Trends in the Incidence and Survival of Intracerebral Hemorrhage by its Location in a Japanese Community

– The Hisayama Study –

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Background: No previous population-based studies have examined secular trends in the incidence of intracerebral hemorrhage (ICH) by its location.

Methods and Results: We established 3 cohorts consisting of residents of Hisayama, Japan, aged ≥ 40 years without a history of stroke or myocardial infarction in 1961 (the first cohort, $n=1,618$), in 1974 (the second cohort, $n=2,038$), and in 1988 (the third cohort, $n=2,637$). Each cohort was followed for 13 years. The age- and sex-adjusted incidence of ICH significantly declined from the first to the second cohort and showed no further change in the third cohort. With regard to the ICH location, the incidence of putaminal hemorrhage decreased steadily, mainly in subjects aged 60–69 years, whereas the incidence of thalamic hemorrhage increased, especially in those aged ≥ 70 years. Both hypertension and alcohol intake were strong risk factors for ICH in the first cohort, but their influence declined with time. Blood pressure levels in hypertensive subjects decreased significantly, and the proportion of current drinkers decreased slightly over the study period.

Conclusions: Our findings suggest that the ICH incidence steeply declined from the 1960s to the 1970s in Japan as a result of the reduced influence of hypertension and alcohol intake, but that this decline has leveled off since then, probably because of the increased incidence of thalamic hemorrhage in the elderly in recent years. (*Circ J* 2014; **78**: 403–409)

Key Words: Epidemiology; Incidence; Intracerebral hemorrhage; Risk factors; Survival

Intracerebral hemorrhage (ICH) is the second most common type of stroke and has high morbidity and mortality.^{1,2} Asian populations, especially Japanese, have been characterized by a higher incidence of ICH than other ethnic groups.^{3–11} Brain imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are useful tools for diagnosing ICH and its location, but their use was not widespread until the 1970s. Therefore, the most reliable population-based data regarding ICH incidence were established in the 1980s or later.³ Some population-based studies have examined secular trends in the incidence and survival of ICH, but their results are inconsistent.^{12–15} In addition, several studies have examined the distribution or incidence of ICH by its

location,^{5,8,16–20} but none has observed long-term trends in location-specific incidence in general populations.

Editorial p315

We have previously reported that the incidence of ICH declined steeply from the 1960s to the 1970s, but showed no further change in the 1980s and 1990s, based on data from the Hisayama Study, a population-based cohort study in Japan.⁴ As the elderly population has been rapidly increasing in Japan, and the prevalence of cardiovascular risk factors has been changing over time, detailed analysis of the ICH incidence and survival by location is considered to be useful for reducing the

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Table 1. Mean (Standard Deviation) or Prevalence of Cardiovascular Risk Factors at Baseline Among 3 Cohorts of the Hisayama Study

	1st cohort (n=1,618)	2nd cohort (n=2,038)	3rd cohort (n=2,637)	P value for trend
Age, years	56 (11)	57 (12)	59 (12)	<0.001
Women, %	56.4	58.1	57.9	0.39
Hypertension, %	37.9	42.7	41.6	0.42
Antihypertensive agents, %	2.2	8.4	15.0	<0.001
Systolic BP, mmHg*	162.1 (20.6)	160.2 (20.1)	153.3 (18.2)	<0.001
Diastolic BP, mmHg*	89.7 (11.7)	86.2 (11.2)	82.2 (11.0)	<0.001
Hypercholesterolemia, %	5.1	17.3	35.9	<0.001
Total cholesterol, mmol/L	4.1 (1.0)	4.9 (0.9)	5.3 (1.1)	<0.001
Glucose intolerance, %	8.0	10.5	35.2	<0.001
Obesity, %	10.5	16.9	23.4	<0.001
Body mass index, kg/m ²	21.6 (2.7)	22.2 (3.1)	22.8 (3.2)	<0.001
Current drinker, %	34.9	30.1	30.5	0.006
Current smoker, %	42.7	36.9	25.0	<0.001

Values are given as the mean (standard deviation) or as percentage. *Mean systolic and diastolic BPs among hypertensive subjects in each examination. BP, blood pressure.

burden of ICH in the future. It was therefore our intent to examine long-term trends in location-specific incidence and survival of ICH in our population.

Methods

Study Population

The town of Hisayama is a suburban community adjacent to Fukuoka City, a metropolitan area in Kyushu, Japan. The population of the town has been stable over the past 50 years and was approximately 8,400 in 2010. Health examinations of the residents have been carried out annually since 1961. The study design has been previously described in detail.⁴ Briefly, we established 3 study cohorts from Hisayama residents aged ≥ 40 years in 1961, 1974, and 1988 after the screening examinations.

In 1961, a total of 1,658 subjects in that age group participated in the screening examination (participation rate, 90.1%). After the exclusion of 28 subjects with a history of stroke or myocardial infarction (MI) and 12 who died or moved out of town during the examination, 1,618 subjects were enrolled as the first cohort. Similarly, after excluding subjects with a history of stroke or MI, we established the second cohort, which consisted of 2,038 subjects from 2,135 participants (participation rate 81.2%), in 1974, and then the third cohort of 2,637 subjects from 2,742 participants (participation rate 80.9%) in 1988. Each cohort was followed based on the repeat health examinations or by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. We also established a daily monitoring system among the study team, local physicians, and members of the town's Health and Welfare

Table 2. Incidence (per 1000 Person-Years) of Intracerebral Hemorrhage and its Location Among 3 Cohorts of the Hisayama Study, With a 13-Year Follow-up for Each Cohort

	1st cohort (1961–1974) (19,681 PY)	2nd cohort (1974–1987) (25,398 PY)	3rd cohort (1988–2001) (32,854 PY)	P value for trend
Total intracerebral hemorrhage				
No. of events	43	33	53	
Incidence (crude)	2.18	1.30*	1.61	0.16
Incidence (adjusted) [†]	2.03	0.96*	1.14*	0.05
Putamen				
No. of events	26	14	13	
Incidence (crude)	1.32	0.55*	0.39*	<0.001
Incidence (adjusted) [†]	1.17	0.45*	0.40*	<0.001
Thalamus				
No. of events	3	8	19	
Incidence (crude)	0.15	0.31	0.58*	0.02
Incidence (adjusted) [†]	0.16	0.23	0.34	0.04
Subcortex				
No. of events	2	4	10	
Incidence (crude)	0.10	0.16	0.30	0.12
Incidence (adjusted) [†]	0.07	0.11	0.15	0.18
Pons				
No. of events	1	2	6	
Incidence (crude)	0.05	0.08	0.18	0.17
Incidence (adjusted) [†]	0.08	0.04	0.08	0.26
Cerebellum				
No. of events	3	3	3	
Incidence (crude)	0.15	0.12	0.09	0.51
Incidence (adjusted) [†]	0.16	0.08	0.04	0.34
Other determined locations				
No. of events	0	1	2	
Incidence (crude)	0	0.04	0.06	0.32
Incidence (adjusted) [†]	0	0.02	0.12	0.28
Undetermined location				
No. of events	8	1	0	
Incidence (crude)	0.41	0.04*	0	0.009
Incidence (adjusted) [†]	0.40	0.02*	0	0.008

*P<0.05 vs. the 1st cohort. [†]Adjusted for age and sex. There are no significant differences between the 2nd and the 3rd cohorts for all. PY, person-years.

Office, through which we gathered information of new events of stroke, including suspected cases. When stroke occurred or was suspected, physicians in the study team, including the neurologist, examined the subject and evaluated his/her detailed clinical information. When the subjects died, autopsy examinations were performed at the Department of Pathology of Kyushu University. During the 13-year follow-up period for each cohort, autopsy examinations were performed on 358 subjects (81.9% of the deceased subjects) in the first cohort, 371 (85.9%) in the second, and 402 (76.1%) in the third. Only 2 subjects in the first cohort and 1 in the second were lost to follow-up.

Definition of ICH and its Location

Stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficit persisting for >24h and was further classified as ischemic stroke, ICH, subarachnoid hemorrhage, or undetermined type. The diagnosis of ICH was determined on the basis of clinical information, including brain imaging (CT and MRI), and autopsy findings. When a patient experienced recurrent stroke episodes, the first ICH event was ana-

lyzed. During the 13-year follow-up for each cohort, the first-ever ICH developed in 43 subjects in the first cohort, 33 in the second cohort, and 53 in the third cohort. Of these patients, brain imaging was conducted for 1 (2%) in the first cohort, 21 (64%) in the second cohort, and 53 (100%) in the third cohort, and autopsy was carried out for 35 (81%), 25 (76%), and 26 (49%) patients, respectively. Consequently, morphological examinations by brain imaging and/or autopsy were available for 35 (81%), 32 (97%), and 53 (100%) patients, respectively. For 9 patients (8 in the first cohort, 1 in the second) without a morphological examination, we diagnosed ICH based solely on clinical information, including rapid evolution of focal neurological signs or coma, signs of meningeal irritation, elevated blood pressure, headache, and frequently blood-stained cerebrospinal fluid. The location of the ICH was classified as the putamen, thalamus, subcortex, pons, cerebellum, other determined locations, or an undetermined location (for patients without a morphological examination). When a hematoma occupied ≥2 brain regions, the location was determined as a single region with the largest hematoma size.

Figure 2. Age-specific incidence of intracerebral hemorrhage (ICH) and its location among 3 cohorts of the Hisayama Study, with a 13-year follow-up for each cohort. (A) Total ICH, (B) putaminal hemorrhage, (C) thalamic hemorrhage.

Risk Factors

Blood pressure (BP) was measured 3 times in a supine position at the baseline examination, and hypertension was defined as a mean BP $\geq 140/90$ mmHg or use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in subjects with glycosuria in 1961, by fasting and postprandial glucose concentrations in 1974, and by a 75-g oral glucose tolerance test in 1988, in addition to medical history or treatment of diabetes. Serum cholesterol levels were measured by the modified Zak-Henly method in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1988. Hypercholesterolemia was defined as total cholesterol level ≥ 5.7 mmol/L (220 mg/dl). Body height and weight were measured in light clothing without shoes, and obesity was defined as a body mass index ≥ 25.0 kg/m². Information regarding antihypertensive treatment, alcohol intake, and smoking habits was obtained with the use of a standard questionnaire and was categorized as current habitual use or not.

Statistical Analysis

The SAS 9.3 (SAS Institute Inc, Cary, NC, USA) was used to perform all statistical analyses. The prevalences or mean values of risk factors were compared among the cohorts by the logistic regression or the linear regression model. The incidence of ICH was calculated by the person-year method and adjusted for age and sex by the direct method using the World Standard Population, and compared among the cohorts by Cox proportional hazards model. Subjects who developed ICH were also followed up for the next 5 years, and survival rates were estimated using Kaplan-Meier methods and tested with the log-

rank test. The age- and sex-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of risk factors for the development of ICH were estimated by the Cox proportional hazards model in each cohort, and the population attributable risk fraction (PAF) was calculated using a formula: $PAF = PD(HR-1)/HR$, where PD indicates the proportion of subjects exposed to a risk factor. Two-sided $P < 0.05$ was considered statistically significant in all analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was given by the participants.

Results

Trends in Risk Factors

Our comparison of the prevalence and mean values of risk factors at the 3 baseline examinations is shown in Table 1. The prevalence of hypertension was stable among the cohorts, but the proportion of individuals using antihypertensive agents increased consistently with time. Consequently, among hypertensive subjects, mean BP levels significantly decreased from the first to the third cohort. The prevalence of glucose intolerance, hypercholesterolemia, and obesity increased progressively with time. The smoking rate declined linearly, and the drinking rate decreased slightly over the study period.

Trends in ICH Incidence by Location

The proportional distribution of hematoma location among ICH

Figure 3. 5-year survival curves after intracerebral hemorrhage (ICH) and its location among 3 cohorts of the Hisayama Study. (A) Total ICH, (B) putaminal hemorrhage, (C) thalamic hemorrhage. * $P < 0.05$.

Table 3. Age- and Sex-Adjusted Hazard Ratios (HR) of Cardiovascular Risk Factors for Development of Total Intracerebral Hemorrhage Among 3 Cohorts of the Hisayama Study

	1st cohort			2nd cohort			3rd cohort		
	HR (95% CI)	P value	PAF	HR (95% CI)	P value	PAF	HR (95% CI)	P value	PAF
Age, per 10 years	1.56 (1.18–2.05)	0.002		2.06 (1.51–2.81)	<0.001		1.89 (1.49–2.40)	<0.001	
Male	4.35 (2.19–8.67)	<0.001		1.82 (0.91–3.63)	0.09		1.52 (0.88–2.62)	0.13	
Hypertension	9.30 (4.03–21.5)	<0.001	0.75	2.38 (1.09–5.21)	0.03	0.40	2.89 (1.57–5.33)	<0.001	0.46
Alcohol intake	2.61 (1.13–6.02)	0.02	0.43	1.82 (0.76–4.40)	0.18	0.19	1.64 (0.82–3.28)	0.16	0.15
Glucose intolerance	1.29 (0.54–3.09)	0.47	0.03	2.08 (0.89–4.86)	0.09	0.11	1.30 (0.76–2.25)	0.34	0.10
Current smoker	1.01 (0.49–2.08)	0.95	0.01	1.05 (0.45–2.43)	0.92	0.02	1.13 (0.57–2.24)	0.73	0.03
Hypercholesterolemia	1.70 (0.52–5.53)	0.36	0.03	0.84 (0.32–2.22)	0.73	–0.03	0.79 (0.43–1.44)	0.44	–0.08
Obesity	0.26 (0.04–1.86)	0.18	–0.07	0.94 (0.32–2.74)	0.91	–0.01	0.88 (0.44–1.77)	0.73	–0.03

CI, confidence interval; PAF, population attributable risk fraction.

patients in each cohort is shown in [Figure 1](#). The proportion of putaminal hemorrhage decreased steadily from the first to the third cohort. Otherwise, the proportions of thalamic, subcortical, and pontine hemorrhage increased with time.

[Table 2](#) shows the trends in the crude as well as the age- and sex-standardized incidences of total ICH and those by location. The incidence of total ICH significantly declined from the first to the second cohort and showed no further change in the third cohort. The incidence of putaminal hemorrhage showed a similar decreasing pattern. Conversely, the incidence of thalamic hemorrhage increased significantly with time. The incidence of subcortical hemorrhage increased slightly, but was not significant.

[Figure 2](#) demonstrates the trends in the age-specific inci-

dences of total ICH, putaminal hemorrhage, and thalamic hemorrhage. The total ICH incidence showed a decreasing trend in the age group <80 years from the first to the second cohort, whereas the incidence in the age group aged ≥ 80 years increased constantly with time. The incidence of putaminal hemorrhage decreased with time mainly in subjects aged ≥ 60 years. In contrast, the incidence of thalamic hemorrhage increased, particularly among subjects aged ≥ 70 years.

Trends in Survival of ICH by Location

As shown in [Figure 3](#), the 5-year survival rate after ICH improved steadily from the first to the third cohorts, mainly as a result of the improvement in the 1-month survival. There were comparable improvements in survival after putaminal and tha-

lamic hemorrhages.

Trends in the Effect of Risk Factors on ICH

The influence of risk factors on the development of total ICH was compared among the 3 cohorts (Table 3). In the first cohort, hypertension was the strongest risk factor for ICH (age- and sex-adjusted HR 9.30, 95% CI 4.03–21.5) and strongly contributed to its occurrence (PAF 75%). The influence of hypertension declined in the second and third cohorts, but was still a significant risk factor and made the largest contribution even in the third cohort (HR 2.89, 95% CI 1.57–5.33, PAF 46%). Alcohol intake was also a significant risk factor for ICH in the first cohort (HR 2.61, 95% CI 1.13–6.02), explaining 43% of ICH events. The effect of alcohol intake on the occurrence of ICH declined with time and was not significant in the second and third cohorts.

Discussion

To our knowledge, this is the first study to examine secular trends in the incidence and survival rates of ICH by its location. Among 3 cohorts established at different times in a Japanese community, the incidence of total ICH declined significantly, mainly from the first to the second cohort. The incidence of putaminal hemorrhage decreased with time, mainly in subjects aged ≥ 60 years, while an increasing trend in the incidence of thalamic hemorrhage was observed mainly in subjects aged ≥ 80 years. The 5-year survival rate after ICH improved significantly with time. Both hypertension and alcohol intake were strong risk factors for ICH in the first cohort, but their influence declined with time.

Although several community-based surveys of secular trends in the ICH incidence have been conducted, the findings have been inconsistent.^{12–15} In a study from Australia, the ICH incidence decreased from 1989 to 2001.¹² A study in the United Kingdom found that the ICH incidence fell in the younger population, with no definite change in the older subjects between 1981 and 2006.¹³ In contrast, the ICH incidence was stable in France (between 1985 and 2004)¹⁴ and in the United States (between 1993 and 1999).¹⁵ None of these studies observed the ICH incidence before the 1970s when brain imaging was not in practical use. In our present study, the ICH incidence decreased significantly from the 1960s to the 1970s, but the decline leveled off thereafter. Inconsistency in the findings from the studies may reflect different patterns in the prevalence of cardiovascular risk factors and ethnic diversity, as well as the different study periods.

Hypertension is the most powerful risk factor for ICH.^{10,21} In our population, BP among hypertensive subjects decreased significantly with time as a result of the increment in the use of antihypertensive medication, though the prevalence of hypertension remained stable. As a result, the influence of hypertension on the development of ICH declined from the first to the second cohort. Alcohol intake was also a significant risk factor for ICH in the first cohort, but its influence decreased with time. We have previously demonstrated that alcohol intake and hypertension increase the risk of ICH in a synergistic manner.²² The improvement in hypertension control might therefore have resulted in the reduced influence of alcohol intake. These changes in risk factors likely resulted in the decline in ICH incidence in our population.

Several studies have found that ICH in the deep brain, such as in the putamen or thalamus, occurs more frequently than in other locations.^{5,8,16–19} Cross-sectional hospital-based studies have shown that the mean age of incident thalamic hemorrhage

is higher than that of putaminal hemorrhage.^{5,23} In the present study, the incidence of putaminal hemorrhage decreased steadily with time, mainly in the relatively young age group (60–69 years), whereas the incidence of thalamic hemorrhage increased, especially in the very old subjects (≥ 80 years). Although putaminal hemorrhage was the most common subtype of ICH, occurring mainly in the relatively young subjects with untreated hypertension in the 1960s, the improvement in hypertension control has reduced the risk of putaminal hemorrhage and subsequent premature death of hypertensive subjects in recent years. The prolonged longevity of hypertensive subjects might increase the probability of ICH in other locations, such as thalamic or subcortical hemorrhage, at a very old age. The precise reasons for these findings are not clear, but the influence of hypertension and aging on the development of ICH may be different among its locations.²³ Relatively mild but prolonged hypertension might cause degeneration of perforating arteries in the posterior circulation, resulting in thalamic hemorrhage. In our population, the decreasing trend in the ICH incidence has slowed since the 1980s, probably because of the increasing incidence of thalamic and subcortical hemorrhages in the elderly.

The 5-year survival rate of ICH improved significantly with time, mainly as a result of improvement in the first 1 month. Improvement in hypertension control before ICH onset and advances in the management of acute-phase ICH such as BP control and surgical procedures are likely to have contributed to this trend.

Study Limitations

Several should be discussed. First, the method of diagnosing ICH has changed remarkably with advances in the diagnostic techniques, and this change may have resulted in an inconsistency of ICH diagnosis and classification among cohorts. In this study, however, morphological evaluations by brain imaging and/or autopsy were performed for most of the ICH cases, even in the earlier cohorts. Therefore, the possibility of information bias in ICH diagnosis and classification was minimized. Moreover, our main conclusions did not change substantially when we excluded ICH events without morphological evaluation from the total ICH (data not shown). Second, because of the small number of events, we could not examine the influence of risk factors on each location. Third, the numbers of ICH events in our cohorts were relatively small, so we could not evaluate sex-specific trends in the incidence and survival of ICH by location. Fourth, we could not show trends in the volume of hematoma. Brain imaging such as CT and MRI is essential to determine hematoma volume, but it was conducted only for 2% of ICH patients in the first cohort and 64% in the second cohort. Finally, we were unable to investigate the influence of antithrombotic medications, which may increase the risk of ICH and affect its location.^{24,25}

In conclusion, our findings suggest that the incidence of ICH steeply declined from the 1960s to the 1970s in Japan as a result of improved hypertension control, but this decline leveled off thereafter. The incidence of thalamic hemorrhage showed an increasing trend, especially in the elderly in recent years; in contrast, we observed a decreasing incidence for putaminal hemorrhage. Our findings indicate that strict management of hypertension is still important for the prevention of ICH, especially in the elderly Japanese population.

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Disclosures

None.

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