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RECURRENT HYPERTENSIVE INTRACEREBRAL HEMORRHAGE AMONG TAIWANESE

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Hypertensive intracerebral hemorrhage (HICH) was once thought to be a one-time event with very rare recurrence, but recent studies have revealed that the recurrent hemorrhage due to hypertension is not unusual. The purpose of this study was to determine the clinical characteristics of HICH among Taiwanese. From June 1988 to December 1999, 1421 HICH patients were admitted to our hospital. Among them, 68 patients (4.8%) had recurrent HICH. We reviewed their medical records and computed tomographic findings. There were 46 males and 22 females (M/F=2.1) with a mean age of 59.9 ± 11.9 years at the onset of the second hemorrhage. The median interval between the first two hemorrhages was 22.5 months (range: 1-107 months). Most of the recurrence was within two years of the first hemorrhage (within 1 year in 27.9%, within 1-2 years in 25%). The location of the second hemorrhage was typical for HICH (putamen in 44. 1%, thalamus in 33.8%, cerebellum in 5.9%, pons in 4.4%, and caudate nucleus in 1.5%) except for 7 patients (10.3%) who had lobar hematoma. Forty-nine patients (72%) had both hemorrhages located in the supratentorium and in most of them (40 patients) the recurrent HICH occurred contralaterally to the first one. Putaminal-thalamic pattern was the most common (23.5%), followed by the putaminal-putaminal pattern (20.6%). The mortality rate of the second HICH was 17.6%. Seven patients (10.3%) experienced more than 2 episodes of hemorrhages. This report found that the recurrent HICH was not rare among Taiwanese. A substantial proportion (19.1%) of recurrence was after 5 years. The male predominance and risk factor for recurrent HICH require further study.

Key words: hypertension, intracerebral hemorrhage, recurrence

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Stroke was the second leading cause of death in Taiwan from 1982 to 1998. Regarding the subtype of stroke, contrary to western countries, intracerebral hemorrhage (ICH) is fairly common in Taiwan. Even though the ratio of ICH to cerebral infarction declined from 0.67 to 0.34 among Taiwanese in a recent decade [1,2], it was still several times higher than that of western countries [3,4]. The incidence of ICH declined in recent decades due to the control of hypertension, but hypertension itself was still the most important risk factor and accounted for 50.5% to 86.7% of cases with ICH [1-4].

Hypertensive intracerebral hemorrhage (HICH) has been considered to be a one-time event with very rare recurrence [5]. Recently, several retrospective studies have demonstrated that the recurrence of HICH was not as rare as had been previously thought [6-11]. The recurrence rate among these studies ranged from 1.8% to 5.4%. However, most of these reports collected only small number of cases or were recorded within a short study period. This study reviewed more than one thousand cases with HICH and looked into the recurrent HICH over a period of eleven and a half years.

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MATERIALS AND METHODS

Using ICD-code (International Classification of Diseases, Ninth Revision), we reviewed the medical records and computed tomographic findings of patients with ICH (ICD-code 431) from June 1988 to December 1999 at National Cheng Kung University Hospital.

The diagnosis of HICH was defined as (1) previous or current use of antihypertensive medication or persistent systolic pressure > 160 mmHg or diastolic pressure > 90 mmHg on more than 2 measurements; (2) bleeding into a site typical for HICH; and (3) exclusion of other potential causes, such as arteriovenous malformation, cavernous hemangioma, aneurysm, brain tumor, blood dyscrasia, anticoagulant use and head injury. Exclusion criteria were patients with hemorrhagic infarction, traumatic ICH and hemorrhage caused by primary subarachnoid hemorrhage or venous thrombosis.

All patients received brain computed tomography (CT) to confirm the presence of ICH. Classification of the hematoma location and laterality was based on the epicenter of the hematoma as putaminal, thalamic, caudate, lobar (frontal, parietal, temporal, occipital), cerebellar, or pontine. Only those patients who were admitted to our hospital during the acute stage of hemorrhage were included.

To determine the risk factor for recurrent HICH, clinical characteristics were compared between patients with and without recurrent hemorrhages after the first HICH. We recruited age, and sex matched subjects with isolated HICH as the control group. Hepatic dysfunction was defined as either glutamic-oxaloacetic transaminase (normal, 5-40 U/L) or glutamic-pyruvic transaminase (normal, 5-55 U/L) exceeding two times of the normal upper limit. Decreased platelet count and hypocholesterolemia were defined as platelet count < 130,000/mL and cholesterol <160 mg/dL respectively. Risk factors of these two groups were compared by chi-squared test.

RESULTS

Sixty-eight patients (46 men and 22 women) had recurrent HICH. They comprised 4.8% of 1421 patients (819 men and 602 women) admitted to our hospital for HICH from June 1988 to December 1999. Six patients had three episodes of HICH and one patient had 7 episodes. The total episodes of hemorrhage were 147. Their mean age was 57.2 ± 12.1 (range: 30-86) years for the first hemorrhage and 59.9 ± 11.9 (range: 34-89) years for the second hemorrhage.

The median and mean intervals between the first and the second hemorrhage were 22.5 and 32.3 ± 27.8 months (range: 1-107 months) respectively. Table 1 shows the distribution of patients according to interval between hemorrhages. The interval between the first and the second hemorrhage was within one year in 19 (27.9%) patients, between 1 and 2 years in 17 (25%), between 2 and 3 years in 11 (16.2%), and between 3 and 5 years in 8 (11.8%). 19.1% of patients had recurrence after 5 years.

The locations of the first and the second hemorrhages are shown in Table 2. All patients had at least one hemorrhage over the typical site for HICH such as putamen, thalamus, pons, cerebellum or caudate nucleus except for one male who had three episodes of hemorrhages over different lobes at the ages of 52, 53, and 55 years. Putaminal hemorrhage was the most common, which contributed to 50% of the first and 44.1% of the second HICH. Thalamus was the second most common location. All the second hemorrhages were located at sites different from the first one.

Table 3 shows the patterns of the first and the second hemorrhage. Putaminal-thalamic hemorrhage was the most common (16 patients; 23.5%), followed by the putaminal-putaminal hemorrhage (14 patients; 20.6%). The location of the second hemorrhage tends to occur contralaterally to the first one. Forty-nine patients (72%) had both hematomas located in the supratentorium and 40 of them the recurrent HICH occurring contralaterally to the first one. In 19 (28%) patients with at least one hemorrhage in the infratentorium, there was no tendency for the second hemorrhage to occur contralaterally to the first one.

The risk factors of 68 patients with recurrent HICH and 68 patients with isolated HICH are listed in Table 4. The risk of recurrent hemorrhage was not significantly associated with smoking, alcoholism, diabetes mellitus, hepatic dysfunction, decreased platelet count or hypocholesterolemia.

Twelve patients (17.6%) died within one month of the second HICH. Of the 56 patients with the second HICH, 7 patients (six men and one woman) experienced further HICHs. The mean interval was 33 (range: 9-77) months between the first and the second hemorrhage, and 25.6 (range:7-83) months between the second and the third hemorrhage (Table

Table 1. Distributions of 68 HICH patients according to intervals of hemorrhages

Intervals between hemorrhage (months)	First and second hemorrhage (%)	Second and third hemorrhage (%)
Interval ≦ 3	6 (8.8)	-
3 < interval ≦ 6	5 (7.4)	-
6 < interval ≦ 12	8 (11.8)	3 (42.8)
12 < interval ≦ 18	8 (11.8)	1 (14.3)
18 < interval ≦ 24	9 (13.2)	1 (14.3)
24 < interval ≦ 36	11 (16.2)	1 (14.3)
36 < interval ≦ 48	2 (2.9)	-
48 < interval ≦ 60	6 (8.8)	-
60 < interval ≦ 72	5 (7.4)	-
72 < interval ≦ 84	4 (5.9)	1 (14.3)
Interval > 84	4 (5.9)	-
Total	68	7
Mean intervals	32.3	25.6

Table 2. Distribution of 68 HICH patients according to locations of recurrent hemorrhage

	Number of patients		
Location of hematoma	First hemorrhage (%)	Second hemorrhage (%)	Third hemorrhage (%)
Putamen	34 (50)	30 (44.1)	4 (57.1)
Thalamus	15 (22.1)	23 (33.8)	0
Lobe	6 (8.8)	7 (10.3)	3 (42.9)
Caudate nucleus	1 (1.5)	1 (1.5)	0
Cerebellum	8 (11.8)	4 (5.9)	0
Pons	4 (5.9)	3 (4.4)	0
Total	68	68	7

2). The locations for the third HICH were 4 in the putamen (57.1%) and 3 in the lobes (42.9%). All had poor outcomes with severe disability and one patient died from the third HICH.

DISCUSSION

National Cheng Kung University Hospital is a university-affiliated general hospital in Tainan, which opened its service in June 1988. In our hospital, neurologists took care of ICH patients unless they underwent surgical intervention.

Although HICH was considered to be a one-time event before [5], this study reveals that recurrent HICHs among Taiwanese are not rare. However, the true incidence of recurrence in patients after the first HICH was not clear because it was difficult to conduct a prospective study and follow up the clinical courses over a long period. Up to now, only one study has reported a recurrence rate of 2.4% per year in patients with primary ICH. Only half of their patients had a history of hypertension and the high recurrence rate was due to lobar hematoma [6]. Several studies recently [7-11] found that the recurrence among HICH patients ranged from 1.8% to 5.4% during a study period of 2 to 9 years (Table 5). These retrospective studies have a

Table 3. Distribution of 68 HICH patients according to patterns of the first and the second hemorrhage

Pattern of location	Contralateral(%)	Ipsilateral(%)	Total(%)
Supratentorial			
Putamen-thalamus	13	3	16 (23.5)
Putamen-putamen	13	1	14 (20.6)
Thalamus-thalamus	8	0	8 (11.8)
Putamen-lobe	3	1	4 (5.9)
Thalamus-lobe	2	2	4 (5.9)
Caudate-putamen	1	1	2 (2.9)
Lobe-lobe	0	1	1 (1.5)
Subtotal	40 (59)	9 (13)	49 (72)
Infratentorial*			
Cerebellum-putamen	4	3	7 (10.3)
Cerebellum-thalamus	1	2	3 (4.4)
Cerebellum-lobe	1	0	1 (1.5)
Pons-putamen	0	5	5 (7.4)
Pons-lobe	0	2	2 (2.9)
Vermis-putamen	0	1	1 (1.5)
Subtotal	6 (9)	13 (19)	19 (28)
Total	46 (68)	22 (32)	68 (100)

* at least one hematoma is infratentorial

Table 4. Comparison of risk factors between 68 patients with recurrent HICH and 68 patients with isolated HICH

Comparison items	Isolated HICH(n=68)		Recurrent HICH(n=68)		Significance
	No. of cases	%	No. of cases	%	p value
Smoking	27	40	26	38	0.860
Alcoholism	1	1.5	1	1.5	1
Diabetes mellitus	7	10	9	13	0.595
Hepatic dysfunction	5	7	3	4	0.466
Decreased platelet count	4	6	4/66	6	0.963
Hypocholesterolemia	17/59	29	22/57	39	0.264

similar study design as ours but they collected fewer cases (5-53) or covered a shorter period (2-9 years) than ours.

Several findings in this study are different from the previous reports. We recruited 68 patients (4.8%) with recurrent HICH among HICH patients during a period of 11.5 years. Most of the studies reported a higher percentage of recurrence than ours (Table 5). According to the inclusion criteria, we included patients who were admitted to our hospital at both episodes of HICH. Those patients with previous HICH but had been admitted to other hospitals were excluded. We also called patients up by telephone to know if they had recurrent ICH. We found that some patients migrated to other places or had stroke recurrence

Table 5. Demographic characteristics of studies on recurrent hypertensive intracerebral hemorrhage*

Author published year	Country	Study period (years)	No. of patients/ total HICH (%)	M/F (ratio)	Mean age (years)	Intervals (months)	Mortality (%)	HCIH ≥ 3 episodes (%)
Lee *et al.*[7], 1990	Korea	4	14/518 (2.7)	1/13 (0.08)	55.4	13.1	21.4	0 (0)
Hirohata *et al.*[8], 1991	Japan	9	9/494 (1.8)	8/1 (8)	60.5	31.9	11.1	0 (0)
Misra *et al.*[9], 1995	India	3	5/105 (4.8)	2/3 (0.67)	46.8	20.4	0	1 (20)
Chen *et al.*[10], 1995	Taiwan	2	47/892 (5.3)	25/22 (1.14)	62	28	25.5	0 (0)
Bae *et al.*[11], 1999	Korea	7	53/989 (5.4)	25/28 (0.89)	58	22.9	28.3	3 (5.7)
Present study	Taiwan	11.5	68/1421 (4.8)	46/22 (2.09)	59.9	32.3	17.6	7 (10.3)

* data in patients with the second HICH.

but admitted to other hospitals. Thus, we may underestimate the actual number of patients with recurrence.

The mean interval between the first and the second HICH was 32.3 months in our study, which is longer than that in previous reports. This is because we collected patients over a much longer period. In agreement with previous findings, most recurrences occurred within first 2 years of the first hemorrhage (within 1 year in 27.9%, within 1-2 years in 25%). Bae et al reported 2 out or 53 (3.8%) patients had recurrence after 5 years of first HICH [11]. We found a substantial proportion (19.1%) of recurrence was after 5 years. This infers that even after a prolonged period, anti-hypertensive treatment for preventing HICH recurrence is still necessary.

Another unusual finding was the male predominance in our HICH patients. The male/female ratio in our HICH patients with and without recurrence was 2.1 and 1.4 respectively. The sex distribution in recurrent HICH varies greatly from different reports. In the studies from India and Korea, females predominated in the recurrent HICH with a female/male ratio of 1.1 to 13.0 [7,9,11]. In a study from northern Taiwan [10], there was a slight male preponderance with a ratio of 1.1 in recurrent HICH patients and 1.4 in isolated HICH patients. Although the male/female ratio in patients with isolated HICH was similar, the male/female ratio of recurrent HICH in our study was nearly twice that in northern Taiwan (2.1 versus 1.1). The male predominance in our finding requires further study to determine whether blood pressure control in male patients is worse than in females.

Although hepatic dysfunction [12], alcohol use [13,14], and smoking [15,16], have been reported to be associated with ICH, the risk factors of recurrent hemorrhage in patients with HICH have not been systematically evaluated. From our study and previous reports [10,11,17,18], the incidence of these risk factors was not significantly higher in recurrent ICH patients than that in isolated ICH patients. Arakawa *et al.* [19] reported that poor control of blood pressure after HICH was associated with an increased risk of recurrence. Reports from clinical trials [20-22] have shown that control of blood pressure can prevent the occurrence of stroke, including ICH [22]. Unfortunately, the Taiwanese have little knowledge about hypertension and the efficacy of blood pressure control [23,24]. Although the status of blood pressure control was not evaluated in our study, poor blood pressure control may play an important role in our patients with recurrent HICH.

Another well-known cause of ICH, especially in elderly nonhypertensive patients, is cerebral amyloid angiopathy (CAA). The locations of hematomas are almost exclusively lobar because amyloid angiopathy has a predilection for the cortical and leptomeningeal arteries [25]. Although CAA accounted for only 2% to 9.3% of ICH [26,27], it was presumed to be the cause for the lobar-lobar pattern of recurrent ICH [17,18, 28]. In our series, lobar hematoma accounted for 10.9% (16/147) of total episodes of hemorrhages and lobar-lobar pattern was noted in only one patient with the onset age of hemorrhages in the early fifties. Five lobar hemorrhages developed in patients aged greater than 65, of whom the other bleeding site was typical for HICH. Although CAA as a cause of ICH cannot be completely excluded in our study, it is unlikely to represent a major one for our cases.

The outcome of recurrent HICH was poor in most studies. The mortality rate in our study was 17. 6%, which was lower than another study [10] in Taiwan (25.5%) and two other studies [7,11] in Korea (21.4% and 28.3% respectively). The outcome was favorable in small series from Japan and India, in which only 1 out of 14 patients died [8,9]. The difference in the mortality rate may be due to selection bias. Those patients who died in the emergency room with severe recurrent HICH may be missed if the study design included only admission cases. Another possible reason was that the patients were sent to another hospital at the recurrence.

The frequency and locations of recurrence in patients after the second HICH has rarely been reported. Of the 56 survivors after the second hemorrhage, seven patients suffered a third attack or even more during a period of 7 to 83 months. Only one of the 7 patients died from the third hemorrhage and one patient even survived after seven episodes of ICH. Brain atrophy after resolution of previous hemorrhages may protect these patients against the raised intracranial pressure and subsequent brain herniation from the third ICH. However, all the survivors were severely disabled due to the accumulated loss of brain tissues.

In conclusion, recurrent HICHs are not rare among Taiwanese. Males outnumbered females with a ratio of 2.1. The location of recurrent bleeding was also typical for HICH and tended to occur contralaterally to the first one. More than half of the recurrence developed within 2 years of first hemorrhage. Nearly one-fifth of recurrenct HICHs developed after 5 years of first hemorrhage. The outcome for recurrent HICH was usually poor and the survivors may suffer further recurrences.

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台灣人高血壓性腦出血再發

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高血壓性腦出血在以往常被認爲只發生一次，很少會再發出血，但是近年來有一些報告顯示高血壓性腦出血再發並不少見。本研究之目的在探討台灣人高血壓性腦出血再發的比例以及這些病人之臨床特徵。從1988年6月到1999年12月，共有1421位病患發生高血壓性腦出血，從病歷記載以及電腦斷層掃描來決定兩次腦出血相隔時間，出血位置以及再發的比例。其中68位(4.8%)病患出現再發，有46位男性，22位女性，男性爲女性的2.1倍。在第二次高血壓性腦出血的平均年齡爲59.9 ± 11.9歲，第一次與第二次出血之間隔從1月到107月(中位數爲22.5月)，病患第二次出血時間大部分是在第一次出血之後兩年以內，其中27.9%在一年內出現，25%在一到兩年之間出現再發。除了7位病患(10.3%)第二次出血的位置是在腦葉，其餘的病患第二次出血位置都在高血壓性腦出血典型的好發位置；被殼44.1%,視丘33.8%,小腦5.9%,橋腦4.4%,尾狀核1.5%。前兩次出血位置都在小腦天幕之上有49(72%)位，而其中40位第二次出血是在第一次出血的對側。在前兩次出血中，被殼-視丘類型是最常見的類型(23.5%)，其次爲被殼-被殼類型(20.6%)。在第二次腦出血一個月內之死亡率爲17.6%。有7位病患發生兩次以上的腦出血。在台灣人中，高血壓性腦出血再發並不少見，且男性較女性爲多，有不少病患(19.1%)在第一次出血的五年以後才發生再出血。男性病患腦出血再發較女性高原因仍不明，值得進一步探討。

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