The Association of Stroke and Family History of Stroke Depends on its Subtypes and Gender: A Family History Study in Taiwan

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Abstract-

Objective: Family history is a risk factor for stroke. The objective of this study was to investigate whether stroke subtypes and gender might have a familial contribution to stroke.

Methods: Detailed family history analysis was used to investigate the parents or siblings of the probands and controls who were classified into 3 groups: probands, outpatient controls, and spouse controls. The lifetime risk (LTR) of stroke was estimated using a Cox proportional hazard model.

Results: The 684 probands and controls yielded 1066 parents and 3247 siblings. Compared to the parents and siblings of the controls, those of the stroke patients had a significantly higher LTR. The findings were consistent between probands with cerebral infarction (CI) or cerebral hemorrhage (CH), independent of diabetes, hypertension, and smoking. With regard to gender, family history of stroke was significant for both parents and siblings of the CH or CI patients, but not for the fathers of CI patients and sisters of CH patients. The family history of stroke was associated with an increased risk of stroke of all subtypes, except cardioembolism.

Conclusions: This study supported the familial contribution to stroke in the case of both CI and CH but not cardioembolism, independent of the established risk factors for stroke. Gender differences in familial clustering of stroke subtypes were also revealed. These results warrant further molecular genetic studies.

Key Words: Cerebral hemorrhage, Cerebral infarction, Family history, Stroke, Taiwan

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INTRODUCTION

Family history has been shown to be a risk factor for stroke[1,2]. In addition, there is speculation that subtypes of stroke and gender offer different familial contribution to stroke occurrence, but reported results are inconsis-

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tent. For example, stroke in a cohort of men was significantly associated with maternal death from stroke[3]. A European stroke registry showed that stroke occurrence in females was associated with a maternal history of stroke[4]. In the Framingham Offspring Study, stroke in offspring was associated with verified parental stroke. The adjusted risk of stroke in probands with a paternal history of stroke was 2-fold that in probands with a maternal history of stroke (2.4 versus 1.4, respectively)[5]. The family history of cerebral hemorrhage (CH) is also a significant risk factor for CH[6,7]. Recent studies have shown that all stroke subtypes except cardioembolism carry familial risks of stroke[8-10]. However, many studies have not shown familial aggregation[11,12].

One of the causes of this inconsistency stems from the methods adopted to investigate the familial clustering of stroke. We conducted a family study using a detailed family history method[13] to compare the lifetime risk (LTR) of stroke in the first-degree relatives of patients with different stroke subtypes and controls.

MATERIALS AND METHODS

Probands and controls

Probands were defined as patients who had experienced stroke within 1 year prior to the interview. We consecutively recruited patients with acute stroke when they were hospitalized or followed-up in the outpatient department (OPD) at Chang Gung Memorial Hospital, a major medical center in northern Taiwan. Critically ill patients were excluded because their hospital stay would probably be too short or they would be discharged from the emergency room; hence, detailed information about them may not be available.

The controls were selected from 2 sources: patients from the OPD and spouses of the eligible probands. The OPD subjects were stroke-free patients who visited the OPD for symptoms unrelated to stroke, such as neuropathy, myofascial pain, headache, or neurosis; those with "stroke-related" symptoms such as dizziness or vertigo, visual problems, weakness, or gait disturbance were excluded. One or two outpatient controls were recruited within 3 days when a proband was hospitalized. The controls were selected such that their age distribution resembled, as closely as possible, that of the probands. Spouses of the probands were eligible as controls if they were alive and available at the time of the interview and consented to release information regarding their relatives. Probands and controls who were adopted were not considered eligible.

Stroke was defined as a sudden neurological deficit of presumed vascular origin. All patients with stroke were examined by neurologists. Computed tomography of the brain was available for all probands; thus, ischemic stroke could be accurately differentiated from CH. Most patients underwent computed tomography of the brain within 1 week after the stroke onset. Stroke was classified into 5 categories according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria[14]: (1) small-vessel occlusion, (2) large-artery atherosclerosis, (3) cardioembolism, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology. Patients with transient ischemic attacks (TIAs) were excluded.

CH included intraparenchymal hemorrhage and intraventricular hemorrhage. Patients with subarachnoid hemorrhage (SAH) or hemorrhage secondary to head injury were excluded because most of these patients were managed by neurosurgeons.

Data collection

The study subjects of interest were the first-degree relatives of the probands and controls and were accordingly categorized into 3 groups: stroke, OPD controls and spouse controls, respectively.

A questionnaire was administered to the probands and controls by qualified nurse assistants. An interview was conducted personally, whenever possible. When the probands were unable to answer the questions (for example, if they were aphasic or unconscious) or when their spouses were deceased, their close relative served as a surrogate and was interviewed to obtain the "best information". The outpatient controls were interviewed in person.

The questionnaire included questions directed to the probands and controls and to their parents and siblings.

These questions were about gender; current age; the use of tobacco; and the presence of diabetes (DM), hypertension (HT), and stroke. The history of stroke for each relative was obtained through the following questions: "Did she/he have a stroke, i.e., abrupt-onset weakness of limbs of one side?" or "Was she/he diagnosed with stroke by a physician?" The relative of a proband or control was considered hypertensive if she/he had ever been diagnosed thus or had ever been under antihypertensive treatment. DM was defined in a similar manner. If the aforementioned medical conditions were present, the age at the onset of the condition (first episode, if multiple) was identified. If a first-degree relative was deceased, the age and cause of death were recorded. Only biological relatives were included in the analysis.

Data analysis

To minimize the bias due to nonrandom sampling of family members, we eliminated the probands and controls themselves from the analysis and treated each relative as an individual subject in the analysis, according to the statistical method suggested by Chakraborty and Hanis[15]. The age of the relatives was compared among the 3 study groups by one-way analysis of variance (ANOVA). The effect of family history of stroke was estimated by calculating the prevalence of stroke among the parents (mothers or fathers) and among the siblings (sisters or brothers) of the probands and controls in the 3 groups; these prevalences were compared using a χ^2 test. We also compared the prevalences between patients with cerebral infarction (CI) and CH.

The LTR of stroke was estimated by survival analysis using the Cox proportional hazards model. The time variable was the age at the onset of stroke. The exposure of interest was being a parent or sibling of the probands and controls. Death was the censoring variable. The subjects were dropped out if their information regarding DM, HT, stroke, smoking status, age, and the age at stroke onset was unavailable. The covariates of interest were smoking, DM and HT that had been present before or at the age of stroke onset. Each relative was treated as a single observation in the analysis.

In each regression model, the outpatient control group data was considered as baseline (non-exposed group). The regression coefficients of the group status denoted the magnitude and significance of the familial contribution of stroke. Association was also examined for CI, CH, and different types of ischemic stroke classified according to their pathogenesis. For parsimony, statistical interaction was not introduced in the model. Instead, each model examined exclusively males or females or both, yielding different models for mothers, fathers, and parents and for sisters, brothers, and siblings.

RESULTS

Demography of probands and controls

A total of 684 probands and controls were recruited. These included 223 stroke patients, 179 spouses of these patients, and 282 OPD controls. Their mean ages were 63.4±11.6, 61.0±10.5, and 61.3±10.3 years, respectively ($p = 0.0356$). A total of 185 probands were diagnosed with CI (83.0%), and the remaining 38 (17%) were diagnosed with CH.

In total, 1066 parents and 3247 siblings of the

Table 1. *Number and age of parents and siblings in the 3 groups of probands and controls*

	Parents		Siblings	
	n (% Male)	Age (y)	n (% Male)	Age† (y)
Probands	340 (47.9%)	70.0 ± 14.3	1001 (53.1%)	57.1 ± 15.0
OPD control	455 (49.5%)	71.0 ± 14.0	1428 (49.2%)	53.9 ± 16.2
Spouse	271 (49.4%)	73.9 ± 13.2	818 (51.0%)	58.1 ± 14.9
Overall	1066 (49.0%)	71.4 ± 14.0	3247 (50.9%)	55.9 ± 15.6

OPD: outpatient department. †Analysis of variance, $p < 0.001$.

probands and controls were analysed (Table 1). No significant difference was observed in the ages of the parents. However, the siblings of the OPD controls were significantly younger than those of the stroke patients and their spouses. In both parents and siblings, the occurrence of stroke did not differ significantly between males and females.

Prevalences and LTRs of stroke

The prevalences of stroke among the parents of the probands and controls are shown in Table 2 and that among the siblings, in Table 3. The LTRs of the parents and siblings are listed in Table 4 and Table 5, respectively.

The mothers, fathers, and parents of the probands with either CI or CH exhibited a significantly higher prevalence than those of the OPD and spouse controls ($p = 0.003$, $p = 0.007$, and $p < 0.001$, respectively; Table 2). A total of 20.1% and 29.5% of the parents of the probands with CI or CH, respectively, were reported to have stroke, while only 11.2% and 13.7% of the parents of the OPD and spouse controls, respectively, had experienced stroke. The prevalence of stroke in the fathers of patients with CI was lower than that in the mothers (17.4% versus 22.5%, respectively), whereas the prevalence in the fathers of patients with CH was higher than that in the mothers (35.5% versus 23.3%, respectively).

As shown in Table 3, 2.0% and 3.4% of the siblings of the OPD and spouse controls, respectively, were reported to have experienced stroke, while such a history was noted in only 6.9% and 4.6% of the siblings of the CI and CH patients, respectively ($p < 0.001$). When men and women were considered separately, the association remained significant, except in the case of the sisters of the probands with CH.

The proportional hazard model using OPD controls, adjusted for DM, HT, and smoking, the association remained significant with hazard ratios (HRs) of 1.75 (95% confidence interval, 1.16~2.63) for being a parent and 2.17 (1.17~4.01) for being a mother. (Table 4) Furthermore, being a parent, a mother, or a father of patients with CH was significantly associated with a high LTR for stroke; the association remained significant even after adjustments for DM, HT, and smoking, yielding adjusted HRs of 2.84 (95% confidence interval, 1.64~4.91), 2.82 (1.18~6.79), and 2.81 (1.39~5.70), respectively.

In the estimation of the LTR of stroke among the siblings (Table 5), being siblings and brothers of the patients with CI and CH and sisters of the patients of CI were shown to be at a significantly higher risk of stroke than these same respective relatives of the OPD controls.

Table 2. *Prevalence of stroke in the mothers and fathers of the subjects of the 3 study groups*

Probands and controls	Parents			Mother			Father		
Infarction	56/279	(20.1%)	**	33/147	(22.5%)	***	23/132	(17.4%)	
Hemorrhage	18/61	(29.5%)	***	7/30	(23.3%)	*	11/31	(35.5%)	**
Spouse	37/271	(13.7%)		21/137	(15.3%)		16/134	(11.9%)	
OPD Controls	51/455	(11.2%)		21/230	(9.1%)		30/225	(13.3%)	

OPD: outpatient department. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, compared to OPD controls; χ^2 test.

Table 3. *Prevalence of stroke in the sisters and brothers of the subjects of the 3 study groups*

	Siblings			Sister			Brother		
Infarction	56/807	(6.9%)	***	21/384	(5.5%)	***	35/423	(8.3%)	***
Hemorrhage	9/194	(4.6%)	*	2/85	(2.4%)		7/109	(6.4%)	
Spouse	28/818	(3.4%)		9/401	(2.2%)		19/417	(4.6%)	
OPD Controls	29/1428	(2.0%)		10/725	(1.4%)		19/703	(2.7%)	

OPD: outpatient department. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, compared to OPD controls; χ^2 test.

After adjustments for DM, HT, and smoking, the association remained significant with HRs of 2.11 (95% confidence interval, 1.30~3.43), 3.11 (1.42~6.80), and 2.28 (1.17~4.45), respectively.

The TOAST subtypes of stroke in the patients were also considered, as shown in Table 6. In the probands, being a parent or a sibling of a stroke patient was associated with an increased risk of all stroke subtypes, except cardioembolism. Even after adjustments for DM, HT, and smoking, the association remained significant in the parents and siblings of patients with small-vessel disease or intraparenchymal hemorrhage and in the siblings of patients with large-vessel disease.

DISCUSSION

This study showed that, compared to the parents and siblings of the outpatient and spouse controls, those of the stroke patients were at an increased risk of stroke. The findings were consistent for both CH and CI, except

Table 4. *Lifetime risk of stroke of being mothers and fathers of the probands and controls*

	Parents				Mother				Father			
	Unadjusted											
Probands and spouse controls	HR	95% CI			HR	95%CI			HR	95%CI		
Infarction	1.86	1.27	2.72	**	2.47	1.43	4.28	**	1.38	0.80	2.39	
Hemorrhage	2.89	1.69	4.95	***	2.82	1.20	6.63	*	2.90	1.45	5.78	**
Spouse	1.05	0.69	1.60		1.51	0.82	2.77		0.73	0.40	1.35	
	Adjusted†											
Probands and spouse controls	HR	95% CI			HR	95% CI			HR	95% CI		
Infarction	1.75	1.16	2.63	**	2.17	1.17	4.01	*	1.34	0.74	2.40	
Hemorrhage	2.84	1.64	4.91	***	2.82	1.18	6.79	*	2.81	1.39	5.70	**
Spouse	1.07	0.68	1.67		1.41	0.73	2.70		0.81	0.43	1.54	

HR: Hazard ratio; estimated by Cox proportional hazard regression using OPD controls as baseline; 95%CI: 95% confidence interval. †Adjusted for hypertension, diabetes, and smoking. ***p < 0.001, **p < 0.01, *p < 0.05.

Table 5. *Lifetime risk of stroke of being sisters and brothers of the probands and controls*

	Siblings				Sister				Brother			
	Unadjusted											
Probands and spouse controls	HR	95%CI			HR	95%CI			HR	95%CI		
Infarction	2.54	1.62	3.98	***	2.34	1.10	5.02	*	2.54	1.45	4.45	**
Hemorrhage	3.01	1.42	6.37	**	2.19	0.48	10.0		3.34	1.40	7.96	**
Spouse	1.22	0.72	2.05		1.11	0.45	2.73		1.27	0.67	2.40	
	Adjusted†											
Probands and spouse controls	HR	95%CI			HR	95%CI			HR	95%CI		
Infarction	2.11	1.30	3.43	**	3.11	1.42	6.80	**	2.28	1.17	4.45	*
Hemorrhage	3.01	1.35	6.69	**	1.40	0.29	6.66		4.65	1.76	12.2	**
Spouse	0.93	0.51	1.69		0.53	0.17	1.65		1.76	0.86	3.60	

HR: Hazard ratio; estimated by Cox proportional hazard regression using OPD controls as baseline; 95%CI: 95% confidence interval. †Adjusted for hypertension, diabetes, and smoking. *** p < 0.001, ** p < 0.01, * p < 0.05.

Table 6. *Lifetime risk of stroke of being parents and siblings of the patients with different stroke subtypes*

	Parents				Siblings			
	HR	95%CI		p	HR	95%CI		p
	Unadjusted							
Large-vessel occlusion	1.85	1.10	3.11	*	2.56	1.42	4.60	**
Embolism	1.23	0.38	3.96		1.95	0.68	5.59	
Small-vessel occlusion	2.32	1.31	4.10	***	4.17	2.40	7.25	***
IPH	3.85	2.26	6.56	***	3.37	1.53	7.44	**
	Adjusted†							
Large-vessel occlusion	1.16	0.68	1.99		1.89	1.04	3.45	*
Embolism	1.30	0.40	4.21		1.22	0.42	3.55	
Small-vessel occlusion	2.06	1.16	3.66	*	3.63	2.08	6.35	***
IPH	2.48	1.42	4.33	**	3.85	1.72	8.59	**

HR: Hazard ratio, estimated by Cox proportional hazard regression using OPD controls as baseline; 95%CI: 95% confidence interval; IPH: intraparenchymal hemorrhage. †Adjusted for hypertension, diabetes, and smoking. ***$p<0.001$, **$p<0.01$, *$p<0.05$.

cardioembolism, and independent of DM, HT, and smoking. The analysis of gender showed that the association was significant for all first-degree relatives of the patients with either CH or CI or both, with the exception of the fathers of CI patients and the sisters of CH patients.

The results of many studies have supported that different subtypes of stroke may have different patterns and degrees of familial clustering. By using death certificate data, a previous study showed that the incidence of deaths due to stroke was high in the index patients with angiographic evidence of occlusive disease of the extra- and intracranial vessels[16]. In the Lausanne Stroke Registry[17], a family history of stroke was associated with large-artery disease rather than with small-artery disease. Jerrard-Dunne P et al.[18] found that the association was present only when stroke occurred at the age of ≤65 years. Our study indicated that all stroke subtypes, except embolism, carried familial risks of stroke, similar to the results of other studies[8,9,19].

Few studies have focused on the familial clustering of intraparenchymal hemorrhage[7,20-22], excluding SAH. Alberts et al.[20] reported that 53% of 144 CH patients had a family history of any type of stroke. Another study found that brothers of women with a history of stroke were at a higher risk of CH; the odds ratio was 3.9[22]. However, a case-control study in Japan[21] that compared SAH, CH, and CI showed that family history of SAH and CH were significantly associated with the occurrence of the individual diseases, whereas a family history of CI was not. The association remained significant only for SAH in multivariate analysis. In our study, CH was associated with the familial occurrence of stroke, except in the sisters of the CH patients.

Our study also showed gender differences in familial aggregation among the stroke subtypes. The mothers of stroke patients were at significantly higher risks of CH and CI, while the fathers were at a minimal risk of CI. Similar findings have been reported in men with a maternal history of stroke: the incidence of stroke was significantly higher in these men than in subjects without such a history[16,3]. A recent population study of women with young-onset stroke showed an increased risk of stroke in mothers but not in fathers, although no significant increase was noted in the family history of stroke in the probands with CI[23]. Our study also found that the risks for both CH and CI were significantly increased in the brothers of stroke patients, while the sisters were at a significantly higher risk for CH only. Likewise, a high incidence of death from CH was reported among the brothers of women with CH[22]. In one study, family history of stroke in any first-degree relative

was an independent predictor of death from ischemic heart disease in elderly men and of death from stroke in elderly women[24]. However, other studies have not shown such gender differences[25,5,9].

Many risk factors of stroke, such as HT and DM, themselves show familial clustering, and familial aggregation of stroke may be a marker of these risk factors[26,27]. Our study showed that the risk of being a first-degree relative of a stroke patient is an independent risk factor for stroke, because it remained statistically significant even after adjustments for HT, DM, and smoking. However, one limitation of this study was that many other confounding factors could not be obtained reliably because such information was indirect from the probands and controls.

An advantage of our study is the method adopted, i.e. detailed family history questionnaire[13,15]. By using age at stroke onset as the time variable, it was assumed the starting point of following up was at age 0. The estimated HR was thus equivalent to the LTR for stroke. With the hazards model, it is possible to control for multiple associations. Many of the studies reported thus far did not adjust for censoring bias. First, they treated family history of stroke as a dichotomic attribute of the probands and controls (an abbreviated family history method was adopted). The resulting estimates of the effect of the family history of stroke might be biased because it increases with sibling size. Second, many siblings are likely to remain at risk later in life, whereas the prevalences in parents may be expected to more closely approximate the LTRs. Only a few studies, including the present study, have considered these factors[28]. Another study for other complex disorders, including Alzheimer disease and Parkinson disease, adopted methods similar to ours[29].

A potential weakness of this study is recall bias. However, we used spouses as alternative controls to minimize this bias[30]. The spouses might have a similar degree of recall bias while providing proxy data about their close relatives and about the patients. They resemble the probands in their sociodemographic characteristics. Furthermore, spouses tend to exhibit a similar prevalence of vascular risk factors[31] and share environmental and cultural exposures in adulthood[32]. Therefore, the use of spouses as controls may contrast the genetic effect of the family history of stroke. In our study, the relative risk of stroke in the spouses of patients with stroke (including various subtypes) did not significantly differ from those in the outpatient controls, suggesting that the effect of the family history of stroke was not a result of information bias. Furthermore, OPD and spouse controls were significantly younger than the stroke group. However, the age of their relatives were comparable (Table 1) except the siblings of the OPD controls. Survival analysis with age as time variable might minimize the selection bias introduced.

Another potential weakness of this study is that many patients might have experienced multiple episodes of different types of stroke. The difference between subtypes might have been underestimated. Furthermore, some strokes might not have presented as focal weakness, and some patients who experience abrupt onset of disturbance of consciousness or sudden death might have been diagnosed with stroke. The confidence intervals of the estimated effects were wide because of the uncertainty regarding case ascertainment using a questionnaire and the heterogeneity of the causes of stroke[33].

This is one of the few studies of the family history of stroke conducted in Asians and the Chinese[34-36]. In summary, we found a significant and independent association between family history of stroke and the occurrence of stroke in first-degree relatives. Our study supported the familial contribution to stroke in the case of both CI and CH but not cardioembolism, independent of the established risk factors for stroke. Gender differences in familial clustering of stroke subtypes were also revealed. These results warrant further molecular genetic studies.

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