The Association of Metabolic Risk Factors and Silent Brain Infarctions in Healthy Taiwanese

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Abstract-

Purpose: Silent brain infarctions (SBI) commonly go unnoticed due to the subtlety of their neurological signs. However, there is the risk of subsequent symptomatic stroke and dementia. A better understanding of the risk factors of SBI may help accurately predict those who will require treatment.

Methods: This one-year retrospective study enrolled 199 adult healthy Taiwanese. Multiple logistic regression analysis was used to evaluate the relationships between baseline clinical factors and the presence of SBI during the study period.

Results: Fifteen (7.5%) healthy subjects had SBI, including 4.9% (5/103) males and 10.4% (10/96) females. Multiple logistic regression analysis revealed that both mean age and hypertension were independently associated with SBI, such that any increase of one year in mean age increased the SBI rate by 7.3%.

Conclusion: In the present study, there is a close relationship between elderly patients and SBI and any increase of one year in mean age increases the SBI rate by 7.3%. Aside from age, hypertension is by far the strongest modifiable risk factor identified to date. Prospective, longitudinal observational studies are warranted to evaluate the relationship between control of hypertension and SBI in this specific population to determine how to prevent subsequent symptomatic stroke.

Key words: Healthy Taiwanese, Metabolic risk factor, Silent brain infarctions

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INTRODUCTION

In clinical practice, silent brain infarctions (SBI) are commonly diagnosed by magnetic resonance imaging (MRI) in both first-ever ischemic stroke and healthy elderly patients[(1)]. It is also common in patients with hypertension and coronary artery disease, and in those undergoing haemodialysis[(2-4)]. In different series, the reported frequency of MRI-defined SBI ranges from 5% to 50%[(5-7)].

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Silent brain infarctions are the most common type of sub-cortical infarction, defined by Fisher as a small, deep cerebral infarction caused by the occlusion of small penetrating cerebral arteries[8]. Its pathogenesis involves arteriosclerotic changes in the cerebral arteries related to aging and is accelerated by hypertension[8]. Although SBI may differ from symptomatic infarcts in terms of the lack of acute stroke-like signs, they do present as subtle deficits in physical and cognitive function that commonly go unnoticed. Moreover, the presence of silent infarcts more than doubles the risk of subsequent stroke and dementia[5,8-9].

To prevent SBI, it is important to identify risk factors, especially those that are treatable. Only two small randomised controlled trials have shown that the risk of SBI is reduced by prophylactic intervention, like antithrombotic agents used in diabetic patients[10,11]. Routine MRI screening of neurologically asymptomatic people is not cost- effective, but may benefit high-risk patients. Thus, there is a need for better delineation of potential treatable risk factors in SBI patients. This study attempted to establish the metabolic risk factors that are strongly associated with SBI in healthy Taiwanese.

MATERIALS AND METHODS

Over a one-year period (January to December 2008), the database of the neurologic health examination center of Chang Gung Memorial Hospital-Kaohsiung, a 2482-bed acute-care teaching hospital and the largest medical center in the southern part of Taiwan providing primary and tertiary referral care, was retrospectively reviewed.

The medical records were reviewed using pre-existing standardized evaluation forms. All patients received complete medical and neurologic examinations, carotid duplex, and brain MRI and magnetic resonance angiography (MRA). The hospital's Institutional Review Committee on Human Research approved the study protocol.

Neurologists and neuro-radiologists integrated the clinical manifestations and neuroimaging findings, respectively.

In this study, infarcts were defined as silent if they lacked stroke-like symptoms[12]. All of the patients were generally in good health. Patients with evidence of cardiovascular events, including symptomatic cerebral infarctions or cerebral hemorrhage, coronary artery diseases and peripheral arterial diseases with or without follow-up at the outpatient clinic, were excluded. Twenty-one patients, including 16 with a history of symptomatic cerebral infarctions and five with coronary artery diseases were likewise excluded. Thus, only 199 of the 220 patients initially enrolled were included in the analysis.

Two neuro-radiologists (Lin W.C. and Lui C.C.) who were experienced in the interpretation of MRI and blinded to the patients' age, sex and clinical status, assessed the presence of SBI on MR images. In cases of disagreement between the two observers, lesions were determined by consensus. The MRI examinations were per-

Table 1. Demographic Data and Vascular Risk Factors

	Male (n=103)	Female (n=96)
Age, y	53.2±12.3	55.9±14.1
Body mass index, kg/m^2	25.0± 3.3	23.8± 4.0
Waist circumference (cm)	88.2± 8.2	84.1±10.1
Waist-to-hip ratio	0.92±0.05	0.89±0.07
Underlying disease		
Diabetes mellitus	11 (10.6%)	13(13.4%)
Hypertension	37 (35.9%)	30 (30.9%)
Smoking	23 (22.3%)	1 (0.1%)
Hyperlipidemia	40 (38.8%)	35 (36.1%)
Obesity	12 (11.7%)	12 (12.4%)
Mean blood pressure on presentation		
Mean Systolic BP (mmHg)	131.9±15.4	129.9±21.9
Mean diastolic BP (mmHg)	81.1±8.5	76.5±9.5
Laboratory data		
Fasting blood sugar, mg/dL	103.5±23.5	101.2±20.1
Uric acid, mg/dL	6.3±1.6	5.2±1.2
Cholesterol, mg/dL		
Total	200.5±40.5	199.8±37.6
HDL-C	50.9±13.8	59.0±14.2
LDL-C	126.6±61.1	113.2±33.3
Triglyceride, mg/dL	136.8±64.1	127.1±113.0
HBA1C	6.4±1.5	6.4±1.6

Note: Values expressed as mean±SD

Table 2. Age distribution of the study subjects and prevalence of silent brain infarction

Age (years)	Prevalence		
	Male, n (%)	Female, n (%)	Total, n (%)
20-29	0/4 (0)	0/6 (0)	0/10 (0)
30-39	0/7 (0)	0/4 (0)	0/11(0)
40-49	0/28 (0)	0/17 (0)	0/45 (0)
50-59	1/36 (2.7)	1/30 (3.3)	2/66 (3)
60-69	2/19 (10.5)	4/22 (18.2)	6/41 (14.6)
>70	2/9 (22.2)	5/17 (29.4)	7/26 (26.9)
Total	5/103 (4.9)	10/96 (10.4)	15/199 (7.5)

formed using a 1.5T scanner (Signa; Horizon GE Medical system, Milwaukee, USA). The imaging protocol included T2-weighted spin-echo [repetition time/echo time (TR/TE = 4,000/96 ms)], T1- weighted spin-echo (TR/TE = 475/minimal ms), and fluid attenuated inversion-recovery (FLAIR) (TR/TE = 9,000/133 ms, inversion time = 2,200 ms) imaging. Images were obtained as 20 trans-axial slices per scan, with 5 mm slice thickness and 2 mm inter-slice gap.

Silent brain infarctions were defined according to previous studies[13,14]. Lesions were defined as a focal lesion if it was at least 3 mm in diameter, with signal intensity corresponding to water, which was hyper-intense on T2-weighted images and hypo-intense on FLAIR images. Lesions of SBI were often surrounded by a hyper-intense gliotic rim on FLAIR images. These were differentiated from peri-ventricular white-matter lesions, which had high signal intensity, and from enlarged perivascular spaces, which were often bilaterally symmetrical, found in the lower third of the basal ganglia, and without gliosis, using FLAIR imaging. Lesions located in the sub-cortical white matter and deep gray matter, as well as cortical silent infarcts, were all enrolled in the diagnosis of SBI. Ultrasound examination was collected using a pulsed Doppler device utilizing a 4-MHz probe for extra-cranial evaluation (TC2-64B, EME, Uberlingen, Germany).

In this study, metabolic syndrome was defined using separated categorical variables based on the 2005 International Diabetes Federation (IDF) criteria for metabolic syndrome, with Asian adaptation, for subsequent multivariate analysis[15]. The modified criteria included central obesity (waist circumference ?90 cm for males and ≥80 cm for females) combined with any two of the following four conditions: (i) hyper-triglyceridemia (triglyceride level ≥1.7 mmol/L [150 mg/dL] or drug treatment for high triglycerides); (ii) HDL-C levels <1.0 mmol/L (40 mg/dL) for males; <1.3 mmol/L (50 mg/dL) for females or as drug treatment for low HDL-C; (iii) glucose level >5.6 mmol/L (100 mg/dL) or diagnosed diabetes; and (iv) elevated blood pressure (BP) (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg).

Patients were considered diabetes mellitus (DM) if they had been previously diagnosed as such or if they had a fasting glucose level ≥7 mmol/l.16 Hypertension was defined by pre-admission history, medical records, and systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg [17]. Blood pressure (BP) was measured with no knowledge of a history of hypertension and was checked by mercury sphygmomanometer after 5 min rest in all subjects. Two readings were taken, separated by two minutes. Hyperlipidemia was defined as hypercholesterolemia, hyper-triglyceridemia, or both, whereas hypercholesterolemia was defined as total venous plasma cholesterol level >5.0 mmol/l and any of the following: (i) increased low density lipoprotein (LDL) cholesterol level (>3.0 mmol/l); (ii) decreased HDL cholesterol level (<1.0 mmol/l); and (iii) ratio of total and high density lipoprotein (HDL) cholesterol >5. Hyper-triglyceridemia was defined as total venous plasma triglyceride concentration >1.6 mmol/l[18,19]. Current cigarette smoking was defined as smoking within the last five years while former cigarette smoking was defined as abstention longer than 5 years.

Variables, including initial clinical manifestations and laboratory and neuroimaging findings associated with underlying problems between those with and those without SBI, were analyzed using the Chi-square test or Fisher's exact test, as appropriate. Stepwise logistic regression analysis was used to evaluate the relationship between metabolic risk factors and SBI after adjusting for other potential confounding factors. Only variables strongly associated with SBI ($p<0.05$) were included in

Table 3. Risk factors of silent brain infarctions among healthy Taiwanese

	Without SBI (n = 184)	With SBI (n = 15)	Crude OR (95% CI)	p value	Adjusted OR (95%CI)	p value
Age, y	53.5±13.0	66.4±8.2		<0.0001	1.07 (1.02-1.13)	0.012
Gender (male/ female)	96/85	5/10		0.182		
Body mass index, kg/m^2	24.4±3.7	24.7±3.0		0.85		
Waist circumference (cm)	86.3±9.4	88.3±8.1		0.41		
Waist-to-hip ratio	0.91±0.07	0.93±0.06		0.16		
Underlying diseases						
Diabetes mellitus	18	5	4.6 (1.4-15.0)	0.018		
Hypertension	54	12	9.6 (2.6-35.5)	<0.0001	5.62 (1.45-21.7)	0.012
Smoking	21	2	1.19 (0.25-5.66)	0.69		
Hyperlipidemia	65	10	3.67 (1.20-11.17)	0.016		
Obesity	23	2	1.08 (0.23-5.08)	0.59		
Mean blood pressure on presentation						
Mean systolic BP (mmHg)	130.0±18.8	140.8±11.9		0.03		
Mean diastolic BP (mmHg)	78.9±99.6	78.8±5.7		0.95		
Fasting blood sugar, mg/dL	102.4±22.1	101.1±12.0		0.84		
Uric acid, mg/dL	5.8±1.5	5.9±1.9		0.86		
Cholesterol, mg/dL						
Total	199.6±38.9	206.8±35.0		0.54		
HDL-C	54.48±14.24	52.9±16.56		0.72		
LDL-C	120.3±51.9	127.9±34.9		0.64		
Triglyceride, mg/dL	131.9±90.6	144.2±67.3		0.66		
HBA1C	6.4±1.5	5.8±0.5		0.40		

Abbreviation: SBI, silent brain infarction

Values expressed as mean±SD

the final model. All statistical analyses were conducted using the SAS software package, version 9.1 (2002, SAS Statistical Institute, Cary, North Carolina).

RESULTS

The 199 healthy subjects included 103 males (mean age: 53.2 years; range, 25-83 years) and 96 females (mean age: 55.9 years; range, 20-82 years). Hyperlipidemia, hypertension, and smoking were the three most common vascular risk factors in males, while hyperlipidemia, hypertension, and diabetes mellitus were the three most common in females.

The age distribution of study subjects and prevalence of SBI were listed in Table 2. The prevalence rate for SBI increased in both males and females, from the age group of 50-59 years old to the age group >70 years old. The prevalence rate was 10.4 among females and

4.9 among males, respectively.

Comparisons of metabolic risk factors and underlying diseases between healthy subjects with and those without SBI were listed in Table 2. Statistical analysis of baseline metabolic risk factors and underlying diseases between the two groups revealed that hypertension ($p<0.0001$; OR 9.6, 95% CI 2.6-35.5) and DM ($p=0.018$; OR 4.6, 95% CI 1.4-15.0) as the underlying disease, mean systolic arterial pressure ($p=0.03$), and mean age ($p<0.0001$) were significant variables. These three, together with DM as underlying disease, were the variables used in the stepwise logistic regression model. After analysis, only mean age ($p=0.012$; OR 1.07, 95% CI 1.02-1.13) and hypertension as the underlying disease ($p=0.012$; OR 5.62, 95% CI 1.45-21.7) were independently associated with SBI. Any increase of one year in mean age increased the rate by 7.3%.

DISCUSSION

The incidence and prevalence of SBI varies widely, depending on the population studied, imaging technique used, infarct definition applied, and inclusion and exclusive criteria[5-7,20-23]. The overall prevalence rate of SBI is estimated to be 8-28% in the general population, with differences mainly explained by age[5,6,20-23]. In this study, SBI occurred in 15 (7.5%) out of 199 healthy subjects, including 4.9% (5/103) males and 10.4% (10/96) females. The incidence of SBI here is lower than those in other reported series[5-7,20], which may be attributed to the inclusion criteria that enrolled only healthy subjects from the neurologic health examination center and excluded the high-risk group of SBI (e.g. patients with pre-existing neurologic deficits and cardiovascular events or end-organ damage related to chronic hypertension like symptomatic cerebral infarctions and coronary artery, peripheral artery, and chronic kidney diseases).

The selection of patients can hamper the identification of risk factors for silent brain infarcts. As such, the assessment of risk factors is best done in the general population. Moreover, risk factors can affect individuals differently by modifying environmental and genetic factors, though little has been reported as to how genetics can affect the risk factors of SBI[24,25]. Aside from age, hypertension is the most widely accepted risk factor that is strongly associated with SBI in most studies, including this one[5,7,21,26,27]. Hypertension has a crucial role in the pathogenesis of SBI, but the association between hypertension and SBI needs to be defined more clearly through further research, particularly in view of the possibility of preventing subsequent stroke by controlling hypertension. To date, the diagnosis of hypertension in most studies is based on isolated blood pressure measurements or on self-reporting[5,7,21,26,27]. The effects of anti-hypertensive drugs on blood pressure may have different effects on the risk of SBI. Therefore, blood pressure monitoring for extended periods may be more important than isolated measurements.

The present study examines risk factors associated with SBI in healthy subjects and has two major findings. First, high mean age is associated with SBI occurrence, which is consistent with other studies[5-7,20-23]. In the present study, there is a close relationship between elderly patients and SBI in, and any increase of one year in mean age increases the SBI rate by 7.3%. Second, hypertension and DM are the major modifiable risk factors in this specific population sub-group.

This study has several limitations. This is a retrospective cross-sectional study and is therefore subject to the bias of unmeasured factors. It is also not possible to assess the effects of treatment for patients with vascular risk factors in preventing subsequent cardiovascular events. There should be care in drawing conclusions. Furthermore, patients with established cardiovascular events (e.g. coronary artery diseases, symptomatic cerebral infarctions or intra-cerebral hemorrhage, chronic kidney diseases or peripheral arterial diseases) and pre-existing neurologic deficits have been excluded. Thus, there is continued uncertainty in assessing the incidence of SBI and the relationship between cardiac and renal damage in non-selected patients. Several healthy subjects in this study have also controlled their risk factors (e.g. hypertension, hyperlipidemia, and DM) with medications. These medications may be confounding factors for the occurrence of SBI and the findings may underestimate the "true" frequency of SBI.

In conclusion, SBI are common among the elderly and presents as subtle neurologic deficits that can go unnoticed. Metabolic risk factors known to increase the risk of SBI, with hypertension being the strongest modifiable risk factor identified. More prospective, longitudinal studies are warranted to evaluate the relationship between the control of hypertension and SBI in this specific group of patients, and to determine the prevention of subsequent symptomatic stroke.

DECLARATIONS

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Ethics approval

The study was approved by Chang Gung Memorial Hospital's Institutional Review Committee on Human Research

Competing interests

All of the authors declare no competing or conflicts of interests.

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