Recurrent Primary Intracerebral Hemorrhage: A Hospital Based Study

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Abstract-

Background: Primary intracerebral hemorrhage (ICH) occurs more commonly in Taiwan than in other western countries. Recurrence of primary ICH after a first episode is not rare. The purpose of this study is to investigate the incidence, risk factors, and prognosis of recurrent primary ICH.

Methods: From the stroke registration data of Kaohsiung Veterans General Hospital (KSVGH), all patients admitted between Jan. 1999 and Dec. 2003 with the discharge diagnosis of ICH were identified. The hospital records and images of each ICH patient were carefully reviewed and the diagnosis was confirmed by one of the investigators. For those patients admitted in this study period with the diagnosis of acute primary ICH who also had past medical history of ICH, the record and image of the past admission were also obtained for review, either from KSVGH or other hospitals. Patients with ICH due to secondary causes were excluded.

Results: 585 patients with primary ICH were reviewed. Among them, 34(5.8%) patients were found to have recurrent primary ICH. The medical records of these 34 patients were obtained for further analysis. Cerebral amyloid angiopathy was diagnosed in 4(11.7%) patients. Mean ages at the onset of the first and second hemorrhages were 64±13 and 66±13 years, respectively. The mean interval between first and second hemorrhages was 33 months (from 1 month to 10 years). The most common location of first-second bleeding was basal ganglion-basal ganglion. The mortality rate in this group was 23.5%. Fifteen (38.2%) patients became totally dependent or vegetative after the second ICH.

Conclusions: Recurrent primary ICH is not uncommon. The main location of recurrent bleeding was basal ganglion. This may implicate hypertension as the main cause of ICH. Hypertension is an important risk factor of recurrent primary ICH. Amyloid angiopathy is another cause of recurrent primary ICH. The prognosis after the second hemorrhage is worse, while the mortality and morbidity after first ever primary ICH were 15.6% and 17.9%, respectively.

Key Words: Recurrence, Intracerebral hemorrhage, Amyloid angiopathy, Outcome

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INTRODUCTION

Cerebrovascular disease is a major public health problem in most countries. Stroke ranks as the second major cause of death according to the data from the Department of Health, Executive Yuan in Taiwan . Although the percentage of intracerebral hemorrhage (ICH) among all strokes was around 10% in most countries[1], a higher incidence of ICH (around 35% of all strokes) has been observed in Taiwan[2] and other Asian countries[3,4]. Recurrence of ICH after a first episode has been considered a rare event in the past[5,6]. However, in some recent studies[7-9], the results showed that recurrent ICH is not rare. As more patients survive their first ICH, the issue of recurrent ICH will become more important. The incidence and characteristic of recurrent ICH had been investigated in many studies worldwide[4,7-17]. However, recurrence of ICH after first hypertensive ICH is still one of the major issues in most Asian studies including some from Taiwan[7,10,15-18]. This study enrolled patients with recurrent primary ICH, including non-hypertensive ICH, from a hospital-based data bank in Taiwan. The analysis included patient characteristics, risk factors, and outcome of recurrent primary ICH. Cerebral amyolid angiopathy (CAA) is another important cause of recurrent primary ICH. Although pathologic finding is the standard criteria for the diagnosis of cerebral amyloid angiopathy, some specific clinical features, including an age greater than 70, recurrent lobar hemorrhage and absence of hypertension, are usually sufficient to make a clinical diagnosis of CAA. This retrospective study also provides some insight into the incidence of CAA in patients with recurrent primary ICH.

PATIENTS AND METHODS

The medical records of all patients with a discharge diagnosis of intracerebral hemorrhage (ICH) admitted to Kaohsiung Veterans General Hospital between January 1999 and December 2003 were reviewed. All patients included must had their intracerebral hematomas demonstrated by CT scan of the brain. A total of 631 patients met the diagnostic criteria of ICH. Primary ICH was defined as spontaneous ICH without secondary causes, such as trauma, coagulation disorders, drug-related issues, vascular malformation, aneurysm, vasculitis, intracranial neoplasm or venous thrombosis. Forty-six patients were considered as having secondary ICH and were excluded from the study. For those patients admitted in this study period with the diagnosis of acute primary ICH who also had past medical history of ICH, the medical records and images of their past admissions were also obtained for review, either from KSVGH or other hospitals.

In all patients, ages at the first and second hemorrhage, interval between the two cerebral hemorrhages, sex, and the location of hematoma were recorded. The locations of hematomas were labeled based on anatomical locations, including basal ganglion (caudate nucleus, putamen, globus pallidus, and internal capsule), thalamus, cerebellum, brain stem, and lobar region. Lobar hemorrhage was defined as ICH located in the subcortical area with or without extension to the cortex. We recorded potential risk factors, including hypertension, diabetes mellitus, smoking, drinking, liver function (AST/ALT), and lipid profile from medical record of each admission period. Hypertension and diabetes mellitus were identified based on past medical history or serial blood pressure and plasma glucose measurements during hospitalization. The diagnostic criteria of hypertension is either systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. The diagnostic criteria of diabetes mellitus is the fasting plasma glucose ≥126 mg/dL according to WHO criteria in 1999. Cerebral amyloid angiopathy were diagnosed by pathological finding or clinical features, including age, recurrent lobar hemorrhage, and the absence of hypertension. The evaluation of clinical outcome was based on scores of Glasgow coma scale and Rankin scale at the time of discharge. Chi-square test was applied to compare sex, location of the hematoma, hypertension, and diabetes mellitus between recurrent and non-recurrent groups of primary ICH patients. Wilcoxon rank sum test was used to compare age, lipid profile, and clinical outcome between the two groups.

Table 1. *Characteristic of 34 patients with recurrent primary intracerebral hemorrhage*

Pt no.	Sex	Age at 2nd ICH	Time between episodes (mon)	Location of ICH		HTN	DM	Hyperli-pidemia	Elevated liver enzyme	Drinking	Smoking	Other
				1st hemorrhage	2nd hemorrhage							
1	M	58	20	Rt thalamus	Lt basal ganglion	Y	N	N	N	N	Y	
2	M	72	54	Rt cerebellum	Lt basal ganglion	Y	N	N	Y	N	N	
3	M	79	40	Rt thalamus	Lt parietal lobe	Y	N	N	N	N	N	
4	M	67	78	Lt basal ganglion	Lt parietal lobe	Y	N	N	N	N	N	
5	M	92	73	Rt basal ganglion	Lt basal ganglion	Y	N	N	N	N	N	
6	M	69	31	Rt thalamus	Pons	Y	N	Y	N	Y	Y	
7	M	70	46	Rt thalamus	Rt thalamus	N	N	N	N	N	N	
8	F	57	5	Lt basal ganglion	Cerebellum & Lt thalamus	Y	Y	N	N	N	N	
9	M	56	2	Rt basal ganglion	Lt thalamus	Y	N	N	N	Y	Y	
10	M	83	120	Lt thalamus	Rt thalamus	Y	N	N	N	N	N	
11	F	54	76	Rt thalamus	Lt thalamus	Y	N	#	N	N	N	
12	M	71	60	Rt basal ganglion	Lt thalamus	Y	N	N	N	N	N	
13	M	90	53	Lt basal ganglion	Rt basal ganglion	N	Y	N	Y	N	N	
14	F	54	11	Lt basal ganglion	Rt basal ganglion	Y	N	N	N	N	N	
15	M	64	29	Rt basal ganglion	Lt cerebellum	Y	N	N	N	N	Y	
16	F	81	89	Rt basal ganglion	Lt basal ganglion	Y	N	N	N	N	N	
17	F	32	24	Rt basal ganglion	Lt basal ganglion	Y	N	#	Y	N	N	
18	M	65	32	Lt basal ganglion	Lt basal ganglion	Y	N	N	N	Y	Y	
19	F	55	36	Lt thalamus	Pons	Y	Y	N	N	N	N	
20	F	78	6	Lt cerebellum	Lt parietal lobe	Y	Y	N	N	N	N	
21	M	42	1	Lt basal ganglion	Lt basal ganglion	Y	N	N	Y	N	Y	
22	M	68	16	Rt thalamus	Rt thalamus, midbrain, pons	Y	N	#	N	N	N	
23	F	64	1	Rt T-P[1] region	Lt basal ganglion	Y	Y	N	N	Y	N	
24	F	78	19	Rt basal ganglion	Lt thalamus	Y	N	N	N	N	N	
25[a]	M	73	23	Rt P-O[2] region	Rt frontal	Y	N	N	N	N	N	CAA*
26[b]	M	77	40	Rt parietal	Lt parietal	Y	Y	N	Y	N	N	CAA*
27[c]	M	60	66	Rt frontal	Lt thalamus	N	N	N	N	N	N	CAA*
28	M	73	1	Rt T-P[1] region	Lt thalamus	Y	N	Y	N	N	N	
29	F	56	2	Lt basal ganglion	Rt basal ganglion	Y	N	N	N	N	N	
30	F	65	0	Rt F-P[3] region	Rt parietal lobe	Y	N	Y	N	N	N	CAA*
31	M	75	1	Rt T-P[1] region	Lt basal ganglion	Y	N	N	N	N	N	
32	M	57	5	Rt frontal	Lt basal ganglion	Y	N	N	N	N	N	
33	M	64	25	Lt basal ganglion	Pons	N	Y	N	N	N	N	
34	M	44	60	Lt cerebellum	Rt basal ganglion	Y	N	Y	N	N	N	

*CAA: cerebral amyloid angiopathy; #No data of lipid profile; [1]Tempero-parietal; [2]Parieto-occipital; [3]Fronto-temporal; [a]Four episodes of hemorrhage: Rt parieto-occipital region, Rt frontal, Rt tempero-parietal region, Lt hemisphere; [b]Three episodes of hemorrhage: Rt parietal region, Lt parietal region, Lt parietal region; [c]Three episodes of hemorrahge: Rt frontal region, Lt thalamus, Lt occipital region.

RESULTS

Among 585 patients with primary ICH, 34 (5.8%) patients had recurrent primary ICH; there were 23 males and 11 females (M/F: 2.1/1). Among the 34 patients, 25 (73.5%) patients had their first hemorrhage treated in our hospital. The mean age of patients with non-recurrent primary ICH was 64±13 years old, and the mean age of patients with recurrent primary ICH was 66±13 years old. The mean interval between the first and the second cerebral hemorrhages was 33 months (range: 1 month to 10 years) in the recurrent primary ICH group. Within 3 years after the first ICH, 21 (61.7%) patients had a second ICH. Among the patients with non-recurrent primary ICH, the sites of hematomas were: basal ganglion (including thalamus) in 351 (65.6%) patients, lobar region in 92 (17.2%), and brain stem or cerebellum in 92 (17.2%). The first and the secondary locations of cerebral hemorrhage were presented in Table 1. The main first-second locations of recurrent cerebral hemorrhage were basal ganglion-basal ganglion in 17 (50%) patients. The recurrent cerebral hemorrhages were located at different sites from the previous one in 31 (91.2%) patients.

Of the 34 patients with recurrent primary ICH, 30 (88.2%) had hypertension; 7 (20.5%) had diabetes mellitus; 6 (17.6%) had a cigarette smorking habit; 4 (11.7%) had a drinking problem; and 5 (14.7%) had elevated liver enzymes. Mean values of triglyceride and cholesterol were 148±73 mg% and 170±39 mg%, respectively. A comparison of the incidences of the potential risk factors between patients with non-recurrent primary ICH and recurrent primary ICH was shown in Table 2. All the incidences of possible risk factors between the two groups showed no statistical differences ($p > 0.05$). Four patients (11.7%) met the criteria of cerebral amyloid angiopathy. Three cases were proved by pathological finding, and one was diagnosed clinically. The overall mortality rate in patients with a second cerebral hemorrhage was 23.5% (n=8). Thirteen patients (38.2%) had severe disability (Rankin scale 5, total dependence or vegetative), and 12 patients (35.3%) had mild-to-moderate disability (Rankin scale 1-4). In the non-recurrent primary ICH patient group, the mortality rate was 15.6%, and the rates of severe and mild-to-moderate disability were 17.9% and 57.9%, respectively. The mean values of Glasgow coma scale and Rankin scale of patients with recurrent cerebral hemorrhage were 9.9±5.2 and 4.4±1.5, compared with those with non-recurrent cerebral hemorrhage were 11.8±5.0 and 3.7±1.6 (Table 2). There was a statistical difference ($p < 0.05$) between the two groups.

Table 2. *Comparison between non-recurrent primary ICH and recurrent primary ICH*

Factors	Non-recurrent primary ICH (n=551)	Recurrent primary ICH (n=34)	p value
Age (mean±SD), years	64±13	66±13	NS
Sex (Male/female)	2.1/1	2.3/1	NS
Location of ICH, n(%)			
Basal ganglion (+thalamus)	351 (65.6)	23 (67.6)	NS
Lobar	92 (17.2)	8 (23.5)	
Brain stem + Cerebellum	92 (17.2)	3 (8.8)	
Risk factor			
Hypertension, n(%)	456 (82.8)	30 (88.2)	NS
Diabetes Mellitus, n(%)	99 (17.9)	7 (19.4)	NS
Triglyceride (mean±SD), mg/dL	156±91	148±73	NS
Cholesterol (mean±SD), mg/dL	173±41	170±39	NS
Outcome at discharge			
Glasgow coma scale (mean±SD)	11.8±5.0	9.9±5.2	<0.05
Rankin scale (mean±SD)	3.7±1.6	4.4±1.5	<0.05

NS: Non-significant (p value> 0.05).

DISCUSSION

A higher incidence of cerebral hemorrhage (around 35% of all strokes) has been reported in Taiwan[2], compared with western countries such as the United States (11%)[1] and Switzerland (11%)[19]. A high incidence of cerebral hemorrhage among all stroke victims was also noted in Korea[3] and Japan[4]. Douglas and Haerer[5] followed 70 consecutive patients with primary hypertensive ICH proved by CT scan for an average of 2.5 years , and recurrent ICH was not found. In the study by Fieschi et al.[7], patients with primary ICH were followed for one year, and none of those patients were found to have recurrent ICH. However, recent studies have shown that recurrence of primary ICH is not uncommon. According to many studies worldwide[8,9,11-14], the incidence of recurrent primary ICH was between 4.9% and 24% (Table 3). In the present study, a similar incidence (5.8%) was found. For recurrent hypertensive ICH, the incidence was between 1.8% and 11% according to the studies from Asia[7,10,15-18], including those (5.3%-4.8%) from Taiwan[7,10].

In the present study, the main sites of the two cerebral hemorrhages were all in the basal ganglion (including thalamus). In other studies[8,11], similar results also were found. Basal ganglion (including thalamus) is the most common location of hypertensive ICH. These findings strongly suggest that hypertension play an important role in recurrent primary ICH. Cerebral amyloid angiopathy (CAA) is a well documented cause of recurrent cerebral hemorrhage. Characteristically, ICH due to CAA occurs in patients without a history of hypertension, and increases with advancing age, especially over 70 years[20]. The sites of hemorrhages in CAA is cerebral lobe because amyloid angiopathy has a predilection for the cortical arteries. CAA accounts for 11.7% of all recurrent primary ICHs in our study. All of them had recurrent lobar hemorrhage. A slightly increased percentage of lobar hemorrhage in this study may reflect the existence of CAA. However, this increase has no statistic significance. In the studies from Italy, France and Canada[9,12,13], either a higher incidence of recurrent primary ICH or a higher percentage of lobar hemorrhage were found. This may imply that CAA is a more common cause of recurrent primary ICH in these studies.

In our study, hypertension has a high incidence in recurrent primary ICH group (88.2%) as well as in non-recurrent primary ICH group (82.8%). There is no statistic difference in incidence of hypertension between non-recurrent and recurrent primary ICH groups. Therefore,

Table 3. *Studies of recurrent intracerebral hemorrahge*

Reference	Year	Country	No. of p't (affected/total)	Incidence %, mean follow-up duration	Mean age (years)	Main recurrent pattern (first-second hemorrhage)
Lee et al[3]*	1990	Korea	14/518	2.7%	54.5	Ganglion-ganglion
Hiroata et al[15]*	1991	Japan	9/494	1.8%	60.5	Ganglion-ganglion
Passero et al[9]	1995	Italy	27/112	24%	67.3	Lobar-Lobar
Chen et al[7]*	1995	Taiwan	47/892	5.3%	62	Ganglion-ganglion
Maruishi et al[8]	1995	Japan	30/509	5.9%	62.9	Ganglion-ganglion
Misra et al[16]*	1995	India	5/105	4.7%	43.5	No description
Neau et al[13]	1997	France	24/375	6.4%	64.7	Lobar-Lobar
Alejandra et al[11]	1998	Mexico	22/350	6.0%	60	Ganglion-ganglion
Arakawa et al[17]*	1998	Japan	8/74	11%, 5.6 yr	54	Ganglion-ganglion
Bae et al[18]*	1999	Korea	53/989	5.4%, 3.2 yr	60	Ganglion-ganglion
Hill et al[12]	2000	Canada	15/172	8.7%, 3.6 yrs	Nil	Lobar[a]
Chen CH et al[10]*	2001	Taiwan	68/1421	4.8%	Nil	Ganglion-Ganglion
Buhl R et al[14]	2003	Germany	48/968	4.9%	67.8	No description
Present study	2003	Taiwan	34/585	5.8%	66	Ganglion-ganglion

*Hypertensive ICH population; [a]No data of location of second cerebral hemorrhage.

hypertension is also a major risk factor for recurrent primary ICH. Similarly, the incidence of hypertension in recurrent primary ICH is also high (50-88%) in many studies[8,9,11-14]. Diabetes mellitus and hyperlipidemia are not the risk factors for primary ICH. This study also showed a low incidence of diabetes mellitus and hyperlipidemia in either recurrent primary ICH group or non-recurrent primary ICH group. Drinking and liver function impairment have been reported as the risk factors for ICH in some epidemiologic studies[21-24]. However , other studies[7,9,13] have reported that these two factors are not the risk factors for ICH. In the present study, drinking and elevated liver enzymes are also not the risk factors for recurrent primary ICH.

A striking feature of recurrent ICH is that the majority of the recurrent cerebral hemorrhages occur at a site different from that of the previous one. In our study, thirty-one (91%) patients with recurrent primary ICH suffered from cerebral hemorrhage in two different sites, and only three (9%) patients had cerebral hemorrhage at the same location. A similar feature was also reported in patients with hypertensive ICH[3,7]. Hypertensive ICH is the result of the rupture of microaneurysms or fibrinoid-weakened vessels in the small penetrating arteries, caused by chronic hypertension[25]. The morbid structure occurs in all susceptible areas of brain. After rupture of the abnormal vessels, the morbid structure is changed. Therefore, the next cerebral hemorrhage will occur at a different site with similarly morbid condition. The mechanism may explain the findings in the present study because hypertension is also the major risk factor for recurrent primary ICH.

Recurrence of cerebral hemorrhage will cause more damage to the brain and have more neurological sequelae than just one hemorrhage. Therefore, recurrent ICH may have a worse prognosis than non-recurrent ICH. In our study, the prognosis was significantly worse in patients with recurrent primary ICH (GCS 9.9±5.2; Rankin scale 4.4±1.5) as compared to those with non-recurrent primary ICH (GCS 11.8±5.0; Rankin scale 3.7±1.6).

This study is retrospective and hospital-based. Hospital-based study will have a bias in sampling, and the retrospective study will limit the interpretation of results. Arakawa et al.[17] in Japan and Bae et al.[18] in Korea have showed that uncontrolled or poorly controlled hypertension is the only predictive factor of recurrent hypertensive ICH. More detailed description of the blood pressure patterns between recurrent and non-recurrent primary ICH groups may improve our result. The prevention of recurrent ICH, aimed at the management of risk factors and predictive factors, is an important issue. Therefore, the primary ICH patients with hypertension should receive regular follow-up and optimal control of their blood pressure.

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