

Clinical features of recurrent stroke after intracerebral hemorrhage

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Abstract

There have been many reports about the prognosis and risk factors of stroke recurrence following brain infarction (BI). However, little is known about the stroke recurrence after primary intracerebral hemorrhage (PICH). Therefore, we explored the recurrent stroke patients after initial PICH retrospectively, to reveal the critical factors of stroke recurrence. Acute BI (n=4013) and acute PICH patients (n=1067) admitted to the hospital between April 2000 and March 2009 were consecutively screened. PICH patients with a history of ICH and BI patients with a history of ICH were then classified into the ICH-ICH group (n=64, age 70.8±9.5 years) and ICH-BI group (n=52, age 72.8±9.7 years), respectively. ICH lesions were categorized into ganglionic and lobar types according to the brain magnetic resonance imaging. Subtypes of BI were classified into cardioembolism, large-artery atherosclerosis, small-artery occlusion and others. There was no difference in incidence of risk factors between ICH-ICH and ICH-BI groups. Distribution of initial PICH lesions was significantly abundant in the lobar type in the ICH-ICH group (P<0.01) and in ganglionic type in the ICH-BI group (P<0.02). Age of onset was significantly older in recurrent lobar ICH compared with recurrent ganglionic ICH (P<0.01: 73.6±10.0 and 59.1±9.0 years, respectively). In conclusion, ganglionic ICH patients may have a chance of recurrent stroke in both brain infarction and ganglionic ICH, suggesting the participation of atherosclerosis in intracranial arteries. Lobar ICH patients were older and prone to recurrent lobar ICH, suggesting the participation of cerebral amyloid angiopathy as a risk of stroke recurrence.

Introduction

In Japan, primary intracerebral hemorrhage (PICH) accounts for about 20% of all strokes and has a mortality rate of 16%, which is about three times higher than that of brain infar-

tion (BI).¹ Currently, the incidence of PICH is higher than that of Western countries.² However, according to the recent meta-analysis, the mortality rate in Japan is lower than in other countries,³ suggesting that stroke is less lethal but more disabling. In fact, stroke is the leading cause of disability.¹ Moreover, after recurrent stroke, recovery of neurological deficits will be worse than that of the first attack, resulting in poor functional outcome. Therefore, it is clinically and socioeconomically important to prevent stroke recurrence after PICH. Although many studies have focused on the risk factors and prevention of stroke recurrence following BI,⁴⁻⁷ the risks and features of recurrent stroke after PICH are still under debate.⁸⁻¹⁰ To identify the effective treatments for preventing recurrent strokes, we explored the difference in clinical features between recurrent PICH and recurrent BI following initial PICH.

Materials and Methods

Patients

After approval from the committee of medical ethics in Research Institute for Brain and Blood Vessels - Akita, Japan, we consecutively screened the inpatients' records in our hospital between April 2000 and March 2009. Acute stroke patients who were admitted to the hospital within 24 h after onset were enrolled in this study (PICH: n=1067 and BI: n=4013). Pure intraventricular hemorrhage was excluded from this study. All stroke lesions were confirmed by a brain computed tomography (Xvigor scanner, Toshiba, Tokyo, Japan) on admission and a brain magnetic resonance imaging (Magnetom Vision 1.5T, GE Medical Systems) within one week of admission. Patients who were admitted with PICH and had a history of PICH were classified into the ICH-ICH group (n=64, 70.8±9.5 years), while

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patients who were admitted with BI and had a history of PICH were classified into the ICH-BI group (n=52, 72.8±9.7 years). All data concerning patients' past history of stroke were collected from clinical records and films. Location and subtype of previous stroke events

Table 1. Clinical backgrounds of all patients.

	ICH-ICH	ICH-BI	P
N.	64	52	
Sex (male/female)	39/25	34/18	0.701
Percentage against total number during the period	6.0 %	1.3 %	0.001
Initial age (average±SD)	63.5±11.2	64.6±11.5	0.299
Recurrent span (years)	7.2±5.1	8.3±7.4	0.117
Risk at recurrent stroke (%)			
Hypertension (without medication)	82.8 (14.1)	86.5 (13.5)	0.999
Diabetes mellitus	10.9	17.3	0.419
Hyperlipidaemia	20.3	21.2	0.999
Atrial fibrillation	3.1	3.8	0.999

ICH, intracerebral hemorrhage; BI, brain infarction; SD, standard deviation.

were confirmed by brain magnetic resonance imaging, using T2 (TR: 4000sec, TE: 92sec) and T2* weighted images (TR: 3100sec, TE: 28sec). ICH lesion was defined as hyposignal area on T2* WI corresponding to the episode. All ICH lesions were classified into lobar (cortical or subcortical), ganglionic (putamen and thalamus), cerebellum and brainstem. BI lesion was defined as high-signal area on T2WI corresponding to the episode. All BI subtypes were classified into cardioembolism, large-artery atherosclerosis, small-artery occlusion and others using the definition of Trial of Org 10172 in Acute Stroke Treatment study.¹¹ Patients diagnosed as transient ischemic attack (TIA) were excluded. The definition of TIA was that neurological symptoms disappear within 24hr rather than evidence from imaging, as used for classical TIA.¹² Clinical risk factors were collected from patient's records with the following criteria: hypertension (>140 mm Hg systolic, >90 mm Hg diastolic or currently prescribed anti-hypertensive medication), diabetes mellitus (spontaneous blood sugar level >200 mg/dL or currently prescribed anti-diabetic medication), hyperlipidemia (>220 mg/dL total cholesterol or >150 mg/dL triglyceride) and atrial fibrillation (confirmed by echocardiogram on admission).

Statistics

Mean age was compared by two group t-test. Distribution of risks and stroke locations were analyzed using Mann-Whitney's U test. All statistics were calculated by computer software, Stat View J 5.0 (SAS Institute Inc., Cary, NC, USA) and $P < 0.05$ was considered significant.

Results

Clinical backgrounds of all patients are shown in Table 1. There were no significant differences in sex distribution, age at initial PICH, periods of recurrence, the incidence of hyperlipidemia and atrial fibrillation between the ICH-ICH group and the ICH-BI group. Hypertension was the most frequent risk factor in both the ICH-ICH and ICH-BI groups. Diabetes was slightly abundant in the ICH-BI group compared with the ICH-ICH group, but there was no significant difference. This study was retrospective and could not calculate the actual recurrence rate following ICH. Nonetheless, recurrence rate of ICH-ICH patients was five times higher than that of ICH-BI patients ($P = 0.001$: 6.0% and 1.3%, respectively). As shown in Figure 1, initial PICH was significantly abundant in the lobar lesion in the ICH-ICH group compared with the ICH-BI group ($P = 0.006$: 31.3% and 9.6%, respectively). Conversely, the location of the initial PICH in

the thalamus was significantly higher in the ICH-BI group than the ICH-ICH group ($P = 0.021$: 40.4% and 31.3%, respectively).

According to the evaluation of the association of stroke lesions between initial and recurrent PICH in the ICH-ICH group, most of the patients who had a lobar lesion as the initial PICH suffered from lobar ICH as recurrent stroke (80%). Patients whose initial PICH was

in thalamus or putamen showed a similar distribution in the lesions of recurrent stroke, *i.e.* the most frequent type was thalamic ICH (52.4% and 66.7%, respectively) followed by putaminal ICH (22.7% and 33.3%, respectively).

Figure 2 shows that, as the recurrent ischemic stroke, large-artery atherosclerosis and small-artery occlusion were abundant in ganglionic lesions of initial PICH. The number

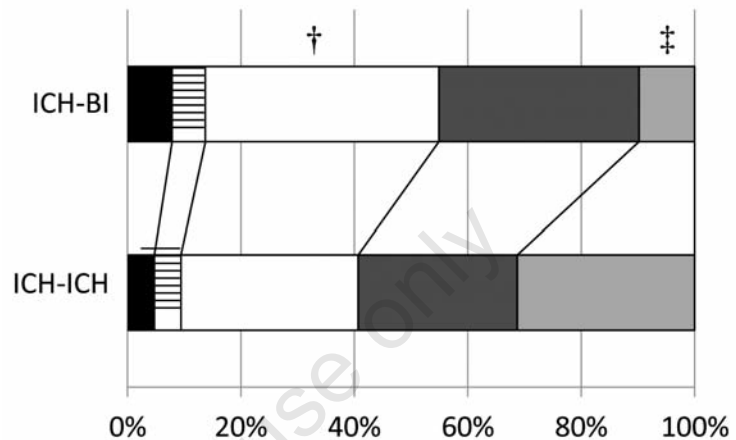


Figure 1. Distribution of initial primary intracerebral hemorrhage (PICH) location. Lobar ICH is significantly abundant in the ICH-ICH group compared with the intracerebral hemorrhage-brain infarction (ICH-BI) group. Percentage of thalamic ICH is significantly high in the ICH-BI group compared with the ICH-ICH group. Black, stripe, white, dark gray and light gray columns indicate brainstem, cerebellar, thalamus, putamen and lobar lesions, respectively. ‡: $P < 0.01$ and †: $P < 0.05$. ICH-BI, intracerebral hemorrhage-brain infarction.

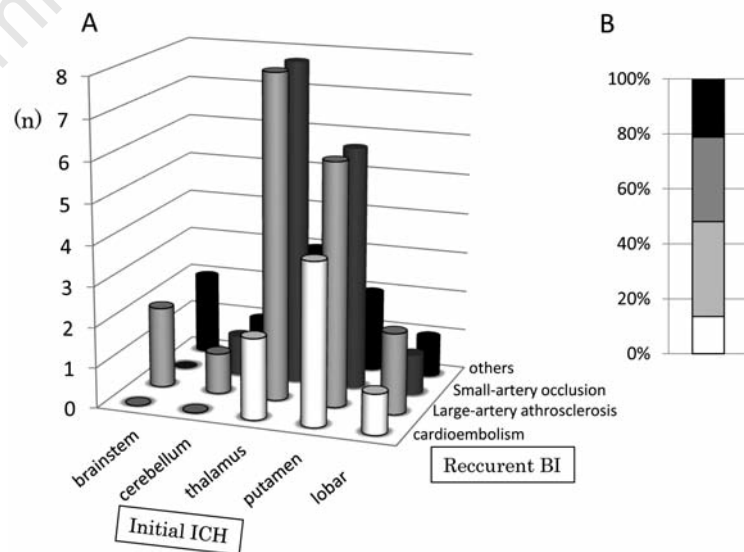


Figure 2. Distributional association between initial intracerebral hemorrhage (ICH) and recurrent brain infarction (BI) subtypes. Lesional correlation between initial ICH and recurrent BI (A), and the proportion of ischemic stroke subtypes (B). White, light gray, dark gray and black bars indicate cardioembolism, large-artery atherosclerosis, small-artery occlusion and others, respectively. Patients with initial primary ICH in ganglionic (putamen and thalamus) exhibit high frequency of large-artery atherosclerosis and small-artery occlusion as recurrent BI. The percentage of cardioembolism is lower than other subtypes. ICH, intracerebral hemorrhage; BI, brain infarction.

of patients with brainstem, cerebellar and lobar lesions as initial PICH was small in this group. The most frequent subtype of recurrent stroke was large-artery atherosclerosis (37.3%) followed by small-artery occlusion (31.4%). Cardioembolism was 13.7%, which was lower than the average in Japan (27.0%).¹³

According to the distributional association between initial and recurrent locations as seen in Figure 3, ganglionic-ganglionic and lobar-lobar lesions were major combinations in the ICH-ICH group. These patients were then classified into decades of age of onset (Figure 4A). The average age was significantly older in lobar-lobar patients compared with ganglionic-ganglionic patients ($P=0.008$: 73.6 ± 10.0 years and 59.1 ± 9.0 years, respectively). In the ICH-BI group, the age of onset of initial PICH was classified into decades depending on the ischemic stroke subtypes of recurrent stroke (Figure 4B). Large-artery atherosclerosis was most frequent in the 70s and small-artery occlusion was in the 60s.

Discussion

It is critically important to prevent stroke recurrence for quality of daily life after initial PICH. Moreover, because the antithrombotic drugs are usually prescribed to patients with ischemic stroke, but may also increase the risk of PICH, the pathogenesis of recurrent stroke after initial PICH should be explored. This study clearly demonstrated the features of recurrent PICH and recurrent BI after initial PICH. There were no differences in clinical risks, such as hypertension, diabetes mellitus and hyperlipidemia, between recurrent PICH and recurrent BI patients after initial PICH. Elderly patients with lobar ICH tended to suffer from lobar lesion as the recurrent PICH. Patients with ganglionic ICH had predominantly recurrence of ganglionic ICH. Moreover, if patients with ganglionic ICH had recurrence of BI, the subtypes were mostly small-artery occlusion and large-artery atherosclerosis.

According to previous studies, the type of recurrent stroke was reported to be more frequent in hemorrhagic stroke than in ischemic stroke,¹⁴ and the recurrence rate of PICH was higher in lobar ICH than in ganglionic ICH.^{9,14-16} Meanwhile, it was reported that there was no difference in stroke recurrent rate for three years following PICH between ICH and cerebral infarctions among the Swedish population.¹⁰ A Japanese study reported that the ganglionic-ganglionic type was the most frequent pattern of ICH recurrence.¹⁷ Our data were not part of a prospective study, so we could not analyze the rate of stroke recurrence after PICH. However, ICH patients may be prone to recurrent hemorrhagic stroke rather than

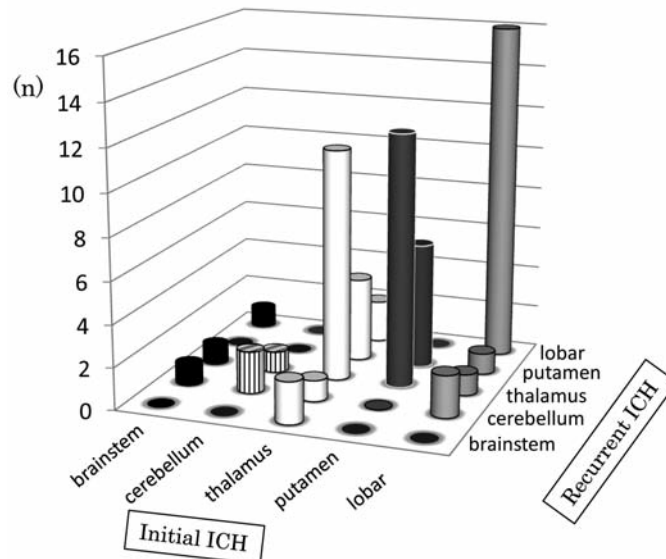


Figure 3. Distributional association between initial and recurrent intracerebral hemorrhage (ICH) locations. Thalamic and lobar lesions as recurrent ICH are dominant. Patients who had lobar lesion in initial ICH mostly suffered from lobar ICH. Patients with ganglionic (putamen and thalamus) lesions in initial ICH showed predominantly ganglionic locations as recurrent ICH. Light gray, dark gray, white, stripe and black columns indicate initial lesions of lobar, putamen, thalamus, cerebellar and brainstem, respectively. ICH, intracerebral hemorrhage

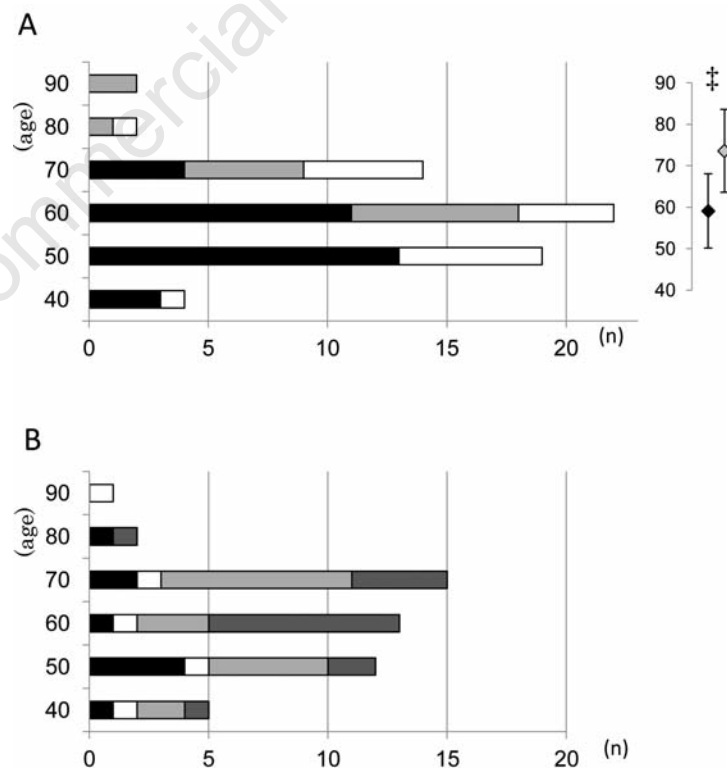


Figure 4. Distribution of age. Mean age of ganglionic intracerebral hemorrhage (ICH) is significantly younger than that of lobar ICH in the ICH-ICH group (A). Black bars indicate patients with ganglionic ICH in both initial and recurrent attack. Gray bars indicate patients with lobar ICH in both initial and recurrent attack. White bars indicate other combination. The mode of small-artery occlusion is 50th and that of large-artery atherosclerosis is 60th in the ICH-BI group (B). White, light gray, dark gray and black bars indicate cardioembolism, large-artery atherosclerosis, small-artery occlusion and others, respectively. ‡: $P<0.01$.

ischemic stroke. Moreover, it can be said that patients of lobar ICH tend to present lobar ICH as recurrent stroke and in particular, that the age of onset of lobar ICH patients with recurrent lobar ICH was significantly older than ganglionic ICH patients with ganglionic ICH as recurrent stroke. In support of this finding, cerebral amyloid angiopathy (CAA) has been reported to be one of the risk factors of lobar ICH accompanied with hypertension,^{8,18} and is often observed in elderly patients with lobar ICH.¹⁹

Generally, ganglionic ICH has a strong association to hypertensive hemorrhage. On the other hand, CAA was reported to have a weak relation to ganglionic ICH.¹⁸ The etiology of ganglionic ICH is the rupture of deep penetrating arteries affected by lipohyalinosis or microaneurysms.²⁰ Thus far, it can be said that the strongest cause of stroke recurrence is uncontrolled risks of atherosclerosis.

In this study, we explored the recurrent stroke of initial PICH cases. Therefore, the number of patients who took anti-coagulation drugs was very small and we did not analyze the role played by the medication in stroke recurrence. Meanwhile, several reports have mentioned that only the treatment of hypertension is significantly effective for prevention of PICH recurrence in CAA patients.^{8,18} In our study, not hypertension but aging was a significantly positive risk factor for the recurrence of lobar ICH. Future studies are needed to determine whether the active treatment of hypertension will decrease the risk of recurrence of lobar ICH or not.

Conclusions

In conclusion, atherosclerosis may play a pivotal role in the pathogenesis of recurrent stroke after ganglionic ICH in middle aged subjects. Hemorrhagic recurrence may be observed in elderly patients with lobar ICH. The clinician should be aware of the critical

treatment of atherosclerotic risks for preventing stroke recurrence after initial PICH.

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