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1. 研 究 テ ー マ

時間衛生学的視点からみた健康増進に係る環境および生活習慣要因に関する疫学研究

2. 本年度の研究業績

(1) 学会・研究会等における発表 ☒ 有 ・ 無 (学会名・演題)

The 26th International Congress of Internal Medicine, Kyoto, Japan, 2002.5

The effects of climate factors on occurrence of subarachnoid hemorrhage in
different seasons

(2) 学会誌等に発表した論文 ☒ 有 ・ 無 (雑誌名・論文名)

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A study of weekly and seasonal variation of stroke onset

地域登録からみた脳卒中発生の週、季節変動および年齢の影響

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ABSTRACT

Background and purpose: A registry-based study was conducted to assess the variation in first onset stroke amongst weekdays and seasons, in relation to age effects. **Method:** Between December 1, 1991 and November 30, 1998, 10,729 first-onset stroke patients aged 25 or more were registered in Toyama Prefecture, Japan. We compared weekly and seasonal variation in first onset stroke by a one-way goodness of fit chi-square test. The relationship between seasonal variation in stroke onset and age was also evaluated by the method of Kendall's tau-b for $R \times C$ tables with ordered categories. **Results:** The onsets of all strokes and cerebral infarction (CI) were significantly higher on weekdays than those at weekend ($p < 0.01$). More men had strokes and CI on Monday ($p < 0.01$), and more women had cerebral hemorrhage (CH) on Monday and CI at the end of the week. Stroke incidence was higher in patients aged < 60 years (20.6%) than in those aged ≥ 60 years (18.7%) on Monday compared to weekend. By chi-square test, comparing observed vs expected number of stroke onsets, which were weighted by the number of days in each 3-month period, the incidence of all strokes, CI and CH were significantly higher in winter and spring than in summer. Seasonal variation in the onset of stroke declined with age: all strokes ($p < 0.001$) and CH ($p < 0.001$) in both genders, with subarachnoid hemorrhage ($p < 0.001$) only in men. **Conclusion:** Our study shows that the onset of stroke is more frequent on weekdays than on weekends, which may be associated with changes in psychophysiological stresses between the working days and the weekend. We also observed a clear negative dose-response relationship between seasonal variations in occurrence with age. It may be speculated that younger people have more chance to work outdoors exposed to the winter environment. Their lifestyle and physiological condition may be very different from older people.

Key Words: Cerebrovascular disease, Season, Week, Age

INTRODUCTION:

The influence of the seasons on the incidence of cerebrovascular disease and mortality from this condition has been reported during the last three decades, generally with some discrepancy in the results. Many studies conducted in different countries have already reported a marked increase in stroke incidence, mortality and stroke hospitalization in winter-spring and a decrease in summer-autumn, related to ambient temperature¹⁻³⁾. However, other investigations have not found evidence linking seasonality or temperature variation to stroke rates. The few population-based studies were conducted on the basis of small numbers of events observed over short periods of time, or were restricted to subarachnoid hemorrhage. Most of the studies have not had sufficient power to analyze the subtypes of strokes. Alternatively, other studies comprising of a larger number of subjects have often been based on routine mortality statistics or hospital admission registers. However, mortality and hospital admission do not necessarily reflect incidence. In Japan, for example, 28-day case fatality is only 10-21%, and the average 1-year case fatality is less than 30%³⁾.

The peak season for the incidence of stroke was almost consistently found in cold weather, from late fall to early spring, with a trough in summer. However, the reverse trend was also reported in countries such as Israel, where more stroke patients occurred in summer than in colder seasons. Data on the effect of age on seasonal variations in stroke are limited. One study, investigating the magnitude of the effect of different age groups on the seasonal variation in stroke mortality, suggested that the seasonal variation in stroke mortality increased with age²⁾. So far, data on the temporal patterns of stroke, in term of age effect in community-based samples, are sparse.

The shift from a leisurely weekend to working on Monday may be unhealthy in some conditions. In contrast to the extensively studied seasonal effects on the incidence of stroke, so far, only a few reports document the pattern of stroke onset by day of the week. Besides Blue Monday effects, the different distribution of stroke occurrence between weekday and weekend is not also well understood²⁾.

The aim of this study was to examine weekly and seasonal variation in the occurrence of stroke by using data from a large community-based stroke register. In addition, the effect of age on the weekly and seasonal variation in first onset stroke was assessed.

SUBJECTS and METHODS:

The Toyama Stroke Registry System project was a prospective, community-based study with an onset date of April 1, 1991. Stroke was defined as the onset of rapidly developing clinical signs of focal or global disturbance in cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than one of vascular origin. The final clinical diagnosis of stroke and subtype of stroke was determined by detailed history, neurological examination, and ancillary diagnostic tests and confirmation at autopsy. All stroke onsets including death cases were required to be registered in three ways. From hospitals, after a patient was clinically diagnosed as stroke or stroke subtype, general information such as sex, birth date, address, day of stroke onset, hospital admission and discharge from hospital (if the patient was discharged or dead), as well as diagnosed subtype of stroke were reported to the local public health center or to the prefecture medical association on a predetermined special form. The death certificate reports were periodically rechecked to find patients with stroke or stroke subtype as the cause of death, which had not been reported from hospital for any reason. These cases were then sent to the local registration teams for evaluation. The families were visited and asked to provide the required information. The physicians in charge were also required to provide related information. Some of the patients went to day-service agents directly after stroke onset, so the administrators of these agents were also required to report information on stroke patients to the local public health center.

This study utilized data from December 1, 1991 to November 30, 1998, which included the data from the complete 7-year period. In the present report, occurrence refers to first onset strokes, i.e., those occurring without any evidence of a clinically recognized previous stroke event in the patient's history. During the study period, 10729 new onsets of stroke patients were registered in the monitored population aged 25 or older. Data were analyzed by season as follows: winter (December to February), spring (March to May), summer (June to August) and autumn (September to November). Stroke onsets by season were corrected for the number of days in each season. Subgroup analyses of seasonal variation were performed by age group: <60, 60 to 69, 70 to 79 and ≥80 years, and by gender.

Statistical Methods

Assuming that the sizes of the monitored populations do not vary by week and season, we examined the null hypothesis that the strokes were equally distributed across the seven days of a week and the four seasons using a one-way goodness of fit chi-square test to compare observed numbers with those expected on the basis of even distribution. The seasonal variation was expressed as a change rate with the difference in stroke onset number between winter and summer divided by the onset number in summer. The trend in seasonal variation by age group was tested by the method of Kendall's tau-b for $R \times C$ tables with ordered categories. All analyses were performed on the all stroke sample and also on individual stroke

types. Furthermore, analyses were performed for sexes combined and separate. The statistical analyses were performed with SPSS (version 10.0J, SPSS Inc. USA).

RESULTS:

Population characteristics

During the study period from December 1, 1991 to November 30, 1998, a total of 10769 first onset of stroke patients aged 25 years or more were registered in the Toyama Stroke Registry System, including 6520 cerebral infarctions (CI) (60.5%), 2803 cerebral hemorrhages (CH) (26.0%), 1229 subarachnoid hemorrhage (SAH) (11.4%) and 217 others (2.0%). Among the patients, there were more men (56.3%) than women (43.7%). For various subtypes, the numbers of CI and CH in men were more than those in women. On the contrary, the number of SAH was higher in women patients. The mean age of all patients was 69.2 years (standard deviation =12.2, range, 25-101 years), and the mean age of CI was significantly higher than that of CH, which was then significantly higher than that of SAH patients ($p<0.001$). The mean ages at stroke onset were also significantly different for men and women. The mean ages of women were much higher than those of men for all strokes and stroke subtypes. CI accounted for 60.5 percent of all strokes. The proportion of CI patients increased linearly from the youngest group, and with the highest proportion of 70.73% in the group aged 80 years. On the other hand, the proportion of CH and SAH decreased with an increase in age.

Weekly variation of stroke occurrence and the effect of age

Table 1 shows the ratios of the number of stroke cases in weekday to that at weekend by stroke subtypes and sexes. For the seven days of the week, significantly different distributions of CI and all strokes in men and women, and CH in female patients were observed ($P<0.05$). Stroke onsets were significantly higher from Monday to Friday than weekend for all strokes (11~19% increased) and CI (14~21% increased). Strokes occurred mostly on Mondays except SAH in men and CI in women. There was a different distribution of stroke among the days of the week between sexes. For men, significantly more strokes occurred on Monday ($p<0.01$) for all strokes, and on Monday and Wednesday for CI ($p<0.01$). On the other hand, women had a similar distribution for all strokes through the weekdays. Although CH was highest on Monday (34% increased when compared to the weekend), the occurrence of CI was significantly high on Thursday and Friday.

Table 1. Ratios of the number of stroke cases in weekday to that at weekend (with Saturday and Sunday averaged as 1.00) by stroke subtypes and sexes, data from the Toyama Stroke Registry System project, 1991-1998

	Total				Men				Women			
	CI	CH	SAH	All	CI	CH	SAH	All	CI	CH	SAH	All
Monday	1.21**	1.13	1.26	1.19**	1.26**	1.01	1.05	1.17**	1.12	1.34**	1.40	1.23**
Tuesday	1.14*	1.11	1.02	1.12**	1.14	1.01	1.02	1.10	1.13	1.27	1.03	1.15*
Wednesday	1.17**	1.01	1.00	1.11**	1.19**	0.94	0.91	1.09	1.15	1.14	1.07	1.14*
Thursday	1.17**	0.99	1.06	1.12**	1.13	0.90	0.91	1.06	1.22*	1.11	1.17	1.20**
Friday	1.15**	1.08	1.12	1.12**	1.10	0.97	0.98	1.06	1.21*	1.25	1.22	1.21**
P†	<0.001	0.082	0.200	<0.001	<0.001	0.844	0.895	0.009	0.007	0.007	0.071	<0.001

†, *, ** by one-way goodness of fit chi-square test comparing the observed vs. expected

† compared among the seven days of a week

* $P<0.05$, ** $P<0.01$ compared with the weekend (Sunday and Saturday averaged)

Seasonal variation of stroke occurrence and the effect of age

Table 2 shows the ratios of the number of stroke cases in winter, spring and autumn to that in summer by sex and by subtype of stroke. It demonstrates that all strokes are unevenly distributed throughout the four seasons ($p<0.001$ in both

genders). The onsets of all strokes, CI and CH were significantly higher in winter and spring than in summer ($p<0.05$ for CI and CH in men, and CI in women; $p<0.01$ for other comparisons). Among total strokes, SAH was also highest in winter compared to other seasons, and significantly higher than that in summer ($p<0.05$).

Seasonal variation in the onsets of CH significantly declined with increasing age in men and women. In those aged <60 years, the seasonal change rate of CH onset was 59.59%, which decreased to 35.29% in those aged 60 to 69, 21.79% for ages 70 to 79, and only 12.17% for ages ≥ 80 years ($P<0.001$ by the test of Kendall's tau-b for $R \times C$ tables with ordered categories). The slope of this trend was a 9.75% decrease in seasonal change rate for every increasing decade in age ($p<0.01$). The seasonal variation in the onsets of all strokes also declined strikingly with increasing age for both genders, although with a less sharp slope than that of CH, respectively. Although the proportion of CI among the various subtypes of stroke increased linearly with age, there were no significantly different seasonal change rates referencing to age in either gender.

Table 2 Ratios of the number of stroke cases in winter, spring and autumn to that in summer (relatively referred as 1.00) by stroke subtypes in men and women aged ≥ 25 years during the 7-year period of the Toyama Stroke Registry System project, 1991-1998

	Season	CI	CH	SAH	Other	All strokes
Total	Winter	1.17**	1.33**	1.23*	0.91	1.21**
	Spring	1.13**	1.32**	1.17	0.91	1.18**
	Summer	1.00	1.00	1.00	1.00	1.00
	Autumn	1.01	1.12	1.13	0.98	1.05
	P †	<0.001	<0.001	0.05	0.951	<0.001
Men	Winter	1.12**	1.28**	1.19	0.97	1.17**
	Spring	1.12*	1.23*	1.08	0.90	1.14**
	Summer	1.00	1.00	1.00	1.00	1.00
	Autumn	1.01	1.14	1.19	0.90	1.05
	P †	0.005	0.002	0.427	0.97	<0.001
Women	Winter	1.24**	1.40**	1.25	0.85	1.27**
	Spring	1.15*	1.46**	1.22	0.93	1.23**
	Summer	1.00	1.00	1.00	1.00	1.00
	Autumn	1.00	1.10	1.09	1.07	1.04
	P †	<0.001	<0.001	0.084	0.865	<0.001

† By one-way goodness of fit chi-square test comparing observed vs expected. The expected numbers were weighted by the number of days in each 3-month period of the season.

* $p<0.05$, ** $p<0.01$ by one-way goodness of fit chi-square test comparing observed vs expected stroke numbers between winter or spring and summer.

DISCUSSION:

We have studied weekly and seasonal variations in stroke occurrence using more than 10000 first onset stroke patients during a 7-year period of registration in the Toyama Stroke Registry System. This is the largest study of seasonal occurrence thus far in Japan. Our study demonstrates that first onset stroke has its own temporal distribution, with more occurrences on weekdays and in colder seasons of spring and winter. A pronounced age effect in the seasonal variations of stroke occurrence was also observed. Winter increases in occurrence of stroke were greater in the younger individuals compared with the elderly, for CH and SAH.

In a previous study, the peak incidence of stroke was observed on the weekend, suggesting that this may be caused by short-term lifestyle changes during the weekend. However, our observation, on the contrary, has demonstrated maximum occurrences during the weekdays, and especially more occurrences on Mondays. Willich⁴⁾ hypothesized that external factors, such as sudden changes in physical and mental activity on transition from the weekend to workdays, may trigger vascular events. In our study, a different weekly distribution of strokes between the two genders was observed. The strokes occurred more on Monday in men, but through the weekdays in women than those at weekend. This phenomenon may be explained, at least partly, by the very different traditional gender role in Japanese family life. The elderly men still have to be more responsible for public life, and face more stress from outside, even after retiring from work, and women are still most in charge of house-keeping. Our analysis points to a need for further exploration in deciphering behavior/risk factor differences, both in terms of daily living habits and the time immediately preceding the acute onset of stroke.

The maximum occurrence of cardio-cerebrovascular disease in winter is a well-documented observation. Our study also confirms a peak for stroke in winter and in spring. Most of the studies in this field have been performed in countries with cold or temperate climates, but in a study from Israel the average daily incidence of stroke was approximately twice as great on hot days as on relatively cold days. This suggests that exposure to extreme temperatures, whether cold or hot, may increase the risk of stroke.

A significant association between season and the occurrence of SAH was found among the total patients and the same tendency was identified in females ($p=0.084$). However, some other researchers have reported no significant association¹⁾. At least in part, these controversies may be due to the small numbers of patients in these studies and to the relative rarity of SAH. The occurrence of SAH also tended to be higher during winter months than during other months in a large population-based stroke registry study from Finland¹⁾, although not significantly so.

The biological reasons for the higher occurrence of strokes during cooler seasons of winter and spring are not well known, but several possible mechanisms may be suggested. The seasonal fluctuation in blood pressure is very similar to that for cerebrovascular disease with a peak in winter and spring and trough in late summer. Hypertension is a recognized factor in the aetiology of all forms of cerebrovascular disease. The difference between summer and winter temperatures in Britain results in a difference of about 5 mm Hg⁵⁾. Sustained differences in blood pressure of this order are associated with at least a 34% difference in stroke event. Furthermore, serum cholesterol, C-reactive protein and factor VII activity, red blood cells and platelet count, and sympathetic tone are all higher under cold temperatures in winter. Elevation of these parameters may contribute to an increased tendency toward arterial thrombosis and a higher winter incidence of cardio-cerebrovascular disease. Perhaps most importantly, plasma fibrinogen concentration and viscosity show considerable seasonal variations, at least in elderly persons⁶⁾ and there is evidence that fibrinogen is a significant predictor of stroke.

We also observed decreased seasonal variation in occurrence with increasing age. So, at younger ages, seasonal changes have a larger effect on occurrence of all strokes, CH and SAH than those with increased age. More seasonal variation in the occurrence of SAH in younger patients than in more elderly patients has not been reported before. There have been only a few reports concerning this phenomenon so far. The greater incidence of ischemic strokes in winter was particularly prominent among men aged 25 to 64 years and less prominent in elderly men¹⁾. The incidence of both CI and CH had a significant seasonal variation in subjects aged <64 years, and a high but not significant seasonal variation in those aged >75 years in another report from Japan³⁾. However, we observed a clear dose-response relationship between age and seasonal variation in the occurrence of stroke, which had not been examined in previous studies.

Sheth²⁾ studied seasonal variations in myocardial infarction and stroke mortality using 300,00 deaths from the Canadian Mortality Database, in which a graded increase in mortality from acute myocardial infarction and stroke with increasing age was observed. However, this result based on mortality data may be much different from that based on occurrence data. Individuals who have had a stroke are more susceptible to die if they develop an acute respiratory infection, and are also at

increased risk of death from influenza, particularly if institutionalized, or if aged 65 or older. The stroke case fatality in the first year after stroke onset is significantly higher in elder than that in younger patients. Although the elderly seem to be more sensitive to environmental changes, with greater increases in blood pressure and coagulation parameters, or a greater likelihood of infection in winter, the younger people have more frequent exposure to cold because of outside work and other physical activities, and are thus more exposed to cold weather and respiratory infections⁷⁾.

Psychological stress was reported as a significant risk for stroke and coronary artery disease, even after adjustment for other established risk factors in middle-aged men. Sudden death in Japan occurred more frequently in April when the new business year starts than in other months. It was supposed that the younger person in Japan might have to face stronger occupational stress at the end of the old financial year and the beginning of the new, from winter to spring. On the contrary, the effective protection of houses with insulation and adequate heating may protect older persons; consequently indoor temperatures might not vary substantially by season in Japan. On the other hand, acute respiratory infections, which are also a kind of disease with strong seasonal variation, may also increase stroke incidence somewhat. Although plausible underlying pathogenetic mechanisms remain to be determined, a number of studies have suggested that infections may trigger stroke, particularly in young and middle patients, but not in older patients⁷⁾.

In conclusion, we observed a significantly weekly and seasonal variation in the occurrence of stroke and stroke subtypes. Stroke occurrences are higher on weekdays than on the weekend, which may be associated with changes in lifestyle between working days and the weekend. We also observed a clear negative dose-response relationship between seasonal variations in occurrence with age. The higher occurrences of all strokes and the subtypes of CH and SAH were particularly prominent in younger patients than in more elderly patients.

REFERENCES:

1. Jakovljević D, Salomaa V, Sivenius J, et al. Seasonal variation in the occurrence of stroke in a Finnish adult population: the FINMONICA stroke register. *Stroke* 1996; 27:1774-1779
2. Sheth T, Nair C, Muller J, Yusuf S. Increased winter mortality from acute myocardial infarction and stroke: The effect of age. *J Am Coll Cardiol* 1999; 33:1916-1919
3. Shinkawa A, Ueda K, Hasue Y, Kiyohara Y. Seasonal variation in stroke incidence in Hisayama, Japan. *Stroke* 1990; 21:1262-1267
4. Willich SM, Löwel H, Lewis M, et al. Weekly variation of acute myocardial infarction: increased Monday risk in the working population. *Circulation* 1994; 90:87-93
5. Wilmsmurst P. Temperature and cardiovascular mortality. *BMJ* 1994; 309:1029-1030
6. Woodhouse PR, Khaw KT, Plummer M, Foley A, Meade TW. Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and deaths from cardiovascular disease. *Lancet* 1994; 343:435-439
7. Syrjänen J, Valtonen VV, Iivanainen M, Kaste M, Huttunen JK. Preceding infections as an important risk factor for ischemic brain infarction in young and middle aged patients. *BMJ* 1988; 296:1156-1160

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