Recurrent Ischemic Stroke is Predicted by Intracranial Large Artery Stenosis Identified by Brain MRA: an Observational Study of 693 Patients from Kaohsiung, Taiwan

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Abstract-

Purpose: This study aimed to explore the incidence, severity and risk factors of recurrent stroke after stroke stratified by intracranial large artery stenosis (ILAS).

Methods: This was an observational study of 693 ischemic stroke patients recruited in a medical center in southern Taiwan. ILAS was identified by MRA. Vascular risk factors, therapeutic conditions and stroke severity were evaluated prospectively. Risk of events was estimated by Kaplan-Meier survival analysis and adjusted for sex, age along with all the variables of interest by Cox proportional hazard models.

Results: The mean observation period was 1.1 year with no lost to follow up. There were 57 (8.2%) patients suffered from recurrent ischemic stroke with 6 (10.5%) dead. Recurrent strokc rate was 2.3% within first month after stroke, 1.5% 31-90 days, 3% 91-365 days, and 1.2% within 365-730 days. Annual stroke recurrence was 8.6% (95%CI, 7.7-9.5). History of ischcmic stroke (HR 2.793, 1.550-5.043) and ILAS (HR 2.193, 1.197-4.018) were associated with increased risk of recurrence.

Conclusion: History of ischemic stroke along with ILAS related to the recurrence. Most of the recurrent stroke was mild in severity. Possibly due to the short interval of observation, recurrent stroke was not related to increased mortality.

Key Words: cerebrovascular disease, recurrence, magnetic resonance image, survival analysis, cohort study, Taiwan

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INTRODUCTION

Stroke is the 2nd-3rd leading cause of mortality in most developed counties since 1981 and is a major cause of adult disability in Taiwan[1]. The aim of treatment after stroke is not only to lessen the sequelae of stroke, but also to prevent further recurrence. However, despite all efforts to reduce the risk of recurrence, 25% of stroke patients are reported to suffer from recurrent stroke[2]. Recurrent strokes increase the risk of disability worsening and death[3]. While acute therapy attracts most attention with most progress, efforts to prevent

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recurrent stroke are still struggling to find better solutions[3].

The recurrent stroke rate varies among different intervals after the index event in different setting of studies and correlates to risk factors control. Community and observational studies offered important information for the recurrence. However, these studies might be limited as segmentation of insurance status or multiple payers or inequality of the resources utilization for the stroke prevention. In community and observational studies, it was reported from 1.2% to 15%[4,5], in 30 days after stroke, 7.4% to 17.3% in 90 days[5,6], 9.3% to 11.2% in the first year[7-9]; 14.1% to 23% in the first 2 years[7,10], 6% to 25% in 3 years[11-13], 16.6% to 30% in 5 years[2,11,14,15]. The risk of recurrent stroke over a 10-year period is six times greater than the risk of a first-ever stroke in the general population of the same age and sex[16,17]. In well controlled trials, recurrent stroke rate was reported as 4% in the first year, 8.4% in the 1.5 years, 9.0% in the 2.5 years and 11.2~13.1% in 5 years after minor stroke or TIA[3,17]. Due to the exclusion criteria applied, mostly minor stroke patients recruited, and attempted controlling multiple risk factors in the trials, the incidence of the recurrence might be less than expected.

Though cerebrovascular disease is abundant, less data were available regarding survival or functional outcome after stroke in Taiwan and Asia[18-23]. Recurrent rate within 30 months after first stroke was reported as 10.5%[24], and 12.7% within 3 years[25]. From a hospital based study, among patients hospitalized for acute stroke, more than 40% of patients were reported to suffer from recurrent stroke[26]. However, information regarding the control of risk factors, severity, and outcomes were not frequently reported.

A universal national health insurance (NHI) program, financed jointly by payroll taxes, subsidies, and individual premiums, commenced in Taiwan in 1995. The analysis based on this universal health insurance system is probably immune from problems arising from the complex setting of segmentation of insurance status or multiple payers, such as the U.S. health care market and neutralize the “ability to pay”. Therefore, this study provided further information about the status of recurrent stroke focused on (a) describing the recurrent stroke rate in a group of patients identified by brain MRI followed in a medical center in Taiwan; (b) exploring the factors related to the recurrent stroke, (c) analyzing the territory and severity of the recurrent stroke, (d) discussing the control rate of risk factors before the recurrence.

METHODS

Patients recruitment

This was a prospective observational study recruiting ischemic stroke patients consecutively admitted for acute management. This study was conducted in Department of Neurology, Chang Gung Memorial Hospital, Kaohsiung, Taiwan. The study protocols were approved by institutional review board of the study hospital and granted by the National Science Committee, Taiwan. The study hospital is a 2,400-bed non-profit proprietary hospital providing medical-center- level health care in Kaohsiung metropolitan area of Taiwan. It has a catchment area of approximately three million inhabitants. There are other hospitals providing services to stroke patients in the same area, including 2 medical centers and 24 community hospitals. The study hospital is the main referral hospital for all kinds of stroke in this area[27-29]. All patients lived in the catchment area of the study hospital and had the same financial arrangement offered by national health insurance.

A patient will be eligible for inclusion in this observational study only if all of the following criteria apply: 1) Patients presented with clinical diagnosis of acute ischemic stroke or TIA according to the WHO criteria. 2) Patient had adequate brain imaging performed and results confirmed no evidence of intracerebral hemorrhage. 3) Patient or his/her legally acceptable representative is willing to provide written informed consent to participate this study.

The scheduled visits of this observational study were every 6 months after enrollment. If patients were not followed in the study hospital, study nurses would have telephone contacts as scheduled if interviews were not possible. All patients were to be followed until death or

end of this study at 31 August 2006.

Intracranial large arteries included 13 segments assessed by brain magnetic resonance angiogram (MRA): bilateral intracranial internal carotid arteries, first and second part of middle cerebral arteries (MCA), anterior cerebral arteries, posterior cerebral arteries, vertebral arteries and basilar artery. MRA data were from the Philips Gyroscan Intera 1.5T or the GE Signa 1.5T. Three dimension time of flight was used. Usually the image was reconstructed from 80 images insonated centered at sella and 19 images from sagital plane. MRA criteria for the ILAS were modified from WASID[9,30]. The cutoff point of ILAS was set as ≥ 50% stenosis. Patients were grouped as with intracranial large artery stenosis (ILAS) or not.

Risk factors and therapeutic conditions

Risk factors and therapeutic conditions were screened between recurrent and index event.

The initial blood pressure, glucose, and lipid were recorded from admission records. Patients with hypertension or diabetes who had not received appropriate medications or lifestyle modification were categorized as untreated. Previously diagnosed hypertension was recognized as controlled when blood pressure was lower than 140/90 mm Hg. Diabetes mellitus was recognized as controlled when fasting serum glucose level was lower than 126 mg/dL or glycosylated hemoglobin lower than 7.0.

The status of dyslipidemia was determined by patients' past history and concurrent high serum cholesterol concentrations, low serum high-density lipoprotein (HDL) concentrations, high serum low density lipoprotein (LDL) concentrations and hypertriglyceridemia after stroke or, by observation of a persistent abnormality of these data 3 months after stroke and before the lipid-lowering agents were employed. High serum cholesterol was defined as values ≥200 mg/dL, low HDL cholesterol as <40 mg/dL in men and <50 mg/dL in women, high LDL cholesterol as ≥130 mg/dL and high serum triglycerides as ≥150 mg/dL. These definitions were in accord with criteria provided by the Bureau of National Health Insurance for diagnosis of lipid disorders.

Therapies to prevent vascular events were similar to prophylactic medical or surgical therapies used for high-risk patients. All the treatment options and adjustment of medication would be according to the practice pattern of the study area and would be NOT altered by any means from this observation study.

Recurrent stroke

Recurrent stroke was defined as: 1) a new focal neurological deficit with no apparent cause other than that of vascular origin (i.e. the deficit could not be ascribed to an intercurrent acute illness, epileptic seizure, or toxic effect) occurring at any time after the index stroke; or, 2) an exacerbation of a previous focal neurological deficit, with no apparent cause other than that of vascular origin (ie. edema, brain shift, hemorrhagic transformation), occurring after the index stroke[31]; 3) early recurrent ischemic lesions were defined as new separate lesions on follow-up DWI outside the region of the acutely symptomatic lesion and which were not detected on initial diffusion weighted image (DWI) of brain MRI[32]. For patients had more than one recurrent episodes; the first recurrence is eligible for the analysis.

All suspected cases went through image studies if available according to the practice pattern in the study hospital. All images were confirmed by one investigator (MHF); and uncertain cases were adjudicated by two investigators (MHF and KCC).

Outcomes

Three kinds of outcomes were prespecified in this study:

Location

The location of recurrent stroke was assessed as involved an anatomic site or vascular territory different from that of index stroke by: a) clinical diagnosis by brain CT without further MRI examinations; b) recurrent acute infarct lesions identified by follow up brain MRI; or, c) clinical diagnosis if no acute lesions identified by brain MRI. Location was identified and assessed by one investigator (MHF). Size difference was not analyzed in this study.

Severity

Stroke severity was assessed with National Institutes of Health Stroke Scale (NIHSS) based on a scale from 0 to 38 (0 = normal). Functional independence status at admission and every 6 month was measured by Barthel Index (BI) based on a scale from 0 to 100 (100 = normal). All measures were ascertained by one investigator (MHF) in patients with recurrent stroke. The impact of the recurrent stroke was computed by the difference of severity of the recurrent and index stroke

Mortality

Difference of the mortality rate among study period was analyzed between patients with and without recurrent stroke among the study period. All mortality cases were confirmed by two investigators (KCC and MHF)

Statistics

Independent-samples T test and Chi-square test was used to determine any significant differences in attributes studied in relation to recurrent stroke. The association between clinical correlates and recurrent stroke time after enrolled was analyzed with a Cox proportional hazards model. In the Cox regression, variables of interest were forward entered the models. All significant tests were two-tailed and differences were considered to be statistically significant at a $p < 0.05$ level. Log Rank test was used to explore the difference between the percentage of outcome events and the existence of ILAS. Cox regression was used to analyze the factors (including ILAS) associated with outcomes.

RESULTS

The mean observation period was 1.1 years with 0% lost to follow up. Among 693 patients enrolled, 57 (8.2%) had recurrent stroke with all were ischemic type. Among patients with recurrent stroke, 39 (68.4%) were male. Their ages ranged from 34 to 85 (67.6±12.1) years. CT examination was performed in 42 (74%) and MRI in 53 (93%) for the recurrent episodes. (Table 1)

There were 16 (2.3%) patients had recurrent stroke within first month, 11 (1.5%) 31-90 days, 21 (3%) 91-365 days, and 9 (1.2%) patients within 365-730 days. Recurrent stroke had occurred at a mean 172 days after the index stroke (median 93 days, range from 8 to 659 days). Annual stroke recurrence was 8.6% (95%CI, 7.7-9.5).

Among those 57 patients with recurrent stroke, 4 (7%) patients had brain CT to confirm the diagnosis of ischemic stroke; and, 53 (93%) patients had brain MRI to confirm the diagnosis of ischemic stroke and attempted identification of the recurrent acute lesions. Among 53 patients had brain MRI for the recurrent stroke, 43 (81%) patients had MRI identified acute infarct lesions by DWI and Apparent Diffusion Coefficient. Patients without MRI or without acute lesion recognized by MRI were adjudicated by clinical presentation to define the recurrent stroke site and involved vessels by investigators (MHF, KCC).

Among 57 patients with recurrent stroke, 43 (75%) patients were assessed as involved in different anatomic sites or vascular territories from the index stroke. Among 38 patients with recurrent stroke and ILAS, the recurrent sites were ipsilateral to ILAS in 21 (55.2%).

Stroke severity assessed by NIH Stroke Scale was 5.8±7.4 for the recurrent stroke as compared with 5.5±6.2 for the index stroke (p=0.741, paired t test). Functional activity assessed by BI was 65.4±31.9 for the recurrent stroke as compared with 61.5±36.2 for the index stroke (p=0.402, paired t test). Baseline NIHSS and BI scores were the same in patients with recurrence or not.

The treatment before the recurrent stroke onset was described in Table 2. The majority of patients had antiplatelet treatment (82.5%) before the stroke recurrence. Among patients with recurrent stroke, prevalence of hypertension, DM, hyperlipidemia was 84.2%, 45.6%, and 59.6%; the control rate was 83%, 77%, and 62%, before the recurrence, respectively.

Demographics of patients with recurrent stroke were demonstrated in Table 1. Among characteristics explored, there was a higher rate of recurrence among patients with history of ischemic stroke (HR 2.793, 1.550-5.043) and patients with ILAS (HR 2.193, 1.197-4.018). (Table 3) (Fig 1.) The annual recurrent stroke

Table 1. *Cumulative stroke recurrence rates by demographic characteristics, selected vascular risk factors, initial stroke severity (NIHSS), and functional level (BI)*

Characteristics	Total	Recurrent stroke		*P*
		Yes	No	
	N=693	57 (8%)	636 (92%)	
Demographics				
Age - yr	66.4±11.7	67.6±12.1	66.3±11.6	0.419
Male sex - n (%)	440 (64)	39 (68)	401 (63)	0.420
Body mass index - Kg/m^2	24.5±3.5	24.6±3.1	24.5±3.6	0.921
≥ 27	150 (22)	11 (19)	139 (22)	0.778
24-26.9	233 (34)	18 (32)	215 (34)	
< 24	310 (45)	28 (49)	282 (44)	
Duplex - n (%)				
≥ 50%	49 (8)	6 (11)	43 (7)	0.425
Uric acid - n (%)				
Abnormal	67 (10)	6 (12)	61 (10)	0.777
Blood pressure - mmHg				
Systolic	147.3±20.4	147.2±22.6	147.3±20.2	0.977
Diastolic	84.5±13.4	86.1±15.5	84.4±13.2	0.345
Risk factors - no.(%)				
History of ischemic stroke	259 (37)	34 (60)	225 (35)	<0.001
Hypertension	486 (70)	48 (84)	438 (69)	0.015
Diabetes mellitus	281 (41)	26 (46)	255 (40)	0.416
History of hyperlipidemia	278 (40)	23 (40)	255 (40)	0.970
Lipid by lab.	391 (56)	34 (60)	357 (56)	0.608
TC ≥ 200 mg/dL	295 (43)	27 (47)	268 (43)	0.487
LDL ≥ 130 mg/dL	312 (46)	30 (53)	282 (45)	0.276
TG ≥ 200 mg/dL	119 (17)	8 (14)	111 (18)	0.484
Heart disease	172 (25)	16 (28)	156 (25)	0.553
Atrial fibrillation	51 (7)	2 (4)	49 (8)	0.422
Alcohol status	122 (18)	10 (18)	112 (18)	0.990
Smoking status	239 (35)	20 (35)	219 (34)	0.921
Image characteristics				
ILAS	334 (48)	38 (67)	296 (47)	0.004
Clinical characteristics				
Baseline NIH stroke scale	6.7±7.1	5.5±6.2	6.8±7.1	0.160
0-6	418 (60)	40 (70)	378 (59)	0.279
7-15	200 (29)	12 (21)	188 (30)	
16-38	75 (11)	5 (9)	70 (11)	
Baselines BI	61.2±35.3	61.5±36.2	61.2±35.3	0.954
95-100	190 (27)	17 (30)	173 (27)	0.836
60-90	230 (33)	17 (30)	213 (34)	
<60	273 (39)	23 (40)	250 (39)	

ILAS: Intracranial Large Artery Stenosis.

Table 2. *Treatment before recurrent stroke*

Recurrent stroke, N=57	Antiplatelets	Anti -hypertensive agents	Lipid lowering agents	Oral hypoglycemic agents
Hypertension, N=48	40 (83)	40 (83)	25 (52)	20 (42)
Diabetes mellitus, N=26	24 (92)	23 (89)	12 (46)	20 (77)
Hyperlipidemia, N=34	28 (82)	26 (77)	21 (62)	12 (35)
Smokers, N=20	17 (85)	14 (70)	7 (35)	6 (30)

Table 3. *Multivariate analysis of factors related to recurrent stroke*

Models	Hazards ratio (95%CI)	*P* Value*	*P* Value†
			0.033
ILAS			
ILAS (-)	1		
ILAS (+)	2.193 (1.197 - 4.018)	0.011	
History of ischemic stroke			
No	1		
Yes	2.796 (1.550 - 5.043)	0.001	
Constant	0.039	<0.001	

§ ILAS: Intracranial Large Artery Stenosis

* Hazards ratios (95% CI) for outcome events were estimated by age, gender, ILAS, body mass index, duplex, uric acid, blood pressure, history of ischemic stroke, hypertension, diabetes mellitus, history of hyperlipidemia, heart disease, alcohol status, smoking status, baseline NIH Stroke Scale at baseline as independent variables in the Cox regression (Logistic regression) analysis: Forward stepwise

† *P* values: Likelihood Ratio test

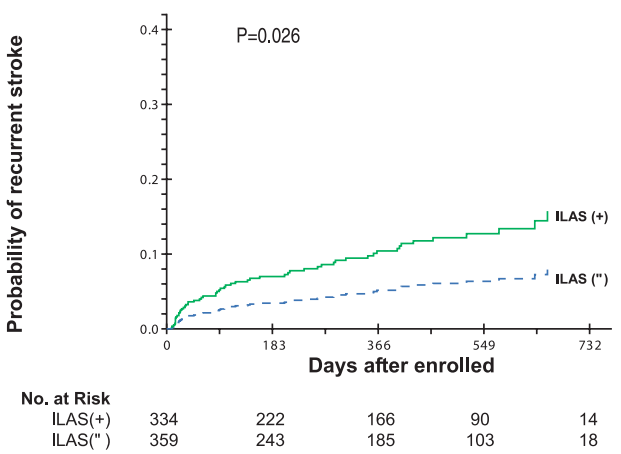

Figure 1. Cumulative incidence of recurrent stroke by Cox regression model according to TILAS groups.

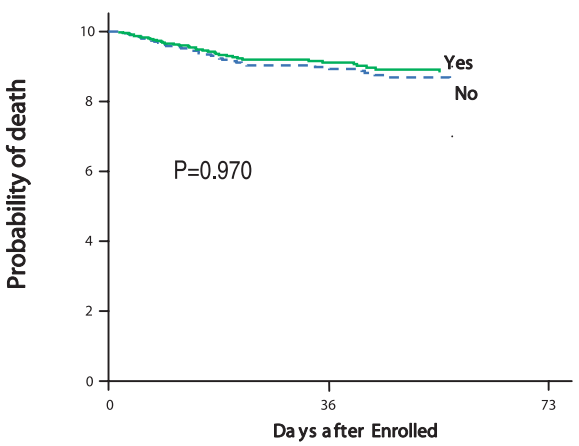

Figure 2. Cumulative incidence of survival according to recurrent stroke.

rate of patients with ILAS was 13% and patients without ILAS 5% (P=0.007)

There were 6 (10.5%) patients with recurrent stroke and 45 (7.1%) without recurrent stroke dead during the study period. In this study, patients with recurrent stroke were not associated with higher mortality rates. (Fig 2.)

DISCUSSION

This hospital-based study described the recurrent stroke rate as 8.6% annually in a group of patients followed prospectively with milder stroke severity and higher incidence of ILAS. History of ischemic stroke along with ILAS related to the recurrence. Most of the recurrent stroke was mild in severity. Possibly due to the short interval of observation, recurrent stroke was not related to the mortality.

There are several limitations of the study. Due to the mild stroke severity, the incidence of recurrence might be less than expected. The intensive factor analyses were limited by the small number of events identified. Even the definition of a recurrent stroke event was challenging[33], the distinction between a truly new stroke lesion, anatomically remote from the index stroke, and stroke progression attributable to the evolution of the ischemic core into the penumbral tissues is not facile. The stroke severity and functional level got worse after recurrent stroke but not significant. Short follow-up duration, small sample size and mild symptoms at first event might partially explain to these findings. Another potential limitation is the assumption, on our part, that diffusion-weighted MR imaging represents a gold standard in defining stroke recurrence. Because progression of the initial lesion was the commonest finding from our study, it might be possible that our findings represented the expected evolution of the infarct lesions over time. This dilemma might be happened by chance when recurrent stroke happens within one month after the index stroke.

Direct comparison between recurrent rates between studies might not be easy. However, patients with ILAS were at risk of higher incidence of adverse events[15,30,34]. Asymptomatic ILAS was reported to be with less incidence of recurrent stroke, however our results supported that patients with ILAS would be at higher risk of recurrent stroke no mater symptomatic or not[35]. From our results, 55% recurrent stroke was assessed ipsilateral to ILAS, as compared with the 73% from WASID[34]. This discrepancy might be from the small number of recurrent stroke patients collected but might be from the different study design as most of recurrent stroke would be explored by brain MRI.

A variety of factors have been previously associated with increased risk of recurrent stroke. The most studied is diabetes mellitus[7,12-14], and some studies reported other independent predictors such as age[12,13], male gender[10], hyperlipidemia[36], and smoking[8,11,37]. As regard to hypertension, several studies found a positive association with stroke recurrence[4,7,8,10,36], but not always[11,14]. ILAS, on the contrary, have been consistently regarded as a negative factor for recurrent stroke, especially in Asians, Hispanics, and African-Americans[30,38-40]. The wide discrepancies among these studies might be related to differences in the duration of follow-up, study design, inclusion criteria or qualifying criteria for a recurrent event. Diabetes mellitus seems to be the key predictor for recurrence in studies with observation period over 2 years[12-14]. Hypertension might play an important role for the recurrence in studies with duration less than 2 years[4,8,10,36]. These findings might suggest time-specific different risk factors for recurrent stroke between early and late recurrences[4,13].

The mortality rate of recurrence group was not higher than those without recurrence in our 1.1 years follow-up probably partly influenced by the mild stroke severity. As higher mortality in recurrent stroke patients might be identified in later follow-up[2,16,41]. Further follow up of this group of patients might be warranted. Detail information about the causes of the death was not available among 45 stroke patients without recurrent stroke. Though, vascular deaths especially the cerebral vascular cause were most attributed cause of death after stroke, future researches explore the death registry from Department of Health, Taiwan to confirm the cause of death are expected[22,23].

Though easy to use and repeatable, the velocity cri-

teria used by TCD to ascertain the stenosis are not universal and mostly middle cerebral arteries explored, with possible interference from the turbulent flow, inability to make angle corrections, and acoustic windows limitation may exist. Though DSA remains the gold standard in diagnosing ILAS, this invasive procedure is not an option of demonstrating ILAS in daily practice. MRA is proved to be feasible in detecting ILAS and capable of detecting more intracranial arteries with different weighted imaging providing detail information and excluding almost all non-stroke causes of stroke syndrome; which are not offered by any other image modalities. MRA can be included with only a few minutes of added scan time. Nowadays, use of MRI along with MRA is frequent in stroke management[15].

Our study contributed with a characterization of risk factors and recurrence prevention in patients with repeated stroke episodes. Recurrence prevention after stroke usually involves antiplatelet, anti-hypertensive agent, oral hypoglycemia agent, and lipid lowering agent. As 82.5% of recurrent stroke patients were on antiplatelet agent, it is obvious that drugs mentioned above failed to prevent recurrent stroke in these patients. Further studies are needed to obtain better prevention strategies.

In conclusion, around 8.2% patients of index stroke experienced a recurrent stroke within two years. The risk of recurrence was highest (6.8%) in one year after the index stroke.

History of ischemic stroke and ILAS are the major risk factors for recurrence. History of ischemic stroke has long been thought of as a risk factor for recurrent stroke. As for ILAS, in spite of the use of anticoagulation and vascular risk factors modification, the recurrent rate was persistent around 10-15% per year[30,38]. Further treatments are needed to be tested in alleviating negative impact of these risk factors.

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