Elevated Levels of Hemoglobin A1c Are Associated With Cerebral White Matter Disease in Patients With Stroke

Michal Rozanski, MD; Tobias B. Richter; Ulrike Grittner, PhD; Matthias Endres, MD; Jochen B. Fiebach, MD; Gerhard J. Junghulsing, MD

**Background and Purpose**—This study was conducted to investigate the association of cerebral white matter disease (WMD) on MRI with vascular risk factors and laboratory findings in consecutive first acute ischemic stroke patients.

**Methods**—Acute ischemic stroke patients underwent MRI ≤24 hours after stroke onset and follow-up on day 2. WMD was scored on fluid attenuated inversion recovery MRI according to the Wahlund score. Vascular risk factors and laboratory parameters were assessed during hospital stay. Univariate and multiple logistic regression analyses were performed.

**Results**—We included 512 patients with first acute ischemic stroke (mean age, 68.5 [SD, 13.2] years; 192 women (37.5%); median National Institutes of Health Stroke Scale on admission, 3 [interquartile range, 1–6]; and median Wahlund score, 4 [interquartile range, 2–9]). WMD was present in 460 (89.8%) patients. In univariate analysis, age, arterial hypertension, reduced estimated glomerular filtration rate, hemoglobin A1c (HbA1c) levels, diabetes mellitus, and female sex were associated with the presence of WMD (P<0.05). In multiple regression analysis, age, arterial hypertension, and elevated levels of HbA1c (P<0.05) remained independently associated with the extent of WMD.

**Conclusions**—Among known risk factors, higher levels of HbA1c were associated with cerebral WMD in stroke patients. This may suggest that chronic disturbance of glycemia measured by HbA1c plays a role in the pathophysiology of WMD.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00715533. (Stroke. 2014;45:00-00.)

Key Words: ischemia ■ leukoencephalopathies ■ magnetic resonance imaging

Cerebral white matter disease (WMD) is detected by hyperintense changes on T2 or fluid attenuated inversion recovery MRI. Histologically, these hyperintensities correlate with spongiosis, gliosis, and patchy demyelination in white matter and are typically caused by ischemia. WMD has gained growing interest, because it may play a role in cognitive decline and as a risk factor for first and recurrent ischemic stroke and death.

The pathophysiology of WMD is not completely understood, and several etiologic mechanisms are discussed. The majority of research and experimental findings suggest chronic ischemic pathogenesis in the development and progression of WMD. Factors consequently found to be associated with WMD were age and arterial hypertension (HTN). The influence of other vascular risk factors such as diabetes mellitus (DM), dyslipidemia, smoking, and renal function remains controversial, because the results of available studies are contradictory. DM type 1 was shown to be a strong risk factor for WMD among young stroke patients. Although there are studies that confirm the association between DM and WMD in the general population, 2 of these were conducted in small cohorts. Metabolic syndrome has been shown to be significantly associated with WMD, but DM prevalence was not analyzed by the authors in this study. In contrast to these findings, a large study showed progress of brain atrophy, but not WMD, in patients with DM. Furthermore, there was no significant association between DM and WMD in studies including ≥2000 participants after adjustment for confounders. Hemoglobin A1c (HbA1c), a biomarker of long-term glycemic control, was not taken into consideration in the aforementioned studies. Few studies conducted in small prespecified cohorts have suggested significant association between levels of HbA1c and WMD. However, these observations were not confirmed when a larger cohort of stroke patients was assessed. The role of renal function in WMD was shown in young stroke patients. In studies on the general population, these results have only partially been replicated.

Stroke is considered a risk factor for WMD and vice versa, that is, WMD predisposes for stroke; therefore, we think that patients with stroke should be thoroughly examined. The purpose of this study was to assess the relationships between the extent of WMD and established laboratory parameters such as HbA1c and estimated glomerular filtration rate (eGFR) in consecutive acute ischemic stroke (AIS) patients. Knowledge
of the possible impact of glycemic disturbances and renal dysfunction reflected by easily controlled parameters might help in the prevention of WMD.

Methods

Study Population
The study population derives from a large prospective stroke MRI study (NCT00715533) approved by the local ethics committee of Charité, Universitätsmedizin Berlin.23 Each patient gave written informed consent. Consecutive patients admitted between May 2008 and October 2011 in the Department of Neurology, Charité, Universitätsmedizin Berlin, Campus Benjamin Franklin, with suspected AIS were screened. Patients were considered eligible for further analysis if MRI was completed <24 hours after stroke onset and past medical history could be obtained. All patients provided serum samples on hospital admission and day 2. Clinical and sociodemographic data, National Institutes of Health Stroke Scale scores, and modified Rankin Scale scores, as well as data on vascular risk factors (DM, HTN, atrial fibrillation, hypercholesterinemia, and current smoking), were collected. The stroke subtype was categorized for every patient using Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.24

Imaging
All patients underwent a standard 3T (Tim Trio; Siemens AG, Erlangen, Germany) stroke MRI protocol as described elsewhere.25 In brief, the protocol consisted of T2*, diffusion-weighted imaging, time-of-flight MR angiography, fluid attenuated inversion recovery, and perfusion imaging. The extent of WMD was analyzed on fluid attenuated inversion recovery using the Wahlund visual rating score (WS) by neurologists experienced in MRI and stroke, blinded to demographics and risk factors (M.R. and G.J.J.).31 In cases of rater disagreement, MRI was discussed with a neuroradiologist (J.B.F.). Patients with WMD were divided into 4 groups depending on WS—0 (no white matter lesions), 1 to 4, 5 to 9, and >9. To assess the possible impact of glycemic disturbances and renal dysfunction, MRI was discussed with a neuroradiologist (J.B.F.). Patients with WMD were divided into 4 groups depending on WS—0 (no white matter lesions), 1 to 4, 5 to 9, and >9. According to TOAST classification, in 117 (22.9%) patients, the cause of stroke was large artery atherosclerosis, in 125 (24.4%) cardioembolism, in 56 (10.9%) small artery occlusion (lacune), in 14 (2.7%) other determined cause, and in 200 (39.1%) undetermined cause.

Of all patients, 394 (77%) had HTN, 253 (49.5%) hypercholesterinemia, 124 (24.2%) atrial fibrillation, and 120 (23%) DM. Demographics, risk factors, frequency of stroke and WMD, and median levels of laboratory parameters according to WS are shown in Table 1. Examples of MRI with WMD are shown in Figure 1.

Univariate analyses revealed a significant association between WMD severity and age, female sex, HTN, and DM (P<0.05; Table 1). Higher HbA1c levels and lower eGFR were the only laboratory parameters significantly associated with WMD (P<0.001; Table 1). After age adjustment, the association between extent of WMD and female sex as well low eGFR was no longer significant.

In multiple ordinal logistic regression analyses, age, HTN, and higher levels of HbA1c remained significantly associated with the extent of WMD (P<0.05; Table 2, model with HbA1c). After additionally including DM, HbA1c was not significantly associated with the extent of WMD any more (P=0.087; Table 2, model with DM and HbA1c), but the goodness-of-fit parameter (~2 Log Likelihood) of both models (model with confounders and HbA1c, model with confounders HbA1c and DM) showed that the additional adjustment for DM did not improve the model. Figure 2 shows the distribution of HbA1c levels in different WMD severity groups.

Discussion
We investigated known and potential risk factors for WMD in a relative large consecutive population of patients with first AIS. Our results underline the high prevalence of WMD in elderly persons and in patients with a history of HTN.12,16

The most important result of our study is that elevated levels of HbA1c were associated with WMD lesion load. To the best of our knowledge, this is the first study showing the possible role of glycemic disturbance as a risk factor for WMD measured by HbA1c. Previous studies assessing the relationship between WMD and DM, metabolic syndrome, dyslipidemia, higher levels of fasting glucose, and increased insulin resistance yielded controversial results.11,12,14,16,17,22,23 In these studies, however, HbA1c was not analyzed. A similar study by Heo et al25 showed rather unexpected negative association between HbA1c and severe WMD in diabetic patients. The authors did not take into consideration DM in
their multivariate analysis, and their statistical methods differed from ours.

In the study of Murray et al.,24 HbA1c was associated with deep white matter hyperintensities. But this study had a relatively small sample size that was comprised primarily of elderly participants. Manschot et al.21 showed that brain atrophy and white matter changes in patients with DM might be responsible for cognitive decline and observed a modest association between HbA1c and white matter hyperintensities in a small cohort of patients with DM. In our study, DM was associated with WMD severity only in univariate analysis, but not in multiple regression analysis. Higher levels of HbA1c seemed to be stronger associated with WMD (−2 Log Likelihood, 1023.5 [df, 3]) compared with the diagnosed DM variable (−2 Log Likelihood: 1027.7 [df, 3], model not shown). This may be explained by the fact that patients with glycemic disturbances, such as prediabetes or impaired glucose regulation, may have HbA1c levels >5.7% but not yet diagnosed with DM according to guidelines.34 Conversely, patients with DM may have tightly controlled glucose levels and, therefore, HbA1c levels below 5.7%. For the majority of patients, higher levels of HbA1c are associated with DM.

Table 1. Association of Demographics, Risk Factors, Laboratory Findings and Imaging Patterns, and the Extent of WMD

<table>
<thead>
<tr>
<th>Demographics N</th>
<th>Total</th>
<th>WS, 0 (n=52)</th>
<th>WS, 1–4 (n=205)</th>
<th>WS, 5–9 (n=139)</th>
<th>WS, &gt;9 (n=116)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD) 512</td>
<td>68 (13)</td>
<td>52 (15)</td>
<td>65 (12)</td>
<td>73 (9)</td>
<td>76 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, n (%) 512</td>
<td>320 (62.5)</td>
<td>38 (73.1)</td>
<td>137 (66.8)</td>
<td>89 (64.0)</td>
<td>56 (48.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.361</td>
</tr>
<tr>
<td>DM 512</td>
<td>120 (23.4)</td>
<td>5 (9.6)</td>
<td>44 (21.5)</td>
<td>33 (23.7)</td>
<td>38 (32.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>HTN 512</td>
<td>394 (77.0)</td>
<td>19 (36.5)</td>
<td>149 (72.7)</td>
<td>119 (85.6)</td>
<td>107 (92.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking 508</td>
<td>125 (24.4)</td>
<td>17 (32.7)</td>
<td>53 (25.9)</td>
<td>29 (20.9)</td>
<td>26 (22.4)</td>
<td>0.114</td>
</tr>
<tr>
<td>HCL 511</td>
<td>253 (49.6)</td>
<td>19 (37.3)</td>
<td>101 (49.3)</td>
<td>74 (53.2)</td>
<td>59 (50.8)</td>
<td>0.173</td>
</tr>
<tr>
<td>AF 512</td>
<td>124 (24.2)</td>
<td>7 (13.5)</td>
<td>46 (22.4)</td>
<td>45 (32.4)</td>
<td>26 (22.4)</td>
<td>0.153</td>
</tr>
<tr>
<td>Laboratory, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR MDRD, mL/min 505</td>
<td>76.5 (64.1–92.2)</td>
<td>83.7 (71.0–100.9)</td>
<td>79.8 (67.2–92.8)</td>
<td>73.7 (61.9–88.2)</td>
<td>70.6 (56.7–88.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol, mmol/L 440</td>
<td>5.05 (4.38–5.78)</td>
<td>4.90 (4.43–5.46)</td>
<td>5.00 (4.20–5.78)</td>
<td>5.05 (4.20–5.91)</td>
<td>5.15 (4.56–5.93)</td>
<td>0.135</td>
</tr>
<tr>
<td>TG*, mmol/L 412</td>
<td>1.25 (0.98–1.77)</td>
<td>1.25 (0.81–1.40)</td>
<td>1.38 (1.01–1.89)</td>
<td>1.21 (0.98–1.61)</td>
<td>1.21 (0.99–1.71)</td>
<td>0.907</td>
</tr>
<tr>
<td>HDL, mmol/L 454</td>
<td>1.3 (1.1–1.6)</td>
<td>1.4 (1.1–1.7)</td>
<td>1.3 (1.0–1.5)</td>
<td>1.3 (1.1–1.6)</td>
<td>1.3 (1.1–1.5)</td>
<td>0.191</td>
</tr>
<tr>
<td>LDL, mmol/L 471</td>
<td>3.0 (2.4–3.7)</td>
<td>2.8 (2.3–3.1)</td>
<td>3.1 (2.5–3.7)</td>
<td>3.0 (2.4–3.8)</td>
<td>3.1 (2.5–3.8)</td>
<td>0.241</td>
</tr>
<tr>
<td>HbA1c*, % 459</td>
<td>5.8 (5.4–6.3)</td>
<td>5.3 (5.1–5.6)</td>
<td>5.7 (5.4–6.1)</td>
<td>5.8 (5.5–6.4)</td>
<td>5.9 (5.5–6.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Univariate analysis, adjusting for age (right column), and WMD extent divided into groups depending on Wahlund score. AF indicates atrial fibrillation; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HCL, hypercholesterinemia; HDL, high-density lipoprotein; HTN, arterial hypertension; IQR, interquartile range; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease; TG, triglycerides; WMD, white matter disease; and WS, Wahlund score.

*Log-transformed values were used in regression models.

Table 2. Multiple Ordinal Regression of Factors Significantly Associated With WMD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model With HbA1c and Confounders (n=459)</th>
<th>Model With DM and HbA1c (n=459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β</td>
<td>SE</td>
<td>P Value</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>HTN</td>
<td>0.73</td>
<td>0.24</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>HbA1c*</td>
<td>4.00</td>
<td>1.34</td>
</tr>
<tr>
<td>Model fit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R² (Nagelkerke)</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>−2LL†</td>
<td>1023.5 (df, 3)</td>
<td>1027.7 (df, 4)</td>
</tr>
</tbody>
</table>

†Likelihood ratio test for comparison of both models; P=0.041.

Figure 1. Cerebral white matter disease in 2 different patients, periventricularly and in basal ganglia (A) in the first example. White matter changes are localized periventricularly and in some extent subcortically in another patient (B).
Endothelial dysfunction in hyperglycemic states may also contribute to small vessel injury.37 The differences in levels of HbA1c in groups of patients with any sign of WMD were 5.7% to 5.9% versus 5.3% in patients without hyperintensities, and hence within the 5.7% to 6.5% range recommended by the American Diabetes Association to diagnose prediabetes or high risk for DM.14 HbA1c is used to approximate serum glucose levels over the past 3 months. It is an end product of nonenzymatic glycation and thus a surrogate marker of glycemia. HbA1c presumably does not play a role in the development of microvascular changes in the brain.14 Whereas, hyperglycemia has been shown to lead to microinfarctions and white matter lesions indirectly.36 These processes could be explained by capillary thickening followed by narrowing of vessel lumen and subsequent chronic ischemia as found in the brains of patients with DM and WMD.1 Endothelial dysfunction in hyperglycemic states may also contribute to small vessel injury.37 The differences in levels of HbA1c were highly significant in our study but rather low, so that further investigations in larger cohorts are needed to explore the subgroup of patients with levels in the prediabetic range and confirm our findings before it could be used as a potential marker for increased WMD risk.

In our study, women had a higher prevalence and extent of WMD, but after adjusting for age, sex differences were no longer significant (Table 1) because of age differences between both sexes, 72 (SD, 14.5) years in women versus 66 (SD, 12) years in men (P<0.05; data not shown). We did not find a significant association between impaired kidney function and WMD after adjusting for age. One reason for this finding could be that our patient cohort was older than that in other studies.13,15 The link between age and both decreased kidney function and WMD severity is well established.38 The possible age-related GFR reduction in our cohort could have been underestimated by the higher age in our cohort. Moreover, the calculation of GFR using the Modification of Diet in Renal Disease formula could overestimate GFR in elderly patients.33 In general population studies, multiple regression models revealed an association between GFR and WMD but either only in patients with severe renal dysfunction or even loss of significance after controlling for risk factors, which is in accordance with our results.12,26,27 We did not find any significant association between levels of triglycerides, low-density lipoprotein, high-density lipoprotein, cholesterol, and WMD. This issue is being discussed by many authors, and its impact on WMD remains vague.12,14,16

Our study has some limitations. The cross-sectional design of our study does not allow assessing factors influencing the development and progression of WMD. Such data should be analyzed in larger epidemiological, longitudinal studies. Our study population is homogenous, but because patients may be especially prone to developing more severe WMD after stroke, AIS patients may constitute a potential target group for more precise glycemic control.5,28 Although the parameters we analyzed are not novel, the few studies that have previously assessed them yielded conflicting results. Moreover, if WMD prevention can be optimized by monitoring simple laboratory values, it is warranted that these parameters be thoroughly investigated.

Conclusions

We demonstrated that WMD in patients with first AIS is associated with age, HTN, and higher levels of HbA1c. This may suggest that stroke patients with prediabetic levels of HbA1c or inadequate glycemic control measured by HbA1c are at risk for WMD. Further studies are needed to establish possible values of HbA1c as a potential marker for increased WMD risk.

Sources of Funding

Supported by the Federal Ministry of Education and Research, grant number (01 EO 0801).

Disclosures

Dr Grittner reports receiving funding from the Center for Rasmiddelforskning Aarhus University, Denmark, and from the Albrecht-Kossel-Institute for Neuroregeneration at Rostock University. Dr Endres receives funding from the DFG (Excellence cluster NeuroCure; SFB TR 43, KFO 247, KFO 213), BMBF (Centre for Stroke Research Berlin), EU (Eustroke, ARISE, WakeUp); Volkswagen Foundation (Lichtenberg Program), Corona Foundation, grant support from AstraZeneca, Roche, and Sanofi; has participated in advisory board meetings of Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, MSD, Pfizer, and Sanofi; and has received honoraria from AstraZeneca, Bayer, Boston Scientific, Berlin Chemie, Bristol-Myers Squibb, Boehringer-Ingelheim, Desitin, Edwards, Ever, Glaxo Smith Kline, MSD, Novartis, Pfizer, Sanofi, Servier, Takeda, and Trommsof. Dr Fiebach reports the following board memberships, consultancies, or payments for lectures including service on speakers’ bureaus: Boehringer-Ingelheim, Lundbeck, Siemens, Sygns, and Synarc. Dr Jungehulsing has received funding from BMBF (Centre for Stroke Research Berlin) and honoraria from Bayer, Pfizer, and Genzyme, and has participated in CEC board meetings of Edwards Life Science. The other authors have no conflicts to report.
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*Stroke.* published online February 25, 2014; *Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2014 American Heart Association, Inc. All rights reserved. Print ISSN: 0039-2499. Online ISSN: 1524-4628

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