인한 병원 입원 발생률 증가와의 관련성 여부를 알아보는 것이었다.

방법
12년의 추적기간 동안 헬싱키대학 중앙병원(뇌졸중 노화 기억 코호트, Stroke Aging Memory cohort)에 입원한 일련의 55~85세 사이 허혈뇌졸중 환자 383명을 포함하였다. 엉덩이 골절, 기타 외상, 생존 자료, 사망 원인 등에 대하여 국가등록자료를 고찰하였다. WMLs는 자기공명영상 사용하여 평가되었고, 경도 이하와 중등도 이상으로 이분화하였다. 이들 데이터는 위험도 및 95% 신뢰구간을 평가하기 위해 Kaplan–Meier 플롯(log-rank)과 항목별 여러 가지 경우에 대한 복잡한 Cox 다변량위험모형을 이용하여 분석하였다.

결과
12년의 추적기간 동안 경도 이하 WMLs군과 비교하여 중등도 이상 군에서 더 많은 엉덩이 골절(13.5% vs 6.5%; log-rank, \( P=0.02 \))과 외상으로 인한 병원 입원(22.2% vs 16.7%; log-rank, \( P=0.04 \))이 있었다. 연령, 성별, National Institutes of Health Stroke Scale, 경색 크기, 뇌졸중 후 치매를 보정한 Cox 다변량모형의 복잡한 표본에서 중등도 이상 WMLs은 엉덩이 골절(HR, 3.98; 95% CI, 1.55~10.21) 및 엉덩이 골절을 포함한 외상(HR, 1.72; 95% CI, 1.03~2.87)으로 인한 병원 입원의 발생률 증가와 관련이 있었다.

결론
허혈뇌졸중 및 중등도 이상 WMLs이 있는 환자는 심각한 외상과 특히 병원 치료를 필요로 하는 엉덩이 골절이 발생할 높은 위험에 처해 있다.

Figure 1. Cumulative risk of first hip-fracture after ischemic stroke in 383 patients of the Helsinki Stroke Aging Memory study cohort followed up for 12 years. Stratified for patients with none-to-mild and for moderate-to-severe white matter lesions (WMLs) on MRI.