Risk Factors for First-ever Ischemic Stroke: A Hospital-based Case-Control Study in Kaohsiung, Taiwan

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Background: Numerous population-based epidemiological studies have shown the prevalence and strength of vascular risk factors for stroke but little is known about risk factors of stroke in Taiwan. The aim of this study was to identify vascular risk factors in a group of first-ever ischemic stroke patients in Taiwan.

Methods: The study consisted of 228 consecutively hospitalized cases of first-ever ischemic stroke and 228 healthy age- and sex-matched control subjects. Conditional logistic regression analyses were performed to evaluate the risk factors.

Results: Significant risk factors included hypertension (odds ratio [OR] 2.7, 95% confidence interval [CI] = 1.53-4.80), atrial fibrillation (OR 14.8, 95% CI = 2.32-94.73), ischemic heart disease (OR 4.4, 95% CI = 1.48-13.38), cigarette smoking (OR 2.3, 95% CI = 1.10-4.96), left ventricular hypertrophy (OR 2.7, 95% CI = 1.18-6.16), and other abnormal electrocardiographic findings (OR 2.1, 95% CI = 1.11-3.80).

Conclusions: Several vascular risk factors of first-ever ischemic stroke were identified. A population-based study involving more vascular risk factors is needed for generalization.

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Key words: **risk factor, first-ever ischemic stroke.**

Stroke has been the second leading cause of death in Taiwan for decades.[1] The rate of incidence of first-ever stroke was reported to be 330 per 100000 and 71% of these events were cerebral infarctions.[2] To reduce the economic burden of stroke, a better understanding of risk factors for stroke prevention is mandatory. Numerous risk factors such as hypertension, cigarette smoking, diabetes mellitus, asymptomatic carotid stenosis, hyperlipidemia, atrial fibrillation, and cardiac diseases have been recognized as well-documented modifiable risk factors for ischemic stroke,[3,4] and numerous population-based epidemiological studies have shown the prevalence and strength of vascular risk factors for stroke.[5-8] Data from hospital-based studies offer important information for the design of future epidemiology studies of the risk factors in Taiwanese stroke patients. The purpose of this prospective hospital-based study was to investigate vascular risk factors in a group of first-ever ischemic stroke patients in Taiwan.

METHODS

The study hospital, Chang Gung Memorial Hospital, Kaohsiung, is a medical center and a main

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referral hospital which serves an area with 3 million inhabitants in southern Taiwan. It is easily accessible for all kinds of stroke patients. In addition, 26 hospitals including two medical centers and 24 community hospitals are located in the same area.[9]

Study population

Patients admitted to the First Department of Neurology of the study hospital from September 1998 through October 1999 were recruited for this study. The cases were patients of first-ever ischemic stroke, defined as the acute onset of a focal neurological deficit consistent with a lesion of vascular origin that persisted for more than 24 hours and without history of cerebrovascular disease or transient ischemic attack. All patients had brain computed tomography (CT) scans to exclude hemorrhages, and brain magnetic resonance image (MRI) scans to confirm ischemic stroke when possible. Information about vascular risk factors of interest was reviewed from their medical records.

Age- and gender-matched control subjects were selected among neurologically healthy people who consulted the study hospital for general physical checkups. The control subjects had no prior strokes.

Risk factors

Eleven vascular risk factors including hypertension, diabetes mellitus, atrial fibrillation or flutter, ischemic heart disease, significant extracranial carotid lesion, cigarette smoking, serum total cholesterol level, serum triglyceride level, left ventricular hypertrophy by electrocardiography (ECG), other abnormal ECG findings, and alcohol consumption were included in the present study. In our analysis, all risk factors were analyzed as categorical variables except for the serum total cholesterol level and serum triglyceride level which were continuous. The occurrence of a risk factor was determined from results of clinical examination, diagnostic procedures, or evidence in the medical records. The definition of each risk factor follows.

Subjects were considered to have hypertension if they were previously diagnosed with hypertension by a clinician, were taking antihypertensive agents, or had systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg on two different occasions measured at least 2 weeks after the acute stage. Diabetes mellitus was diagnosed if a subject had the diagnosis documented on the medical record, was receiving oral hypoglycemic agents, or if the fasting blood glucose level was (126 mg/dL. The blood glucose levels were rechecked for the patients during the chronic stage to confirm the diagnosis of diabetes mellitus. Subjects were considered to have atrial fibrillation or flutter if the diagnosis was documented in ECG reports (episodes of atrial fibrillation that alternated with periods of sinus rhythm as well as lone atrial fibrillation or flutter was included). Subjects were considered to have ischemic heart disease if they either had the diagnosis of myocardial infarction or angina pectoris, or were treated for myocardial infarction or angina pectoris as documented in their medical records.

Subjects were considered to have significant extracranial carotid lesions only if there was internal carotid artery (ICA) >50% stenosis or an occlusion. We considered only those who currently smoked cigarettes, which was defined as smoking more than 10 cigarettes per day for more than 6 months prior to the stroke or from the date they enrolled.

Left ventricular hypertrophy was coded as being present when it was documented in an ECG report. Subjects were considered to have other abnormal electrocardiographic findings if they had atrial premature beats, ventricular premature beats, completed and incomplete bundle branch block, or atrioventricular block of any degree documented in ECG reports. We defined alcohol consumption as regular consumption of > 30 g of alcohol per day or > 210 g of alcohol per week for more than 6 months prior to the stroke or from the date they enrolled.

Statistical analysis

Conditional logistic regression analyses were performed to estimate the odds ratios (OR) along with two-sided 95% Confidence Intervals (CI) for matched case-control differences. In univariate analyses, this method gives a result equivalent to a McNemar's test.[10] Multivariable conditional multiple logistic regression analysis was performed by initially including all risk factors considered, to avoid overfitting the data and to reduce the potential risk due to variables selection.[11,12] In evaluating risk factor, significant *p*-values were set at 0.05.

In our analysis, the logistic procedure eliminated pairs in which either the case or the control had missing values for a particular variable. Unknown or

missing data occurred in the following variables: diabetes mellitus in one patient, cholesterol levels in nine patients and 19 control subjects, triglyceride levels in 11 patients and 19 control subjects, smoking in one control subject, and atrial fibrillation in one patient. STATA for Windows 7.0 (Stata Corp., College Station, Tex) was used for all analyses.

RESULTS

In total, 228 cases were included in this study and they were individually matched for age and sex with 228 control subjects. Among the cases, 145 (63.6%) were men. The mean age was 61.7 ±11.8 years (median, 63 years; range, 18-87 years). Table 1 shows the proportions of cases and control subjects by risk factors that were studied. It was noted that the study subjects had a high frequency of hypertension (57.9% for cases and 36.4% for control subjects). The mean and median serum total cholesterol levels were slightly greater for the control subjects than for the patients, whereas the mean and median serum triglyceride levels were slightly greater among the patients than the control subjects.

Univariate analysis revealed that patients with first-ever ischemic stroke were significantly associated with hypertension, diabetes mellitus, atrial fibrillation or flutter, ischemic heart disease, significant extracranial carotid lesion, cigarette smoking, serum total cholesterol, and left ventricular hypertrophy (Table 1). No significant differences between the patients and control subjects were observed in the risk factors such as serum triglyceride levels, other abnormal ECG findings, or alcohol consumption.

Table 2 shows the results of multivariable conditional logistic regression analyses. Risk factors that were identified to be significantly associated with increased risk of first-ever ischemic stroke included: hypertension, atrial fibrillation or flutter, ischemic heart disease, cigarette smoking, left ventricular hypertrophy, and other abnormal ECG findings. Additionally, none of the OR estimates of these significant risk factors materially changed after we excluded the variables with p-value > 0.1 to obtain a reduced model.

Table 2. Multivariable Conditional Logistic Regression Analysis*

Study factors	Odds Ratio	95% CI	p
Hypertension	2.7	1.53- 4.80	0.001
Diabetes mellitus	1.7	0.93- 3.15	0.086
Atrial fibrillation or flutter	14.8	2.32-94.73	0.004
Ischemic heart disease	4.4	1.48-13.38	0.008
Internal carotid stenosis >50%	1.9	0.73- 4.89	0.190
Cigarette Smoking	2.3	1.10- 4.96	0.026
Serum total cholesterol, mmol/L	0.8	0.62- 1.07	0.144
Serum triglyceride, mmol/L	1.2	0.99- 1.57	0.064
Left ventricular hypertrophy	2.7	1.18- 6.16	0.019
Other abnormal ECG findings	2.1	1.11- 3.80	0.021
Alcohol	0.5	0.18- 1.35	0.172

*Matched for age and gender

Table 1. Univariate Analysis of Case-control Differences in Risk factors for First-time Ischemic Stroke *

Study factors	Patients, n=228	Control Subjects, n=228	Odds ratio (95% CI)	p
Hypertension	132 (57.9)	83 (36.4)	2.8 (1.81- 4.37)	<0.001
Diabetes mellitus	63 (27.6)	38 (16.7)	1.9 (1.20- 2.99)	0.006
Atrial fibrillation or flutter	18 (7.9)	2 (0.9)	9.0 (2.09-38.79)	0.003
Ischemic heart disease	32 (14.0)	8 (3.5)	4.4 (1.95-10.06)	<0.001
Internal carotid stenosis >50%	24 (10.5)	12 (5.3)	2.1 (1.02- 4.29)	0.044
Cigarette Smoking	56 (24.6)	33 (14.5)	2.3 (1.31- 3.96)	0.004
Mean (median) serum total cholesterol, mmol/L	4.9 (4.8)	5.1 (5.0)	0.8 (0.64- 0.96)	0.018
Mean (median) serum triglyceride, mmol/L	1.8 (1.4)	1.5 (1.3)	1.2 (1.00- 1.43)	0.050
Left ventricular hypertrophy	43 (18.9)	14 (6.1)	3.6 (1.87- 7.09)	<0.001
Other abnormal ECG findings	42 (18.4)	30 (13.2)	1.4 (0.88- 2.36)	0.142
Alcohol	17 (7.5)	21 (9.2)	0.8 (0.40- 1.55)	0.494

Values are numbers (percentage) of patients unless otherwise specified.

* Unknown or missing data occurred in the following variables: diabetes mellitus in 1 patient, atrial fibrillation or flutter in 1 case, cigarette smoking in 1 control subject, total cholesterol level in 9 patients and 19 control subjects, triglyceride level in 11 patients and 19 control subjects.

DISCUSSION

This, to the best of our knowledge, is the first case-control study to examine the risk factors for ischemic stroke in Taiwan. Based on our hospital data, increased risk was found to be associated with hypertension, atrial fibrillation, ischemic heart disease, cigarette smoking, left ventricular hypertrophy shown on ECG, and other abnormal ECG findings. No significant independent association with the risk of ischemic stroke was found for diabetes, significant extracranial carotid lesion, serum total cholesterol level, serum triglyceride level, or alcohol consumption. Overall, the identified risk factors mirrored those in other populations and cohorts.[5,7,8,13,14,20,27]

Our study indicated that hypertension was associated with increased risk of ischemic stroke. It is commonly agreed that hypertension is a major risk factor for stroke and has the highest attributable risk.[3,4] Our findings, in agreement with the population-based case-control studies done in Australia and Russia,[13,14] indicated that the Taiwanese population is no exception. Since controlling blood pressure has been shown to benefit high-risk patients regardless of having had a stroke or not,[15,17] lowering blood pressure is crucial in stroke prevention.

Atrial fibrillation or flutter, ischemic heart disease, cigarette smoking, and left ventricular hypertrophy as risk factors for ischemic stroke have been previously reported. Compared with a review study,[4] the frequency of atrial fibrillation or flutter in the present study was not low (18 of 227 cases or about 8% vs. 2 of 228 control subjects or 0.9%). Although it had the highest OR, the impact on ischemic stroke should be interpreted cautiously due to its wide range of 95% CI. In our univariate as well as the multivariable analyses, the large CI was likely attributed to the small number of subjects with atrial fibrillation or flutter in this study. The frequency of ischemic heart disease in this study (14% for cases) was low in contrast to a hospital-based registry in Taiwan,[18] in which researchers reported that 26% of their ischemic stroke patients had ischemic heart disease.

In this study, we found neither serum total cholesterol nor serum triglyceride independently increased the risk of ischemic stroke. However, researchers noted mixed results in previous studies of the association between triglyceride levels and stroke.[19-22]

Using univariate analysis, there was no evidence that patients were more or less likely than control subjects to have other abnormal ECG findings (OR=1.4, $p = 0.142$). However, using multivariable conditional logistic regression, we found that the variable of other abnormal ECG findings was associated with a significantly higher risk of ischemic stroke (OR=2.1, $p = 0.017$ according to the full model). Further exploration using more specific data of ECG findings is needed.[23]

In this study, after controlling for other factors associated with the risk of ischemic stroke, our model did not identify significant associations between diabetes mellitus and ischemic stroke even though they were demonstrated on univariate analyses. We noted that in a study of risk factors for hemorrhagic stroke Zodpey et al. reported similar results.[24] However, other researchers reported that those with diabetes mellitus were at greater risk for stroke than control subjects.[3,4] Among Hawaiian Japanese men in the Honolulu Heart Program, those with diabetes had twice the risk of thromboembolic stroke than those without diabetes, which was independent of other risk factors.[25]

Using univariate analysis, significant extracranial carotid lesion was a marginally significant risk factor, however, its significant association with risk of ischemic stroke was not confirmed in our multivariable analysis. The severity of carotid atherosclerosis evaluated using ultrasonography is a useful indicator of the risk of ischemic stroke in symptomatic patients, and is a major risk factor predicting occurrence of neurological and other vascular events in asymptomatic patients. However, no significant association had been found between the severity of stroke and the severity of extracranial internal carotid artery atherosclerosis in Taiwanese patients.[26] In this study, the prevalence of significant extracranial internal carotid artery stenosis appeared to be low compared with others,[27] but similar to the results in a study in Northern Taiwan.[18]

The positive relation between total and low density lipoprotein (LDL) cholesterol, and a protective influence of high density lipoprotein (HDL) cholesterol on extracranial carotid atherosclerosis has been shown.[6] In this study, we did not find any association between total cholesterol and risk of ischemic stroke, but more than 75% of patients and 80% of control subjects had serum total cholesterol levels

higher than 5.18 mmol/L (200 mg/dL). Additionally, the relations between total and LDL cholesterol and HDL cholesterol were not considered in this study. To determine whether and to what extent serum total cholesterol levels were associated with risk of ischemic stroke requires further study.

This study has several potential limitations, primarily owing to being a hospital-based study, and the results cannot be generalized to the Taiwanese population. We did not start with specifications of any odds ratio worth detecting at given levels of type I error and power because only a little information about the prevalence or the incidence rate of the potential risk factors in patients with ischemic stroke or in patients free of ischemic stroke in Taiwan was available. Our results should therefore be confirmed by a population-based study in which the sample size is determined to produce the required number of informative pairs. Another limitation was that other potential risk factors such as obesity and lifestyle factors were not included in this study. Furthermore, we did not have the information about cardiac abnormalities as documented by cardiac echo to be included as risk factors. Despite the limitations, our approach is justified by the fact that the study risk factors can easily be assessed and are modifiable or potentially modifiable during clinical practice. This is of utmost importance with respect to primary stroke prevention in this area.

In summary, our analyses identified several vascular risk factors that were significantly associated with increased risk of first-ever ischemic stroke. The results have implications for clinical practice and are helpful for devising stroke prevention strategies in Taiwan. We suggest that a population-based study involving more vascular risk factors should be performed in the future for generalization.

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初次缺血性腦中風的危險因子：以醫院爲基礎之病例對照研究

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背 景： 針對腦中風危險因子的研究很多，但是針對台灣本土初次缺血性腦中風的危險因子的研究卻罕見。本研究之目的是希望能找出台灣本土初次缺血性腦中風病人的危險因子。

方 法： 本研究共連續登錄228位因初次缺血性腦中風住院的病人，同時每一位病人配對一位年齡及性別相符的對照組。我們利用條件式邏輯迴歸的統計方法來評估危險因子。

結 果： 本研究找出了以下幾個有意義的危險因子，包括高血壓，心房顫抖，缺血性心臟病，抽煙，左心室肥大及不正常的心電圖檢查。

結 論： 針對台灣本土初次缺血性腦中風病人危險因子的研究，共發現了6個危險因子。因本研究的侷限性，更大型及全國性的研究是有必要的。

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關鍵字：危險因子，初次缺血性腦中風。

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