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【 ORIGINAL ARTICLE 】

Differentiation between Stroke Subtypes and the Causes of Monthly Variations: The Akita Stroke Registry

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Abstract:

Objective It has been established that stroke occurrence is influenced by seasonality. Stroke is divided into three subtypes: cerebral hemorrhage (CH), cerebral infarction (CI), and subarachnoid hemorrhage (SAH). The purpose of this paper was to analyze stroke events by subtype and month, in order to clarify the biggest factors that affect seasonal differences and thereby gain insight into stroke prevention.

Methods Initial stroke events in the Akita Stroke Registry from 1991 to 2010 (58,684 cases; male 30,549, female 28,135) were classified by subtype and the month of onset, and correlations were estimated based on 115 healthy volunteers' monthly mean resting blood pressure (BP) at home and outdoor temperature measured by the Akita Meteorological Observatory in 2001.

Results Systolic BP showed monthly variation in both morning and evening measurements. BP and outdoor temperature showed significant correlations with hemorrhagic stroke events by month (CH: r=0.87, r=−0.82; SAH: r=0.68, r=−0.82). Among the stroke subtypes, seasonal differences were the greatest in CH. Systolic BP was the most important factor for monthly and seasonal variation in stroke events. By comparing monthly BP variations with CH incidence throughout the year, we concluded that a decrease in home BP of 5 mmHg can reduce the risk of CH by 35%.

Conclusion Our findings suggest that lowering BP would be the best strategy for CH prevention. Simple daily actions may be affected by cold stress. As physicians, we must strive to help patients lower their BP throughout the year not only with medication but with lifestyle guidance, especially in winter.

Key words: monthly variation, blood pressure, stroke epidemiology, intracerebral hemorrhage, stroke registry

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Introduction

Although a large number of studies have reported on stroke prevention measures, stroke is still a leading cause of death and disability around the world. Stroke prevention is considered one of the best strategies for improving public health, on which a great deal of effort has been made. What seems to be lacking, however, is research on the variations in blood pressure on a daily, monthly, and yearly basis under an array of various conditions (1-5).

Stroke occurrence is generally known to increase when the weather gets colder. Blood pressure (BP) is the strongest risk factor for stroke and may be increased by the overconsumption of salt and less physical activity during the cold season (6-8). Stroke is divided into three subtypes: cerebral hemorrhage (CH), cerebral infarction (CI), and subarachnoid hemorrhage (SAH). The magnitude of seasonal variation may differ by subtype, but only a few studies have been carried out on the differences in stroke occurrence by month and by subtype (9). Such an analysis requires the use of large amounts of data. However, there were few reports based on such large amounts of data from a single location. Therefore, the purpose of this paper was to use a large number of stroke events in single location (Akita Prefecture) categorized by subtype and month, to clarify the factors that have the biggest impact on seasonal differences and can be utilized for stroke prevention.

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Materials and Methods

The monthly number of initial stroke events were extracted from the Akita Stroke Registry from 1991 to 2010 (58,684 cases; male 30,549, female 28,135). As described in our previous papers, the Akita Stroke Registry consists of all patients with a stroke event who provided informed consent and were admitted to a hospital, and also includes all stroke events and stroke-related deaths that required immediate hospitalization in all emergency medical facilities in Akita Prefecture (10-13). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committees of the Akita prefectural organization. All stroke events that were referred to a hospital and stroke-related deaths were included in our registry. It was difficult to differentiate between the cases of asymptomatic and symptomatic stroke without reviewing documentation from hospital visits; however, the Japanese health insurance system provides easy access to nationwide data without economic variables, so hidden events in our study population were small enough to be negligible. The WHO MONICA diagnostic criteria for stroke were used in this registry. Based on computed tomography (CT) or magnetic resonance imaging (MRI), strokes were divided into 3 subtypes: CH, CI, and SAH.

In 2001, home BP measurements were collected by 115 healthy volunteers living in Akita Prefecture (55 men, mean age 66.5 years; 57 women, mean age 64.6 years). They were recruited from a community health survey in which they reported no subjective symptoms. Those taking medication for hypertension, hyperlipidemia, and diabetes mellitus were excluded from this study. Their morning and night BP were measured on a daily basis for one year. Morning BP was measured within 30 minutes of waking up, before breakfast and taking medicine (14, 15). Night BP was measured just before going to bed. Each time, BP was measured only once on the upper arm and recorded**.**

The number of stroke incidents per month, the average temperature across Akita Prefecture each day in 2001 as recorded by the Akita Meteorological Observatory, and the average home BP among the volunteers were measured and analyzed for correlative relationships using SPSS for Windows (Ver. 12.0; SPSS Japan, Tokyo, Japan). Reductions in risk and 95% confidence intervals were estimated using the Cox proportional hazards model and applied to the number of patients, not the number of stroke events. The data were adjusted for cohort fixed effects and the fixed model approach was applied with the cohort effects included as dummy variables.

Results

The mean monthly morning and night BP and outdoor temperature are shown in Table 1. Night BP is lower than morning BP across all months, with BP in August being the lowest. The outdoor temperature was also highest in August.

The number, proportions, and confidence intervals of initial stroke events per month, both totaled and divided by subtype, are shown in Table 2. The proportion of total stroke events was the lowest in August, and significantly differed from January, March, and April. Each proportion represents each event for total events per month. Compared with European and American stroke data, the ratio of hemorrhagic stroke (CH and SAH) in this registry was significantly higher (13). This distribution of stroke subtypes in Japan is similar to that in our previous report (16).

Of the subtypes, only CI seemed to display no seasonal trends. However, CH and SAH showed similar behavior, such as a decrease in August and an increase in April. CI was divided into three subtypes: atherosclerotic, cardiac emboli and lacunar. We know each subtype had different risk factors. BP has tendency to elevate with climate getting colder, however, dehydration has a tendency to the contrary. Each risk factor balanced out total seasonal variation of “Ischemic stroke”. The correlations between stroke subtypes are shown in Table 3. The correlation index among the stroke subtypes were: CH and SAH, 0.9; CH and CI, 0.64; SAH and CI, 0.63. At this point of view, seasonal behavior of CH and SAH were significantly more similar to each other than to CI. In other words, hemorrhagic stroke (CH and SAH) may be more susceptible to seasonal changes than ischemic stroke.

Correlations among BP, the subtypes, and outdoor temperature are shown in Table 4. BP and outdoor temperature showed significant correlations with monthly hemorrhagic stroke events (CH: r=0.87, r=-0.82; SAH: r=0.68, r=-0.82, respectively). The correlation between systolic BP and CH was within a 1% significant difference and between systolic BP and SAH was within 5% significant difference, but ischemic hemorrhage showed no significance at all. We recognize the similarity between resting BP and CH incidence. This similarity could be a clue to the mechanism of seasonal trends in stroke (Figure). By comparing monthly variations in BP with CH incidence throughout the year, we estimated that a decrease in home BP of 5 mmHg could reduce the risk of CH by 35%.

Outdoor temperature showed a negative correlation with hemorrhagic stroke. The partial correlation coefficient of BP and CH controlling for temperature was 0.60 (p=0.05), and that between outdoor temperature and CH controlling for BP was -0.39 (p=0.23). This shows that home resting BP is a stronger risk factor for CH than cold temperatures in winter.

Discussion

In this study, we elucidated that monthly trends in total stroke incidence most closely followed the pattern of monthly CH incidence (Figure). Resting systolic BP at home may be the best predictor for a CH event (17-18). In comparison with BP measurements taken in a clinical setting, home BP measurements have the advantage of allow-

Table 1. Mean Home BP and Outside Temperature by Month.

Month	Morning BP (mmHg)		Evening BP (mmHg)		Temperature
	Systolic	Diastolic	Systolic	Diastolic	
Jan	132.9	78.1	125.6	72.5	-0.5
Feb	132.1	78.5	124.5	73.0	-0.3
Mar	133.1	77.3	125.3	71.9	2.7
Apr	132.3	77.1	125.4	72.3	8.8
May	131.9	78.6	126.0	73.9	14.1
Jun	130.3	78.2	123.7	73.1	18.5
Jul	127.8	76.3	121.3	71.3	22.6
Aug	127.4	76.2	121.1	71.2	24.0
Sep	130.9	78.0	123.7	73.0	19.4
Oct	132.7	79.2	126.0	74.1	13.1
Nov	134.5	79.1	126.7	73.7	7.3
Dec	133.9	78.7	126.4	73.4	2.3

Temperature: mean outside temperature across Akita Prefecture (°C)
Morning BP: mean blood pressure within 1 hour of waking up

Table 2. Monthly Numbers, Proportions, and Confidence Intervals of Stroke Subtypes and Total Stroke from 1991 to 2010.

	Cerebral hemorrhage			Subarachnoid hemorrhage			Cerebral infarction			Total stroke		
Month	N	%	95%CI	N	%	95%CI	N	%	95%CI	N	%	95%CI
Jan	1,341	9	7.4-10.3	616	9.2	6.8-11	3,366	9	8-9.9	5,323	9	8.1-9.7
Feb	1,295	8.7	7.3-10.3	586	8.8	6.6-11	2,833	7.7	7-8.7	4,714	8	7.3-8.9
Mar	1,451	9.8	8.1-11.1	634	9.5	7.1-12	3,330	9	8-9.8	5,415	9.2	8.2-9.8
Apr	1,332	9	8.1-11.3	599	9	7.2-12	3,067	8.2	8-10	4,998	8.5	8.3-10
May	1,293	8.7	7.1-10	539	8.1	5.7-10	3,168	8.5	7-9.3	5,000	8.5	7.6-9.1
Jun	1,123	7.5	6.1-9.1	504	7.6	5.4-10	3,161	8.5	8-9.6	4,788	8.2	7.5-9.1
Jul	1,022	6.9	5.2-8.3	517	7.8	5.4-9.9	3,035	8.2	7-9	4,574	7.8	6.9-8.4
Aug	960	6.5	4.8-8	477	7.1	4.8-9.3	2,942	7.9	7-8.7	4,379	7.5	6.6-8.1
Sep	1,158	7.8	6.4-9.4	510	7.7	5.5-10	2,891	7.8	7-8.9	4,559	7.8	7.1-8.7
Oct	1,283	8.5	7-9.9	530	8	5.6-10	3,102	8.4	7-9.2	4,915	8.4	7.5-9
Nov	1,296	8.7	7.3-10.3	554	8.3	6.1-11	3,080	8.3	7-9.4	4,930	8.4	7.7-9.3
Dec	1,324	8.9	7.3-10.2	598	8.9	6.6-11	3,167	8.5	7-9.3	5,089	8.7	7.8-9.3
Total	14,878	25.3		6,664	11.4		37,142	63.3			100	

N: Cumulative number of stroke events that occurred in all 20 iterations of a given month across the study period
%: Percentage of stroke events that occurred in all 20 iterations of a given month across the study period, over total stroke events
95%CI: 95% confidence interval

Table 3. Correlations by Stroke Subtype.

	SAH	CI	Total stroke
CH	0.9**	0.64*	0.91**
SAH	1	0.63*	0.87**
CI	0.63*	1	0.75**

*<5% CI, **<1% CI
CH: cerebral hemorrhage, SAH: subarachnoid hemorrhage, CI: cerebral infarction

ing subjects to take measurements at any time and accumulate substantially more data through daily records (14, 15). Further, we used this technique not to evaluate the BP of individuals, but to analyze the trends in BP for an entire population. CH onset is directly triggered by high BP, in the form of both resting BP and abrupt increases in BP (ambulatory BP), and a perforating artery in the brain rupturing when it overtakes vessel wall stiffness.

Monitoring ambulatory BP can reveal large variations in systolic and diastolic BP throughout the day. However, direct measurement of arterial pressure (in patients undergoing rehabilitation) has revealed the dynamic swings in BP that occur in daily life (18).

Tominaga measured the maximum abrupt changes in systolic BP in hypertensive patients during daily events: an increase of 129 mmHg during urination, 142 mmHg during defecation using a squat toilet (traditionally used in Japan), 120 mmHg during a short medical interview with a doctor, 123 mmHg during a cough, and 104 mmHg during a sneeze (Table 5) (18). Real daily BP is made up of these abrupt in-

Table 4. Correlation and Determination by Stroke and BP, Temperature.

	Hemorrhagic subtypes						Ischemic subtype		Total		
	CH			SAH			CI				
	C		D	C		D	C	D	C		D
Morning SBP	0.87	**	0.76	0.68	*	0.46	0.51	0.26	0.77	**	0.59
Morning DBP	0.45		0.2	0.15		0.02	0.11	0.01	0.31		0.1
Evening SBP	0.83	**	0.69	0.6	*	0.53	0.53	0.28	0.75	**	0.56
Evening DBP	0.34		0.12	0.04		0.02	0.07	0.05	0.24		0.06
Temperature	-0.82	**	0.67	-0.82	**	0.67	-0.45	0.2	-0.74	**	0.55

*5% CI, **1% CI

SBP: systolic blood pressure, DBP: diastolic blood pressure, CH: cerebral hemorrhage, SAH: subarachnoid hemorrhage, CI: cerebral infarction, C: correlation coefficient, D: coefficient of determination

Morning: home BP measurement within 1 hour of waking up

Evening: home BP measurement before going to bed

Temperature: monthly average temperature in Akita

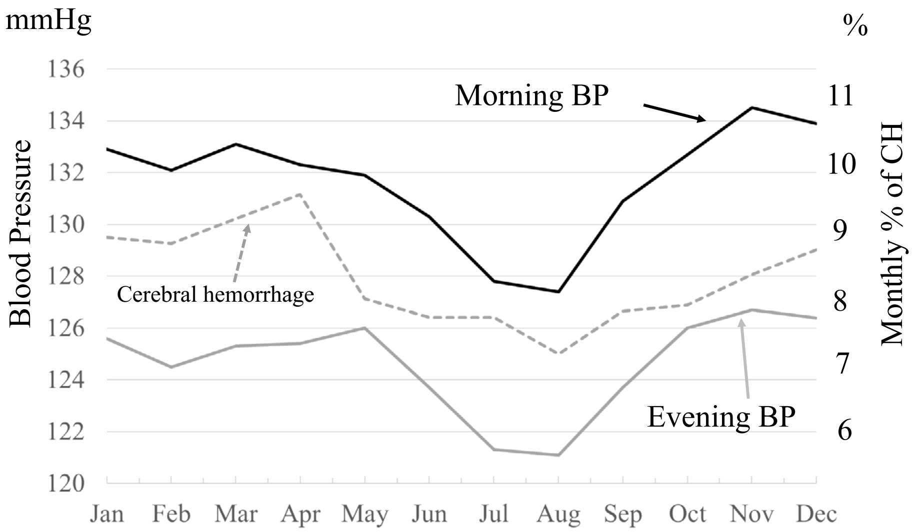

Figure. The monthly distribution of BP and cerebral hemorrhage from 1991 to 2010. The monthly resting BP (morning and evening) was higher in winter than in summer. The ratio of monthly occurrences of cerebral hemorrhage mirrors the trends of BP throughout the year.

Table 5. Abrupt Increases in Systolic BP after Certain Actions (Re-editing from References).

Action	Mean	(Min-Max)	Number	Times
Waking up	23	4-62	13	14
Defecating				
Squat toilet	77	25-142	8	11
Western style toilet	62	32-97	4	9
Urinating	32	3-129	13	47
Climbing stairs	57	24-124	11	12
Coughing	81	26-123	4	10
Sneezing	48	4-104	4	6
Speaking				
with doctor	37	12-120	11	18
with family	36	4-70	7	12
Smoking	38	21-60	3	7
Eating	33	3-73	16	45

Mean: mean elevation of systolic blood pressure (mmHg)

Min: minimum elevation of systolic blood pressure

Max: maximum elevation of systolic blood pressure

Number: number of cases recorded

Times: number of behavior recorded

creases in BP with resting BP as a baseline. If a hypertensive patient with a resting BP of 160 mmHg defecated in a squat toilet, systolic BP could rise to 302 mmHg (Table 5). If a perforating artery in the brain has a limit of 300 mmHg, then CH could occur in an individual when using the toilet. Even if the threshold of 300 mmHg is breached only for an instant, it can be enough to potentially rupture the perforating artery and cause CH.

In the present study, monthly resting BP in winter was 4 to 6 mmHg higher than in summer. Many previous studies reported the relation between seasonal variation and stroke incidence and mentioned about meteorological factors (6-8). We think that seasonal variation of resting blood pressure is not high, however, it has a sufficiently high value to perforate the cerebrovascular artery, because small seasonal blood pressure variation with additional abrupt elevation of blood pressure among daily performance increase the chances to reach the limitation point of perforation for artery. Cerebral hemorrhage was triggered with an abrupt elevation of blood

Table 6. Linear Regression Analysis between Blood Pressure Variation and Stroke Incidence by Stroke Subtypes.

	Cerebral hemorrhage	Subarachnoid hemorrhage	Cerebral infarction	Total stroke
number	14,878	6,664	37,142	58,684
monthly average	1,239.8	555.3	3,095.1	4,890.3
coefficient of correlation	0.906	0.717	0.419	0.759
coefficient of determination	0.821	0.515	0.176	0.576
beta	58.8	16.3	30.3	105.4
probability	0.00	0.009	0.175	0.004
beta/monthly average (%)	4.74	2.93	0.98	2.16

pressure, and increased chances of critical situation increase the incidence of CH in general population in winter. Thus, in this meaning, small seasonal blood variation is not negligible and it is therefore a crucial factor among stroke seasonal variation.

This means the chance of rupturing a perforating artery increases during the cold season and it mirrors the trends of resting systolic BP as shown in Figure.

The correlation coefficient and determination coefficient between morning systolic BP and the proportion of CH events per month were 0.87 and 0.76, respectively. This result suggests that both factors have strong causality. We tried to estimate the proportional reduction in CH events as a result of lowering BP, as follows.

A linear regression analysis between blood pressure variation and stroke incidence by stroke subtypes are shown in Table 6. A large size population can create this value. CH and SAH had a significantly high coefficient of correlation (CH: 0.906 and SAH: 0.717, respectively). Amazingly, the value of CH was extremely high. With this analysis, we could conclude 4.74% as a value that decreasing 1 mmHg of morning systolic BP could reduce the onset of cerebral hemorrhage events. On the contrary, cerebral infarction (CI) had little correlation with the blood pressure. However, a large number of ischemic stroke events were included in this study population, total stroke had significant correlation with blood pressure variation, because of extremely high correlation between CH and BP. Large number of study population and monthly data could reveal the impact of BP among stroke subtypes.

BP measured at home is one of the best methods for estimating stroke risk. A quantitative reduction in CH risk can be achieved by decreasing resting home BP. As physicians, we must strive to help patients lower their BP throughout the year not only with medication but with lifestyle guidance, especially in winter

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committees of the Akita prefectural organization.

The authors state that they have no Conflict of Interest (COI).

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