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Same Pattern of Circadian Variation According to the Season in the Timing of Ischemic Stroke Onset: Preliminary Report

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Background and Objective Stroke occurrence shows a chronobiological variation, which is considered to be related with waking in the morning. We hypothesized that its seasonal difference would also exist because individual life activity including sleep-wake pattern can be influenced by interseasonal variability. The objective of this study was to investigate the seasonal difference of circadian variation in the timing of onset in patients with acute ischemic stroke.

Methods We studied 1486 patients with acute ischemic stroke. Stroke onset time was defined as the earliest time the patient or a witness noted definite neurological symptoms. The patients with clear onset stroke were enrolled. Frequency of onset was analyzed for four 6-hour and twelve 2-hour intervals from 0 to 24 hour per day.

Results The clear onset time was known in 968 patients (65.1%). Mean age of the patients was 67.63 ± 12.65 years and 589 patients (60.9%) were male. Stroke occurred in spring (26.5%), summer (27.2%), fall (24.1%), and winter (22.3%). In all cases, ischemic stroke showed a significant circadian variation in time of onset ($p < 0.001$). High peak period was between 6:01 AM to 12:00 PM (37%) with the same pattern in each season.

Conclusions Seasonal difference was not significant despite circadian variation in time of onset of ischemic stroke. Thus, exogenous factors such as environmental factors and life styles may have less influence on inter-seasonal variability of circadian rhythms, which are related with chronobiological factors of stroke onset in this regional population. **Sleep Med Res 2015;6(2):72-76**

Key Words Stroke, Circadian, Season.

INTRODUCTION

Several types of cardiovascular events, including myocardial infarction and sudden cardiac death, display significant circadian variation in the timing of symptom onset. Stroke onset also shows a diurnal variation with a peak occurrence during the mid to late-morning hours.[1-3] Several physiological systems and parameters, such as the cardiovascular system, blood pressure, platelet function, serum concentrations of circulating hormones and coagulation factors, blood viscosity, and cerebral vasomotor activity have a pattern of circadian rhythmicity, predominantly peaking during the morning.[4-7] Likewise, seasonal differences of hospital- or community based ischemic stroke incidence have been reported in many countries.[8-14] Several studies concluded that stroke incidences significantly increase in winter.[8-12]

However, environmental factors have undergone significant changes such as abnormal weather and global warming. Lifestyles have undergone change due to electrical instruments; most houses and workplaces are equipped with lights and heating/cooling system. These changes can affect human sleep-wake patterns, and may also affect circadian and seasonal variations of ischemic stroke onset. Moreover, in comparison to studies regarding circadian pattern of timing of stroke onset and seasonal difference of stroke incidence, a few studies have systematically investigated whether the circadian pattern varies according to each season relatively. We investigated the presence of a circadian variation according to seasonal difference

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in the timing of ischemic stroke onset.

METHODS

From March 2008 to February 2012, 1486 consecutive patients with acute ischemic strokes or transient ischemic attacks (TIA) who were admitted to Soonchunchang University Cheonan Hospital were prospectively registered in Soonchunchang University Cheonan Hospital (SCH) Stroke Registry. The SCH stroke registry contained demographic data, medical history including coronary artery diseases, atrial fibrillation, valvular and other heart diseases, previous TIA or strokes, hypertension, diabetes mellitus, hyperlipidemia, peripheral arteriopathies, cigarette smoking, the situation at stroke onset, time of stroke onset, lesion location, stroke subtype, acute and maintenance treatments, and laboratory findings. All patients underwent computed tomography within the first 48 hours and most patients underwent magnetic resonance imaging and contrast-enhanced magnetic resonance angiography within 5 days of stroke onset. In all patients, laboratory investigations included blood tests, 12-lead electrocardiogram, and echocardiography (transthoracic or transesophageal), in order to determine the cause of stroke.

We used Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment classification criteria to determine 5 subtypes of acute ischemic stroke: large artery atherosclerosis (LAA), small artery occlusion (SVO), cardioembolism (CE), stroke of other cause, and stroke of undetermined causes, which include patients with multiple potential causes.[15] TIA was defined as a focal neurologic deficit that lasted for < 24 hours and of presumed vascular origin.[16]

The onset time of stroke, defined as the earliest time that the patient or a witness noted definite neurological symptoms or signs, was obtained from patients, their relatives, or bystanders. The time of onset was classified into 3 categories: clear onset, unclear onset, and undetermined onset. If the patients or bystanders knew the exact time of symptom onset, it was defined as clear onset. If patients or bystanders knew the last normal time that patients were at their previous baseline or symptom-free state, the first observed abnormal time was defined as unclear onset. If the last-known normal time or the first observed abnormal time were unknown, it was defined as undetermined time. Patients with unclear and undetermined onset times were excluded because the exact time of stroke onset could not be accurately established. Frequency of stroke onset was analyzed for the four 6-hour intervals (12:01 to 6:00 AM, 6:01 to 12:00 PM, 12:01 PM to 6:00 PM, and 6:01 PM to 12:00 AM) and twelve 2-hour intervals in a day. Seasons were divided into spring (March, April, and May), summer (June, July, and August), autumn (September, October, and November), and winter (December, January and February).

Data were analyzed using chi-squared test for goodness of fit to the null model of equal distribution of strokes to evaluate the circadian variations in stroke onset. Differences were considered statistically significant with p-values < 0.05. All data were analyzed using STATA (version 11; StataCorp, College Station, TX, USA).

RESULTS

Among the 1486 consecutive patients who were identified with an acute ischemic or TIA, 518 patients who had an unclear onset time (n = 208) and undetermined onset time (n = 310) were excluded. Finally, we analyzed 968 patients with clear onset time. The mean age was 67.63 ± 12.66 years, and this category included 589 men (60.9%) and 379 women (39.1%). The clinical characteristics of patients with clear onset were shown in Table 1. There were 256 individuals with LAA (26.5%), 276 with SVO (28.5%), 155 with CE (16.0%), 191 with other determined/undetermined causes (19.7%), and 90 with TIA (9.3%). The incidence of ischemic strokes was highest between 6:01 AM to 12:00 PM when divided into four 6-h intervals (p < 0.001) (Table 2). The circadian variation showed the highest

Table 1. Clinical characteristics of ischemic stroke with clear onset time

No. of patients	968
Age (mean ± SD)	67.6 ± 12.7
Male, n (%)	589 (60.9)
Weight, kg	62.7 ± 12.7
Height, cm	162.2 ± 11.0
Body mass index, kg/m^2	23.5 ± 3.2
Systolic blood pressure, mm Hg	142.3 ± 23.2
Diastolic blood pressure, mm Hg	83.6 ± 13.2
Hypertension, n (%)	704 (72.7)
Diabetes, n (%)	313 (32.3)
Hyperlipidemia, n (%)	115 (11.9)
Total cholesterol, mg/dL	186.8 ± 45.1
High-density lipoprotein, mg/dL	43.4 ± 12.5
Low-density lipoprotein, mg/dL	101.0 ± 29.5
Triglyceride, mg/dL	154.5 ± 98.5
Stroke subtype, n (%)	
LAA	256 (26.5)
SVO	276 (28.5)
CE	155 (16.0)
SOC/SUC	191 (19.7)
TIA	90 (9.3)

SD: standard deviation, LAA: large artery atherosclerosis, SVO: small vessel occlusion, CE: cardioembolism, SOC: stroke of other cause, SUC: stroke of undetermined causes, TIA: transient ischemic attack.

Table 2. Circadian and seasonal distribution of ischemic stroke with clear onset time by 6-hour period

	Overall	Spring	Summer	Autumn	Winter
0:01–06:00 h	104 (10.7)	29 (11.3)	35 (13.3)	16 (6.9)	24 (11.1)
06:01–12:00 h	363 (37.5)	95 (37.1)	85 (32.3)	101 (43.4)	82 (38.0)
12:01–18:00 h	299 (30.9)	71 (27.7)	90 (34.2)	70 (30.0)	68 (31.5)
18:01–24:00 h	202 (20.9)	61 (23.8)	53 (20.2)	46 (19.7)	42 (19.4)
No. (%)	968 (100)	256 (26.5)	263 (27.2)	233 (24.1)	216 (22.3)

$p < 0.001$ for overall circadian distribution. $p = 0.124$ for overall seasonal distribution. $p = 0.194$ for circadian distribution according to season by 6-h period.

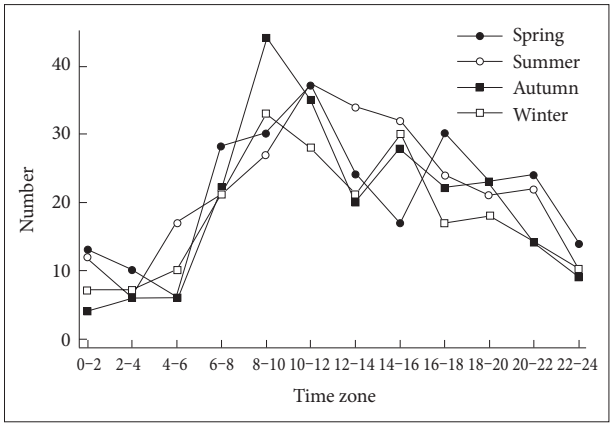

Fig. 1. Circadian distribution of ischemic stroke with clear onset time by 2-hour period according to each season. The circadian variation showed the highest peak during the period from 8:01 AM to 10:00 AM when divided into twelve 2-h intervals ($p < 0.001$).

peak during the period from 8:01 AM to 10:00 AM when divided into twelve 2-h intervals ($p < 0.001$) (Fig. 1).

Two-hundred and fifty-six patients experienced ischemic strokes in spring (26.5%), 263 patients in summer (27.2%), 233 patients in autumn (24.1%), and 216 patients in winter (22.3%). The seasonal difference in the incidence of ischemic stroke was not statistically significant ($p = 0.124$) (Table 2). Seasonal differences in the occurrence time of ischemic stroke were also not significant when analyzed in 6-h intervals ($p = 0.194$) (Table 2). Fig. 1 showed the time-specific onset patterns of ischemic stroke according to a season in 2-h intervals. There was no significant seasonal difference in the onset time of ischemic stroke ($p = 0.892$, Kruskal-Wallis rank test).

DISCUSSION

The present study demonstrated that the onset of ischemic stroke was significantly higher between 6:01AM and 12:00 PM and there was no significant seasonal difference in the incidence of ischemic stroke. Previous studies have shown that the onset of ischemic stroke follows a circadian pattern.[1,17-19] A meta-analysis of 31 publications supported the presence of a circadian pattern in the onset of stroke, with a significantly higher risk in the morning.[1] According to these data, the risk for all subtypes of stroke was significantly higher between 6:00 AM and 12:00 PM whether divided into 3-, 4- or 6-h periods. Other studies also showed that stroke onset peaked in the morning with highest incidence between 10:00 AM and 12:00 PM,[20] most commonly between 6:00 AM and 8:00 AM on weekdays, and between 8:00 AM and 10:00 AM on weekends.[21] A hospital-based study showed that both ischemic stroke and stroke subtype followed a circadian rhythm during the early morning hours, similar to the findings in our study, with highest frequency between 06:00 AM and 12:00 PM and lowest in the late hours of the evening.[18] Moreover, this tendency was observed irrespective of whether the stroke occurred for the first time or was recurrent. A Korean single-center study likewise showed that stroke occurred most frequently at times of 6:00 AM and 12:00 PM and the peak time for stroke onset was 12:22.[22] Several possible factors have been reported including circadian pattern of physical activity, blood pressure, plasma catecholamines, plasma cortisol, and platelet aggregation.[1,23-25] Blood pressure is one of the most important factors for ischemic stroke that follow a circadian pattern with highest values during mid- to late morning. Moreover, low blood pressure during sleep, when the cerebral blood flow becomes insufficient, can also cause hemodynamic stroke.[5,26] Changes of the coagulative balance follow this circadian pattern. Platelet aggregation is also at its highest level in the morning. Platelet activity is lowest in a supine position and highest in an upright position.[23,24] Plasminogen activator-inhibitor 1 activity increases in the morning and tissue-type plasminogen activator decreases. Thus, thrombogenic tendency can occur in the morning.[27]

In stroke onset, in addition to circadian rhythm, seasonal variations have also been observed. Many epidemiological and clinical studies have examined the seasonal variation of stoke occurrence.[8-14] Several studies concluded that the incidence of stroke significantly increased in winter.[8-12] An analysis of seasonal variations showed that ischemic stroke and cerebral hemorrhage occur primarily during winter and fall, respectively.[28] One retrospective study showed a seasonal variation in which a higher incidence of stroke occurred during winter and an inverse correlation between the average atmospheric temperature and total number of hospitalizations for ischemic stroke and TIA.[8] In another study of three geographical areas of Finland, the rate of occurrence of ischemic stroke events was 12% higher in men and 11% higher in women in winter than in summer.[10]

Cold exposure increased the platelet count, red blood cells, blood viscosity and arterial pressure.[9] Plasma fibrinogen concentrations were 23% higher in the coldest six months, as compared with summer months.[4,8,29] These results could explain the relationship between cold weather and coronary/cerebral thrombosis. On the other hand, Japanese studies showed that the seasonal difference in incidence was not statistically significant, but the incidence in summer was significantly higher than in winter.[30,31] Hot summers may cause dehydration that could lead to hyperviscosity of blood and enhanced platelet aggregation. Some recent studies showed no seasonal difference of stroke onset, as shown in our result.[14,32-34] Oxfordshire Community Stroke study also failed to show a seasonal variation in the incidence of ischemic stroke and there was no significant relationship between temperature and the incidence of ischemic stroke; this suggested that the widely reported seasonal difference of stroke incidence might be related to the referral bias in hospital-based studies.

Finally, we also investigated circadian distribution of onset time according to four seasons. Seasonal difference was not significant although circadian variation was observed. High peak period was between 6:01 AM to 12:00 PM with the same pattern in each season. The previous study also showed that all subtypes of ischemic stroke occurred most frequently in the morning, similar to the finding of our study.[30] Another study reported that transition to or from daytime saving time was coupled with an immediate shift in the time pattern of stroke onset.[35] Exogenous factors associated with awakening were suggested as important determinants of the pattern of diurnal variation of stroke onset. Environmental factors have undergone significant changes such as abnormal weather and global warming. There are fewer differences in seasonal physical activities because most houses and workplaces are equipped with lights and heating/cooling system. Furthermore, life styles are not much different in each season. Thus, the sleep-wake patterns may be less influenced by seasonal environment in modern society.

There were some limitations in this study. First, the present study was of retrospective design and included one regional tertiary hospital. Sleep-wake patterns and life styles can vary based on individual and regional differences. Second, we did not evaluate the socio-economic factors related to individual circadian pattern, such as personal physical activities, sleep-wake habit, jobs, educational, and economic levels, which could lead to seasonal or circadian differences. Third, differences of stroke subtypes were not addressed because of insufficient data. Thus, our result may be influenced by heterogeneous characters of each stroke subtype. Fourth, the time interval of frequency might be too long to investigate the circadian variation according to season time onset of stroke; hence, we cannot exclude the possibility of a fine difference. Further studies with shorter time interval (ex, minutes) and large sample size are needed.

In conclusion, ischemic stroke occurs primarily in the mid- to late-morning hours with the same pattern in the four seasons and no seasonal difference in its incidence. Thus, exogenous factors such as environmental factors and life styles may have less influence on inter-seasonal variability of circadian rhythms that are related to chronobiological factors of stroke onset in this regional population.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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