Neuroimaging Markers for Early Neurologic Deterioration in Single Small Subcortical Infarction

Han-Gil Jeong, MD; Beom Joon Kim, MD, PhD; Mi Hwa Yang, RN; Moon-Ku Han, MD, PhD; Hee-Joon Bae, MD, PhD

Background and Purpose—Early neurological deterioration (END) occurs in ≥20% of single small subcortical infarctions (SSSIs; axial diameter ≤20 mm in the perforator territories) and deters functional recovery. Both microvascularopathies and atherosclerosis have been proposed to independently contribute to the occurrence of END in SSSI cases. We hypothesized that the occurrence of END in SSSIs differs according to the pathological process.

Methods—We collected data from 587 patients with SSSI within 48 hours of onset from a prospective stroke registry containing 4961 case records. Independent reviewers, blinded to END information, rated neuroimaging characteristics, including relevant artery stenosis (0% to 50% stenosis of the adjacent arteries on magnetic resonance angiography), branch atheromatous lesions (≥4 consecutive axial cuts or extensions from the basal surface of the pons), white matter hyperintensities, old lacunar infarctions, and cerebral microbleeds.

Results—END occurred in 79 (13.5%) cases, including 6 recurrences, 68 progressions, 1 symptomatic hemorrhagic bleed; and acute phase parameters such as leukocyte count.4,8–16

Conclusions—Our analysis indicated a potential contribution of the localized atherosclerotic process to END in SSSIs.

Key Words: atherosclerosis ■ early neurologic deterioration ■ lacunar infarct ■ single small subcortical infarct ■ stroke

Single small subcortical infarctions (SSSIs), traditionally called lacunar infarctions or small vessel occlusions, usually have a small infarction volume, and thus SSSI cases show relatively limited functional deficits.1–3 However, early neurological deterioration (END) also occurs in 20% to 30% of SSSIs during hospitalization, which hampers functional recovery.4,6 END in SSI is a frustrating event for both stroke physicians and patients.7 Thus, elucidating the pathological mechanisms and potential predictors of END in SSSI is the first and foremost step to effectively cope with the progression of neurological deficits.

Efforts have been made to determine reliable predictors for the occurrence of END in patients with SSSI, and the following have been suggested: metabolic factors such as hemoglobin A1c and hypertriglyceridemia; characteristics of ischemic lesions such as ischemic volume, topographical location, shape, or perfusion state; the occurrence of cerebral microangiopathy including microbleeds; and acute phase parameters such as leukocyte count.8–16 However, these studies were conflicting and mostly conducted in a retrospective manner. A potential breakthrough about this issue may come from a detailed analysis of imaging findings that implicate 2 different pathological processes that contribute to the occurrence of SSSIs.5 In this context, we hypothesized that the atherosclerotic process would produce a greater contribution to END compared with small vessel pathologies and sought to investigate the associations between concomitant neuroimaging markers and END by analyzing a large stroke registry that has prospectively and systemically gathered information on END.

Methods

Collection of Patient Data

A total of 4961 patients with stroke were admitted to Seoul National University Bundang Hospital between July 2007 and July 2013. Among them, the authors collected analyzable cases using the following inclusion criteria, such as (1) arrived within 48 hours after...
symptom onset (n=3702); (2) ischemic stroke cases (n=3043); (3) ischemic lesions documented by a neuroimaging study (n=2893); (4) ischemic lesions located in the striatocapsular, thalamic, or brain stem area (n=788); and (5) single ischemic lesions with an axial diameter ≤20 mm with a patent adjacent relevant artery (degree of stenosis ≤50%) and without atrial fibrillation (n=589). Our exclusion criteria consisted of (1) ischemic strokes because of other determined etiologies (n=2), (2) MRI that could not be analyzed, and (3) missing information on END. Finally, a total of 587 cases were eligible for analysis. Acute stroke management, including the process of hyperacute recanalization, was performed according to the current clinical practice guidelines and institutional protocols and at the discretion of the individual physicians with direct liability. This study was approved by the Institutional Review Board at the Seoul National University Bundang Hospital (Institutional Review Board approval No. B-1408-264-109).

Definition of Clinical Information
We collected baseline demographic and clinical information for all study participants, including age, sex, body mass index, initial systolic and diastolic blood pressure, history of previous stroke, and cardiovascular risk factors such as hypertension (previous use of antihypertensive medication), systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg at discharge), diabetes mellitus (previous use of glucose-lowering medication or hemoglobin A1c ≥6.5%), hyperlipidemia (previous use of lipid-lowering medication, fasting low-density lipoprotein cholesterol >160 mg/dL, or fasting total cholesterol >240 mg/dL), and habitual smoking (current or past regular smoking). We obtained laboratory information, including initial glucose level, hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, triglycerides, low-density lipoprotein cholesterol, leukocyte count, hemoglobin, and prothrombin time from the patients. Stroke characteristics included the time interval between the onset of symptoms and time of arrival, National Institutes of Health Stroke Scale (NIHSS) score at admission and treatment information.

END: Definition and Collection of Data
We prospectively and systemically collected END data starting in 2007. The NIHSS scores of every patient with stroke were rated by certified nurses and attending physicians every 4 hours in the stroke unit and at least once a day in the general ward. END is defined as any new neurological symptom/sign or any neurological worsening occurring within 3 weeks after stroke onset. In our stroke center, we collected END cases using the following criteria: (1) an increment in the total NIHSS score of ≥2 points, (2) an increment in the consciousness score (1a–1c) of ≥1, (3) an increment in the motor score (5a–6b) of ≥1, or (4) any new neurological deficit (even unmeasurable by NIHSS scores). Then, the causes of END were analyzed and classified into (1) stroke recurrence, (2) stroke progression, (3) symptomatic hemorrhagic transformation, (4) other, and (5) unknown.

(1) Stroke recurrence was defined as any neurological deterioration within 3 weeks in patients with acute stroke whose initial neurological status had been stabilized for ≥24 hours and that was not caused by the progression of the initial ischemic lesion. Diffusion-weighted imaging after END demonstrated discrete new ischemic lesions explaining the neurological deterioration. However, cerebral edema, mass effect, herniation syndrome, or hemorrhagic transformation of the infarction was not classified as stroke recurrence. (2) Stroke progression was defined as neurological deterioration caused by progression of the initial lesion, which was confirmed in the follow-up imaging study as an enlargement of the infarct size or the presence of significant perilesional edema. In the cases of END within 24 hours of stroke onset, those cases showing discrete new lesions were also assigned to the stroke progression group. (3) Symptomatic hemorrhagic transformation was defined as the presence of hemorrhagic transformation in follow-up images that could explain END. (4) The other category included any probable medical complication, such as infection, electrolyte disturbance, myocardial infarction, or medication side effects. (5) The unknown category included cases in which the causes of END could not be classified into any of the above categories.

END was reported immediately to the on-duty residents or staff physicians. In weekly Stroke Center meetings, all END cases were discussed and evaluated by experienced staff and team members, and the cases were registered in the prospective END database.

Evaluation of Neuroimaging Information
All cases underwent MRI on a 1.5 or 3.0 Tesla scanner within 24 hours after admission. The following neuroimaging information was gathered using the initial MRI scans. White matter hyperintensities (WMH) were visually evaluated by a 4-point score as proposed by Fazekas et al. A cerebral microbleed (CMB) was defined as a black, round lesion with a blooming effect on gradient echo MRI, devoid of T1- or T2-weighted hyperintensity, with at least half of the lesion surrounded by brain parenchyma. Potential mimics such as iron or calcium deposits, bone, or vessel flow voids were excluded. An old lacunar infarction was defined as a focal lesion in deep perforator territory, ≥3 mm in diameter, with hyperintense signal on T2-weighted or fluid attenuation inversion recovery images and hypointense signal on T1-weighted images, which was often surrounded by a hyperintense signal rim on fluid attenuation inversion recovery images. Two trained neurologists (B.J.K. and H.G.J.), blinded to the clinical information, assessed the degree of WMH, CMBs, and old lacunar infarctions on the first MRI (κ values, 0.71, 0.75, and 0.84, respectively). Any disagreement was resolved by re-evaluation and discussion. Relevant artery stenosis was defined as the presence of 0% to 50% narrowing at the adjacent major arteries feeding the corresponding territory on magnetic resonance imaging study as an enlargement of the infarct size or the presence of significant perilesional edema. In the cases of END within 24 hours of stroke onset, those cases showing discrete new lesions were also assigned to the stroke progression group. (3) Symptomatic hemorrhagic transformation was defined as the presence of hemorrhagic transformation in follow-up images that could explain END. (4) The other category included any probable medical complication, such as infection, electrolyte disturbance, myocardial infarction, or medication side effects. (5) The unknown category included cases in which the causes of END could not be classified into any of the above categories.

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Figure. Representative figures from cases with early neurological deterioration (END). A. A branch atheromatous lesion in the right lenticulostriate territory (documented on ≥4 consecutive axial sections on 5-mm thick diffusion-weighted images) and growth of infarction with END. B. Relevant extracranial stenosis (≤50% stenosis) in the midbasilar artery and expansion of pontine infarction involving basal surface of the brain stem after END.
angiography (k value, 0.86). Branch atheromatous lesions were defined when they were visible for 4 axial MRI cuts at a slice thickness of 5 mm in the lenticulostriate territory or infarcts that extended from the basal surface of the pons (k value, 0.92).13

Statistical Analyses
We analyzed differences among the groups with χ2-tests for categorical variables and with independent sample t-tests. Binary logistic regression analysis models were used to evaluate the association between the occurrence of END and exposure variables. We constructed multivariable logistic models using END as a dependent variable with adjustment for confounding variables with bivariate P<0.20 (thrombolytic treatment, time delay from symptom onset to hospital arrival, NIHSS score at admission, body mass index, and initial systolic blood pressure) and clinically relevant factors (age and initial glucose). The number of covariates was less than one tenth of the number of outcome events. Significance levels were set at a P<0.05 for 2-tailed tests. Statistical analyses were performed using Stata 13 (StataCorp LP, College Station, TX).

Results
Of the 4961 cases with acute ischemic stroke evaluated from July 2007 to July 2013, 587 cases met the eligibility criteria. Men comprised 59% (n=347) of the sample, and the mean age was 65±12 years. The risk factors included hypertension in 412 (70%) patients, diabetes mellitus in 193 (33%) patients, habitual smoking in 248 (42%) patients, and hyperlipidemia in 147 (25%) patients. The average NIHSS score at admission was 3.4±2.7 points, and the time delay from symptom onset to arrival was 16.7±13.6 hours. Twenty-five (4.3%) patients received thrombolytic treatment. Relevant artery stenosis (0% to 50% narrowing) was observed in 159 (27.1%) patients, and branch atheromatous lesions were observed in 220 (37.5%) patients, WMH was graded as 0 in 123 (21.0%) patients, 1 in 209 (35.4%) patients, and 2 in 97 (16.5%) patients, and 3 in 58 (10.0%) patients. Old lacunar infarctions were observed in 288 (49.1%) patients, and CMBs were observed in 162 (27.6%) patients.

END occurred in 79 (13.5%) cases; progression of the initial stroke occurred in 68 (86.1%) cases; stroke recurrence was seen in 6 (7.6) cases; symptomatic hemorrhagic transformation occurred in 1 (1.2%) case; other cause was found in 1 (1.2%) case; and unknown were 3 (3.8%) cases. The average NIHSS score at END onset was 6.2±2.1 points, which increased by 2.3±1.4 points after END. The time interval from admission to END and from onset to END were 30.0±32.6 and 40.3±36.0 hours, respectively.

Subjects with END had a higher body mass index and arrived earlier than those without END (Table 1). Functional dependency or death (modified Rankin Scale score, 3–6) at 3 months was more prevalent in the END group (49.3%) than in the non-END group (23.2%). Branch atheromatous lesions and relevant artery stenosis were more prevalent in the END cases, but the frequencies of WMH, old lacunar infarctions, and CMBs were comparable.

Multivariable logistic regression models adjusted for relevant confounders showed that relevant artery stenosis (adjusted odds ratio, 1.91; 95% confidence interval, 1.13–3.21) and branch atheromatous lesions (adjusted odds ratio, 2.98; 95% confidence interval, 1.80–4.93) remained significantly associated with END (Table 2; Figure). In contrast, WMH, old lacunar infarctions, and CMBs did not have a significant association with END.
Discussion

In our SSSI population, END occurred in 13.5% of all cases 40.3±36.0 hours after stroke onset with an NIHSS score increment of 2.3±1.4 points. We documented that relevant artery stenosis and branch atheromatous lesions, which both suggest a potential contribution from large vessel pathologies, were significantly associated with the occurrence of END. However, there was no association with WMH, previous lacunar infarction or microbleeds as markers of small vessel disease.

The methodological strength of our study is because of the prospective and systematic collection of END events from the entire study population. With the implementation of quality improvement programs in our stroke center, we have been able to gather reliable information on the occurrence, cause, characteristics, and consequences of any END case. Previous studies have usually been limited to retrospective data collection and smaller sample sizes. From our research experience in collecting the acute complications of acute stroke cases, we established detailed definitions and protocols about END and successfully implemented these into our daily clinical practice. When a nursing staff member or duty resident detected END, the information was readily spread via a texting service to the on-duty doctors and attending physicians. We attempted to capture every END event and secure rapid responses to END cases through this alerting system.

Traditionally, SSSIs were considered a category of small vessel disease, caused by the lipohyalinosis or fibrinoid necrosis of small arteries or arterioles to the deep structures. However, evidence has accumulated indicating the potential contribution from atherosclerotic processes including the formation of a microatheroma or hemodynamic compromise of an infarction. Owing to the two distinct entities of lacunar infarction, SSSIs from atherosclerotic pathologies have been suggested to be larger in size and located in the proximal basal ganglia. Our results, in view of the current theory, propose that the biological characteristics of arterial occlusive lesions and the localized parenchymal responses after the occlusion of arterioles would vary according to the nature of the occlusion. A recent result from a randomized trial of dual antiplatelet treatment for minor ischemic stroke could be explained by our results because suppressing antiplatelet activities to a greater degree in earlier periods may lead to the prevention of END in the study population. It could be hypothesized further that the atherosclerotic occlusion of perforating arteries would cover the more extensive surfaces of large arteries or that thrombus propagation would be ongoing within a couple of days after initiation.

A few points should be clarified in our study. First, the direct visualization of different pathological processes was not available in our clinical practice environment. Second, coronal images of diffusion-weighted sequences were not available, and the definitions of branch atheromatous lesions were different in the basal ganglia and brain stem. Third, the small vessel disease markers in our study design were only concomitant findings and not directly related to the infarction itself. Fourth, we used magnetic resonance scanners with different magnetic fields (1.5 and 3.0 Tesla), but the incidences of END and detection rate of neuroimaging markers were not different. Fifth, statistical issues in multiple testing should be considered. Finally, because the prevalence of intracranial atherosclerosis is higher in the Asian populations, readers should use their caution in application of our results to their clinical practice.

From our study, we documented that the patients with SSSIs with relevant artery stenosis and branch atheromatous lesions are more likely to develop END but that the association was not documented in the SSSI patients with WMH, old lacunar infarctions, or CMBs. Our study may provide new insights into the underlying pathology of these small but prevalent infarctions. Moreover, it could be inferred from our results that precautionary measures might be used in clinical practice for small infarctions with large vessel pathology markers. Further clinical research involving a large set of SSSI cases from various clinical environments is warranted to determine the feasibility and use of our findings.

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Disclosures

None.

References


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Abstract

単一皮質下小梗塞における早期神経学的悪化の脳神経画像マーカー

Neuroimaging Markers for Early Neurologic Deterioration in Single Small Subcortical Infarction

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背景および目的：早期神経学的悪化（END）は、单一皮質下小梗塞（SSSI）の20%以上で発症しており、その発症は脳の機能回復を妨げている。微小血管病は一方でレントゲン検査がの一因であると考えられているが、物性病変による脳梗塞の発症は、かねてよりSSSIとされるENDの原因であろうとされてきた。本研究では、SSSI患者におけるENDの発症率を検討し、その病理解剖的所見を明らかにすることを目的とした。

方法：本研究では、4,961症例の記録を含む前向きの群調査で、発症後48時間以内にSSSI患者が587例のデータを収集した。ENDに関する情報が検索された。END診断の基準を、SSSIの発症は、脳梗塞の0〜50%の狭窄、分枝血管性病変（5〜10の5mm以上の狭窄病変または横断面での拡張）、自覚性異常、頭部CT、MRI、脳血管造影、および脳血管病変を含む神経画像診断を評価した。

結果：ENDは79例（13.5%）で発症し、このうち6例は再発性脳卒中、68例は進行性脳卒中、1例は悪性脳卒中、2例は他の原因、3例は原因不明であった。ENDにより、米国国立衛生研究所脳卒中スケール（National Institutes of Health Stroke Scale）スコアが2.3±1.4ポイント上昇した。END患者はENDのない患者と比較して、3ヶ月後検査でスコアが2.3±1.4ポイント上昇したが、END患者では、ENDを示すセリクスが有意に高かった。ただし、このような関連性は小血管病変マーカーでは特微されなかった。

結論：本解析により、SSSIにおける局在性血管性病変の形成がENDの一因となっている可能性が示された。また、血管性病変が疑われるSSSIに対しては予防的対策を講じるべきである。

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Key Words: atherosclerosis ■ early neurologic deterioration ■ lacunar infarct ■ single small subcortical infarct ■ stroke

Table 2. Associations Between Neuroimaging Markers and Early Neurological Deterioration

<table>
<thead>
<tr>
<th></th>
<th>Univariate Models</th>
<th>Multivariable Models*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR [95% CI]</td>
<td>P Value</td>
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<tr>
<td>Relevant artery stenosis</td>
<td>1.92 [1.17–3.14]</td>
<td>0.01</td>
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<tr>
<td>Branch atheromatous lesion</td>
<td>2.84 [1.75–4.62]</td>
<td>&lt;0.01</td>
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<tr>
<td>1</td>
<td>0.89 [0.49–1.59]</td>
<td>0.68</td>
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<tr>
<td>2</td>
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<td>0.67</td>
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<td>3</td>
<td>0.41 [0.13–1.25]</td>
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<tr>
<td>Old lacunar infarctions</td>
<td>1.14 [0.71–1.83]</td>
<td>0.54</td>
</tr>
<tr>
<td>Cerebral microbleeds</td>
<td>1.16 [0.69–1.94]</td>
<td>0.55</td>
</tr>
</tbody>
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BMI indicates body mass index; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*Multivariable models were adjusted for thrombolytic treatment, time delay from onset to hospital arrival, NIHSS score at admission, BMI, initial systolic blood pressure, age, and initial glucose.