Causes, Risk Factors, and Clinical Outcomes of Stroke in Korean Young Adults: Systemic Lupus Erythematosus is Associated with Unfavorable Outcomes

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Background and Purpose The incidence of ischemic stroke (IS) in young adults is increasing, and the associated large socioeconomic impact makes understanding IS in young adults important. We investigated the causes of and risk factors for IS in young adults, and their impact on outcomes.

Methods The Stroke in Korean Young Adults (SKY) study is a standardized multicenter prospective study involving eight medical centers of the Republic of Korea. First-ever IS patients aged 18 years to 44 years were prospectively included in this study within 7 days of stroke onset. Their outcomes at 3 months were analyzed.

Results This study enrolled 270 patients from April 2014 to December 2018, most (67.8%) of whom were male. About 41.5% of the patients had one or more vascular risk factors from among hypertension, diabetes mellitus, and dyslipidemia. However, only half of them had received regular treatment. Arterial dissection was more common in males, and systemic lupus erythematosus (SLE) and Moyamoya disease were more common in females. The outcome was favorable (modified Rankin Scale score of 0 or 1) in 81.9% of the patients at 3 months after stroke onset. More severe initial symptoms, higher initial glucose level, and SLE as a comorbidity were associated with unfavorable outcomes.

Conclusions Young adult IS patients in Korea exhibit low awareness and poor management of their risk factors. Although the short-term outcome was relatively favorable in those patients, having SLE was associated with unfavorable outcomes. More attention needs to be paid for improving awareness and controlling risk factors in this population.

Key Words ischemic stroke, young adults, outcome, systemic lupus erythematosus.

INTRODUCTION

The incidence of ischemic stroke (IS) in young adults is increasing substantially worldwide. Since young adults have long lifespans ahead of them and are productive members of the labor force, knowledge about IS in young adults deserves more attention. However, investigating the causes of and risk factors for stroke in young adults is often challenging. Current guidelines provide limited information on the clinical management of stroke in young adults. In addition, most studies involving young stroke victims have had retrospective designs and been limited by missing data, nonstandardized evaluations, and high dropout rates during follow-up.

The prevalence of traditional vascular risk factors is increasing in young adult patients with IS, and their origins differ from those of older adults. IS in young adults is associated with arterial dissection, Moyamoya disease (MMD), primary and secondary central ner-
vous system vasculitis, antiphospholipid syndrome (APS), reversible cerebral vasoconstriction syndrome (RCVS), cerebral venous thrombosis (CVT), and genetic diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and Fabry disease. However, the causes of 15–35% of the strokes in young adults are still unidentified. In addition, the connection between these etiological factors and stroke outcomes remains unclear.

The Stroke in Korean Young Adults (SKY) study aimed to evaluate the traditional and emerging risk factors for stroke in young adults. We also investigated the etiologies, treatments, and outcomes of stroke in these patients.

**METHODS**

**Study design and diagnostic workup**

The SKY study is a standardized multicenter prospective study performed in eight medical centers in the Republic of Korea. Details of the rationale and design of this study have been reported previously. From April 2014 to December 2018, 270 patients with first-ever IS visited the Department of Neurology, and those aged 18 years to 44 years were consecutively enrolled as case subjects. We intended to include 470 case subjects and 470 age- and sex-matched community control subjects. However, we stopped adding patients after enrolling 270 case subjects because an interim analysis of the association between job strain and IS produced somewhat positive results.

Demographic data were collected, and brain imaging, cardiac evaluations, and laboratory studies were performed as described previously. For the cardiac evaluations, all of the available patients underwent 24-hour Holter monitoring, transthoracic echocardiography, and transesophageal echocardiography. We sought to identify well-supported risk factors and uncommon etiologies among the young patients with IS. In addition, the acute management and 3-month outcomes of acute IS were investigated. The study was approved by the ethics committee at each participating center, and is registered at clinicaltrials.gov under the number NCT02682914.

**Stroke classification, definition of other etiologies, and follow-up**

The IS subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. The classification was reviewed independently by two neurologists, and a consensus approach was applied if there were discrepancies. Stroke in a patient with both high- and moderate-risk cardiac sources of embolism and no other cause of stroke was considered a case of cardioembolic stroke.

Arterial dissection was diagnosed by angiography if there was a double lumen, intramural hematoma, nonatherosclerotic tapered, flame-shaped stenosis/occlusion or pearl-and-string sign, or a dissecting aneurysm at a nonbranching site. MMD was diagnosed if there was chronic, occlusive cerebrovascular disease with Moyamoya vessels. Systemic lupus erythematosus (SLE) was diagnosed according to the classification criteria of the Systemic Lupus International Collaborating Clinics group, and was regarded as the culprit etiology when an event was not assigned to a conventional stroke etiology. The updated Sapporo classification criteria were used for APS. RCVS was characterized by thunderclap headaches and diffuse segmental constriction of the cerebral arteries that resolved within 3 months. If a thrombus in a venous sinus was detected by magnetic resonance or computed tomography venography in clinically suspected patients, CVT was diagnosed.

Two patients died, and the remaining 268 of the 270 patients were followed up to 3 months in the outpatient clinic of each hospital. Modified Rankin Scale (mRS) scores were obtained at 3 months.

**Statistical analysis**

Mean±SD values were calculated for continuous variables, and numbers with percentages were calculated for discrete variables. We used Student’s t-tests, the chi-square test, and the Mann-Whitney U test to evaluate differences between groups. Correlations between clinical characteristics and a favorable outcome (mRS score of 0 or 1) were measured by logistic regression analysis, adjusting covariates for which p<0.2 in the univariate analysis. The adjusted variables were the initial National Institutes of Health Stroke Scale (NIHSS) score, a patent foramen ovale (PFO), SLE, RCVS, white-blood-cell count, and blood urea nitrogen, fasting glucose, and fibrinogen levels.

**RESULTS**

**Demographic data and risk factors**

The 270 enrolled patients were aged 37.1±6.3 years, of which 183 were males. The median NIHSS score was 2 [interquartile range (IQR)=0–4] at admission and 1 (IQR=0–2) at discharge. At discharge, 30.0% of the patients had hypertension, 12.2% had diabetes mellitus (DM), and 17.4% had dyslipidemia. However, the risk factors had been known and treated regularly for only half of the patients. In addition, 47.8% of them were current smokers and 17.8% were obese [body mass index (BMI) ≥30.0 kg/m²].

The baseline characteristics including demographic data and risk factors are presented in Table 1. The males were significantly older than the females (mean age=37.9 years vs. 35.4 years, p=0.002) and they had significantly higher rates of hy-
pertension ($p=0.021$) and current smoking ($p<0.001$), and a higher BMI ($p<0.001$). There were no other sex-related differences.

### Subtypes of ischemic stroke and other determined etiologies

The IS subtypes according to the TOAST classification are

| Table 1. Baseline characteristics including classification of ischemic stroke in the study patients |
|-----------------------------------------------|
| Demographics                                  |
| Total (n=270)  | Males (n=183)  | Females (n=87)  | p     |
| Age, years | 37.1±6.3 | 37.9±5.8 | 35.4±7.0 | 0.002 |
| Risk factor                                   |
| Hypertension (p=0.021) | 63 (34.4) | 18 (20.7) | 0.021 |
| Diabetes mellitus (p=0.065) | 27 (14.8) | 6 (6.9) |
| Dyslipidemia (p=0.280) | 35 (19.1) | 12 (13.8) |
| Current smoking (p<0.001) | 19 (21.8) |
| Atrial fibrillation (p=0.087) | 2 (1.1) | 4 (4.6) |
| Coronary artery disease (p=1.000) | 1 (1.1) |
| PFO (p=0.784) | 15 (8.2) | 8 (9.2) |
| Chronic kidney disease (p=0.183) | 5 (2.7) | 6 (6.9) |
| BMI, kg/m² (p<0.001) | 26.3±4.4 | 23.8±5.7 |
| Obesity (p=0.617) | 34 (18.6) | 14 (16.1) |
| Medication history                            |
| Antihypertensives (p=0.186) | 35 (19.1) | 11 (12.6) |
| Antidiabetes (p=0.641) | 10 (5.5) | 6 (6.9) |
| Statins (p=0.490) | 22 (12.0) | 8 (9.2) |
| Stroke subtype (p=0.065)                      |
| Large-artery disease (p=0.021) | 35 (19.1) | 7 (8.0) |
| Small-vessel occlusion (p=0.126) | 20 (10.9) | 14 (16.1) |
| Cardioembolism* (p=0.087) | 2 (1.1) | 0 (0.0) |
| Undetermined, two or more (p=1.000) | 33 (18.0) | 22 (25.3) |
| Undetermined, negative (p=0.002) | 1 (0.5) | 0 (0.0) |
| Other determined (p=0.490) | 55 (30.1) | 31 (35.6) |
| Dissection (p=0.112) | 30 (16.4) | 8 (9.2) |
| SLE† (p<0.001) | 1 (0.5) | 9 (10.3) |
| Moyamoya disease (p=0.002) | 2 (1.1) | 8 (9.2) |
| APS without SLE (p=0.443) | 7 (3.8) | 1 (1.1) |
| Cerebral venous thrombosis (p=0.391) | 3 (1.6) | 3 (3.4) |
| RCVS (p=1.000) | 3 (1.6) | 1 (1.1) |
| CADASIL (p=1.000) | 2 (1.1) | 0 (0.0) |
| Primary angiitis of CNS (p=1.000) | 2 (1.1) | 0 (0.0) |
| Thrombosed aneurysm (p=1.000) | 2 (1.1) | 0 (0.0) |
| Others‡ (p=1.000) | 3 (1.6) | 3 (1.6) |
| Lesion location (p=0.469)                     |
| Anterior circulation (p=0.001) | 95 (52) | 52 (60) |
| Posterior circulation (p=0.001) | 45 (25) | 33 (38) |
| Combined (p=0.001) | 3 (2) |
| Initial NIHSS score (p=0.908) | 1 (–4) | 2 (0–4) |

Data are mean±SD, median (interquartile range), or n (%). Obesity was defined as BMI ≥30.0 kg/m². Pearson’s chi-square test, Student’s t-test, Fisher’s exact test, and the Mann-Whitney U test were used as appropriate.

*One patient had both SLE and dilated cardiomyopathy, if both SLE and APS were present, SLE was considered the etiology, Others include radiation-induced angiopathy, hyperhomocysteinemia, Fabry disease, aortic aneurysma, hyperesinophilic syndrome, and calcium pyrophosphate deposition. APS: antiphospholipid syndrome, BMI: body mass index, CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CNS: central nervous system, NIHSS: National Institutes of Health Stroke Scale, PFO: patent foramen ovale, RCVS: reversible cerebral vasoconstriction syndrome, SLE: systemic lupus erythematosus.
Clinical outcomes and factors associated with unfavorable outcomes

The characteristics of patients according to favorable and unfavorable outcomes at 3 months are presented in Table 2. Patients with an unfavorable outcome had a higher initial NIHSS score, SLE and higher white-blood-cell count. Intravenous thrombolysis (IVT) and/or intra-arterial thrombectomy (IAT) were applied to 24 patients (8.9%). Early neurological improvement (NIHSS score of 0 to 1 or improvement of ≥8 at discharge) occurred in 56% of those who received IVT alone and in 73% of those who received IAT with or without IVT. However, the proportion of patients receiving IAT or IVT did not differ between the two subgroups (Table 2).

During the 3-month follow-up there were five (1.8%) stroke events (four IS and one hemorrhagic stroke), and two (0.7%) patients died. There were no myocardial infarction events, and post-stroke seizure occurred in four (1.4%) patients. At 3 months after stroke onset, 81.9% of the patients (213 of 260) had a favorable outcome (mRS score of 0 or 1), while more than 90.4% of them had an mRS score of ≤2 (Fig. 1). After adjusting for potential confounding variables, higher initial NIHSS score, higher initial glucose level, and having SLE were associated with an unfavorable outcome (Table 3).

**DISCUSSION**

This study found relatively favorable outcomes in young-adult IS patients. More than 80% and 90% of the included patients had mRS scores of ≤1 and ≤2, respectively, at 3 months after stroke onset. This proportion was much higher than in patients of all ages, 50% of whom reportedly had an mRS score of 0 or 1 at 3 months. An unfavorable outcome was associated with higher initial NIHSS score, higher initial glucose level, and SLE as comorbidity. IS was more common in males than females (67.8% vs 32.2%). About 41.5% of the patients had one or more of the vascular risk factors among hypertension, DM, and dyslipidemia, but only half of them had been aware of their risk factors and received regular treatment. We consider that neglect of these risk factors could be an important cause of IS in young patients.

Poststroke mortality occurred in only two (0.7%) patients during the 3-month follow-up, and five (1.8%) patients suffered recurrent stroke. These outcomes are more favorable than in previous reports. In a Swiss prospective study involving 624 IS patients, 61% and 85% had mRS scores of ≤1 and ≤2, respectively. In a French study, mRS scores of ≤2 were present in 87% of 287 young adults with IS after 3 years of follow-up. The higher rate of favorable outcomes in our study may have been due to improved stroke treatments including the use of mechanical thrombectomy. Fourteen of the 15 patients who received IAT showed recanalization more than Thrombolysis in Cerebral Infarction (TICI) grade 2b, and 11 patients showed early neurological improvement. The patients who benefited from IAT may have shifted from poor outcome patients to favorable-outcome patients. Thus, investigating the IAT outcomes of young IS patients would be useful.

Our detailed and standardized evaluation of the etiologies of stroke in young adults classified 31.9% of the patients as other determined etiologies. Arterial dissection was more common in males, and SLE and MMD were more common in females. Having SLE was associated with poor outcome.

According to our results, the initial NIHSS scores did not differ between patients with and without SLE (median=2 vs. 2, IQR=1–6 vs. 0–4; p=0.393). However, SLE was associated with poor functional outcome at 3 months after stroke onset. We can therefore speculate that cerebrovascular inflammation due to autoantibodies leads to poor recovery after IS. In addition, inflammation may damage diverse other organs such as the kidneys, lungs, and heart, and lead to poor stroke outcome. In contrast to our results, there are previous reports of outcomes being similar in patients with and without SLE after stroke onset. However, those studies had retrospective designs, included all age groups, and had low proportions of patients with SLE (0.2–0.3%). Our study included only young adult patients, and had a much higher proportion of SLE patients (4.1%). Although SLE itself could not be an independent risk factor for IS, we believe that having SLE may be a poor prognostic factor for IS in young patients,

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and so more careful management may be called for.

We found that a higher initial glucose level was independently associated with poor outcome. This is consistent with previous studies showing an association between hyperglycemia on admission and a worse clinical outcome of IS.\textsuperscript{18,19} The release of catecholamine and inflammatory cytokines

Table 2. Baseline characteristics of patients with favorable and unfavorable outcomes at 3 months

| Demographics                      | mRS score=0 or 1 at 3 months | p     |
|-----------------------------------|------------------------------|-------|
|                                    | Yes (n=213)                  | No (n=57) |   |
| Age, years                        | 37.2±6.3                     | 36.8±6.3 | 0.636  |
| Sex, male                         | 146 (69)                     | 37 (65) | 0.602* |
| Risk factor                        |                              |        |       |
| Hypertension                      | 60 (28)                      | 21 (37) | 0.204* |
| Diabetes mellitus                 | 24 (11)                      | 9 (16)  | 0.355* |
| Dyslipidemia                      | 37 (17)                      | 10 (18) | 0.976* |
| Current smoking                   | 99 (47)                      | 30 (53) | 0.409* |
| Atrial fibrillation               | 4 (2)                        | 2 (4)   | 0.610* |
| Coronary heart disease            | 4 (2)                        | 0 (0)   | 0.582* |
| PFO                               | 22 (10)                      | 1 (2)   | 0.059* |
| Chronic kidney disease            | 7 (3)                        | 4 (7)   | 0.252* |
| Body mass index, kg/m\(^2\)       | 25.5±4.8                     | 25.4±5.7 | 0.899 |
| Clinical findings                 |                              |        |       |
| Initial NIHSS score               | 1 (0–3)                      | 4 (2–8) | <0.001\(^1\) |
| Initial SBP, mm Hg                | 147.2±32.7                   | 150.5±27.3 | 0.484 |
| Initial DBP, mm Hg                | 88.2±19.9                    | 91.0±19.3 | 0.339 |
| Other etiologies                  |                              |        |       |
| Dissection                        | 31 (15)                      | 7 (13)  | 0.661* |
| SLE                               | 6 (3)                        | 5 (9)   | 0.043* |
| APS without SLE                   | 7 (3)                        | 1 (2)   | 1.000* |
| Cerebral venous thrombosis        | 6 (3)                        | 0 (0)   | 0.348* |
| RCVS                              | 2 (1)                        | 2 (4)   | 0.197* |
| Laboratory findings               |                              |        |       |
| White-blood-cell count, 10\(^7\)/mm\(^3\) | 8.5±2.8                     | 9.5±3.1 | 0.030  |
| Hemoglobin, g/dL                  | 14.7±2.0                     | 14.3±2.0 | 0.191  |
| Blood urea nitrogen, mg/dL        | 13.4±5.8                     | 15.4±10.8 | 0.196  |
| Creatinine, mg/dL                 | 0.9±1.0                      | 0.9±0.8 | 0.881  |
| Total cholesterol, mg/dL          | 188.3±45.4                   | 185.7±63.9 | 0.727  |
| Low-density lipoprotein, mg/dL    | 115.8±38.8                   | 110.6±40.6 | 0.373  |
| Glucose, mg/dL                    | 118.7±44.3                   | 133.0±73.1 | 0.187  |
| Hemoglobin A\(1c\), %             | 5.9±1.5                      | 6.1±1.6 | 0.335  |
| C-reactive protein, mg/dL         | 1.1±2.5                      | 2.0±5.3 | 0.208  |
| Erythrocyte sedimentation rate, mm/hour | 14.5±18.1                   | 16.8±19.4 | 0.387  |
| Homocysteine, mmol/L              | 10.3±5.7                     | 10.7±6.7 | 0.709  |
| Fibrinogen, mg/dL                 | 323.0±101.1                  | 355.2±153.7 | 0.069  |
| Thyroid-stimulating hormone, mIU/mL | 2.2±5.7                     | 2.5±8.2 | 0.814  |
| Acute management                  |                              |        |       |
| IVT only                          | 6 (2.8)                      | 3 (5.3) | 0.290* |
| IAT with/without IVT              | 11 (5.2)                     | 4 (7.0) | 0.393* |

Data are mean±SD, median (interquartile range), or n (%). Student’s t-test was used except where indicated otherwise.

\(^*\)Pearson’s chi-square test, \(^*\)Mann-Whitney U test, \(^*\)Fisher’s exact test.

APS: antiphospholipid syndrome, DBP: diastolic blood pressure, IAT: intra-arterial thrombectomy, IVT: intravenous thrombolysis, mRS: modified Rankin scale, NIHSS: National Institutes of Health Stroke Scale, PFO: patent foramen ovale, RCVS: reversible cerebral vasoconstriction syndrome, SBP: systolic blood pressure, SLE: systemic lupus erythematosus.
after IS might increase the glucose level, and an elevated glucose level can exacerbate ischemic brain injury by enhancing edema, diminishing vascular reactivity, promoting disruption of the blood–brain barrier, and provoking lactic acidosis and the production of free radicals.

Previous Korean studies had a male preponderance, as in our study. Higher prevalence rates of hypertension and smoking and a higher BMI in males seem to be the reasons for this difference. A previous multicenter study of IS in young Korean adults (aged between 15 and 45 years) from 2007 to 2010 found hypertension in 18.0%, DM in 7.8%, and dyslipidemia in 2.6% of the enrolled patients. Since the diagnostic criteria for risk factors were not described in detail in that report, direct comparisons might not be justified. However, most of the risk factors including HTN, DM, dyslipidemia, and BMI (mean: 24.1 kg/m²→25.5 kg/m²) appear to have increased in frequency. In our study, the rates of traditional risk factors were increasing but the awareness and treatment rates were relatively low, which might increase the incidence of stroke. Sustained efforts are required to improve the awareness and treatment of traditional vascular risk factors.

This study was subject to some limitations. First, we enrolled patients from a single ethnic group (Korean) and observed them for only 3 months. However, the study data might be applicable at least to all Asians, and ongoing follow-up may provide further significant results. Second, we only included IS patients. However, information about this single group is also meaningful. Third, mostly metropolitan centers were included in this study, and lifestyle and risk factors may differ between rural and urban areas. However, young adults tend to live in cities and we believe that the data for the total population of young patients would not differ greatly. Fourth, since SLE was diagnosed in only 4.1% of the participants and this condition is accompanied by many systemic problems, caution is needed when interpreting the results. Finally, excluding patients with recurrent stroke and those admitted to departments other than neurology due to a need for surgery or the presence of severe trauma may have been responsible for the relatively good prognoses in our study.

In conclusion, the findings of this study emphasize the importance of improving the awareness and prevention of traditional vascular risk factors for IS in young adults, including...
hypertension, DM, dyslipidemia, smoking, and obesity. Although the outcomes tended to be favorable with a good response to thrombolysis, SLE was associated with poor functional outcome.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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