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Special Article - Ischemic Stroke

Recurrence Rate of Ischemic Stroke: A Single Center Experience

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Abstract

Background: Stroke is a key public health problem worldwide, with the majority of patients suffering from ischemic strokes. Recurrent ischemic stroke, with its concordant high morbidity and mortality, is therefore a principal target of secondary prevention. This study aims to present the rates of ischemic stroke recurrence and its possible determinants.

Methods: This is a hospital-based retrospective cohort study of patients seen at our Center diagnosed with ischemic stroke from 2010 to 2012. Data on consecutive patients who had a follow-up of at least three years were collected. The annual incidence of stroke recurrence was determined during the 1st, 2nd and 3rd year of consultation. Multivariable logistic regression was employed to determine the predictors of ischemic stroke recurrence.

Results: The study comprised 1155 first-onset ischemic stroke patients with a total of 280 recurrences recorded over the 3-year period, 24.2% (95% CI, 21.8-26.7). The incidence of recurrence was highest during the first year after index stroke, 12.8% (95% CI, 11.0-14.8) with a declining annual rate, 6.3% (95% CI, 5.0-7.9) during the second year and 5.1% (95% CI, 4.0-6.5) during the third year after the index stroke. Multivariate logistic regression of the different risk factors showed no significant association with ischemic stroke recurrence.

Conclusion: The 1155 first onset ischemic stroke patients, 12.8% had a second ischemic event within the next year, with an average of 8% annual risk for stroke recurrence over three years. Urgent initiation and consistent monitoring of secondary preventive measures are extremely important to prevent stroke recurrence and improve the long-term outcome after an ischemic stroke.

Keywords: Ischemic stroke; Recurrence; Risk factor

Introduction

Stroke is the leading cause of mortality and the third cause of morbidity especially in developed countries [1]. Majority of strokes are ischemic [2]. It has been reported in hospital-based data that the over-all risk of stroke recurrence within five years after a first episode is approximately between 15-40% [3,4]. Within the first year after the initial stroke, the risk of stroke recurrence is higher (between 6-14%) as opposed to risk in subsequent years (4% annually) [4-6]. The maximum incidence of recurrent stroke is in the first 30 days after initial stroke [7].

The most significant predictors of stroke recurrence include advancing age, arterial hypertension, atrial fibrillation, diabetes mellitus (DM), hyperlipidemia, smoking, heavy alcohol consumption, and obesity [8-12]. Most of these risk factors are modifiable. The recognition of these risk factors and institution of preventive measures reduce stroke recurrence [13].

Majority of the studies comparing the relationship between patients' demographic profile and the long-term post-stroke outcomes such as stroke recurrence were conducted in Western countries [14-17]. Few comparisons have been made amongst Asians and none among Filipinos [18-21]. Filipinos are descendants of the Malay race which is an ethnic group indigenous also to other countries including Malaysia, Singapore, Indonesia and Brunei [22]. Research findings from this population may reflect a significant burden of disease especially in Southeast Asia. Therefore, this study aims to determine the rate of recurrence of ischemic stroke and factors for recurrence among Filipinos, and to compare our results with published data from other populations.

Methods

This is a hospital-based retrospective cohort study of patients seen at our Center, a state-owned public hospital in central Manila, and diagnosed with ischemic stroke between 2010 and 2012. Our Center attends to about 900 stroke patients per year. The surviving patients were subsequently followed up on a regular basis at the Out Patient Section of our Center. We reviewed the records of surviving, consecutive patients during these years who had ischemic stroke with consistent neuroimaging; had first ever stroke during the specified period; and with regular follow-up defined as monthly visits after the onset of symptoms for 3 months, then every 3 months thereafter for at least one year up to three years. Patients who had previous multiple (>1) ischemic stroke prior to the initial consultation were excluded.

The sample size was calculated as follows: assuming a recurrence rate of 8.5% (7-9%) per year, utilizing a single proportion, with 5% margin of error and 80% power, the sample size needed is 385 per

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Table 1: Baseline Characteristics of Ischemic Stroke Patients.

Characteristics (n=1155)	Mean±SD or n (%)
Age (year)	55.4 (±10.4)
Sex Males Females	 617 (53.4) 538 (46.6)
Hypertension	1,098 (95.0)
Atrial fibrillation	195 (16.9)
Diabetes mellitus	288 (24.9)
Hyperlipidemia	418 (36.2)
Smoking	175 (15.2)
Heavy alcohol consumption	94 (8.1)
Obesity	91 (7.9)
Initial mRS 0 1 2 3 4	 35 (3.0) 363 (31.4) 391 (33.9) 354 (30.6) 12 (1.0)
Initial NIHSS Mild stroke (<8) Moderate stroke (8-16) Severe stroke (>16)	 476 (41.2) 628 (54.4) 51 (4.4)

year, with a total of 1155 patients. A logistic regression analysis was performed to determine any significant risk factors associated with stroke recurrence. To be able to determine if there is significant difference in time of recurrence, the odds of recurrence at year one were compared at the 2nd and 3rd year. The Institutional Review Board of our Center has approved the study protocol.

Stroke recurrence is defined as a clinical event characterized by new onset focal neurologic deficit that is vascular in etiology or worsening of a former deficit not attributed to drug effects or a concurrent illness, with neuroimaging consistent with recent infarction [4]. The rates of stroke recurrence in each year were determined during the 1st, 2nd and 3rd year of follow up consultation in the years 2010, 2011 and 2012. The average number of stroke recurrences was calculated by adding the recurrences in each year (stroke recurrence per year) and the 95% confidence interval was calculated.

Baseline characteristics, including age, sex, vascular risk factors, initial National Institutes of Health Stroke Scale (NIHSS) [23] and modified Rankin Scale (mRS) scores [24], and the number of stroke recurrence were determined. Vascular risk factors included arterial hypertension defined as previousmedical treatment with anti-hypertensive or detected persistent blood pressure >140/90 mmHg [10], atrial fibrillation as evidenced by electrocardiography (ECG) or 24-hour Holter monitoring [25], smoking defined as current pipe, cigar or cigarette smoking during index stroke [4] and heavy alcohol consumption defined as drinking 5 or more drinks on the same occasion on each of 5 or more days in the past 30 days [26]. Diabetes mellitus (previous medical treatment with anti-diabetic or detected fasting plasma glucose level of ≥7 mmol/L or with symptoms of diabetes plus random plasma blood sugar of ≥11.1 mmol/L or HBA1C >6.5%) [27], hyperlipidemia (previous medical treatment with anti-hyperlipidemic or detected total cholesterol ≥240 mg/dl or low-density lipoprotein (LDL) ≥160 mg/dl) [28] and obesity (body mass index ≥30) [10] were also regarded as possible predictors of stroke recurrence. Multivariable logistic regression analysis was employed to compare the factors that were possible predictors of recurrence amongst these patients with ischemic stroke. Data was analyzed using Epi Info™ 7.

Results

The study comprised1155 first onset ischemic stroke patients where 385 consecutive patients were identified for each year: 2010, 2011 and 2012, the records of these patients were then reviewed. The mean±SD age was 55.5±10.4 years and 617 (53.4%) were males. Other demographic data were also recorded. Majority of the index strokes had an initial mRS between 1 and 3 and were classified as mild to moderate based on initial NIHSS (Table 1). The mean number of follow-ups within three years was 12.

During the 3-year period of each year, a total of 280 ischemic stroke recurrences were recorded, 22 of which had a second recurrence and 3 had a third. The incidence of stroke recurrence was highest during the first year after an initial ischemic stroke, i.e. 12.8% (95% CI, 11.0-14.8). The annual rate of stroke recurrence during the succeeding years showed a declining pattern, 6.3% (95% CI, 5.0-7.9) during the second year and 5.1% (95% CI, 4.0-6.5) during the third year after the index stroke, with a mean of 8% per year (95% CI, 7.2-9.0) (Table 2).

Stroke recurrence during the first year was significantly higher compared to succeeding 2nd and 3rd years. There is a 2.42 higher odds of a stroke occurring in the first year after an index stroke ($p<0.0001$), compared to subsequent years. Following logistic regression analysis, none among the risk factors showed significant association with ischemic stroke recurrence but male gender and hyperlipidemia exhibited a trend towards significance (Table 3).

Discussion

In this single center experience, we have shown in 1155 with first onset ischemic stroke that there is a 12.8% rate of first recurrence within the first year, with an average of 8% annual risk for stroke recurrence up to three years. Additionally, the risk factors identified in this study to be associated with recurrence did not show to be significant. The population included in this study is all of Filipino

Table 2: Recurrence of Stroke, 2010-2012 (with 3 year follow-up for each year).

	Year 1	Year 2	Year 3	Average of 3- year follow-up
2010 (n=385)	54 14.0 % (10.9-17.9)	25 6.5% (4.4-9.4)	24 6.2% (4.2-9.1)	103 8.9% (7.4-10.7)
2011 (n=385)	49 12.7% (9.8-16.4)	27 7.0% (4.9-10.0)	20 5.2% (3.4-7.9)	96 8.3% (6.8-10.0)
2012 (n=385)	45 11.7% (8.8-15.2)	21 5.5% (3.6-8.2)	15 3.9% (2.4-6.3)	81 7.0% (5.7-8.6)
Recurrence rate (n=1155)	148 12.8% (11.0-14.8)	73 6.3% (5.0-7.9)	59 5.1% (4.0-6.5)	280 8.1% (7.2-9.0)

Table 3: Risk Factors for Stroke Recurrence within 3 Years.

Demographics and risk factors	With Recurrence n=280 (%)	Without Recurrence n=875 (%)	OR with 95% CI	P value
Mean±SD	56.02±10.59	55.37±10.39		0.389
Age≥65 yrs old	54 (19.3)	178 (20.3)	0.94 (0.67-1.31)	0.699
Sex			1.09 (0.83-1.43)	0.543
Male	154 (55.0)	463 (52.9)		
Female	126 (45.0)	412 (47.1)		
BMI				
Mean±SD	24.62 ±2.89	24.49 ±2.78		0.509
>30	20 (7.1)	71 (8.1)	0.87 (0.52-1.46)	0.597
Hypertension	261 (93.2)	837 (95.7)	0.62 (0.35-1.1)	0.100
Atrial fibrillation	45 (16.1)	150 (17.1)	0.93 (0.64-1.33)	0.680
Diabetes mellitus	58 (20.1)	230 (26.3)	0.73 (0.53-1.01)	0.061
Hyperlipidemia	106 (37.9)	312 (35.7)	1.10 (0.83-1.45)	0.507
Smoking	33 (11.8)	142 (16.2)	0.69 (0.46-1.03)	0.071
Alcohol drinking	17 (6.1)	77 (8.8)	0.67 (0.39-1.15)	0.146

Results of logistic regression with any recurrence within a 3-year follow-up as dependent variable (recurrence=1, non-recurrence =0).

Table 4: Rate of Ischemic Stroke Recurrence According to Different Sources.

Research	Rate of Ischemic Stroke Recurrence
[14]	11.1% within 1 year
[15]	3.6% within 1 year
[16]	16.6% within 5 years
[17]	9.4% within 1 year
[18]	9.6% within 1 year in 2000 7.8% within 1 year 2011
[19]	18% within 2 years
[20]	14.6% within 5 years
[21]	20.9% within 1 year (elderly group) 15.4% within 1 year (younger group)
[30]	11.2% within 1 year

descendancy. The patients included come from a referral center attending to about 900 stroke patients a year.

Currently, there is variability in the reported rate of ischemic stroke recurrence by different investigators as shown in Table 4. Most of these are conducted among Caucasians. It has been shown that the over-all recurrence within 5 years after initial stroke is about 15-40% [3,4]. In a meta-analysis and systematic review performed by Mohan, et al. the populations were mainly Caucasians from North America and Europe. Two studies came from Asia i.e. Japan and China. In the 16 studies identified the cumulative risk of stroke recurrence in 9115 patient survivors are as follows: 3.1% at 30 days, 11.1% at 1 year, 26.4% at 5 years and 39.2% at 10 years. Our results are consistent with the previous finding that the risk of stroke recurrence is highest in the first year following a first ever-ischemic stroke [4-6]. In this study, the odds of a stroke recurrence in the first year after the index stroke is 2.4 times higher than in subsequent years.

The findings in the study conducted by Lee, et al. showed that the one-year ischemic stroke recurrence rate declined from 9.61% in 2000 to 7.27% in 2011. The same trend was seen in our study wherein the incidence of stroke recurrence for those with first onset ischemic strokes in 2012 was substantially lower compared to those who had their index strokes in 2010. The variation in incidence of recurrence during this period may be explained by better implementation of secondary stroke prevention strategies.

Several investigators have studied the relationship of potentially modifiable risk factors and stroke recurrence to guide interventions for secondary prevention; often, their results have been inconsistent [16,18,29,30]. None of the risk factors included in our study showed significant association with increased risk for recurrent ischemic stroke. Our observations show that most stroke recurrences in the population remain unexplained by conventional risk factors, suggesting a multi-factorial causation of recurrence. This may probably be due to the different ethnic origin of Filipinos (i.e. Malay race) which may be poorly represented in the previous studies regarding ischemic stroke recurrence.

The main advantage of this study is its large sample size, the recruitment of consecutive cases, and close follow-up of study subjects. However, we acknowledge that not all potential risk factors of the index stroke were encompassed in this research due to non-availability of data. The quality of data gathered in a retrospective study such as ours is a limiting factor. Data, for instance, such as whether diabetes mellitus, hypertension or atrial fibrillation were controlled or uncontrolled with medication could have shed more light or explained variations in stroke recurrence, are not available. In addition, the effect of acute stroke management as well as compliance to secondary preventive measures on the risk of stroke recurrence was also beyond the scope of this study. Further investigation is therefore suggested in these areas.

In conclusion, this single center experience, we have shown that of the 1155 first onset ischemic stroke patients, 24.2% (95% CI, 21.8-26.7) had a second ischemic event within the next three years. The incidence is high in the first year and decreases with time. Traditional risk factors do not appear to significantly affect the risk of recurrence. Further studies are needed to uncover factors that affect stroke

recurrence, as secondary preventive measures are paramount to hinder stroke recurrence and improve the long-term outcome after an ischemic stroke.

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