Prevalence and Risk Factors of Silent Cerebral Infarction in Apparently Normal Adults


Abstract—Cerebrovascular disease is a major cause of death and disability in adults. Silent cerebral infarction (SCI) portends more severe cerebral infarctions or may lead to insidious progressive brain damage resulting in vascular dementia. This study was designed to evaluate the prevalence and risk factors of SCI in an apparently normal adult population. Nine hundred ninety-four consecutive symptom-free adults (mean age 49.0 ± 7.7; men:women 830:164) who underwent brain magnetic resonance imaging at the Center for Health Promotion at Samsung Medical Center were assessed. All were neurologically normal in history and physical examination. A total of 121 SCI lesions was observed in 58 subjects. The lesion prevalence adjusted for patient age was 5.1%. There was no gender difference in prevalence. Ninety-nine lesions were <1 cm in diameter, 15 were between 1 and 2 cm, 3 were between 2 and 3 cm, and 4 were >3 cm in diameter. The most frequent site of the SCI lesion was basal ganglia, after which the periventricular white matter, cerebral cortex, and thalamus were the most frequent sites. Old age, hypertension, a history of coronary artery disease, evidence of cardiomegaly in chest radiographs, and high fasting glucose/hemoglobin A1c levels were associated with SCI on univariate analysis. Multivariate analysis demonstrated old age and hypertension to be independent risk factors for SCI, and mild alcohol consumption was revealed as an independent protective factor against SCI. (Hypertension. 2000;36:73-77.)

Key Words: cerebral infarction • risk factors • hypertension, essential • elderly • alcohol

Silent cerebral infarction (SCI) is defined as a brain lesion that is presumably a result of vascular occlusion found incidentally by magnetic resonance imaging (MRI) or computed tomography (CT) in otherwise healthy subjects or during autopsy.1–3 It is considered a precursor of symptomatic stroke patients, that prevalence ranged from 10% to 38%.4,5 A comprehensive study of SCI in a relatively large population of normal subjects,6 and in a study on a large number of elderly subjects, the prevalence was 33% in patients ≥65 years.7 Because such variance in study subjects has led to different conclusions in regard to the prevalence and risk factors of SCI,8–10 we attempted to present a more comprehensive study of SCI in a relatively large population of apparently normal adults of all ages.

Methods

Subjects
We studied 994 healthy consecutive subjects who visited the Center for Health Promotion at Samsung Medical Center, Seoul, Korea, from September 1994 through October 1996 and who underwent MRI of the brain as part of their routine health check. Their age ranged from 20 to 78 years; 54 subjects were <40 years, 572 subjects were between 40 and 49 years, 271 subjects were between 50 and 59 years, 81 subjects were between 60 and 69 years, and 16 subjects were between 70 and 79 years. The mean age of the subjects, who consisted of 830 men and 164 women, was 49.1 years. Clinical information was gathered by means of a personal interview and a physical examination performed by physicians at the Center for Health Promotion. The term “healthy” was defined as having no symptoms or signs of neurological manifestations before and at the time of study enrollment, and all of our subjects satisfied that criterion. All of the patients gave informed consent, and the study was approved by Samsung Biomedical Research Institute, Seoul, Korea.

Clinical and Laboratory Data
Data on body mass index, history of hypertension, smoking, diabetes mellitus, history of coronary artery disease, family history of cardiovascular disease, and frequency of alcohol consumption were obtained by means of a personal interview and a physical examination. Obesity was defined as having a body mass index of >25 kg/m². Blood pressure was measured with no knowledge of history of hypertension. A family history of cardiovascular disease included a history of stroke, coronary artery disease, hypertension, or sudden cardiac death. Alcohol consumption was graded by current drinking frequency in 3 categories: nondrinkers; mild drinkers, alcohol

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consumption 1 to 2 times per week; and frequent drinkers, alcohol consumption ≥3 times per week. Data regarding smoking history was divided into 3 categories: nonsmokers; past smokers, defined as subjects who quit smoking ≥1 year before enrolling in the study; and current smokers. Laboratory data evaluated in the study were as follows: evidence of cardiomegaly on chest radiograph (cardiothoracic ratio ≥50%); left ventricular hypertrophy and atrial fibrillation on ECG; and serum creatinine, fasting blood glucose, hemoglobin (Hb) A1c, total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol levels.

Definition and Evaluation of SCI Lesions
MRI was performed with a 1.5 Tesla MRI unit (Signa, General Electric Co). SCI lesions were defined as high-intensity areas identified on a T2-weighted image coinciding with low-intensity areas on a T1-weighted image. MRI images were evaluated independently by a neuroradiologist and a neurologist who were both blinded from the clinical and laboratory data of the subjects. The Kappa value of agreement was 0.91, and the final diagnosis of SCI was made by consensus. The subjects were divided into 2 groups: those with SCI lesions (the SCI group) and those without any lesions (the non-SCI group).

Statistical Analysis
The age-standardized prevalence rate (ASR) for SCI was estimated with the formula of
\[ \text{ASR} = \frac{\text{Prevalence in age group } i \times \text{Population of age group } i}{\text{Total population}} \]
The variance of the ASR was estimated with the formula of
\[ \text{Variance of ASR} = \frac{\text{Prevalence in age group } i \times \text{Population of age group } i}{\text{Total population}^2} \]
Variance of the ASR was adjusted for the population structure of Korea in 1996. Multivariate analysis was performed separately in each gender group. None of the subjects <40 years of age exhibited SCI lesions.

Performing analysis of risk factors was performed separately in each gender group. None of the subjects <40 years of age exhibited SCI lesions. Of the total 121 lesions, the vast majority (99) were <1 cm in diameter. Among the lesions >1 cm in diameter, there were 15 lesions that ranged in size from 1 to 2 cm, 3 lesions from 2 to 3 cm, and 4 lesions >3 cm in diameter. Forty-six lesions were found in the basal ganglia, 31 in the periventricular white matter, 18 in the cerebral cortex, 15 in the thalamus, 11 in thepons, and 5 in the cerebellum. Thirty subjects had lesions in the left hemisphere only, 14 had lesions in the right only, and the remaining 14 subjects had bilateral SCI lesions.

Univariate Analysis of Risk Factors
Clinical characteristics of the subjects were assessed individually by univariate analysis. Table 2 shows the clinical characteristics of our study population. A history of hypertension was observed in 42.9% of the SCI group and in 9.9% of the non-SCI group, and the difference between the 2 groups was statistically significant (P<0.01; OR 6.86; 95%
CI 3.87, 12.16). There was also a significant excess in the number of subjects with systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg in the SCI group (63.8% versus 27.1%, \( P<0.01 \)), regardless of the history of hypertension.

A history of coronary artery disease was also a risk factor for SCI on univariate analysis (7.1% versus 1.8%; OR 4.31; 95% CI 1.39, 13.36). There were no significant differences among the SCI group and the non-SCI group with regard to a history of smoking or diabetes mellitus or a family history of cardiovascular diseases. Also, the proportion of subjects with obesity was not significantly different between the 2 groups.

Alcohol consumption was significantly lower in the SCI group (54.0% versus 74.2%, \( P<0.01 \)). Further analysis was performed with regard to these data. In the SCI group, the proportions of subjects in the nondrinker, mild drinker, or frequent drinker group were 46.0%, 22.0%, or 32.0%, respectively, and in the non-SCI group, those proportions were 25.7%, 52.1%, and 22.2%. Nondrinkers were more frequently observed in the SCI group and mild drinkers less frequently observed in the SCI group than in the non-SCI group (\( P<0.01 \)). These data were further assessed with regard to age. In the group with subjects whose age was <50 years, the proportions of nondrinkers, mild drinkers, and frequent drinkers were 33.3%, 11.1%, and 55.6%, respectively, in the SCI group and 19.4%, 58.5%, and 22.1% in the non-SCI group. This indicates a significant excess of mild drinkers in the non-SCI group compared with that number in the SCI group (\( P<0.01 \)). However, in the group with subjects whose age >50 years, the same proportions were 48.8%, 24.4%, and 26.8%, respectively, in the SCI group and 38.4%, 39.5%, and 22.1% in the non-SCI group. This indicates no significant difference in the frequency of drinking between the 2 groups.

Laboratory data of our subjects are also shown in Table 2.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.13</td>
<td>1.09–1.18</td>
</tr>
<tr>
<td>Gender</td>
<td>2.04</td>
<td>0.74–5.64</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.47</td>
<td>1.71–7.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.89</td>
<td>0.51–7.00</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.08</td>
<td>0.97–4.47</td>
</tr>
<tr>
<td>Past smoking</td>
<td>0.45</td>
<td>0.09–2.26</td>
</tr>
<tr>
<td>CAD</td>
<td>2.22</td>
<td>0.53–9.34</td>
</tr>
<tr>
<td>FHx</td>
<td>1.02</td>
<td>0.51–2.04</td>
</tr>
<tr>
<td>Mild alcohol consumption</td>
<td>0.31</td>
<td>0.12–0.78</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.00</td>
<td>0.49–2.03</td>
</tr>
<tr>
<td>Cardiomegaly on chest radiograph</td>
<td>2.52</td>
<td>0.64–9.95</td>
</tr>
<tr>
<td>High plasma total cholesterol</td>
<td>1.07</td>
<td>0.45–2.56</td>
</tr>
</tbody>
</table>

All variables included in the multiple logistic analysis are listed. CAD indicates history of coronary artery disease; FHx, family history of cardiovascular disease.

TABLE 3 Multivariate Analysis of Risk Factors by Multiple Logistic Regression

Fasting plasma glucose and hemoglobin A1c levels were significantly higher in the SCI group (104.3±34.2 versus 91.9±26.7 and 6.0±1.2 versus 5.6±0.8, respectively, \( P<0.05 \) for both values). No other laboratory data demonstrated any significant difference between the 2 groups.

Multivariate Analysis of Risk Factors

In the analysis of independent risk factors for SCI (Table 3), age and a history of hypertension were significantly associated with SCI (\( P<0.01 \) in all). A history of mild alcohol consumption was independently associated with a low risk for SCI (\( P<0.01 \)). The analysis was performed again after the study subjects had been divided into 2 groups according to age. In the relatively younger group (those who <50 years), a history of hypertension was the only significant independent risk factor, and mild alcohol consumption was a significant protective factor (\( P<0.01 \) in both). However, in the group ≥50 years, age and hypertension were significant independent risk factors of SCI (\( P<0.01 \)), but there was no association of mild alcohol consumption with SCI lesions.

Discussion

SCI is usually considered to be a precursor of symptomatic stroke or insidious brain damage,1–3 and from a public health standpoint, it seems important to evaluate its prevalence and risk factors in the general population. To the best of our knowledge, this study is the first to address these issues on a large scale in healthy adults with a wide range in age. Our study demonstrates that the age-adjusted prevalence of SCI in apparently normal Korean adults is 5.1% and that the prevalence increases with age.

There have been a few previous reports on the prevalence of SCI among neurologically normal subjects. In a population-based autopsy study2 and in another study6 that focused primarily on the relationship of SCI with cerebral blood flow, the prevalence of SCI was reported to be ~13%. In a report on lacunar infarcts in a large group of elderly subjects who were ≥65 years of age, the prevalence was 23%,12 but that report included subjects with a history of transient ischemic attack or stroke and cannot be a true estimate of the prevalence of clinically “silent” brain lesions. There have been a number of large-scale studies on asymptomatic white matter brain lesions,13–17 sometimes noted as leukoaraiosis.18,19 However, unlike the lesions in our study, the lesions in those studies produced high signals on T2-weighted images only, and did not consider the morphology in T1-weighted images. These lesions cannot all be considered true infarct lesions, and their clinical significance has yet to be clearly defined.
study population. In a report dealing with a large number of elderly subjects in the United States, the prevalence of SCI has been reported to be 33\% in those $\geq 65$ years,\textsuperscript{7} which resembles the results of our study that indicate a prevalence of 29.1\% among the same age population. A recent report\textsuperscript{20} on the prevalence of SCI in adults that range in age from 55 to 70 indicates that the prevalence in that particular elderly population is 11\%. This is a lower estimate than those of previous reports concerning the elderly population, and it also differs from the prevalence in the same age group (17.8\%) in our report. The difference may have resulted from differences in the definition of the SCI lesions, for in the other study cited, the criteria limited the SCI lesions to those in the cerebrum and the brain stem only, which probably excludes intracerebellar lesions, which we chose to include in our report. Also, the variance of results from relatively old reports may have been associated with improvements in technology in the detection of intracranial lesions. The use of MRI, which is a more sensitive measure of detecting the lesions than CT, and the improvement of CT resolution over time are the most important technical developments that account for the improvement.

In most previous reports, no difference in clinical manifestations was found in patients with SCI and those without.\textsuperscript{10} However, Krishnan et al\textsuperscript{21} reported that deep white matter lesions were more common in subjects with senile depression than in control subjects. Fujikawa et al\textsuperscript{22} reported that SCI could be identified in 66\% of patients with presenile-onset depression and in 94\% of patients with senile-onset depression, which suggests an association between SCI and the development of depression. Matsubayashi et al\textsuperscript{23} reported an association of neurologically silent periventricular white matter lesions in subjects with neuropsychological dysfunction.

As shown in our study, the clinical “silence” of SCI lesions may be related to their location. The lesions are most frequently found in the basal ganglia\textsuperscript{9} and periventricular white matter, which are not major areas that govern motor and sensory functions, but rather sites associated with coordination and the relay of signals through parts of the brain. However, the presence of cortical lesions and large lesions of $>3$ to 4 cm in diameter in subjects without noticeable neurological deficits still awaits elucidation.

Age and a history of hypertension have been the most consistently observed risk factors for SCI in most of the studies dealing with normal subjects.\textsuperscript{1,6,7,24–26} A low plasma HDL-cholesterol level and a high degree of blood viscosity have also been reported as possible risk factors in studies dealing with hypertensive subjects.\textsuperscript{25,26} Risk factors for SCI in studies on symptomatic stroke patients have been more variable. Age was the most consistent risk factor,\textsuperscript{7–10} and other risk factors included hypertension,\textsuperscript{5,10} male gender,\textsuperscript{5,9,10} glucose intolerance,\textsuperscript{4} ischemic changes on ECG,\textsuperscript{5} and left atrial enlargement.\textsuperscript{9} In our study, independent risk factors of SCI were an increase in age and a history of hypertension, which are in accord with most of the previously described small-scale studies. A history of coronary artery disease, cardiomegaly on chest radiographs, and high levels of blood hemoglobin A1c and fasting plasma glucose may summon a certain interest as being potential risk factors for SCI, because those characteristics were identified as risk factors on univariate analysis.

Mild alcohol consumption (1 to 2 times per week) was an independent protective factor against SCI in both univariate and multivariate analyses, and abstinence from alcohol or frequent alcohol drinking were both not associated with the risk of SCI. The explanation for this result is unclear. However, it may be in line with a long list of previous studies on the incidence of ischemic stroke and cardiac mortality rates associated with drinking.\textsuperscript{27,28} A lower risk of ischemic stroke was observed in moderate drinkers when compared with that risk in nondrinkers or heavy drinkers,\textsuperscript{27} and there was a U-shaped curve phenomenon in the mortality rate produced by coronary artery disease associated with alcohol consumption.\textsuperscript{28} Large-scale observational studies\textsuperscript{29–31} also demonstrated a lower incidence of coronary artery disease and cardiovascular and overall mortality in moderate alcohol consumers among hypertensive subjects and the general population. This has been partially ascribed to the fact that mild-to-moderate alcohol consumption increases the plasma HDL-cholesterol level and especially the levels of HDL-2 and HDL-3 subfractions.\textsuperscript{27,31–33} However, in this study, there was no significant correlation between the frequency of alcohol consumption and the blood HDL-cholesterol level. There is also a possibility that alcohol may exert some influence through the coagulation system, but there was no significant correlation between the blood fibrinogen level and the frequency of alcohol consumption in this study. In our study, the protective effect of mild alcohol consumption was abolished in the group whose age was $>50$ years, which suggests that the increment of the risk of SCI with age overrides the effect of alcohol consumption on the risk of SCI.

This study has some limitations. Our population, though consecutive, was recruited from subjects who visited our Center for Health Promotion for the purpose of checking their general health status, and therefore we might have dealt with a population overly concerned about their health. Furthermore, because we dealt with volunteers who were willing to pay for the MRI study, which is relatively expensive, the socioeconomic status of our population may have left out the group whose socioeconomic status is relatively low, which could have resulted in a selection bias. In addition, the subjects’ age, gender, and racial distribution in this study are different from those of previous studies on SCI, because most of our subjects (most of whom were men) were $<70$ years and were primarily Korean ($>99\%$). These facts may also limit generalization of the study results.

In conclusion, the age-adjusted prevalence of SCI is 5.1\% in apparently normal Korean adults, and independent risk factors for SCI include old age and a history of hypertension. Mild alcohol consumption may be an independent protective factor against SCI, especially in relatively younger age groups.

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References


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