Association of Leukoaraiosis With Convalescent Rehabilitation Outcome in Patients With Ischemic Stroke

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Background and Purpose—We investigated the factors influencing inpatient convalescent rehabilitation outcomes in patients with ischemic stroke, particularly severity of leukoaraiosis on magnetic resonance imaging.

Methods—Participants included 520 patients with ischemic stroke (317 men and 203 women; mean age, 72.8±8.4 years) who were transferred from acute care hospitals for inpatient convalescent rehabilitation. Ischemic stroke subtypes included lacunar infarction (n=41), atherothrombosis (n=223), artery-to-artery embolism (n=67), cardiogenic embolism (n=97), undetermined embolism (n=76), and uncategorized ischemic stroke (n=16). Leukoaraiosis was graded according to periventricular hyperintensity (PVH) and deep white matter hyperintensity on magnetic resonance imaging. Functional Independence Measure scores were assessed on admission and at discharge.

Results—Multiple regression analysis revealed that rehabilitation outcomes, measured as total Functional Independence Measure scores, were significantly associated with leukoaraiosis estimated by PVH grade. This association was observed after adjustment for factors such as severity, age, and poststroke history. In all patients, PVH grades were associated with Functional Independence Measure motor scores (P<0.001), whereas in patients with artery-to-artery embolism or cardiogenic embolism and deep white matter hyperintensity grades were associated with Functional Independence Measure cognitive scores (P<0.05).

Conclusions—Our study revealed that the degree of leukoaraiosis was associated with inpatient convalescent rehabilitation outcome in patients with ischemic stroke. Furthermore, the PVH grade was associated with motor function outcome, whereas the deep white matter hyperintensity grade correlated with cognitive function outcome, likely because the progression patterns and anatomic backgrounds of PVH and deep white matter hyperintensity differ according to ischemic stroke subtype. (Stroke. 2016;47:160-166. DOI: 10.1161/STROKEAHA.115.010682.)

Key Words: convalescent rehabilitation ischemic stroke leukoaraiosis magnetic resonance imaging

Although the care and diagnosis of patients with acute ischemic stroke have progressed dramatically,1 large numbers of these patients still cannot directly return from an acute care hospital to a preclinical environment, such as their home. These patients require convalescent rehabilitation because of poststroke-related functional impairments. Convalescent rehabilitation units for postacute stroke patients with ischemic stroke, particularly severity of leukoaraiosis on magnetic resonance imaging. Functional Independence Measure scores were assessed on admission and at discharge.

Rehabilitation units for postacute stroke patients with ischemic stroke, particularly severity of leukoaraiosis on magnetic resonance imaging. Functional Independence Measure scores were assessed on admission and at discharge. These imaging modalities have enabled implementation of therapies that are more aligned with a particular disease subtype. Lacunar infarction (LI), atherothrombosis, and cardiogenic embolism (CE), as defined by the National Institute of Neurological Disorders and Stroke III criteria,4 are widely used as classifications of ischemic stroke subtype. Although the pathologies of these subtypes are described by these criteria, no diagnostic methods or standards exist for neuroimaging and other examinations. The current diagnostic standards for ischemic stroke subtype used in clinical trials are from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classifications.5 According to the TOAST classification system, artery-to-artery embolism (A-to-A) can be distinguished from atherothrombosis,6 and both can be distinguished from CE. However, these concepts are not well

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understood in the convalescent rehabilitation stage. MRI and MRA can be used to detect and assess leukoaraiosis, white matter hyperintensities, that are thought to affect both cognitive and motor functions; however, the relationship between leukoaraiosis and rehabilitation outcome, especially in acute ischemic stroke survivors in the convalescent rehabilitation stage, has not been clarified.

In this study, we investigated the factors influencing convalescent rehabilitation outcomes in patients with acute ischemic stroke. We assessed their ADL prognosis in terms of disease subtype and performed radiological assessments, including intracranial MRI and MRA, along with various other examinations mainly during the acute care stage. We paid special attention to possible relationships between rehabilitation outcomes and degree of leukoaraiosis on MRI.

Patients and Methods

Patients
This retrospective study included consecutive patients with ischemic stroke who had been hospitalized for convalescent rehabilitation at the Kami-iida rehabilitation hospital between January 2008 and December 2013. A total of 520 patients (317 men and 203 women; mean age, 72.8±8.4 years) who fulfilled the following inclusion criteria were enrolled in the study: (1) no premature discharge because of changes in their condition or other circumstances; (2) complete independence in ADL (at a level such that the patient could live alone) before the current ischemic stroke according to scores on both the modified Rankin Scale (score of 0) and the Barthel Index (score of 100); (3) no dementia, including Alzheimer disease or mild cognitive impairment, before the current ischemic stroke; (4) right-hand dominant; and (5) underwent intracranial MRI/MRA to diagnose ischemic stroke. The average number of days from onset of the current ischemic stroke to transfer to our hospital, including the period at the acute care hospital, was 32.8±10.3 days. The daily rehabilitation time at our convalescent hospital was 112±20 minutes/d. Total FIM score (including both FIM motor and FIM cognitive scores) was measured in all patients both on admission and at discharge from our convalescent hospital.

Ischemic Stroke Subtype Evaluation

In addition to the National Institute of Neurological Disorders and Stroke III classifications of LI, atherothrombosis, and CE, we appended A-to-A embolism. According to the TOAST classification system, A-to-A, which involves atherothrombotic mechanisms, can be distinguished from CE and atherothrombosis. Although difficult, we did differentiate A-to-A from atherothrombosis, as we considered it beneficial to diagnose the different disease subtypes using the TOAST classification system. A flaw in the TOAST classification system is that it indicates a single cause, which cannot be specified when ≥2 causes are implicated; thus, in some cases, the conditions were not diagnosed completely because multiple causes were indicated. Consequently, we performed the following detailed classification with the objective of adopting only cases with clear evident causes: (1) LI: ischemic stroke of the deep brain, basal ganglia, or brain stem, <15 mm on MRI; (2) atherothrombosis: ischemic stroke based on a cortical atherosclerotic lesion or caused by an atherosclerotic lesion extending into multiple perforating branches, ≥15 mm; (3) A-to-A: cerebral embolism in which an atherosclerotic lesion of its proximal artery is confirmed to be the embolism source on a carotid artery echogram or intracranial MRA; and (4) CE: cerebral embolism resulting from a thrombus formed in the heart caused by its disease, such as atrial fibrillation. Furthermore, embolic cases in which A-to-A and CE could not be distinguished or in which the embolism source was unknown were all classified as undetermined embolism. Ischemic stroke caused by specific mechanisms such as vasculitic or postoperative ischemic stroke was classified as other.

The disease subtype for all patients was determined using blood test findings, carotid artery and cardiac echograms, electrocardiograms, intracranial MRI/MRA findings, and any other relevant data provided by the acute ischemic stroke care hospitals. The use of medications to treat hypertension, diabetes mellitus, and hyperlipidemia was also determined. If a patient’s information from the acute care hospitals was insufficient, we requested more information; in some cases, diagnostic assessments to determine ischemic stroke subtype were performed again based on data from the acute care stage.

MRI/MRA Assessments

Intracranial MRI/MRA findings were assessed in all 520 patients. White matter lesions were classified on admission to our hospital using the Fazekas criteria for periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) on T2-weighted or fluid-attenuated inversion recovery images (Figure). PVH was graded from 0 to 3 as follows: grade 0, none or rim only; grade 1, localized lesion depicted in pencil-thin lining or caps; grade 2, irregular hyperintensity, a smooth halo; and grade 3, lesion spreading into the deep white matter and periventricular region. DWMH also was graded from 0 to 3 as follows: grade 0, none; grade 1, punctate hyperintensity; grade 2, punctate hyperintensity with fusion tendency; and grade 3, large fused punctate hyperintensity. For MRA, the presence of ≥50% stenosis or occlusion in the intracranial trunk arteries in the visible range was considered stenosis positive.

Statistical Analysis

For statistical analysis, quantitative variables were expressed as mean±SD. After excluding the undetermined embolism and other ischemic stroke groups, the χ² test was used to analyze multigroup qualitative variables, whereas the Kruskal–Wallis test (with the Scheffé method as a subtest) was used for quantitative variables, in which P values of <0.05 were considered significant. Stepwise multiple regression analysis was performed to characterize the relationships.

Periventricular hyperintensity (PVH)

[Figure. Grading of periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) was performed using axial T2-weighted or fluid-attenuated inversion recovery images according to the Fazekas scale.]
between (1) total FIM score on admission and at discharge, (2) FIM motor score on admission and at discharge, and (3) FIM cognitive score on admission and at discharge. The dependent variables were total FIM, FIM cognitive, and FIM motor scores at discharge. The independent variables were total FIM, FIM cognitive, and FIM motor scores on admission and use of various medications including those for hypertension, diabetes mellitus, and hyperlipidemia; age; sex; history of stroke; history of heart disease; history of tobacco use; lateralization of ischemic stroke lesion (right or left side); whether the lesion was unilateral or bilateral; the presence of atrial fibrillation; PVH grade; DWMH grade; and the presence of stenosis ≥50% or occlusion on MRA. History of stroke did not include the current ischemic stroke requiring convalescent rehabilitation. This history was determined from interviews with the patient or his/her family and was not diagnosed by information from the past attending neurologists or neurosurgeons. However, we established strict criteria that all patients with a positive history of stroke also had complete independence in ADL before the current ischemic stroke. The undetermined embolism and other ischemic stroke groups were excluded from multiple regression analysis. Multiple linear regression analysis using a stepwise approach was performed in this study to make direct prediction formulas of functional recovery as rehabilitation outcome using variable factors in our data for each patient; however, we understand the increase in type I errors using the stepwise method. SPSS version 20.0J (SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

Demographics of the study participants are summarized in Table 1. No significant differences in age, sex, or hospital stay were observed among disease subtypes. Hypertension medication was used in a little more than half of all patients, and in >80% of the LI group. Although only about one quarter of all patients used diabetes mellitus medication, it was used in >40% of the A-to-A group. Hyperlipidemia medication was used in ~40% of the LI and atherothrombosis groups, but there was no significant difference in its use among disease subtypes. In addition, there was no significant difference in the laterality of ischemic stroke (right or left side) among disease subtypes, and ischemic stroke occurred bilaterally in =10% to 25% of the embolic groups. There were no significant differences in histories of tobacco use, stroke, or heart disease, or in PVH or DWMH grade among disease subtypes; however, the LI and A-to-A groups tended to have slightly higher grades. Arterial stenosis or occlusion occurred more frequently in the A-to-A group.

There were no significant differences in FIM scores on admission or at discharge among disease subtypes; however, all FIM scores both on admission and at discharge tended to be lower in the undetermined embolism group than in those with other disease subtypes (Table 2).

Finally, we examined how the status and clinical factors of patients on admission were related to their rehabilitation outcome at discharge. Various assessments on admission, including prescribed medications; age; sex; focus site (right or left side, unilateral or bilateral); histories of tobacco use, stroke, and heart disease; PVH and DWMH grades; and the presence of ≥50% stenosis or occlusion on MRA, were used as independent variables. Stepwise multiple regression analysis was performed to identify the relationships between these factors and all ischemic stroke subtypes combined, as well as the relationships between these factors and each disease subtype separately. When total FIM score at discharge was considered as a measure of rehabilitation outcome, increases in PVH grade and age, in addition to total FIM score on admission, were significant factors worsening rehabilitation outcome in all 520 patients. When each disease subtype was considered separately, positive history of stroke was a significant factor worsening rehabilitation outcome in the A-to-A group (Table 3). When only FIM motor scores on admission and at discharge were considered, PVH grade, bilateral ischemic stroke lesions, and positive history of stroke were significant factors worsening rehabilitation outcome in patients overall; the presence of

Table 1. Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>All</th>
<th>LI</th>
<th>AT</th>
<th>A-to-A</th>
<th>CE</th>
<th>UN</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>520</td>
<td>41</td>
<td>223</td>
<td>67</td>
<td>97</td>
<td>76</td>
<td>16</td>
</tr>
<tr>
<td>Men/women, n</td>
<td>317/203</td>
<td>25/16</td>
<td>133/90</td>
<td>44/23</td>
<td>57/40</td>
<td>50/26</td>
<td>8/8</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>72.8±8.4</td>
<td>75.6±6.4</td>
<td>71.9±8.7</td>
<td>74.5±7.7</td>
<td>74.0±8.2</td>
<td>71.8±8.2</td>
<td>70.1±10.5</td>
</tr>
<tr>
<td>Hospital stay, mean±SD, d</td>
<td>82.2±26.8</td>
<td>76.7±25.1</td>
<td>83.4±25.9</td>
<td>78.3±28.2</td>
<td>84.1±28.7</td>
<td>84.5±24.8</td>
<td>77.5±28.1</td>
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<tr>
<td>Hypertension, %</td>
<td>62.5</td>
<td>80.5</td>
<td>63.7</td>
<td>64.2</td>
<td>58.8</td>
<td>53.9</td>
<td>56.3</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>28.3</td>
<td>24.4</td>
<td>31.8</td>
<td>44.8</td>
<td>25.8</td>
<td>21.1</td>
<td>6.3</td>
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<tr>
<td>Hyperlipidemia, %</td>
<td>35.2</td>
<td>39.0</td>
<td>44.4</td>
<td>25.4</td>
<td>25.8</td>
<td>32.9</td>
<td>6.3</td>
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<tr>
<td>Right-sided infarction, %</td>
<td>42.5</td>
<td>51.2</td>
<td>44.5</td>
<td>40.3</td>
<td>42.2</td>
<td>38.2</td>
<td>50.0</td>
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<tr>
<td>Left-sided infarction, %</td>
<td>47.2</td>
<td>49.8</td>
<td>52.0</td>
<td>38.8</td>
<td>49.5</td>
<td>36.8</td>
<td>31.2</td>
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<tr>
<td>Bilateral infarction, %</td>
<td>10.3</td>
<td>0</td>
<td>3.5</td>
<td>20.9</td>
<td>10.3</td>
<td>25.0</td>
<td>17.8</td>
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<tr>
<td>History of tobacco use, %</td>
<td>39.2</td>
<td>41.5</td>
<td>38.6</td>
<td>38.8</td>
<td>30.9</td>
<td>53.9</td>
<td>25.0</td>
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<tr>
<td>History of stroke, %</td>
<td>25.2</td>
<td>41.4</td>
<td>19.3</td>
<td>28.4</td>
<td>24.7</td>
<td>26.3</td>
<td>12.5</td>
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<tr>
<td>History of heart disease, %</td>
<td>10.2</td>
<td>9.8</td>
<td>8.5</td>
<td>6.0</td>
<td>14.4</td>
<td>14.5</td>
<td>6.3</td>
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<tr>
<td>PVH grade on MRI, mean±SD</td>
<td>1.33±0.80</td>
<td>2.00±0.63</td>
<td>1.33±0.76</td>
<td>1.37±0.76</td>
<td>1.12±0.65</td>
<td>1.19±0.82</td>
<td>1.31±1.02</td>
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<td>DWMH grade on MRI, mean±SD</td>
<td>1.40±0.77</td>
<td>2.05±0.56</td>
<td>1.42±0.73</td>
<td>1.48±0.69</td>
<td>1.18±0.69</td>
<td>1.22±0.82</td>
<td>1.44±0.92</td>
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<tr>
<td>MRA stenosis ≥50% or occlusion (+), %</td>
<td>42.5</td>
<td>34.1</td>
<td>33.2</td>
<td>74.6</td>
<td>41.2</td>
<td>50.0</td>
<td>31.2</td>
</tr>
</tbody>
</table>

A-to-A indicates artery-to-artery embolism; AT, atherothrombosis; CE, cardiogenic embolism; DWMH, deep white matter hyperintensity; LI, lacunar infarction; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PVH, periventricular hyperintensity; and UN, undetermined embolism, unable to differentiate A-to-A from CE.
≥50% stenosis or occlusion on MRA was a significant worsening factor in the atherothrombosis group; and PVH grade was a significant worsening factor in the A-to-A group (Table 4). When only FIM cognitive scores on admission and at discharge were considered, age and use of hypertension medication were significant factors worsening rehabilitation outcome in patients overall; history of tobacco use was a significant worsening factor in the atherothrombosis group; and DWMH grade was a significant worsening factor in the CE and A-to-A groups (Table 5). Moreover, we statistically tested the difference in total FIM score at discharge associated with PVH and DWMH grades among disease subtypes by including an interaction term (PVH or DWMH grade×disease subtype) in the regression model. This analysis revealed that there were no significant differences in PVH or DWMH effect among the 4 disease subtypes. In addition, there were mild but significant correlations between age and PVH grade (r=0.296; P<0.001) and between age and DWMH grade (r=0.293; P<0.001) from the standpoint of multicollinearity. However, in each stepwise multiple regression model, the variance inflation factor values of PVH or DWMH were relatively low (<1.1 in each analysis); thus in this study, we used each independent variable factor, including PVH and DWMH grades, directly.

### Discussion

Our results revealed that convalescent rehabilitation outcome after ischemic stroke, expressed as total FIM score, was influenced by several factors. In particular, rehabilitation outcome was affected by the presence of leukoaraiosis on MRI. Total FIM score at discharge correlated with degree of PVH. When total FIM score was subdivided into motor and cognitive components, PVH grade correlated with motor function, whereas DWMH grade was associated with cognitive function in the A-to-A and CE groups based on an embolic mechanism. Furthermore, our results demonstrated that the worsening factors and their effects differed in each disease subtype. To the best of our knowledge, the relationship between degree of leukoaraiosis and rehabilitation outcome in patients with ischemic stroke has not been clearly described for the 5 disease subtypes used in this study.

Although not statistically significant, leukoaraiosis tended to be more severe in the LI group than in the other groups, based on PVH and DWMH grades on MRI. PVH is defined as hyperintensity continuous with the periventricular region, whereas DWMH is described as a lesion in the subcortical region but not continuous with the periventricular region. In terms of pathology, clarification of the myelin sheath and dilation of the perivascular space are common in both PVH and DWMH; however, age and hypertension are risk factors for PVH, whereas DWMH is associated with risk factors of the vascular system, such as thrombosis.11,12 In this study, >80% of patients with LI had been prescribed medication for hypertension. This trend supports the consideration that lipohyalinosis—microscopic vessel arteriosclerosis induced by hypertension—is a primary factor in LI occurrence10 and suggests a link with intense white matter lesions, as indicated by the high PVH and DWMH scores. Our findings also revealed that hypertension was related to decreased FIM cognitive score in patients with LI, suggesting a relationship between hypertension and cognitive impairment, even at the convalescent rehabilitation stage.15

Degree of PVH or DWMH on intracranial MRI does not necessarily coincide with pathological severity of the

### Table 2. FIM Scores of the Study Participants on Admission and at Discharge

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Total FIM Score</th>
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<tr>
<td></td>
<td>Admission</td>
<td>Discharge</td>
<td>Admission</td>
<td>Discharge</td>
<td>Admission</td>
<td>Discharge</td>
</tr>
<tr>
<td>All (n=520)</td>
<td>80.06±23.28</td>
<td>91.73±21.58</td>
<td>55.69±19.38</td>
<td>65.99±18.17</td>
<td>24.17±7.10</td>
<td>25.63±4.48</td>
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<tr>
<td>LI (n=41)</td>
<td>85.93±19.45</td>
<td>96.71±16.80</td>
<td>63.31±14.63</td>
<td>72.51±12.24</td>
<td>21.16±6.68</td>
<td>22.66±6.05</td>
</tr>
<tr>
<td>AT (n=223)</td>
<td>83.51±21.02</td>
<td>95.34±18.80</td>
<td>51.87±15.98</td>
<td>63.91±20.54</td>
<td>21.96±7.42</td>
<td>23.48±7.48</td>
</tr>
<tr>
<td>CE (n=97)</td>
<td>83.52±23.27</td>
<td>93.55±21.56</td>
<td>59.40±18.35</td>
<td>69.05±15.90</td>
<td>24.51±6.77</td>
<td>26.12±5.97</td>
</tr>
<tr>
<td>UN (n=76)</td>
<td>70.01±23.40</td>
<td>83.25±23.06</td>
<td>48.96±20.06</td>
<td>60.72±19.05</td>
<td>21.16±6.68</td>
<td>22.66±6.05</td>
</tr>
<tr>
<td>Other (n=16)</td>
<td>79.56±25.48</td>
<td>92.87±22.53</td>
<td>61.33±19.26</td>
<td>72.61±16.78</td>
<td>25.06±7.49</td>
<td>27.72±6.03</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD. A-to-A indicates artery-to-artery embolism; AT, atherothrombosis; CE, cardiogenic embolism; FIM, Functional Independence Measure; LI, lacunar infarction; and UN, undetermined embolism, unable to differentiate A-to-A from CE.

### Table 3. Multiple Linear Regression Analysis of Rehabilitation Outcome as Total FIM Score at Discharge and Clinical Factors

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>β</th>
<th>P Value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=520)</td>
<td>0.901</td>
<td>0.847</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVH grade</td>
<td>-0.052</td>
<td>-1.443</td>
<td>0.004</td>
</tr>
<tr>
<td>Age</td>
<td>-0.043</td>
<td>-0.103</td>
<td>0.023</td>
</tr>
<tr>
<td>LI (n=41)</td>
<td>0.909</td>
<td>0.806</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AT (n=223)</td>
<td>0.914</td>
<td>0.888</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVH grade</td>
<td>-0.111</td>
<td>-3.297</td>
<td>0.016</td>
</tr>
<tr>
<td>A-to-A (n=67)</td>
<td>0.921</td>
<td>0.840</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of stroke (+)</td>
<td>-0.112</td>
<td>-5.710</td>
<td>0.021</td>
</tr>
<tr>
<td>CE (n=97)</td>
<td>0.868</td>
<td>0.842</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVH grade</td>
<td>-0.135</td>
<td>-4.909</td>
<td>0.001</td>
</tr>
</tbody>
</table>

A-to-A indicates artery-to-artery embolism; AT, atherothrombosis; CE, cardiogenic embolism; FIM, Functional Independence Measure; LI, lacunar infarction; and PVH, periventricular hyperintensity.
white matter lesions, and it is difficult to predict impaired cognitive function from the degree of cerebral white matter hyperintensity. It has also been reported that in elderly individuals, the presence of PVH or DWMH alone does not necessarily lead to decrements in cognitive function. However, increases in PVH and DWMH grades have been associated with decreases in both motor and cognitive functions in nondisabled patients. In lesions in which PVH borders the lateral ventricle, length association and projection fibers that connect the different lobes are present in large numbers, and reduced motor function may easily be caused by injury to these fibers. Furthermore, white matter lesions indicated by PVH are thought to cause walking and balance impairments because motor, sensation, and balance functions of the lower extremities decrease after injury to the superior longitudinal fasciculus fibers, which connect the frontal lobes to the sensorimotor area. In contrast, for the portions of DWMH located in the subcortical region, injury to the short association fibers, which connect between or within the cerebral lobes, in addition to the long association and projection fibers, leads to impaired cognitive function. Furthermore, these small-sized abnormalities in the subcortical region, rather than large cortical cerebral infarction, are more important for the development of vascular cognitive impairment although various cardiovascular risk factors also are related to occurrence of ischemic stroke. These brain tissue changes, which characterize Alzheimer disease with amyloid plaques and neurofibrillary pathology, occur more often in patients with cerebrovascular disease than in those with no ischemic lesion. As a result, a combination of Alzheimer-type pathological changes and these subcortical diseases can worsen cognitive function. Therefore, the development of DWMH has been shown to strongly influence cognitive function. In addition, several reports have indicated that both atherosclerosis in the carotid artery and other risk factors for cardiovascular disease are associated with cognitive impairment. Overall, these results support our study that the degree of DWMH influenced cognitive functional outcome in patients with A-to-A or CE stroke because we subdivided the ischemic stroke subtypes thoroughly in terms of their embolic mechanism. Thus, we think that the patterns of these white-matter abnormalities influence the different functional outcomes of convalescent rehabilitation.

The presence of stenosis or occlusion of the trunk arteries seemed to significantly affect convalescent rehabilitation outcome only in patients with atherothrombosis and only when measured by FIM motor score. It has been established that trunk artery occlusion or stenosis itself causes hypoperfusion in the region of the dominant vessels, which impairs various neurological functions. We speculate that in stroke caused by atherothrombosis, which had the second highest frequency of stenosis or occlusion after the A-to-A group, the hypoperfusion that occurs because of these arterial deficits results in progression of PVH. White matter lesions indicated by PVH can reduce motor function and, consequently, influence FIM motor score at discharge. To summarize, it seems that in conjunction with stenosis or trunk artery occlusion, degree of white matter lesions may influence the presence of aphasia and spatial neglect, foci size, and lesion site, as well as ADLs prognosis after convalescent rehabilitation. Therefore, assessment using intracranial MRI/MRA is necessary in convalescent rehabilitation patients.

The primary finding of this study is that white matter lesions according to PVH predicted convalescent motor

Table 4. Multiple Linear Regression Analysis of Rehabilitation Outcome as FIM Motor Score at Discharge and Clinical Factors

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>β</th>
<th>B</th>
<th>P Value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=520)</td>
<td>0.842</td>
<td>0.826</td>
<td>&lt;0.001</td>
<td>0.591</td>
</tr>
<tr>
<td>FIM motor score on admission</td>
<td>+0.842</td>
<td>+0.826</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PVH grade</td>
<td>-0.063</td>
<td>-1.415</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Bilateral infarction</td>
<td>-0.049</td>
<td>-1.538</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>History of stroke (+)</td>
<td>-0.057</td>
<td>-2.410</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.051</td>
<td>-0.009</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

A-to-A indicates artery-to-artery embolism; AT, atherothrombosis; CE, cardiogenic embolism; FIM, Functional Independence Measure; LI, lacunar infarction; MRA, magnetic resonance angiography; and PVH, periventricular hyperintensity.

Table 5. Multiple Linear Regression Analysis of Rehabilitation Outcome as FIM Cognitive Score at Discharge and Clinical Factors

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>β</th>
<th>B</th>
<th>P Value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=520)</td>
<td>0.849</td>
<td>0.825</td>
<td>&lt;0.001</td>
<td>0.837</td>
</tr>
<tr>
<td>FIM motor score on admission</td>
<td>+0.849</td>
<td>+0.825</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.127</td>
<td>-0.301</td>
<td>0.012</td>
<td></td>
</tr>
</tbody>
</table>

A-to-A indicates artery-to-artery embolism; AT, atherothrombosis; CE, cardiogenic embolism; DWMH, deep white matter hyperintensity; FIM, Functional Independence Measure; and LI, lacunar infarction.
function, whereas lesions indicated by DWMH predicted cognitive function after ischemic stroke rehabilitation. Similar to previous studies, we also found that the age of the patient and bilateralism of the ischemic stroke lesion were linked to the functional prognosis; in particular, we showed that bilateralism correlated with worse rehabilitation outcome, especially in regard to FIM motor score.

In our set of patients, the use of medication for diabetes mellitus or hyperlipidemia and history of tobacco use were relatively high when compared with another large-scale cohort study in Japan. This trend suggests that the use of diabetes mellitus or hyperlipidemia medication may be a factor in ischemic stroke caused by broadly defined atherothrombotic mechanisms. Because diabetes mellitus itself is a poor prognostic factor for acute ischemic stroke, we speculate that diabetic patients with ischemic stroke caused by atherothrombotic mechanisms tend to have more severe sequelae after the acute care stage and, therefore, require convalescent rehabilitation.

Previous reports have suggested that diabetes mellitus and hyperlipidemia decrease cognitive function, but these factors were not related to measures of convalescent rehabilitation outcome in our study, including FIM cognitive score. History of tobacco use was also associated with worse cognitive functional outcome in patients with atherothrombosis, an effect that cannot be clearly explained. However, smoking has been shown to be a risk factor for dementia and to increase the levels of serum markers for coagulation and inflammation, which consequently induces leukoaraiosis; thus, we assume that a similar mechanism exists for the apparent effect of smoking history on decreased cognitive functional outcome in patients with atherothrombosis.

The premorbid ADLs of the study participants were assessed only through medical history interviews; more accurate assessments and compilations using cognitive function scales, such as the Mini-Mental State Examination, were not performed. Furthermore, assessments of stenosis or occlusion of the trunk arteries were limited to the intracranial arteries; assessments of the extracranial arteries using carotid artery echograms or cervical MRA were not performed. These will be good topics for future research.

We examined the factors that might influence convalescent rehabilitation outcome in patients with ischemic stroke by combining diagnostic elements in the acute care stage and ADLs assessments after the convalescent stage. We demonstrated that degree of leukoaraiosis estimated on MRI seems to represent a significant confounder in the outcome of stroke. This study demonstrates the importance of using intracranial MRI/MRA not only to determine ischemic stroke in the acute care stage but also to understand the severity of white matter abnormalities in terms of leukoaraiosis and the state of stenosis or occlusion of the trunk arteries in the convalescent rehabilitation stage.

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Disclosures

None.

References


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