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 microvasculopathies 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 (≥24 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 doublets; 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 neurological 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 SSSI 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.1 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...
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 mm Hg, or diastolic blood pressure >90 mm Hg 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).18-20 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 systematically 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).21,22 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.23 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.24 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.25 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.

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 artery stenosis (≤50% stenosis) at 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 220 (37.5%) 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 228 (41.9%) 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±1.3 points, which increased by 2.3±1.4 points after END. The time intervals 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, WML, 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,\(^5\) 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.\(^5,8,10–12,14,16,27–30\) From our research experience in collecting the acute complications of acute stroke cases,\(^21\) 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.\(^31\) However, evidence has accumulated indicating the potential contribution from atherosclerotic processes including the formation of a microatheroma or hemodynamic compromise of an infarction.\(^14,32\) Owing to the two distinct entities of lacunar infarction,\(^33\) SSSIs from atherosclerotic pathologies have been suggested to be larger in size and located in the proximal basal ganglia.\(^1,34\) 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.\(^35\) It could be hypothesized further that the atherothrombotic 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.\(^4,36\)

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.\(^37\)

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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This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI10C2020) and grant No. 02-2014-039 from the Seoul National University Bundang Hospital Research Fund.

Disclosures

None.

References

Diffusion- and perfusion-weighted imaging in acute lacunar infarction: is there a mismatch?


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背景および目的：早期神経学的悪化（END）は、単一皮質下小脳塞（SSSI）, 穿通枝領域の横断面の直径 ≤ 20 mm)の 20% 以上で発症しており、患者の機能回復を妨げている。微小血管病とアテレローム性動脈硬化症は、いずれも SSSI 患者の END 発症の独立した要因であるとされてきた。本研究では、SSSI 患者における END 発症は脳塞の病理的過程によって異なるという仮説を立てた。

方法：本研究では、4,961 症例の記録を含む前向きの脳塞中登録から、発症後 48 時間以内の SSSI 患者 587 例のデータを収集した。END に関する情報は不評価、強化、独立した評価者の関連性の関係（差異的共鳴血管撮影法で検出した近接動脈の 0 ～ 50% の狭索）、分枝アテロローム性病変（4 連続以上の立体断面または横断面からの進展）、白質高信号病変、陳旧性走行病変、および脳微小出血を含む神経画像的特性を評価した。

結果：END は 79 例（13.5%）で発症し、このうち 6 例は再発性脳塞（68 例は進行性脳塞中、1 例は症状性出頭性脳塞）である。END 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塞中スケール（National Institutes of Health Stroke Scale）スコアが 23 ± 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 カ月後の改善 Rankin Scale（mRS）スコアが 3 ～ 6 である頻度が高かった（49% 対 23%）。関連動脈の狭索（補正オッズ比 = 1.91, 95% 信頼区間（CI）1.13 ～ 3.21）および分枝アテロローム性病変（補正オッズ比 = 2.98, 95% CI : 1.80 ～ 4.93）を有する患者では、END を呈するオッズが有意に高かった。ただし、このような関連性は小血管疾患マーカーでは特定されなかった。

結論：本解析により、SSSI における局在性アテロローム硬化の形成が END の一因となっている可能性が示された。アテロローム硬化性病変が疑われる SSSI に対しては予防的措置を講じるべきであろう。

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개요
본 연구는 초기 신경학적 악화(early neurological deterioration, END)와 관련된 단일 피질경색(single small subcortical infarctions, SSSIs)의 발생 및 진행의 원인과 경로에 대한 이해를 높이기 위해 계획되었다.

정의
END는 발병 6주 내에 악화되어 발생한 뇌졸중의 예시로, 신경학적 악화를 나타내며, 이를 통해 뇌의 구조와 발전을 이해하는 데 도움이 된다.

연구 방법
본 연구는 2015년 3월부터 2016년 3월까지 12개월간의 지속시간 동안 진행되었다. 연구 대상자가 587명으로, 이 중 2893명이 SSSIs로 진단되었다. END의 발생과 진행은 각각의 영역별로 발생하여, 이를 통해 뇌의 구조와 발전을 이해하는 데 도움이 된다.

결과
END는 제발 6주 후, 악화 6주 후, 증상성 출혈변화 1주 후, 기타 1주 후, 원인에 따라 발생하여 79건(13.5%)에서 발생하였다. END는 NIHSS 점수를 2.3±1.4점 증가시키며, END가 발생한 환자들은 END 발생 전 낮은 낮았으나, END 발생 후의 환자들은 3개월 후 mRS 3~6점의 인도가 높았다(49.2±23.3). 연관된 관협 혈관(보기 OR, 1.91; 95% CI, 1.13~3.21)과 분지혈관의 증증성 혈관(보기 OR, 2.98; 95% CI, 1.30~4.93)이 있는 환자들은 END를 나타내는 대상임. maRk가 유의하게 높았다. 하지만, 이러한 관협성은 다른 혈관 질환(small vessel disease) 인자들에게는 나타나지 않았다.

결론
이 연구의 본격은 국소적 동맥경화 과정이 SSSIs에서 END에 임해적으로 기여하는 것을 보여주었다. 동맥경화 병변이 의심되는 SSSIs에서는 예방책들이 사용될 수 있을 것이다.

Table 2. Associations Between Neuroimaging Markers and Early Neurological Deterioration

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<tr>
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<td>Adjusted OR [95% CI]</td>
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<tr>
<td>Cerebral microbleeds</td>
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<td>0.55</td>
</tr>
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</table>

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.