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Risk Factors for Hemorrhagic Stroke in Wonju, Korea

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Although stroke is a great public health challenge in Korea, there have been few epidemiologic studies of the risk factors for stroke. A case-control study was performed to evaluate the risk factors for hemorrhagic stroke in Wonju, Korea. Ninety-five subarachnoid hemorrhage (SAH) and 102 intracerebral hemorrhage (ICH) patients aged 21~86 years, and 267 controls were recruited among the inpatients of Wonju Christian Hospital during 1994~1995. Information was gathered through interviews and examinations. After adjustment for age and sex, family and past history of hypertension, drinking habits, age of menarche, height, weight, body mass index, waist and hip circumference, earlobe crease, prothrombin time, white blood cell count, hemoglobin, and total cholesterol were all found to be significantly associated with both SAH and ICH. The risk factor significantly associated only with ICH was smoking habits. In multiple logistic analyses, the independent risk factors for SAH and ICH were the same. Those included family and past history of hypertension, age of menarche, earlobe crease, prothrombin time, white blood cell count, hemoglobin and total cholesterol. In general, the risk factors for SAH and ICH were similar with each other, except smoking habits. Risk factors found in this study congruent with previous studies were family and past history of hypertension, drinking habits, body mass index, prothrombin time, white blood cell count, and hemoglobin. Those incongruent or rather newly found were age of menarche, a big physique, earlobe crease, and total cholesterol.

Key Words: Case-control study, subarachnoid hemorrhage, intracerebral hemorrhage, hemorrhagic stroke, risk factor

Control of stroke is a great public health challenge in the Republic of Korea. It is a major cause of mortality and accounts for more than 37,000 deaths per year in Korea. This is more than five times the number who die from ischemic heart disease in Korea (Nam, 1996). However, the risk factors for stroke are less well defined and documented than those of coronary heart disease.

The pathological patterns of stroke in Korea are different from those noted in most western countries. A nationwide multi-hospital registration study in Korea showed that the relative frequency of stroke by type was: thrombosis (27.2%), lacunar infarction (11.2%), transient ischemic attack (3.0%), embolism (7.0%), intracerebral hemorrhage (31.4%), subarachnoid hemorrhage (18.0%), intraventricular hemorrhage (1.5%), and others (0.7%) (The Korean Neurological Association, 1993). In western countries, ischemic stroke is considered twice as common as hemorrhagic stroke. The reasons for the differences in the patterns of stroke in Korea compared with western countries are unknown. Differences in the prevalence and treatment of hypertension, preva-

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lence of hypercholesterolemia, smoking and drinking habits, as well as differences in mean dietary protein and lipid intake, may all play a role (Kuller and Reisler, 1977; The Korean Neurological Association, 1993). Since the pathogenesis underlying the various types of stroke differs, it is reasonable to expect that the risk factors for thromboembolic stroke differ from those for hemorrhagic stroke (HS). However, none of the epidemiologic reports published in Korea distinguishes between thromboembolic stroke and HS (Park, 1993).

To help promote a better understanding of HS risk factors, we attempted to examine these factors by means of a case-control study. In doing so, we considered not only known major risk factors, but other possible risk factors as well.

MATERIALS AND METHODS

Prospectively, from March 1, 1994 to November 30, 1995, 95 subarachnoid hemorrhage (SAH) and 102 intracerebral hemorrhage (ICH) patients aged 21 ~86, having their first attack and identified at the department of neurosurgery, Wonju Christian Hospital were selected. Two hundred sixty seven controls were selected among the patients admitted to the same hospital without prior history of stroke (In fact, this control group was a pool for studying the risk factors of various types of stroke including atherothrombotic stroke.). The illnesses of these controls were of an acute surgical or nonsurgical nature.

HS was diagnosed on the basis of a focal neurologic deficit accompanied by headache, loss of consciousness, and bloody spinal fluid obtained from a non-traumatic lumbar puncture, or on the basis of computed tomography or magnetic resonance imaging. Among the cases of HS, there were no cases with SAH or ICH alone. Therefore, we subdivided HS into SAH and ICH according to the major site of hemorrhage.

We collected clinical and anamnestic information from the subjects or from their relatives. A detailed family and personal history and physical examination were conducted on each subject by two medical doctors in the neurosurgery department. The interview involved the use of a structured questionnaire covering the following characteristics and experiences of the patients data (age, sex, marital status, education, and economic status, age of menarche, and age of menopause), cigarette consumption (amount and duration), drinking frequency, snoring habits, ever having clinically-diagnosed acute myocardial infarction, stroke, hypertension, and diabetes mellitus; a history of stroke, hypertension, diabetes mellitus, and acute myocardial infarction among first-degree relatives; physical measurements (height, weight, waist and hip circumference), and hematologic data (white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, total cholesterol, alkaline phosphatase, and prothrombin time). Blood samples were collected immediately after subjects were admitted to the hospital.

We calculated age and sex adjusted odds ratios (ORs), and 95% confidence intervals (CIs) to estimate risk. To account for possible confounding factors (other than age and sex) simultaneously, a more

Table 1. Age and sex distribution of cases and controls*

Age	Controls			Subarachnoid hemorrhage			Intracerebral hemorrhage		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
~39	33 (21.0)	21 (19.1)	54 (20.2)	12 (50.0)	14 (19.7)	26 (27.4)	13 (30.9)	6 (10.0)	19 (18.6)
40~49	32 (20.4)	26 (23.6)	58 (21.7)	8 (33.3)	17 (23.9)	25 (26.3)	12 (28.6)	18 (30.0)	30 (29.4)
50~59	57 (36.3)	31 (28.2)	88 (33.0)	3 (12.5)	26 (36.6)	29 (30.5)	12 (28.6)	26 (43.3)	38 (37.3)
60~	35 (22.3)	32 (29.1)	67 (25.1)	1 (4.2)	14 (19.7)	15 (15.8)	5 (11.9)	10 (16.7)	15 (14.7)
Total	157 (100)	110 (100)	267 (100)	24 (100)	71 (100)	95 (100)	42 (100)	60 (100)	102 (100)

*: Data are presented as number(%).

Table 2. Odds ratios(ORs)[a] and 95% confidence intervals(95% CIs) of potential risk factors

Variables	SAH		ICH	
	OR	95% CI	OR	95% CI
Family history of stroke (yes/no)	1.33	0.65~2.71	1.25	0.64~2.45
Family history of hypertension (yes/no)	8.25†	3.89~17.47	10.00†	4.98~20.09
Past history of hypertension (yes/no)	29.52†	10.67~81.67	63.39†	23.91~168.07
Education(years)				
<6	1.00		1.00	
7~9	1.74	0.83~3.67	2.25*	1.20~4.24
10<	1.11	0.50~2.47	1.01	0.49~2.11
Economic status (middle or high/low)	1.65	0.95~2.86	1.55	0.93~2.56
Drinking habits (current/no)	2.10*	1.09~4.05	2.01*	1.11~3.64
Smoking habits (current or stopped /no)	1.37	0.64~2.91	0.36†	0.19~0.70
Age of menarche (y.o.[b])				
<15	1.00		1.00	
16~17	0.46*	0.23~0.93	0.37†	0.18~0.78
18<	0.34*	0.15~0.76	0.21†	0.08~0.53
Age of menopause (y.o.[b])				
<46	1.00		1.00	
47~49	1.96	0.86~4.44	2.55*	1.15~5.66
50<	1.04	0.49~2.19	0.80	0.36~1.76
Height (cm)				
<157	1.00		1.00	
157~162	1.87	1.00~3.48	2.32†	1.25~4.31
>162	11.81†	3.11~44.78	5.21†	2.09~12.98
Weight (kg)				
<56	1.00		1.00	
56~64	2.44†	1.26~4.71	2.35*	1.22~4.50
>64	6.38†	3.09~13.18	7.70†	3.87~15.32
Body mass index (kg/m^2)				
<21.1	1.00		1.00	
21.1~24.0	3.84†	1.96~7.52	3.10†	1.71~5.62
>24.0	4.56†	2.29~9.11	3.94†	2.12~7.32
Waist circumference (cm)				
<79	1.00		1.00	
79~86	3.79†	1.81~7.93	3.77†	1.88~7.57
>86	6.07†	2.99~12.31	6.22†	3.17~12.18
Hip circumference (cm)				
<88.6	1.00		1.00	
88.6~95.9	3.05†	1.51~6.14	2.25*	1.16~4.39
>95.9	7.86†	3.85~16.01	8.76†	4.60~16.68
Earlobe crease (yes/no)	4.90†	2.49~9.65	2.93†	1.58~5.43
Snoring (frequent/sometimes or never)	0.54	0.28~1.05	1.29	0.77~2.15
Prothrombin time (delayed/normal)	1.91*	1.12~3.25	2.99†	1.84~4.83
White blood cell (10^9/l)				
<7.9	1.00		1.00	
7.9~12.3	4.08†	1.99~8.4	4.40†	2.13~9.10
>12.3	10.15†	4.89~21.08	12.49†	6.10~25.54
Hemoglobin (g/dl)				
<12.0	1.00	1.00		
12.0~13.4	2.46†	1.30~4.68	3.86†	1.96~7.60
>13.4	3.75†	1.94~7.25	6.45†	3.31~12.60
Total cholesterol (mg/dl)				
<150	1.00		1.00	
150~188	1.97	0.99~3.91	7.41†	3.51~15.67
>188	5.39*	2.81~10.33	10.88†	5.07~23.35

[a]: adjusted with age and sex through logistic analysis, [b]: years old, *: $P<0.05$, †: $P<0.01$

Table 3. The results of logistic regression analysis

Variables	SAH		ICH	
	OR	95% CI	OR	95% CI
Family history of hypertension (yes/no)	4.37†	1.63~11.75	4.35†	1.44~13.13
Past history of hypertension (yes/no)	14.74†	4.03~53.91	43.61†	13.35~142.51
Age of menarche (y.o.)[a]	0.52*	0.29~0.95	0.38†	0.15~0.97
Earlobe crease (yes/no)	6.72†	2.49~18.11	4.52†	1.51~13.57
Hemoglobin (g/dl)	1.32†	1.07~1.63	1.35†	1.09~1.67
White blood cell	1.15†	1.07~1.24	1.18†	1.10~1.27
Total cholesterol (mg/dl)	1.02†	1.01~1.02	1.02†	1.01~1.03
Prothrombin time (normal/delayed)	4.86†	2.26~10.45	5.68†	2.49~12.97

[a]: Estimated from another analysis adjusting age, past history of hypertension, prothrombin time, white blood cell, and total cholesterol in women, *: $P<0.05$, †: $P<0.01$

refined analysis was carried out using a logistic regression model.

RESULTS

The distribution of the cases and controls by age and sex is shown in Table 1. The proportion of females was lower in the control group than in the case groups. The mean age of controls, SAH, and ICH were 55.7 years, 51.7 years, and 54.3 years, respectively.

In Table 2, the ORs (and 95% CIs) for risk factors, adjusted with age and sex, are summarized. This table shows all the significant risk factors, as well as those considered to be of interest but which showed no association with both SAH and ICH. Continuous variables in this table were trichotomized by tertile cut points of the entire distribution of subjects. Family and past history of hypertension, drinking habits, age of menarche, height, weight, body mass index, waist circumference, hip circumference, earlobe crease, prothrombin time, white blood cell count, hemoglobin, and total cholesterol were significantly associated with both SAH and ICH. The risk factor significantly associated only with ICH was smoking habits. The potential risk factors not associated with both of the two diseases were family history of stroke, education, economic status, age of menopause, and snoring.

Using SAH and ICH each as dependent variables, two multiple logistic regression models were estimated (Table 3). These were obtained after fitting a series of possible models, with good fit and significant ORs (significance level of 0.05) as criteria for the most appropriate model. The independent risk factors for SAH and ICH were the same. Those were family and past history of hypertension, age of menarche, earlobe crease, prothrombin time, white blood cell count, hemoglobin, and total cholesterol.

DISCUSSION

Recently, the incidence of stroke in western countries has been decreasing due to the successful control of hypertension, but in Korea, stroke is still considered to be the most important cause of death. Although the mortality rate of stroke has been decreasing since 1984, the proportion of people among age groups at higher risk is progressively increasing because of the changing demographic structure.

Though the number of patients in case groups was rather small, the age distribution was similar to that of a nationwide multi-hospital registration study in Korea (The Korean Neurological Association, 1993). A family history of stroke was recently reported as a risk factor for stroke, with puzzling sex differences (Khaw and Barrett, 1986; Welin *et al.* 1987). This factor, however, did not differentiate those at greater risk of both SAH and ICH in this study. As would be expected, family and past history of hypertension

were significant independent risk factors for both SAH and ICH.

Different from the findings in western countries, educational status is not significantly associated with both SAH and ICH in this study. Conflicting results have been reported regarding the association of socioeconomic level with stroke morbidity (Chapman *et al.* 1966; Johnson *et al.* 1967; Pell and D'Alonzo, 1970). In this study, this factor was not correlated significantly with both SAH and ICH. Alcohol consumption is believed to increase the occurrence of stroke, especially the hemorrhagic type, mainly as a result of alcohol-induced hypertension (Beaglehole and Jackson, 1992). Some studies suggest a possible health-protective effect of light and moderate alcohol use, particularly against ischemic stroke. In this study, drinking was a significant risk factor for both SAH and ICH. The role of cigarette smoking in causing stroke remains contested. Although some studies have been unable to demonstrate a relationship between smoking and stroke (Johnson *et al.* 1967; Nomura *et al.* 1974; Doll and Peto., 1976), others have reported varying degrees of association (Herman *et al.* 1982; Abbot *et al.* 1986; Colditz *et al.* 1988; Wolf *et al.* 1988). This study showed a significant negative relationship between cigarette smoking and ICH, but not between cigarette smoking and SAH. We cannot explain this phenomenon, especially between cigarette smoking and ICH.

Late menarche was a significant independent risk factor for both SAH and ICH, though the age of menopause was not. The higher the age of menarche, the higher the risk of HS. This result has not, as far as we know, been reported previously. Early menarche in well- nourished and obese women, and the effect of estrogen in raising blood pressure may explain this result, though confirmation of such results remains to be achieved. Obesity has been positively and independently associated with stroke incidence in several studies, including the Framingham Study (Hubert *et al.* 1983). However, several studies in Japan reported negative or no correlation between relative weight and stroke (Okada *et al.* 1976; Ueshima *et al.* 1980). In this study, body mass index was an independent risk factor for both SAH and ICH. Moreover, all the body dimensions measured (height, weight, waist and hip circumference) were positively related to both SAH and ICH. This result suggests that a big physique, including obesity, may be a risk factor for HS.

Earlobe crease was reported as a risk factor for ischemic heart disease. The mechanism by which earlobe crease occurs appears unclear, but it has so far been reported to be associated with hypertension (Moncada *et al.* 1979; Kristensen, 1980; Shoenfeld *et al.* 1980; Kobayashi *et al.* 1987), hypercholesterolemia (Kobayashi *et al.* 1987), abnormal funduscopic findings (Moncada *et al.* 1979), smoking (Lichstein *et al.* 1974; Doering *et al.* 1977), obesity (Doering *et al.* 1977), diabetes (Andresen *et al.* 1976; Doering *et al.* 1977; Shoenfeld *et al.* 1980), snoring (Roger, 1989) and atherosclerosis (Mochio *et al.* 1990). Despite the fact that the intimate origin of this association remains unsolved, we found that earlobe crease was independently associated with both SAH and ICH. A number of studies have demonstrated an association between habitual snoring and stroke. Pressman suggested that snoring not only increased the statistical risk of stroke, but could be the proximal trigger that precipitates these events during sleep (Pressman *et al.* 1995). However, our study did not show this kind of relationship.

As would be expected, prothrombin time was independently associated with both SAH and ICH. One report has suggested an association between increased white blood cell count and an increased incidence of cerebral infarction (Prentice *et al.* 1982). Other studies, including the Framingham Study, have demonstrated a relationship between high-normal hematocrit level and incidence of cerebral infarction (Kannel *et al.* 1972). This study showed an independent positive relationship of WBC count and hemoglobin to both SAH and ICH.

A surprisingly consistent finding from Japan has been the relationship between low total cholesterol and the increased incidence of HS. The Framingham Study also reported a significant inverse association between low density lipoprotein cholesterol and stroke (both thromboembolic stroke and other types) in a multivariate analysis, but only for women (Gordon *et al.* 1981). However, this study showed an independent positive association between total cholesterol and both SAH and ICH. In this study, stroke events themselves may affect the total cholesterol levels. However, acute ICH appeared to have little effect on the serum lipid profile (Woo *et al.* 1990),

and total cholesterol levels at the time of stroke may be more representative of usual total cholesterol levels because poor nutrition or newly developed liver or renal dysfunction poststroke may result in lower total cholesterol levels (Jacobs and Iso, 1991).

Several possible limitations of the current study should be considered in interpreting the results. Since the design of this study is case-control, some of the risk factors found in this study (white blood cell count, hemoglobin, prothrombin time, and total cholesterol) may be affected by stroke events themselves. In fact, leukocytosis is a common phenomenon of subarachnoid hemorrhage(Toole, 1990). However, acute HS appeared to have little effect on the hemoglobin level and prothrombin time because the volume of the extravasated blood in HS is usually not more than 30 ml.

Not all HS patients under hospital care were interviewed, largely because of death. This might lead to a bias in the study outcome if the factors being considered influenced one's chances of dying from HS a short time after the initiation of such care. It is possible that if such bias were present, this effect would be an underestimation of the associations noted because the study variables are more than likely to reduce one's survival chances. One of the most important requisites for a case-control study is the selection of controls from an appropriate population, in order to obtain unbiased relative risk estimates. Here, controls were selected among patients admitted to the same hospital, in order to obtain study groups that were broadly similar with regard to the area of residence and socioeconomic status.

A classification bias could have occurred since the baseline information on various health behaviors was based on self-reports, and the observers were aware of the clinical status of the patients. A structured questionnaire was used in order to overcome this potential bias, and not all study variables were found to be associated with HS, making interviewer bias less suspected. Since stroke can affect blood pressure levels, we excluded this information from the analysis. Bias due to disease misclassification is also unlikely because well defined criteria were used and no stroke events occurred in the controls. There is little direct evidence in this study concerning the effect of this source of bias. Because of the large number of comparisons performed, it is possible that our findings may be the result of chance.

In general, the risk factors for SAH and ICH were similar with each other except for smoking habits. Risk factors found in this study congruent with previous studies were family and past history of hypertension, drinking habits, body mass index, prothrombin time, white blood cell count and hemoglobin. Those incongruent or rather newly found risk factors were age of menarche, a big physique, earlobe crease, and total cholesterol. Potential risk factors for both SAH and ICH were family history of stroke, education, economic status and snoring.

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