CLINICAL ARTICLE

Recurrent Spontaneous Intracerebral Hemorrhage

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Objective : Recently, the survival rate and prognosis of spontaneous intracerebral hemorrhage(S-ICH) has improved, and their enhanced survival has become associated with a consequent rise in the recurrence of S-ICH. The aim of this study is to improve the prevention of recurrent S-ICH.
Methods : Between January 1999 and March 2004, we experienced 48 cases of recurrence. We classified the patients into the two groups; a double ICH group and a triple ICH group. We investigated their brain CTs, MRIs, cerebral angiographies, and medical records, retrospectively.
Results : Majority of patients had the intervals at least 12 months, and most of patients underwent conservative treatment. The most common hemorrhage pattern of recurrence was ganglionic-ganglionic (basal ganglia - basal ganglia), and the second attack was contralateral side of the first attack in a large percentage of all patients. Prognosis of patients was worsened in recurrent attack. Nearly all patients had medical history of hypertension, and most patients have taken antihypertensive medication at the arrival of emergency room.
Conclusion : In treating hypertension for S-ICH patients, we stress that blood pressure must be thoroughly controlled over a long period of time.

KEY WORDS : Spontaneous intracerebral hemorrhage · Recurrence · Hypertension.

Introduction

Spontaneous intracerebral hemorrhage(S-ICH) is a disease that can cause severe permanent neurological deficits and complications with just a single attack. It is also known as a highly lethal disease entity[19]. Recently, the survival rate and prognosis for S-ICH has improved due to greater use of computerized tomography(CT) and magnetic resonance imaging (MRI), with the 30-day survival rate increasing from 8% to 44%[23]. This enhanced survival has become associated with a consequent rise in the recurrence of S-ICH, reported to be between 1.8 and 11.7%[2,6,12,18,20].

In our hospital, we define recurrent S-ICH as a re-attack of S-ICH occurring after one month of the initial attack. We performed a retrospective study in all patients at our department experiencing S-ICH over a five-year period to identify clinical factors that might contribute to recurrence. The aim of this study is to improve the prevention of recurrent S-ICH.

Materials and Methods

Between January 1999 and March 2004, we evaluated brain CTs, MRIs, cerebral angiographies, and medical records of 577 patients with S-ICH. We excluded patients with cerebral hemorrhage that resulted from intracranial aneurysms, arteriovenous malformations, bleeding diathesis, trauma, intracranial brain tumors, and anticoagulant use. Among the 577 patients, 48 (8.3%) had recurrent S-ICH.

We classified the patients into the two groups; a double ICH group and a triple ICH group. Among the 48 patients with recurrent S-ICH, 41 had two S-ICH attacks and were grouped into the double ICH group. The remaining 7 patients experienced three hemorrhages and were classified into the triple ICH group. We investigated each patient's chief complaint, mental status, past medical history, history of alcohol use or medication, treatment modality, neurological status at discharge, and final prognosis. In particular, we focused on patients' histories with

respect to hypertension and antihypertensive medications.

We investigated hemorrhages with regard to location, direction of recurrence, and amount of hemorrhage in a patient's CT and MRI. The amount of hemorrhage can be estimated using the formula of , $V=(1/2) \times A \times B \times C cm^3$ which is used for calculating the capacity of ellipsoids[21]. We classified hemorrhages by site into 5 groups, basal ganglia, thalamus, cerebellum, brain stem, and subcortex. Patients' prognoses were rated using the Glasgow outcome scale(GOS).

Results

Double ICH group

Forty-one of 48 patients had experienced two episodes of S-ICH. The mean age at the time of first S-ICH attack was 57.3 years and the mean age at the second attack was 62.5 years. Twenty-three patients were male and 18 were female. Only 12 patients (29.2%) were younger than 50 years old at the time of initial hemorrhage (Table 1). Thirty patients (73.2%) in the double ICH group had a history of hypertension. A small number of patients had experienced diabetes, liver disease,

Table 1. Age, systolic blood pressure at emergency room, and volume of hematoma in double and triple ICH groups
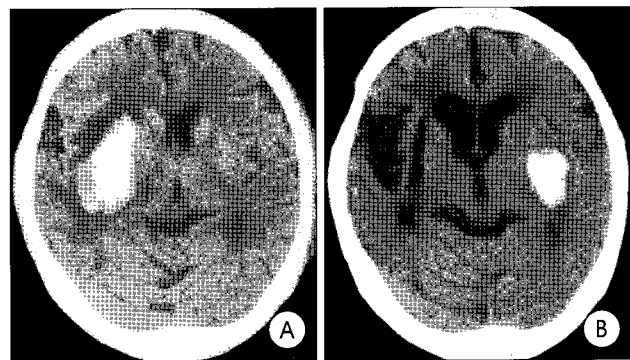
	Double ICH group		Triple ICH group		
	1st ICH*	2nd ICH	1st ICH	2nd ICH	3rd ICH
Age (year)					
< 51	12	7	6	3	1
51~60	12	9	1	4	5
61~70	10	16	0	0	1
71~80	7	8	0	0	0
80 <	0	1	0	0	0
Systolic BP(mmHg)					
< 141	14	7	0	1	3
141~160	12	12	1	3	1
161~180	10	16	2	2	2
180 <	5	6	0	1	1
Volume (ml)					
< 11	15	21	0	3	4
11~20	15	4	2	4	2
21~30	7	2	0	0	1
31~40	2	2	1	0	0
40 <	2	12	1	0	0

*ICH : intracerebral hemorrhage, **BP : blood pressure

Table 2. Intervals of hemorrhagic attacks in double and triple ICH group

	Double ICH group	Triple ICH group	
	1st~2nd ICH*	1st~2nd ICH	2nd~3rd ICH
< 12 Months	9	2	2
1~5 Years	18	3	1
6~10 Years	9	2	3
10 Years <	5	0	1

*ICH : intracerebral hemorrhage

Fig. 1. An example of the double intracerebral hemorrhage(ICH) group in a 68-year-old woman. A : Computed tomography(CT) scan revealing hematoma in the right basal ganglia at the first attack. B : CT scan after 24 months showing recurrent ICH in the left basal ganglia and encephalomalasia in the opposite side with hydrocephalus due to previous hematoma, at the second attack.

alcoholism, or stroke in addition to hemorrhage. An example is shown in Fig. 1.

The average interval between the first and second hemorrhage was 62.6 months (range 4 months -20 years). In most patients (32 cases, 78%), the interval was greater than 12 months (Table 2). Upon arrival at the emergency room, systolic blood pressure was below 140mmHg in 14 patients (34.1%) at the first attack and in 7 patients (17.1%) at the second attack. Mean systolic blood pressures were 158.3mmHg at the first attack and 163.1mmHg in the second attack (Table 1). Twenty-four patients (58.5%) had taken medication for hypertension.

The most common location of hemorrhage was the basal ganglia. At the time of first hemorrhage, 24 patients (58.5%) presented with a hematoma at the basal ganglia. At the second hemorrhage, 14 patients (34.1%) had the basal ganglionic hematoma. The most common hemorrhage pattern by location was the ganglionic-ganglionic type (9 cases, 21.0%), followed by the ganglionic-thalamic type (8 cases, 19.5%), the ganglionic-subcortical type (5 cases, 12.2%), and the subcortical-subcortical type (5 cases, 12.2%). In the majority of patients, the second instance of hemorrhage occurred at a similar location to the first bleeding. Twenty-four patients (58.5%) had hemorrhages located at the basal ganglia or thalamus in both the first and second attacks. For most patients (65.7%) the secondary hem-

Table 3. Location of hemorrhage in double ICH group

		2nd ICH					
		BG	Thal	Cbll	Pons	SC	Total
1st ICH*	BG**	9	8	1	1	5	24
	Thal	4	3	1	0	0	8
	Cbll	0	1	0	0	1	2
	Pons	0	0	0	0	0	0
	SC	1	0	0	1	5	7
	Total	14	12	2	2	11	41

*ICH : intracerebral hemorrhage **BG : basal ganglia, Thal : thalamus, Cbll : cerebellum, SC : subcortical
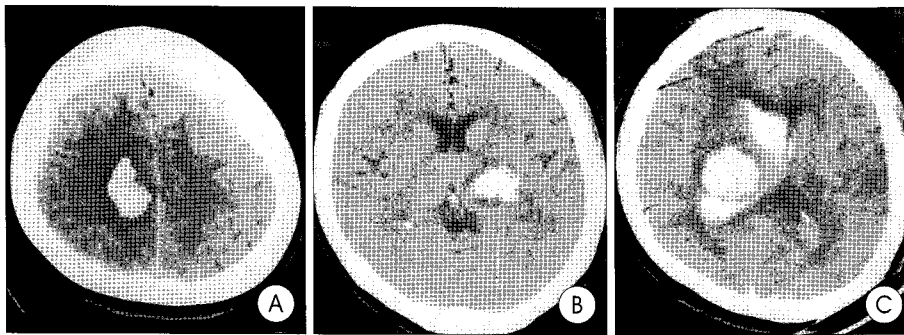
Fig. 2. An example of the triple intracerebral hemorrhage(ICH) group in a 56-year-old woman. A : Computed tomography(CT) scan showing a small amount of hemorrhage in right centrum semiovale at the first attack. B : Left thalamic hemorrhage is found in CT scan after 4 months, at the second attack. C : At the last attack, CT scan demonstrating spontaneous thalamic ICH and IVH (intraventricular hemorrhage) in contralateral side of the second attack.

orrhage was in the opposite direction, and the others of the double ICH group had hemorrhage in the ipsilateral direction (Table 3).

The mean amount of hemorrhage was 16.6ml at the first attack and 25.6ml at the second attack. While the amount of hemorrhage appeared to be in direct proportion to the number of occurrences, this trend was not statistically significant. Most patients had a small amount of hemorrhage, below 20ml for 30 patients (73.2%) at the first attack and below 25ml for patients (61.0%) at the second attack (Table 1). Therefore, most of these patients were treated conservatively at both the

Table 4. Location of hemorrhage in triple ICH group

Patient	1st ICH*	2nd ICH	3rd ICH
1	Lt** BG***	Cbll	Rt BG
2	Cbll	Thal	Cbll
3	Lt BG	Rt. Thal	Lt. Thal
4	SC	Lt Thal	Rt Thal
5	Lt BG	Rt BG	Rt Thal
6	Rt BG	Rt BG	Lt BG
7	Rt BG	Lt Thal	Lt BG

*ICH : intracerebral hemorrhage, **Lt : left, Rt : right, ***BG : basal ganglia, Thal : thalamus, Cbll : cerebellum, SC : subcortical

Table 5. Treatment methods and prognosis in double and triple ICH groups

	Double ICH group		Triple ICH group		
	1st ICH*	2nd ICH	1st ICH	2nd ICH	3rd ICH
Treatment					
Craniotomy or craniectomy	4	2	1	0	0
Burr hole trephination	6	7	2	0	1
EVD**	2	5	0	2	1
Conservative treatment	29	27	4	5	5
Prognosis					
Good Recovery	17	6	4	2	0
Moderate Disability	19	11	2	2	0
Severe Disability	5	9	1	3	3
Vegetative state	0	9	0	0	4
Death	0	6	0	0	0

*ICH : intracerebral hemorrhage, **EVD : external ventricular drainage

first attack (29 cases, 70.7%) and the second attack (27 cases, 56.9%) (Table 5).

At the time of first S-ICH, the majority of patients (36 cases, 87.8%) were discharged from the hospital with neurological conditions that scored better than moderate disability by GOS, with no mortality. At the time of second S-ICH, however, 6 patients (14.6%) died and only 17 patients were discharged from hospital with conditions rated better than moderate disability (Table 5). We found that the prognosis was significantly worse (P<0.05) with S-ICH recurrence.

Triple ICH group

Seven patients experienced two recurrences of S-ICH. Their mean age was 46.7 years, and 6 of the 7 patients (85.7%) had their first hemorrhagic attacks prior to 50 years old (Table 1). These patients included 2 males and 5 females. All had a history of hypertension, without any other complicating medical history. An example is shown in (Fig. 2).

Most triple ICH patients had intervals of over 12 months between S-ICH attacks, just as in the double ICH group. Five patients (71.4%) had their second hemorrhagic attacks at least 12 months following the first hemorrhage, and 5 patients (71.4%) also had their third attacks at least 12 months following the second attack (Table 2).

Mean systolic blood pressures were 170mmHg, 161.4mmHg, and 160mmHg at the first, second, and third attacks (Table 1). Four patients (57.1%) were taking antihypertensive medications at the times of the second and third hemorrhagic attacks. This suggested that recurrence of S-ICH could occur even when the patient was taking antihypertensive medicine.

The most common location of hemorrhage in this group was the basal ganglia which was same as for the double ICH group. Basal ganglionic hemorrhage occurred in 5 (71.4%), 4 (57.1%), and 3 patients (42.9%) at the first, second, and third attacks, respectively. Bleeding was predominantly in contralateral side to the previous hemorrhage, as summarized in (Table 4).

The mean volumes of hemorrhage were 27.6ml, 11.1ml, and 10.4ml at the first, second, and third attacks.

Hematomas of more than 20ml occurred in only two cases at the first attack, no cases at the second, and in only one case at the third attack (Table 1). Patients who were treated conservatively totaled 4 (57.1%) at the first attack and 5 (71.4%) at the second and third attacks, respectively (Table 5).

A good prognosis better than moderate disability by GOS was obtained for 6 patients at the first attack, but for only 4 patients after the second attack. Following the third attack, the prognosis for all patients was scored at worse than severe disability (Table 5). This was similar to our findings for the double ICH group, although it did not achieve statistical significance (P > 0.05).

Discussion

While the incidence of S-ICH varies in different countries, it occurs in 10~32% of all stroke patients[5,14,19]. Hypertension, intracranial arteriovenous malformation, Moyamoya disease, cerebral hemangioma, vasculitis, and systemic diseases such as leukemia and hemophilia are known as primary causes of S-ICH. In Korea, hypertension is the most common reported cause of S-ICH, occurring in 40~90% of cases[7,11,13,15].

Regional differences have been described in the etiology of recurrence. In some studies from Europe, the rate of recurrence of S-ICH has been reported to be about 6.4~24%, and recurrence were most often attributed to uncontrolled hypertension and amyloid angiopathy[17,21]. In studies from Korea, inadequate treatment of hypertension has been indicated as the most common cause of recurrence[12,18]. In Park's study[18], 88.4% of recurrent S-ICH patients had hypertension, but only one patient was being treated with an antihypertensive drug. In another study, patients who have had a secondary S-ICH attack failed to regularly treat hypertension[10]. In our study, 37 patients (77%) had a history of hypertension, and patients' systolic blood pressures were high at the time of recurrence. We agree that hypertension is the most important contributing factor in recurrent S-ICH, but we suggest that adequate continuing control of hypertension is more important than routine medication with antihypertensive drugs in preventing recurrence. We recommend that patients should be followed for a long time period with thorough monitoring and control of hypertension, as the maximum interval between occurrences of S-ICH in our study was 20 years.

In some studies, diastolic blood pressure was found to be very meaningful. In studies by Arakawa[2] and Araki[3], there was no difference in systolic blood pressure between the recurrent and non-recurrent groups, but diastolic blood pressure was significantly different in the two groups. These studies also investigated a number of other known risk factors for recurrence, but none of these showed statistical significance.

In our study, the first attack of hemorrhage was most common in the sixth decade, with the first attack after 50 years of age for most patients. In Park's study[8], the mean ages at the first and second attacks were 55.3 and 55.6 years, respectively, with the most common age at first attack in the sixth decade. Gonzàlez-Duarte[8] reported that the mean age for recurrent S-ICH caused by hypertension was 60 years, but recurrence caused by amyloid angiopathy was at over 70 years of age. In hypertensive S-ICH, especially recurrent cases, the sixth decade of age was common because of the initiation of vascular degenerative changes, although patients were able to maintain their physical and mental activities. We found that most patients had their secondary attack in the seventh decade.

Substantially, different intervals of recurrence have been reported in various studies[1-3,8,12,16,18]. In some studies[12,16,18], intervals of recurrence were less than 12 months in 50~67% of patients. However, in our study, most patients (37 cases, 77.1%) had recurrence intervals of at least 12 months. Arakawa[2] reported that all of his patients had recurrences more than 12 months following the first attack, and Gonzàlez-Duarte[8] reported that only 36% of patients experienced recurrence of S-ICH prior to one year after the first attack. Araki[3] found that 48% of patients had their secondary attacks between one and two years following the first attack, and in Suzuki's study[22], most recurrences were between 3 and 4 years after the first attack. Yet another study observed that recurrence was most common at least 5 years after the first attack[1]. In summary, there is not good consensus about the timing of recurrence, so in our opinion, strict and thorough control of hypertension even one year after first attack should be deemed critical in patients experiencing S-ICH.

The reported volumes of recurrent hemorrhages have also been discordant between studies[4,12,18,24]. Some studies have found that the volume of a recurrent hematoma is much greater than in the first attack, but another report, observed no difference in hematoma volumes between first and second hemorrhages. In Yoji's report, the volumes of secondary hemorrhages were smaller than the first hemorrhages. In our study, mean hematoma volume was increased from 16.6ml to 25.6ml at the time of recurrence, but this difference was not statistically significant. Large hemorrhage volumes of over 40ml were found in only 2 patients (4.8%) at the time of first S-ICH, but this increased markedly to 12 patients (29.3%) at the time of second S-ICH. We found that recurrence of S-ICH is associated with increased hematoma volumes. However, in our triple ICH group, the mean volume for the second attack of S-ICH was smaller than for the first attack, and the volume for the third attack was smaller than for the second. This phenomenon, the reverse situation of the double ICH group, may be a consequence of low survival for patients who had larger hematomas

with their second S-ICH. Patients with large hematomas in their second attacks may have been unable either to endure a third attack or to survive until a third attack could occur.

We found that the most common location of hemorrhage was the basal ganglia, whether at the time of the first, second or third attack. In our double ICH group, the ganglionic-ganglionic type was most common (22.0%). In Kim's report[10], it was observed that 7 among 25 patients (28%) had a putamenal-putamenal type. Other studies were similar to our results that the ganglionic-ganglionic type is the most common type of hemorrhage, ranging between 27.8 and 50%[12,18]. Gonzàlez-Duarte[8] reported that 12 patients (55%) had hematomas at the basal ganglia or thalamus at both the first and second attacks, and these patients had secondary attacks at the opposite side from the first hemorrhage. This phenomenon has been reported by many authors. Because the lenticulostriatal artery branches away from the middle cerebral artery at an acute angle, the blood pressure in this artery is very high compared with that in smaller arteries, so it exhibits a tendency to be ruptured more easily than small arteries[9]. This fact likely has close relationship to the site of recurrence.

Direction of recurrent hemorrhage has also been a subject of discrepant opinions. In some reports[8,18], 54.8~66.6% of patients had recurrence at the side ipsilateral to the first hemorrhage. Another group[4], however, reported that recurrence was on the side opposite to the first hematoma. Our finding also showed that recurrence was more common at the side opposite to the first hemorrhage. It seems reasonable that in the case of ganglionic hemorrhage, recurrence would have a tendency to occur on the side opposite the first attack, because the lenticulostriatal artery on the ipsilateral side tends to collapse as a result of thromboembolization or decreased blood flow[25]. Reports in which ipsilateral recurrence was found to be more common were based on heterogeneous groups including hemorrhages other than those at the basal ganglia.

Most patients admitted to our hospital underwent conservative treatment. This result is predictable, because patients with hemorrhage volumes below 20ml accounted for 32 cases among our 48 patients (66.7%) at the times of first and second attack of hemorrhage, and for 6 cases among 7 patients (85.7%) at the times of third attack. This phenomenon has also been described by others[10,18].

Yoji[24] reported that prognosis following the second attack was better than for the first attack because of smaller volume of hematoma in second attacks. In contrast, Gonzàlez[8] asserted that in recurrent cases, prognosis was worse than following the first attack, because only 27% of recurrent S-ICH patients experienced good functional recovery, compared to 37~55% of nonrecurrent S-ICH patients. In Kim's study[10], patients more frequently had poor prognoses at the time of recurrence than

at first attacks. Park and colleagues[18] reported a prognosis worse than severe disability was 44.5% of patients with recurrence, with a mortality rate of 27.8%. They also found that in patients with additional recurrent hemorrhages, prognosis was worse regardless of treatment method, and this phenomenon had statistical significance. In our study as well, the double ICH group had a statistically significant worse prognosis with the recurrent S-ICH than for the first attack, so we can say the recurrence of S-ICH worsens the prognosis of patients.

Conclusion

We can stress that in treating hypertension for S-ICH patients, blood pressure must be thoroughly controlled over a long period of time. And physicians should schedule follow-up care for patients periodically for more than one year. If a patient experiences recurrence of S-ICH, his prognosis will be severely worsened. So it is imperative to pay careful attention to preventing recurrence of S-ICH.

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