Supratentorial Age-Related White Matter Changes Predict Outcome in Cerebellar Stroke

Eva Grips, MD; Oliver Sedlaczek, MD; Hansjörg Bätzner, MD, PhD; Michael Fritzinger, MD; Michael Daffertshofer, MD, PhD; Michael Hennerici, MD, PhD

Background and Purpose—Little is known about the relevance of age related white matter lesions (WMLs) concerning outcome after first-ever territorial stroke. Based on an index patient, we hypothesized that age and pre-existent WMLs rather than infarct volume and topography determine outcome.

Patients and Methods—Thirty-four consecutive patients with magnetic resonance diffusion-weighted imaging–proven isolated acute cerebellar infarction were prospectively entered on our stroke data registry. Patients with pre-existent neurological deficits, hemorrhagic, or malignant cerebellar infarction were excluded. Patients were stratified using Rankin and Barthel disability scales into groups: I complete recovery, II moderate, and III significant disability 14 days after stroke onset.

Results—Initial neurological and functional scores were similar among all the groups with vertigo, nausea, unsteadiness, and limb ataxia being the most common. Infarct volume, vascular territories, and comorbidity did not predict clinical outcome. In contrast, presence and severity of supratentorial WMLs and age significantly determined outcome by functional tests.

Conclusions—In patients with isolated cerebellar infarction functional outcome correlated with the coexistence of age-related WMLs rather than stroke volume and topography. This reflects the loss of compensatory network integrity as the equivalent of functional incapacity beyond local lesion disturbances. (Stroke. 2005;36:1988-1993.)

Key Words: aging ■ outcome ■ stroke ■ white matter

Stroke signs and symptoms have traditionally been analyzed with regard to lesion localization, infarct size, and underlying stroke mechanism. However, more recently, based on the steadily increasing quality of acute stroke imaging, the concept of an immediate relationship of clinical signs and expected anatomical lesion sites is often challenged in patients with multiple lesions. In this context, several situations are principally conceivable: (1) The synchronous occurrence of acute lesions in nonadjacent cerebral territories may cause syndromes such as “hemianopia–hemiplegia” in patients with double infarct in 1 hemisphere. Here, symptoms are consistent with anatomically related function, and unusual findings result from simultaneous infarction in distant vascular territories; (2) the synchronous occurrence of acute lesions in anatomically and functionally related regions either adjacent or remote but symmetrically resulting in more severe deficits than might be expected from the simple addition of 2 infarct syndromes; (3) unexpected symptoms in the context of an acute infarct, a situation reported previously as synergistic infarct. In a published case, a posterior cortical infarct (aggravated in a patient with a previous frontal lesion) elicited frontal features that had not been expected from a simple sum of effect of these lesions. In a series, a patient exhibited clinical deterioration with a subcortical pattern of deficits fitting with his chronic lacunar lesions rather than with the acute cortical infarct; (4) an acute lesion in exact anatomical symmetry to a previous lesion in the contralateral hemisphere that may induce the reappearance of the previous deficit in addition to the newly acquired symptoms. Thus, concepts of remote network mediated lesions were within reach.

In light of these observations, the hypothesis was promoted that new lesions may generate symptoms unrelated to the specific anatomic or functional area affected through the breakdown of widespread neuronal networks. Patients with isolated cerebellar stroke could be considered an ideal model to test whether a disruption of the cerebellar gating function with its influence on supratentorial networks predicts functional outcome. Pre-existing supratentorial white matter lesions (WMLs) could then be considered vice versa to account for a poor prognosis in isolated cerebellar infarction. In consistence with this model, anatomical–functional networks have been proposed for a long time and (pre) frontal–subcortical circuits have been established. Recently, growing evidence from primate studies confirm the existence of vast anatomical–functional circuits through transneuronal trans-
port of neurotropic viruses, additionally integrating cerebellar nuclei. Following this model, the persistence of vivid by-
port of neurotropic viruses, additionally integrating cerebellar nuclei. Following this model, the persistence of vivid by-
port of neurotropic viruses, additionally integrating cerebellar nuclei. Following this model, the persistence of vivid by-
port of neurotropic viruses, additionally integrating cerebellar nuclei. Following this model, the persistence of vivid by-

and is based on the adjusted mortality risk associated with each comorbid diagnosis; it is a strong predictor of 1-year survival after hospitalization.

Stroke imaging in this study was performed on a 1.5-T magnetom vision (Siemens) for 24 to 48 hours after symptom onset and included standard T2, DWI, FLAIR, and MR angiography. MRI was read and evaluated by an independent experienced reader blinded to the clinical outcome. Apart from the identification of pre-existent cerebral lesions, small vessel changes of supratentorial subcortical WM were determined and classified by prominent features such as lesion extent, rims, and frontal caps, from none to severe according to the classification of Fazekas.26 Cerebellar infarcts were categorized according to the vascular territories as published by Tatu.20

Results are expressed as the mean \pm SD. Error probabilities were calculated by comparing 2 patient groups using the Mann—Whitney U test and were intended for exploratory data analysis because no Bonferroni correction was performed. The \( \chi^2 \) test was used for multiple categorical comparisons. Logistic regression was used to perform a prediction of dichotomous variables from interval or categorical data.

### Statistics
Results were expressed as the mean \( \pm \) SD. Error probabilities were calculated by comparing 2 patient groups using the Mann—Whitney U test and were intended for exploratory data analysis because no Bonferroni correction was performed. The \( \chi^2 \) test was used for multiple categorical comparisons. Logistic regression was used to perform a prediction of dichotomous variables from interval or categorical data.

### Results
Of the 34 patients included, 8 patients fulfilled the criteria of group I, 20 of group II, and 6 of group III (Table 1). Clinical symptoms leading to presentation were vertigo (91%), nausea (68%), unsteadiness (68%), and limb ataxia (62%; Table 1). There was no correlation between initial symptoms and outcome and no difference between the frequency of specific symptoms between groups. Symptoms persisting after 2 weeks were mainly vertigo, dysarthria, and unsteadiness. Barthel, Rankin, and National Institutes of Health Stroke Scale (NIHSS) results measured 2 weeks after stroke onset are given in Table 2. Clinical scores at presentation were significantly worse in group III compared with group I (Table 2). The distribution of the infarct territories between the groups was similar. This was particularly true for superior cerebellar artery (SCA) infarctions. There was no significant difference in infarct size among the groups; however, there was a trend toward larger infarct volumes in group III (\( P<0.08 \); Table 3). Silent territorial infarctions were detected in 6 patients only, again with no intergroup difference.

General vascular risk factors and hypertension in particular were much more frequent in group II (\( >50\% \)) and group III (100%), with large vessel disease being the suggested etiology of the acute stroke in most of the cases, whereas cardiac embolism (atrial fibrillation, patent foramen ovale) was the leading etiology of stroke in group I (Table 1).

However, subcortical WM changes were more frequent in patients with worse outcome: whereas no patient in group I exhibited any WMLs, 7 patients in group II and all of the patients in group III showed subcortical damage (Table 4). Severity of WM damage itself was not identical in groups II and III: mild (grade I) and moderate (grade II) WMLs were each present in 10% of the patients of group II; in group III, half of the patients had moderate (grade II) and the other 50% severe (grade III) WM damage. The overall frequency of WMLs was significantly higher in groups II and III compared with group I (\( \chi^2; P<0.01 \) and 0.05, respectively). There was a high correlation between the detection and the degree of WML load and the age of patients (\( r=0.65; \ P<0.001 \)). Age also predicted patients’ group assignment (\( r=0.41; \ P<0.05 \)).

In a logistic regression combining moderate (group II) and severe persistent disability after 14 days (group III), early recovery (group I) was predicted by the absence of WMLs (Z score 5.591; \( P<0.018 \)) to a slightly higher degree compared with lower age (Z score 4.514; \( P<0.034 \)). In a multivariate regresional analysis identifying age and WML-associated initial symptoms, only unsteadiness was predicted by patients’ older age (\( t=2.52; \ P<0.021 \)) and by the detection and degree of WMLs (\( t=2.90; \ P<0.007 \)).

### TABLE 3. Tentative Outcome Predictors

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Mean Age (range)</th>
<th>Cerebellar Territories Affected, no.</th>
<th>Infarct Volume, mL</th>
<th>Pre-Existing Cortical Lesions</th>
<th>Charlson Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>8</td>
<td>44 \pm 13 (29–67)</td>
<td>1.2</td>
<td>17 \pm 23</td>
<td>1 of 8</td>
<td>1</td>
</tr>
<tr>
<td>Group II</td>
<td>20</td>
<td>55 \pm 17 (23–88)</td>
<td>1.3</td>
<td>21 \pm 18</td>
<td>3 of 20</td>
<td>1.7</td>
</tr>
<tr>
<td>Group III</td>
<td>6</td>
<td>70 \pm 7 (61–77)</td>
<td>1.2</td>
<td>38 \pm 26</td>
<td>2 of 6</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Mean \( \pm SD; ^*P<0.01 \) vs group I; \( ^\dagger P<0.05 \) vs group II; \( ^\ddagger P<0.08 \) vs group I.

### TABLE 4. Frequency of WMLs

<table>
<thead>
<tr>
<th>WML Grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group II</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Group III</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

\( \chi^2 \ P<0.03 \).
Imaging examples characteristic for each group are shown in the Figure (A through F).

**Discussion**

This study presents a second level analysis of the prospective Mannheim Stroke Registry, with data on 34 highly selected patients with acute isolated cerebellar infarction. Except for patients’ age, which cannot be seen as an illness in itself, there is no significant role for comorbidity, the number of cerebellar territories affected, pre-existent silent territorial strokes, or cerebellar infarct size in the prediction of early outcome after first-ever cerebellar stroke. However, the presence and degree of subcortical WM damage was a strong predictor of early recovery. None of the 8 patients experiencing complete clinical restitution within 48 hours after stroke onset exhibited any WMLs. However, 35% of the patients in group II and all of the patients in group III had mild to severe WMLs that were not associated with any clinically apparent
neurological deficits before the acute cerebellar stroke. Strongly correlated with the presence of subcortical changes, outcome in these patients was significantly worse, with WMLs being a slightly stronger predictor of nonbeneficial outcome than age.

Apart from age, the presence of WMLs was well matched by the identification of vascular risk factors: none of the patients of group I were experiencing hypertension, 50% in group II, and all of the patients in group III. Other vascular risk factors such as diabetes, hyperlipidemia, smoking, and hyperhomocysteinemia were distributed similarly between the 3 groups. Although stroke etiology differs among groups, we did not consider this to be a relevant parameter for outcome in this specific model. Whereas in the study of Kelly et al., the Charlson comorbidity index did significantly predict long-term outcome, no such association was seen in our study population. Therefore, the degree of subcortical damage seems to be a major factor determining recovery from acute cerebellar lesions, suggesting a mutual compensatory function of the cerebellum for progressive vascular damage.

To our knowledge, no study has investigated the association of WMLs with acute cerebellar stroke and vice versa with regard to functional outcome. With regard to supratentorial lesions, Boon et al. identified the presence of silent subcortical infarcts and its relation to outcome after acute supratentorial stroke. However, they found no influence of subcortical damage to the degree of initial handicap, 30-day fatality and 1-year mortality.

To our understanding, the mechanisms underlying the persistence of neurological deficits, namely vertigo, dysarthria, and unsteadiness after acute cerebellar infarcts in patients with WM disease, are related to pre-existing network disruption. Such missing compensation is evident for the motor loops (the cerebellum receiving information from the cerebral cortex via pontine nuclei and cerebellar afferences projecting to the primary motor cortices via the ventrolateral thalamus as part of a feedback control) and their control. In SVE, the disturbance of the circuitry from frontal and parietal cortex to the basal ganglia via VM tracts causes disturbance of gait, disconnecting supplementary motor cortex, and therefore planning and initiating of locomotion from basal ganglia by multilocular diffuse network destruction. Considering the known complexity of motor circuits, the concept of synergistic lesions is very appealing. However, the proof of single lesions and their network disruptions is rarely described, comprising of only a few patients. One of the few established concepts of remote effects is the crossed cerebellar diaschisis, which is defined as depression of blood flow and metabolism in the cerebellar hemisphere contralateral to the focal supratentorial lesion. First observed in positron emission tomography, the phenomenon has been confirmed by means of functional MRI. Although mutual aspects of crossed cerebellar diaschisis are evident, no study has identified primarily infratentorial lesions.

Despite the limited absolute number of patients recruited in a monocenter study from a large stroke population reflecting the high degree of selection and exclusion criteria, these data support our hypothesis of a network concept for stroke prognosis. WMLs were a strong predictor of the persistence of symptoms such as vertigo, dysarthria, and unsteadiness after 14 days; this was independent of infarct size or territory of the acute cerebellar infarct but highly correlated with age. These unspecific clinical signs can be secondary to various pathologies, both non-neurological disorders (acid base disturbance, endocrinological or cardiological problems, etc) and multilocular neurological disease (supratentorial and infratentorial, subcortical and cortical, left and right hemispheric). This nonfocal character suggests an important function of subcortical relay stations and connecting fibers to compensate for cerebellar lesions evidenced by loss of network compensation in age-related WM disease. If the prevention or treatment of WMLs could be shown to be associated with risk factor modulation, this would have an important impact on the burden of stroke-associated disability.

**References**


13. Baezner H, Oster M, Daffertshofer M, Hennerici M. Assessment of gait disturbance, dementia, and urinary incontinence. The fact that isolated cerebellar infarctions in general have a good functional outcome compared with infarctions in other vascular territories is also well established. To our knowledge, no study has investigated the association of WMLs with acute cerebellar stroke and vice versa with regard to functional outcome. With regard to supratentorial lesions, Boon et al. identified the presence of silent subcortical infarcts and its relation to outcome after acute supratentorial stroke. However, they found no influence of subcortical damage to the degree of initial handicap, 30-day fatality and 1-year mortality.

To our understanding, the mechanisms underlying the persistence of neurological deficits, namely vertigo, dysarthria, and unsteadiness after acute cerebellar infarcts in patients with WM disease, are related to pre-existing network disruption. Such missing compensation is evident for the motor loops (the cerebellum receiving information from the cerebral cortex via pontine nuclei and cerebellar afferences projecting to the primary motor cortices via the ventrolateral thalamus as part of a feedback control) and their control: in SVE, the disturbance of the circuitry from frontal and parietal cortex to the basal ganglia via VM tracts causes disturbance of gait, disconnecting supplementary motor cortex, and therefore planning and initiating of locomotion from basal ganglia by multilocular diffuse network destruction. Considering the known complexity of motor circuits, the concept of synergistic lesions is very appealing. However, the proof of single lesions and their network disruptions is rarely described, comprising of only a few patients. One of the few established concepts of remote effects is the crossed cerebellar diaschisis, which is defined as depression of blood flow and metabolism in the cerebellar hemisphere contralateral to the focal supratentorial lesion. First observed in positron emission tomography, the phenomenon has been confirmed by means of functional MRI. Although mutual aspects of crossed cerebellar diaschisis are evident, no study has identified primarily infratentorial lesions.

Despite the limited absolute number of patients recruited in a monocenter study from a large stroke population reflecting the high degree of selection and exclusion criteria, these data support our hypothesis of a network concept for stroke prognosis. WMLs were a strong predictor of the persistence of symptoms such as vertigo, dysarthria, and unsteadiness after 14 days; this was independent of infarct size or territory of the acute cerebellar infarct but highly correlated with age. These unspecific clinical signs can be secondary to various pathologies, both non-neurological disorders (acid base disturbance, endocrinological or cardiological problems, etc) and multilocular neurological disease (supratentorial and infratentorial, subcortical and cortical, left and right hemispheric). This nonfocal character suggests an important function of subcortical relay stations and connecting fibers to compensate for cerebellar lesions evidenced by loss of network compensation in age-related WM disease. If the prevention or treatment of WMLs could be shown to be associated with risk factor modulation, this would have an important impact on the burden of stroke-associated disability.


Supratentorial Age-Related White Matter Changes Predict Outcome in Cerebellar Stroke
Eva Grips, Oliver Sedlaczek, Hansjörg Bätzner, Michael Fritzinger, Michael Daffertshofer and Michael Hennerici

Stroke. 2005;36:1988-1993; originally published online August 4, 2005;
doi: 10.1161/01.STR.0000177869.02361.dc

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/36/9/1988

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/