Diurnal and seasonal variations in the onset of primary intracerebral hemorrhage in individuals living in Izumo City, Japan

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Object. Little is known about the temporal patterns of primary intracerebral hemorrhage (ICH) among the general population. The aim of this study was to examine diurnal and seasonal variations in the onset of ICH in a community-based series.

Methods. The study population consisted of 350 patients who presented with primary ICH for the first time and were treated between 1991 and 1998 in Izumo City, Japan. Among the entire patient population, the onset of hemorrhage was rarely observed during the night and a peak was observed in the late afternoon. In men 69 years of age or younger, the onset of ICH exhibited a bimodal distribution, with an initial high peak between 8:00 and 10:00 a.m. and a second, lower peak between 6:00 and 8:00 p.m. In contrast, in men 70 years of age or older and in women regardless of age, only a single evening peak, between approximately 6:00 and 10:00 p.m., was found, and no morning peak was observed. For the entire patient population (for both sexes), and for men alone, seasonal variations—a peak in winter and a trough in summer—were significant for all age groups combined. This factor was significant for patients 69 years of age or younger, during the daytime hours (8:00 a.m.–8:00 p.m.), and for patients with untreated hypertension; however, it was not significant for patients 70 years of age or older, during nighttime hours (10:00 p.m.–8:00 a.m.), or for treated hypertensive and normotensive patients. In women, no significant seasonal patterns were found, regardless of patient age, time of day at onset of ICH, or the presence of risk factors. Seasonal variations were statistically significant for patients with hematomas larger than 5 ml, but not for those with hematomas 5 ml or smaller.

Conclusions. Temporal distributions in the onset of ICH seem to be influenced by patient sex and age. The seasonal patterns of ICH occurrence may result mainly from changes that occur during the daytime, and may also be modified by the presence of untreated hypertension and by the volume of the hematoma.

KEY WORDS • intracerebral hemorrhage • diurnal variation • seasonal variation • epidemiological study

Over the past decade, diurnal and seasonal variations in the onset of primary ICH have been examined in many community- and hospital-based studies. Nevertheless, there remains little understanding of the temporal patterns of onset of primary ICH among the general population. The results of our previous study conducted in Izumo City, Japan, indicated that, although temporal patterns in the onset of ICH could be observed with respect to the time of day and season, their distributions differed according to patient sex and age. Furthermore, in a recent study on seasonal variations in the incidence of aneurysmal SAH in Izumo City, showed that the seasonal pattern may be derived mainly from SAH occurring in the morning, but may also be modified by patient age and SAH risk factors, resulting in masking significant patterns when all patients are investigated together. In the present study, I collected data on a relatively large number of patients from Izumo City who had experienced primary ICH, and investigated not only the influence of patient sex and age, site and volume of the hematoma, and risk factors on diurnal and seasonal variations of ICH occurrence, but also the seasonal pattern of ICH onset in relation to the time of day at which the bleeding occurred.

Clinical Material and Methods

Patient Population

Izumo City is located in the western part of Japan, covering a rural area of approximately 175 km², and has 80,000 inhabitants. There are no large industries and the social and demographic composition of the population is relatively stable. The present study included residents of Izumo City who had experienced primary ICH sometime during an 8-year period (January 1, 1991–December 31, 1998). Izumo City has four hospitals, all of which offer CT scanning. Two hospitals have both neurosurgical and neurological departments and are designated as emergency centers, whereas the other two facilities do not have these specialized departments. Patients in whom primary ICH was verified by CT scanning or MR imaging were eligible for this study, but those with a history of ICH were excluded. Regarding the diagnosis of primary ICH, patients whose hemorrhages...
Diurnal and seasonal variations in intracerebral hemorrhage

were caused by aneurysms, arteriovenous malformations, moyamoya disease, cavernous hemangioma, hemorrhagic transformation of a previous cerebral infarction, head trauma, brain tumor, severe bleeding tendency or coagulation disorder, or malignant disease (including leukemia) were not included in the study. Patients receiving anticoagulant or antiplatelet therapy, and those with severe late-stage diseases involving a bleeding tendency or coagulation disorder were also excluded. The site of ICH was classified, according to the location of the largest blood hematoma, as the putamen, thalamus, caudate nucleus, subcortex, cerebellum, or brainstem. The hematoma volume was calculated on the basis of findings on the CT scan.29

Risk Factors

I collected data on the following risk factors for primary ICH: hypertension, cigarette smoking, alcohol consumption, diabetes mellitus, total serum cholesterol level, and BMI. Hypertension was defined as a history of treatment with antihypertension medication, systolic and/or diastolic pressures greater than 160 and 95 mm Hg, respectively, and roentgenographic or electrocardiographic evidence of left ventricular hypertrophy or cardiomegaly. Data about risk factors were collected from the hospital charts at the time the patients were admitted. Definitions of risk factors and details of the methods used for collecting the data have been given elsewhere.18,20 To focus on the physical state of the patients at the onset of ICH, I divided the patients into two groups according to each risk factor. Patients with hypertension were classified according to whether it was uncontrolled or controlled at the onset of ICH; patients were categorized as those with untreated hypertension or as those with treated hypertension or normotension. For smoking, patients were classified as current regular smokers or as former smokers or nonsmokers. With regard to alcohol consumption, patients were classified according to whether they drank daily, occasionally, or not at all. It was recorded whether the patient had diabetes mellitus, and whether the patient’s total serum cholesterol level was greater than or equal to 220 mg/dl or lower than 220 mg/dl; the BMI of the patient was listed as greater than or equal to 24 or as less than 24.

Statistical Analysis

For statistical analyses of patient age and the volume and site of the ICH between men and women, an unpaired t-test or a chi-square test was used. Diurnal and seasonal variations in primary ICH were examined with respect to the patient’s sex and age, the sites and volume of the ICH, and the presence of any risk factors. To investigate circadian patterns of variation, the times of onset of ICH were plotted within 12 2-hour intervals. I then divided the total number of events by 12 to obtain an expected frequency based on an even distribution throughout the day. I applied the chi-square test to compare the observed frequency of onset against the expected frequency within each of the 12 2-hour intervals. Seasonal variations in ICH were also examined in relation to the time of day when the primary ICH occurred. Statistical analysis for cyclic trends was performed using the method developed by Roger,42,45 to allow for comparisons with data from recently published studies, including one of mine and my colleagues,18,20 in which we evaluated the annual variation of ICH by using this method.

Table 1

<table>
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<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td>All (mean ± SD)</td>
<td>68.3 ± 12.9</td>
<td>65.3 ± 12.1</td>
<td>71.9 ± 13.1</td>
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<tr>
<td>Age in yrs</td>
<td></td>
<td></td>
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<tr>
<td>Hypertensive</td>
<td>257 (73)</td>
<td>144 (75)</td>
<td>113 (72)</td>
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<tr>
<td>Normotensive</td>
<td>70 (20)</td>
<td>38 (20)</td>
<td>32 (20)</td>
</tr>
<tr>
<td>Unknown</td>
<td>23 (7)</td>
<td>11 (6)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Location of ICH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>120 (34)</td>
<td>69 (36)</td>
<td>51 (32)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>115 (33)</td>
<td>59 (31)</td>
<td>56 (36)</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>7 (2)</td>
<td>4 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Subcortex</td>
<td>53 (15)</td>
<td>29 (15)</td>
<td>24 (15)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>25 (7)</td>
<td>14 (7)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>30 (9)</td>
<td>18 (9)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Vol of hematoma in ml (mean ± SD)</td>
<td>19.8 ± 28.5</td>
<td>21.1 ± 30.9</td>
<td>18.3 ± 25.1</td>
</tr>
</tbody>
</table>

* SD = standard deviation; vol = volume.

Results

Between 1991 and 1998, primary ICH was diagnosed in 350 patients; the presence of ICH was verified using CT scanning alone in 345 patients, by MR imaging alone in three, by using both methods in one, and by CT scanning and autopsy in one patient. The mean ages of these patients were 68.3 years (range 34–97 years) for patients with all types of ICH and 67.3 years (range 39–97 years) for those in whom the ICH was due to hypertension (Table 1). The ratio of men to women was 1.2 for all types of ICH and 1.3 for hypertension-induced ICH. There were no significant differences in patient age or in the location and volume of the hematoma between the sexes.

Diurnal Variations

The precise time of onset was recorded for 244 patients with primary ICH. In an additional 106 patients, the exact time of onset could not be confirmed; 66 of these patients became aware of their symptoms on waking or were found unconscious, whereas in the other 40 patients, the time of onset could not be determined at all. For 283 patients, it was possible to categorize the time of ICH onset as daytime (8:00 a.m.–8:00 p.m.; 197 patients) or nighttime (8:00 p.m.–8:00 a.m.; 86 patients).

Figure 1 shows the frequency distributions of the known times of onset in 244 patients with ICH, stratified by sex within the 12 2-hour study intervals. The frequency distributions of the known times of onset for 182 patients with hypertension-induced ICH are also demonstrated. When both sexes were taken into account, the onset of hemorrhage was rarely observed during the night, and a peak was observed during the late afternoon. There was a clear difference in the diurnal variation in the onset of ICH between men and women, however. In the men, ICH exhibited a bimodal distribution, with an initial peak between 8:00 and
10:00 a.m., and a second one between 6:00 and 8:00 p.m. Intracerebral hemorrhage was least likely to occur between 8:00 p.m. and 8:00 a.m. In contrast, no bimodal distribution was found for women, in whom there was a single evening peak in the occurrence of ICH between 6:00 and 10:00 p.m., and ICH was least likely to occur between 10:00 p.m. and 6:00 a.m.

In relation to the age of the patient, there were noticeable differences in the diurnal patterns of ICH between those 69 years of age or younger and those 70 years of age or older (Fig. 2). When both sexes were included, a bimodal distribution of ICH was apparent in patients 69 years of age or younger, whereas in those 70 years of age or older, a single evening peak was found. In men 69 years of age or younger, a bimodal distribution was also found, and the initial peak between 8:00 and 10:00 a.m. was more prominent, compared with that documented in individuals of all ages. In men 70 years of age or older, however, the number of patients between 8:00 and 10:00 a.m. decreased, and an initial peak was no longer observed. In contrast, in women, the distribution pattern of the single evening peak between 6:00 and 10:00 p.m. was not changed regardless of age. The daily variation patterns in the incidence of hypertensive ICH were basically similar to those for all types of ICH combined. When data were analyzed by treating the 66 patients with unknown onset times (those whose symptoms were first noted on waking or who were found unconscious) as though their ICHs had been randomly distributed throughout the preceding 6 or 8 hours, the distribution patterns for both sexes were no different from those in patients in whom exact times of onset could be confirmed.

Seasonal Variations

When all age groups were analyzed together, statistically significant seasonal variations were found for the total patient population (including both sexes) and for men alone (Fig. 3). A graph plotting the occurrence of all types of ICH or only hypertensive ICH throughout the year revealed a sinusoidal pattern for the total patient population and for men alone, with a peak in winter and a trough in summer. For women, however, no significant seasonal patterns were found, regardless of whether the ICH was due to hypertension.

Seasonal variations in the occurrence of ICH, stratified by patient age, are shown in Table 2. Although no statistically significant seasonal variation in ICH was found among the total patient population, the RSCCs were definitely higher in groups of patients younger than 70 years of age than in older patient groups. In men, the RSCCs were significant in the subgroups 59 years or younger and 60 to 69 years, whereas no significant seasonal patterns were found in the subgroup 70 years or older. Therefore, when patients were separated into two groups (age ≤ 69 years and ≥ 70 years), statistically significant seasonal fluctuations were found only in the former group in the total patient population and in men with all types of ICH and those with hypertension-induced ICH (Fig. 4). In contrast, for women, even in patients 59 years of age or younger who had a relatively high RSCC, the plot of ICH occurrence throughout the year did not reveal a typical sinusoidal pattern. When women with all types of ICH and those with hypertension-induced ICH were stratified into two groups in the same way as for men, no statistically significant seasonal variations were observed in either age group.

In the present study, seasonal variations in the onset of primary ICH as they relate to the time of day were analyzed for 283 patients by dividing the day into daytime and nighttime periods. Using this classification, the two diurnal peaks in the incidence of ICH were both included within the daytime period. In previous studies of the Izumo City population, similar diurnal tendencies were found in the onset of aneurysmal SAH, and seasonal variations in SAH were significant during daytime hours, but not during the night.

In this study, during the daytime, statistically significant seasonal variations were found in the total patient population and also in men with all types of ICH (Fig. 5). In relation to the age of the patients, during the daytime, seasonal patterns for the total population were significant in patients 69 years of age or younger (r = 10.26; p < 0.01), but not in those 70 years of age or older (r = 1.41). For men, statistically significant seasonal patterns occurred during the daytime period in patients of both age groups (r = 18.03 and 8.86, respectively; p < 0.001 and p < 0.05, respectively), but not in women, regardless of their age (r = 0.35 and 2.49, respectively). In contrast, no significant fluctuations were found in either sex during the nighttime period, regardless of the age of the patient or whether the ICH was due to hypertension.
Site and Volume of Hemorrhages

Daily variations in the onset of hemorrhage were significant for putaminal and thalamic hemorrhages ($\chi^2 = 34.55$ and 34.16, respectively; both $p < 0.001$); both types of hemorrhage were least likely to occur between midnight and 6:00 a.m., and were highest during working hours between 8:00 a.m. and 8:00 p.m., with a peak in the late afternoon. In patients with ICHs at other sites, similar tendencies were observed, but did not reach statistical significance, probably because of the small number of patients. When patients were classified according to the volume of their hematoma ($\leq 5$ ml and $> 5$ ml), and diurnal patterns of ICH were evaluated separately, no apparent differences were observed between them and only a single evening peak was observed in both groups ($\chi^2 = 26.29$ and $p < 0.01$ for patients with $\leq 5$-ml hematomas, and $\chi^2 = 55.25$ and $p < 0.001$ for patients with $> 5$-ml hematomas).

With respect to seasonal variations in the onset of primary ICH as they relate to the site of ICH, significant seasonal fluctuations—a peak in winter and a trough in summer—were observed for putaminal and subcortical hemorrhages ($r = 9.11$ and $6.07$, respectively; both $p < 0.05$). For thalamic hemorrhage, however, although a similar weak tendency was found, the RSCC did not reach statistical significance ($r = 2.59$). In patients with cerebellar or brainstem hemor-
rhage, no statistically significant seasonal variations were found (r = 0.72 and 2.16, respectively). For these hemorrhages, however, because the number of patients was small, additional work is needed.

Figure 6 shows seasonal variations in the onset of all ICHs and in putaminal or thalamic hemorrhage stratified by hematoma volume. These analyses were not performed in patients with hemorrhages at other sites, because of the small sample number. In patients with hematomas 5 ml or smaller, the RSCC did not reach statistical significance for all ICHs or for putaminal and thalamic hemorrhages, whereas it was statistically significant for those with hematomas larger than 5 ml, regardless of hemorrhage site. The difference by volume of hematoma was more apparent in patients with thalamic hemorrhage than in those with putaminal hemorrhage.

**TABLE 2**

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<th>Month</th>
<th>≤59 Yrs</th>
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<th>70–79 Yrs</th>
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<th>≤59 Yrs</th>
<th>60–69 Yrs</th>
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<td>37</td>
<td>43</td>
<td>49</td>
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</tbody>
</table>

| r value* | 4.70    | 5.94      | 1.57      | 4.25    | 10.91†   | 6.64‡     | 3.44      | 2.65    | 5.32    | 0.48      | 0.03      | 1.92     |

* RSCC.
† p < 0.005.
‡ p < 0.05.

**FIG. 4.** Bar graphs showing seasonal variations in the occurrence of primary ICH in patients 69 years of age or younger (upper) and in those 70 years of age or older (lower). Left: Total patient population. Center: Men. Right: Women.
Risk Factors

With respect to the influence of known risk factors for ICH on diurnal variations in its occurrence, a morning peak was found in current smokers ($\chi^2 = 23$, $p < 0.001$). Daily patterns of ICH, however, did not lead to apparent links with untreated hypertension and daily drinking of alcohol. In patients with untreated hypertension or daily drinking of alcohol, and in those who had no risk factors, a single peak was found in the late afternoon.

Table 3 demonstrates seasonal patterns in the onset of primary ICH in relation to the presence or absence of risk factors. For the entire patient population including both sexes and for men alone, significant seasonal variations were observed in those patients with untreated hypertension at the onset of their ICH, whereas no significant seasonal fluctuations could be found in individuals with treated hypertension or normotension. Nevertheless, cigarette smoking, alcohol consumption, and the BMI did not appear to affect seasonal variations in ICH. With respect to diabetes mellitus and total serum cholesterol levels, although there were significant differences in seasonal patterns between men with and without these risk factors, no definite conclusions can be drawn because of the relatively small number of patients who had these risk factors. No significant seasonal fluctuations were found for women, regardless of their risk factor status.

Discussion

Brief Review of Literature on Variations in BP

It has long been widely recognized that BP exhibits a circadian pattern in patients with either normotension or hypertension, with a diurnal increase and a nocturnal decrease. According to Degaute, et al., BP and heart rate follow a typical bimodal pattern, in which there is a morning peak (at ~ 10:00 a.m.), a small afternoon nadir (at ~ 3:00 p.m.), an evening peak (at ~ 8:00 p.m.), and a profound nocturnal nadir (at ~ 3:00 a.m.). In other words, two natural increases in BP occur during a 24-hour period: once in the morning and once in the evening. Blood pressure is also well known to rise during the morning shortly after waking, and a remarkable rise in BP in the early morning has been referred to as the morning surge. Many recent studies have indicated that the morning surge in BP is associated with the occurrence of ischemic stroke and myocardial ischemic events.

With some exceptions, a seasonal influence on BP, with the highest levels demonstrated in winter and the lowest in summer, has been observed in both normotensive individuals and hypertensive patients, regardless of their sex or age. Cold exposure is known to increase BP by activating the sympathetic nervous system, and seasonal differences in BP correlate with changes in outdoor temperature. With respect to seasonal variations in the 24-hour BP pattern, most authors have demonstrated that daytime BP is higher in winter than in summer, whereas nighttime BP is either lower in winter than in summer or does not differ between these seasons. Thus, the circadian amplitude is higher in winter than in summer, and the morning elevation in BP becomes steeper in winter than in summer.

Regarding the effects of risk factors on BP, it is well known that alcohol consumption is closely associated with...
hypertension. Current drinkers, especially episodic heavy drinkers, display higher BP levels than nondrinkers, and a dose-response or J-shaped relationship between alcohol intake and BP levels has been observed in these individuals.\(^{15,21,31}\) Smoking a cigarette causes an acute rise in BP, especially in the systolic pressure.\(^{7}\)

**Diurnal Variations**

In patients suffering from hemorrhagic stroke, an abrupt increase in BP is likely to play an important role,\(^{18,20}\) and the diurnal pattern of onset of ICH has been explained by the circadian rhythm in BP.\(^{20,46,51}\) In a previous study on diurnal variations in the incidence of ICH in Izumo City, we\(^{20}\) suggested that there were indeed bimodal patterns in its onset; an initial peak occurred during the morning hours and a second one was observed in the late afternoon. In three other community-based studies, however, although a morning peak was demonstrated for ICH onset, no significant bimodal distribution was found.\(^{26,40,55}\) In reports of hospital-based studies on the onset of ICH, some authors have described a bimodal circadian distribution with a preponderance of episodes in the morning and a somewhat lower peak in the evening.\(^{36,46,51}\) whereas others indicated only a peak during the morning waking hours.\(^{22,28}\) or no significant daily variation at all.\(^{1,37}\) In other community- and hospital-based studies concerned with the impact of sex differences on diurnal variations in ICH, no significant differences have been reported between men and women.\(^{13,20,38,46}\)

In this study, when analyses were performed by dividing the patients according to sex and age, there was a clear difference in the diurnal variation of ICH onset. For men, ICH exhibited a bimodal distribution, with an initial peak between 8:00 and 10:00 a.m. and a second one between 6:00 and 8:00 p.m. Therefore, when the existence of a bimodal diurnal variation in BP is considered,\(^{4}\) this pattern of ICH occurrence is also highly suggestive of a strong relationship between BP and ICH. Nevertheless, it is noteworthy that when male patients were separated into two groups according to age (≥ 69 years and ≥ 70 years), the daily patterns of ICH clearly differed between them. In men 69 years of age or younger, the initial peak in the bimodal distribution became more prominent than that for patients of all ages, whereas in men 70 years of age or older, only a single evening peak was found, and a morning peak was no longer observed. In contrast, for women, the diurnal pattern of ICH was similar to that in men 70 years of age or older, regardless of the age of the women. In other words, there were two different patterns in the diurnal variation of ICH, which cannot be explained only by diurnal changes in BP. This raises the question of why a morning peak was found only in men 69 years of age or younger. It has been shown that the difference between daytime and nighttime BPs is significantly lower in elderly hypertensive patients (65–90 years of age) than in younger patients (20–39 years of age).\(^{46}\) In addition, most younger men have to go to work in the morning, and it is well known that stressful events and physical activities produce an acute and substantial increase in BP. These factors may mean that the initial peak of BP becomes more prominent in younger patients, but is obscured in elderly patients. Therefore, not only the morning peak of BP, but also strenuous activity in the morning seem to play an important role in the initial peak of ICH occur-

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**Fig. 6.** Bar graphs showing seasonal variations in the occurrence of primary ICH in patients with a hematoma 5 ml or smaller (upper), and in those with a hematoma larger than 5 ml (lower). Left: All ICHs. Center: Putaminal hemorrhage. Right: Thalamic hemorrhage.
rence in men 69 years of age or younger. In Izumo City, most women are housewives and may have their most stressful and busy time in the evening as they prepare dinner and engage in other activities. This lifestyle may lead to an enhanced evening peak in the incidence of ICH, while making a morning onset less likely in these women. From these findings, it may be concluded that the peaks of ICH occurrence become predominant when BP increases acutely due to strenuous physical activity, in addition to a natural increase in BP.

Seasonal Variations

In community-based studies, Shinkawa, et al.,45 and my colleagues and I20 found significant seasonal patterns in the incidence of ICH, with a peak in the winter months and a trough in the summer, whereas Ricci, et al.,40 reported that the peak incidence of ICH occurred in the autumn. In four other published community-based studies, however, no significant seasonal variation was found.16,26,44,47 In hospital-based studies, several investigators have reported that the incidence rate of ICH demonstrates a peak in winter and a nadir in summer,1–3,6,13,22,37–39,49,52 whereas other investigators have indicated peaks at other times, such as August through September36 and April,43 or have failed to demonstrate any significant seasonal variation.12,14,34,36–39,43,46,49,53 Regarding death rates due to ICH, a similar cyclical fluctuation, with a peak in winter and a trough in summer, has been also reported.17,35,50 With respect to the causes of seasonal patterns in stroke occurrence, climatological factors have been proposed following observations of relationships with ambient temperature,3,6,25,35,45,50 barometric pressure,35 relative humidity,6,35 and hours of sunshine.6 Most reports that have demonstrated a peak in the incidence of cerebrovascular disease in winter and a nadir in summer have stressed the negative correlation between ambient temperature and the incidence of stroke.3,6,18,20,25,35,45,50 The climate in Izumo City is characterized by cold, cloudy, windy, and snowy winters and hot, humid summers.18,20 In other published studies from Japan, the average BP values have been higher when measured in winter than in summer.33,50 Thus, raised BP due to low ambient temperatures may perhaps explain why the incidence of ICH peaks in winter and decreases in summer.

The influence of sex and aging on the seasonal pattern of ICH has not been well investigated to date. In our previous Izumo study, a peak in winter and a trough in summer were found for men, but not for women, and when analyzing patients including both sexes, a statistically significant seasonal fluctuation was observed in individuals younger than 65 years of age, but not in those 65 years or older.20 Nevertheless, there have been no community-based studies in which seasonal patterns of ICH have been investigated separately for men and women who were stratified by age. In a hospital-based study by Gallerani, et al.,13 an annual pattern with a noticeable peak in February was found for men, but not for women. Regarding the influence of aging, Jakovljević, et al.,22 have reported that, for men, the incidence of ICH displays a clear seasonal variation in those 65 to 99 years of age, but not in those 25 to 64 years of age. In other hospital-based studies, however, an influence of sex or aging on the seasonal pattern of ICH was either not found or not investigated at all.1–3,12–14,34,36–39,43,46,49,53

In the present study, the incidence of ICH exhibited a peak in winter and a nadir in summer for the total patient population and for men alone. Why should the incidence of ICH exhibit a significantly seasonal pattern for men, but not

TABLE 3

Seasonal variations in the occurrence of primary ICH stratified by the presence or absence of risk factors*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Total</th>
<th>r Value†</th>
<th>Men</th>
<th>r Value†</th>
<th>Women</th>
<th>r Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>untreated hypertension</td>
<td>83</td>
<td>8.08‡</td>
<td>59</td>
<td>12.62$</td>
<td>24</td>
<td>0.20</td>
</tr>
<tr>
<td>treated hypertension or normotension</td>
<td>185</td>
<td>4.29</td>
<td>90</td>
<td>3.79</td>
<td>95</td>
<td>1.19</td>
</tr>
<tr>
<td>cigarette smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>current smokers</td>
<td>88</td>
<td>8.12‡</td>
<td>77</td>
<td>7.82‡</td>
<td>11</td>
<td>0.56</td>
</tr>
<tr>
<td>former or nonsmokers</td>
<td>242</td>
<td>7.86‡</td>
<td>104</td>
<td>7.97‡</td>
<td>138</td>
<td>2.33</td>
</tr>
<tr>
<td>alcohol intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daily drinking</td>
<td>123</td>
<td>7.37‡</td>
<td>115</td>
<td>10.42$</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>occasional or no drinking</td>
<td>211</td>
<td>9.11‡</td>
<td>70</td>
<td>7.78$</td>
<td>141</td>
<td>3.05</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>37</td>
<td>2.02</td>
<td>30</td>
<td>1.24</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>absent</td>
<td>303</td>
<td>11.96§</td>
<td>157</td>
<td>13.95**</td>
<td>128</td>
<td>3.63</td>
</tr>
<tr>
<td>total cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥220</td>
<td>51</td>
<td>1.91</td>
<td>23</td>
<td>4.53</td>
<td>28</td>
<td>0.54</td>
</tr>
<tr>
<td>&lt;220</td>
<td>186</td>
<td>6.75‡</td>
<td>111</td>
<td>10.47$</td>
<td>75</td>
<td>0.22</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥24</td>
<td>35</td>
<td>1.97</td>
<td>30</td>
<td>2.13</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>&lt;24</td>
<td>82</td>
<td>2.02</td>
<td>49</td>
<td>3.05</td>
<td>33</td>
<td>2.07</td>
</tr>
</tbody>
</table>

* Statistical analyses were not performed in groups in which there were too few patients. — = not performed.
† RS CC.
‡ p < 0.05.
§ p < 0.005.
¶ p < 0.01.
** p < 0.001.
for women? One of the most important reasons would seem to be that men are much more likely to work outdoors than women, resulting in greater exposure to environmental changes.\(^{20}\) In our previous Izumo study, however, no significant differences in seasonal variations in aneurysmal SAH were observed between men and women.\(^{18,20}\) At present, the reasons for the sex-related differences in seasonal pattern between these two types of hemorrhagic stroke remain unknown, and additional studies in this area are needed to clarify this issue.

Seasonal variations in BP have been reported to affect all age groups, including the elderly population.\(^{4,5}\) Indeed, Brennan, et al.,\(^{4}\) reported that seasonal variations in BP in older patients were greater than those in younger patients, at least up to the age of 64 years. This raises the question of why the RSCC showed a definite difference between patients younger than 70 years of age and those 70 years of age and older during the present study. In recent epidemiological studies, the incidence of ICH has continued to increase as individuals become older.\(^{19,20}\) The most prominent increase in prevalence occurs after the age of 70 years, when the incidence rate of ICH increases almost linearly with advancing age. Thus, there is no doubt that advancing age is a major risk factor for ICH. It also appears likely that the pathophysiological factors associated with aging may play a role in modifying the seasonal variations in hemorrhagic stroke, masking the seasonal patterns of ICH in the elderly. In our previous study on aneurysmal SAH in Izumo City, the RSCCs were definitely higher in groups of patients younger than 60 years of age than in older patient groups, and when patients were separated into two groups (age \(\leq 59\) years and \(\geq 60\) years) statistically significant seasonal fluctuations were found only in the former group, regardless of sex.\(^{18}\) Whereas seasonal variations in both ICH and SAH seem to be influenced by aging, the demarcation age might therefore differ between them.

During the daytime in this series, significant seasonal variations in ICH were found only for men, regardless of age, whereas no significant fluctuations were observed during the night, regardless of sex and age. It can be speculated that the seasonal patterns in ICH onset observed in the daytime pattern resulted from the seasonal differences in BP during the daytime or working hours. As speculated in patients with SAH,\(^{18}\) considering that no significant seasonal fluctuations in ICH could be found during the night, the daytime fluctuations in the onset of ICH may contribute largely to the development of a seasonal variation in ICH occurrence. When male patients were divided by age and seasonal patterns were analyzed during the daytime, however, significant fluctuations were found not only in younger men but also in older men. That is, even in older men with apparently lower levels of physical activity, seasonal patterns were significant. Therefore, the influence of sex on the seasonal variation in ICH might outweigh the age-related difference.

**Site and Volume of the Hemorrhage**

The result of this study failed to clarify whether there are differences in the diurnal and seasonal variations of the incidence of each ICH subtype and to demonstrate any relationship between the diurnal pattern of ICH and the hemorrhage volume. At present, no definite conclusions could be reached because of the small numbers of patients. When patients with thalamic hemorrhage were classified according to the volume of their hematoma and seasonal patterns were evaluated separately, the RSCC did not reach statistical significance for patients with a hematoma 5 ml or smaller, whereas it was statistically significant for those with a hematoma larger than 5 ml. The current use of CT scanning has detected small hematomas, which previously might have been diagnosed clinically as cerebral infarction, and has provided their correct anatomical location. As demonstrated in this series, many small hemorrhages were identified in the thalamic area. When considering the difference in seasonal patterns between patients with smaller and larger thalamic hemorrhages, the causes of bleeding might have differed according to the volume of hematoma. In patients with larger hematomas, an elevation in BP seemed to be the main causative factor. In patients with smaller hemorrhages, however, bleeding might not necessarily have been directly related to a rise in BP and changes in the vessel walls, such as degeneration, might have played an important role.

**Risk Factors**

A history of hypertension and alcohol consumption are well-known risk factors for ICH.\(^{3,9,20,22,24}\) In the present study, a predominant morning peak was found in current smokers, which was similar to the diurnal pattern for men 69 years of age or younger. This seems to be explained by the fact that 77 (88%) of the 88 smokers in this study were men. In this study, with respect to the role of hypertension, diurnal variations in hypertensive ICH were similar to those in all types of ICH combined. Similarly, Tsamentzis, et al.,\(^{51}\) and Passero and colleagues\(^{38}\) reported that there were no differences in the time of onset of ICH between normotensive and hypertensive patients.

In the present study, when the patients were classed as those with untreated hypertension or as those with treated hypertension or normotension at the onset of their ICH, significant seasonal variations for the total patient population and for men alone were observed only in the former group. Therefore, it is possible that the effects of the high BP in winter are more severe in patients with untreated hypertension than in patients with treated hypertension or normotension, resulting in a higher incidence of ICH in the former group. Seasonal patterns in ICH do not appear to be affected by risk factors other than hypertension, however. In our previous study on aneurysmal SAH in the population of Izumo City, although statistically significant seasonal patterns were found among patients 59 years of age or younger, patterns tended to be absent or of unclear significance in patients of the same age group who had untreated hypertension, were current smokers, or drank alcohol on a daily basis.\(^{18}\) The conclusions of that study were that seasonal variations in aneurysmal SAH, which are possibly related to changes in BP, are likely to be outweighed by the effects of certain highly influential risk factors, resulting in the obscuration of significant fluctuations. Comparing these findings with those of the present study, it is apparent that the influences of risk factors on seasonal variations in ICH are different from those for SAH. Indeed, ICH and aneurysmal SAH are different entities, and each has an individual risk factor profile. Further studies therefore need to be under-
Diurnal and seasonal variations in intracerebral hemorrhage

taken to elucidate the differing effects of risk factors on each type of hemorrhagic stroke.

Conclusions
The results of this study suggest that there are diurnal and seasonal variations in the occurrence of primary ICH, and that they are influenced by patient sex and age. For men 69 years of age or younger, ICH exhibited a bimodal distribution, with an initial peak between 8:00 and 10:00 a.m. and a second one between 6:00 and 8:00 p.m.; significant seasonal variations, with a peak in winter and a trough in summer, were also found. In contrast, for men 70 years of age or older and for women regardless of age, only a single evening peak between approximately 6:00 and 10:00 p.m. was found, and seasonal patterns were not significant. Analyses of the seasonal pattern of occurrence of ICH as it relates to the time of day at onset indicates that the overall seasonal pattern seen in men may result from the pattern of seasonal changes observed during the daytime (8:00 a.m.–8:00 p.m.). In addition, seasonal variations may also be modified by the presence of untreated hypertension and the volume of hematoma. These may, in turn, be related to the diurnal and seasonal pattern of changes in BP. It is important to note, however, that diurnal and seasonal variations in the occurrence of ICH cannot be ascribed to a single cause, and one should bear in mind that temporal variability may be affected by a complex combination of pathophysiological changes, environmental factors, aging, and modifiable risk factors. In addition, hormonal differences should also be considered to explain sex differences in the variations of ICH occurrence.

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