Risk Factors for Vascular Dementia: A Hospital-Based Study in Taiwan

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Abstract-

Background: In Taiwan, next to Alsheimer's, vascular dementia (VD) is the second leading cause of dementia in the elderly. Few studies have examined cardiovascular risk factors and their association with VD in Taiwan.

Methods: This is a case-control study using a sampling of subjects from the outpatient memory clinics of two hospitals. Identified cases were those patients diagnosed with VD based on the DSM-IV criteria. The controls were subjects with Clinical Dementia Rating Scale as 0, i.e. no dementia from the same dementia registry database. Exposure was recorded by means of a risk factor questionnaire or medical examination.

Results: There were a total of 190 patients with VD and 155 controls in this study. Significant risk factors were age, hypertension, diabetes and hyperlipidemia. There was no correlation with sex, education, cigarette smoking or alcohol consumption.

Conclusions: This study confirmed reported cardiovascular risk factors contributing to VD as in Western countries.

Key Words: Vascular dementia, Cardiovascular risk factor, Case-control, Taiwan

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INTRODUCTION

With increasingly aged populations in most countries, vascular dementia (VD) will probably become the most common type of dementia[(1)]. In Taiwan, VD is the second leading cause of dementia in the elderly, responsible for more than 20% of all the dementia cases next to Alzheimer's disease (AD)[(2-3)].

There is evidence of the interactions between stroke and dementia. Cardiovascular disease may also cause VD or worsen degenerative dementias by compromising perfusion within the brain. Previous studies have demonstrated that risk factors for VD are age[(4)], hypertension[(5)], diabetes[(6)], cigarette smoking[(7)], coronary heart

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disease[8], congestive heart failure[9] and hyperhomocysteinemia[10].

There are several epidemiological studies of dementia in Taiwan[3,11]. However, none of them investigated vascular risk factors associated with VD. A report indicated that predictors of post-stroke dementia were old age, being a laborer, prior stroke, left carotid vascular territory stroke, cognitive impairment and initial poorer function status following stroke. However, vascular risk factors including prior hypertension, diabetes and hypercholesterolemia had no significant association because the authors used stroke samples as a base population[12].

Identification of the risk factors for VD is essential to provide prevention and reduction of severity from VD. We conducted a hospital-based case-control study in two hospitals in northern Taiwan to examine the association between vascular risk factors and VD.

METHODS

The study subjects were recruited from specialized dementia clinics at the Chang Gung Memorial Hospital (CGMH) and St. Paul's Hospital. The former is a medical center with more than 3000 inpatient beds. The latter is a regional hospital with approximately 400 beds. Both are located in northern Taiwan.

In the dementia clinics, all patients with memory complaints, memory disorders or dementia were registered. A series of assessments were administered, including a clinical history review, physical and neurological examinations and the Mini-Mental Status Examination (MMSE), the Clinical Dementia Rating (CDR) scale[13], laboratory examinations, neuroimaging studies and/or neuropsychological assessments (NPA). We collected the information by interviewing the patients and their caregivers. A team including neurologists and neuropsychologists evaluated all patients.

Dementia was diagnosed based on the Diagnostic and Statistic Manual of Mental Disorder, 4th edition (DSM-IV) criteria[14], so too with the diagnosis for VD. The diagnosis of AD was based on the NINCDS-ADRDA Criteria[15]. Normal subjects were sampled from the registry of the clinics, as those with a CDR score of 0. Since those with a CDR score of 0.5 might suggest normal, mild cognitive impairment or very mild AD[16], they were excluded deliberately to reduce the bias of misclassification.

Study variables were classified into two categories: demographic and medical factors. The former included age, sex and education level from patients or informants. Medical factors include hypertension, diabetes, hyperlipidemia, smoking, and alcohol consumption. Hypertension was defined if the patient had ever been so diagnosed, is taking antihypertensive agents or presently has documented high blood pressure (140/90 mmHg) in at least two occasions in one week during the visits. Diabetes was defined if the patient had ever been so diagnosed, is taking antidiabetic medications or has a documented fasting blood sugar level greater than 126 mg/dl during the visits. Hyperlipidemia was defined as a total cholesterol level greater than 200 mg/dl or a triglyceride level greater than 150 mg/dl or current use of lipid lowering agents. Smoking and alcohol consumption were assessed as present or past/never.

Statistical methods

For statistical tests, p-value with a level of less than 0.05 was considered significant. All tests were two-sided. For univariate comparisons of cases and controls, chi-square test was used for categorical variables and two-sample t test for continuous variables. Mantel-Haenszel odds ratios were calculated. For multivariate analyses, significant variables found in univariate analyses were included in a logistic regression model to determine the effect size and significance as risk factors for VD.

RESULTS

A total of 773 subjects were included as the population base of this study between July 1, 2003 and October 31, 2005. Among them, 155 (20.0%) were normal, 74 (9.6%) mild cognitive impairment, 252 (32.6%) AD, 190 (24.6%) VD and 102 (13.2%) other types of dementia or dementia with undetermined etiology. For the current study, only the subjects with the diagnosis of "normal"

(as the controls) and those with VD (as the cases) were analyzed.

The age distributions were 76.4±9.0 (mean±SD) years old (range from 46 to 102) for VD case group and 66.6±11.0 years old (range from 45 to 93) for control group (Table 1). Controls were significantly younger than the cases. There was no statistical difference in the proportion of men and women. The controls had a higher education level compared with the cases (6.6±4.6 vs 4.4 ±4.9 years, p<0.001). In both study groups, age was significantly correlated with years of education (Pearson correlation coefficiency -0.144 with p=0.047 and -0.258 with p<0.001 for the cases and controls, respectively). The distribution of both groups is not different between the two hospitals (67.4% is to 32.6% in cases and 65.2% is to 34.8% in controls, p=0.67).

The prevalence of hypertension, diabetes, and hyperlipidemia were all significantly higher in the cases than in the controls (Table 2). There was no statistically significant difference in cigarette smoking and alcohol consumption. Smoking was not a risk factor when men and women were considered separately (15.6% in cases versus 25% in controls for men, p=0.129 and 4% versus 5.1% for women, p=0.732). Multivariate logistic analysis determined the independent risk factors (Table 3). Age, hypertension, diabetes and hyperlipidemia were significant risk factors for VD, while gender and education were not.

Table 1. *Demographic data*

Variable	VD cases	Normal controls	p
n	190	155	
Male, %	47.4%	49.0%	0.83
Education, years	4.42±4.86	6.59± 4.61	<0.001
Age, years	76.38±9.04	66.58±11.01	<0.001
Hospital (CGMH), %	67.4%	65.2%	0.73

VD: vascular dementia; CGMH: Chang Gung Memorial Hospital; Mean±SD.

Table 2. *Univariate analyses of medical factors*

Variable	VD cases	Normal control	Odds ratio†
n	190	155	(95% CI)*
Hypertension	131 (68.9%)	49 (31.6%)	4.80 (3.04-7.59)*
Diabetes	76 (40.0%)	17 (11.0%)	5.41 (3.03-9.68)*
Hyperlipidemia	79 (41.6%)	22 (14.2%)	4.30 (2.52-7.35)*
Smoking	18 (9.5%)	23 (14.8%)	0.60 (0.31-1.16)
Alcohol consumption	30 (15.8%)	36 (23.2%)	0.62 (0.36-1.06)

VD: vascular dementia; †Mantel-Haenszel odds ratio; *p<0.001.

DISCUSSION

To our knowledge, this study is by far the largest hospital-based study on vascular dementia in Taiwan. In this study, we found that age, hypertension, diabetes, and hyperlipidemia were related to VD, whereas gender, education, smoking and alcohol consumption were not. Some reports pointed out that risk factors for VD were similar to those for cardiovascular disease, carotid atherosclerosis and stroke, including hypertension, hyperlipidemia, diabetes and smoking[17,18]. Our study showed consistent findings.

Age was associated with increased risks of VD in many incidence studies[3,4,11]. Although age was associated with many vascular factors, the association between age and VD remained significant after adjustment for these factors, thus supporting age as an independent risk factor for VD.

There is a controversy about whether education may provide protection against dementia. Some suggested that higher education compensates the neurodegenerative changes instead of protection from dementia[19]. A lower education level may place one at greater risk of dementia. Recently, a meta-analysis of 19 studies also supported this finding[20,21]. In our study, education was significantly lower in the cases than in the controls.

Table 3. *Multivariate analysis of risk factors for VD*

Variable	Odds ratio† (95%CI)
Gender, male vs female	1.02 (0.55-1.89)
Age, years	1.10 (1.07-1.14)*
Hypertension	3.16 (1.81-5.52)*
Diabetes	3.75 (1.89-7.46)*
Hyperlipidemia	3.65 (1.92-6.95)*
Smoking	1.00 (0.40-2.48)
Alcohol consumption	0.70 (0.32-1.52)
Education, years	0.95 (0.90-1.01)

VD: vascular dementia; *p<0.001; †Adjusted for hospitals.

However, the association between VD and education disappeared in the multivariate model. Age was a confounding factor because the correlation of education with age was higher in the controls than in the cases.

Many epidemiologic studies have shown that men have a higher risk of stroke than women, so too with VD[22-23]. Gender differences in risk profiles, endocrine and stress burden may play a role. Surprisingly, our study showed no association between VD and gender. There were two hypotheses. Traditionally, older men were retired with reduced functional requirement, whereas women still took more responsibility in household jobs than men when they were old. Older women may more easily manifest impaired functions than men. On the other hand, there have been neuropathology findings of AD observed in the patients with clinical diagnosis of vascular dementia in recent studies[24]. Since women are prone to AD[25], the gender effect was subsequently biased toward the null by the nondifferential misclassification, as in our study.

Smoking is associated with many diseases such as atherosclerosis or cardiovascular disease as well as stroke[26]. The relationship between VD and smoking was positive in some studies[7,27], but our study has not shown a statistically significant association between the presence of VD and a history of smoking. One should be careful to interpret this finding. In 2001, the prevalence rate of smoking was 46.8% among adult males in Taiwan; and, the smoking rate among females was about 4.3%[28]. In our study groups, the rate of smoking history was relatively low, 9.5% in cases and 14.3% in controls, that fact may cause the underestimation of the power of smoking as a risk factor. Further investigation is needed to clarify this questionable point.

Several studies showed regular light to moderate drinking seemed to be associated with a decreased risk for dementia[4,29]. In a Rotterdam study[30], one to three drinks of alcohol per day was significantly associated with a lower risk of any dementia and vascular dementia. Alcohol consumption in our study was of a similar effect size, although not significant. It may have resulted from a small sample size.

The strength of this study is that a diagnosis of VD was based on standardized diagnostic criteria and made by neurologists. The ascertainment of normal controls was based on a detailed history inquiry in performing a CDR assessment. In addition, the diagnosis of comorbid diseases, such as hypertension and diabetes, is more precise than that among a community-based sample.

This study has some limitations. The mean age of controls was significantly lower than the cases. Factors associated with older age people may be falsely identified as risk factors. Although the confounding bias might be reduced by adjustment in the multivariate model an age-comparable or -matched control group would be required. Some variables such as smoking and alcohol exposure history and the missing data could be another source of biases. The retrospective informant interview may not measure the exposure adequately/accurately. We should design another standardized detailed screening questionnaire for the assessment of clinical symptoms and medical history. Further, a prospective study is needed with a larger sample size selected from multiple hospitals, detailed interview and appropriate controls. Such a new prospective study should also investigate level of exposure to risks, as well as any possible relationships between risk exposures and genetic factors. Finally, our study design is unable to investigate whether the risk factors studied are related to VD independent of stroke history. Because they are highly correlated with both stroke history and VD, it is difficult to distinguish their effects from stroke history in the statistic models due to collinearity.

The more vascular risk factors we have, the higher our chances of having a stroke or VD. Many risk factors can be controlled if we attend to the matter properly. Prevention or adequate management of vascular risk factors such as hypertension, diabetes and hyperlipidemia is the available way to prevent stroke and VD.

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