# Circadian, circaseptan and circannual rhythms in acute ischemic stroke*

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*Most of the biologic activities in organism show periodic variation. It is considered that the endogenous and exogenous rhythms, and the interactions between diseases are effective on periodicity in stroke incidence. It is known that the precipitant factors affect the onset of stroke as well as the long-term risk factors. This study was planned to investigate the circadian, circaseptan and circannual rhythms of stroke, and to evaluate their relation with some risk factors. Patients with acute ischemic stroke admitted into our clinic between May, 28, 1992 and May, 28, 1993 were included to this study. Patients with a previous stroke history were excluded from the study. The patient group consisted of 214 subjects, 106 female and 108 male. Their mean age was 62.47± 14.71. The statistical analyses were performed at intervals of one hour, two hour and four hour. The onset of infarcts were more frequent between the hours of O^-OS°°, 08°°-10°°, 10°°-12°° and W^-W°°. The frequency was higher on weekdays than weekends and the peak was on Monday. We found the peak of the occurrence of stroke in April according to months and in Spring according to seasons. We investigated the relation between circadian, circaseptan, circannual rhythms and smoking, obesity, hypertension, antihypertensive therapy, atrial fibrillation, diabetes mellitus, age, sex, the activity degree, activity type. Identification of the periodicity of the onset of stroke might lead to measures that could help prevent stroke and to determine the pathophysiological mechanism. [Turk J Med Res 1995, 13(3): 101-105]*

Key Words: Biological rythms, Stroke, Circadian rhythms, Circaseptan rhythms, Circannual rhythms

The presence of circadian rhythms in organisms has been known since the Hipocrat time. It has been proved lately biological rhthms can affect most systems. Organism that is an open system to the environmental effects has a dynamic equilibrium in itself. Living beings show variations depending on time and changing periodic-aperiodic surrounding factors. These variations are influential on molecule, cell, tissue, organ or organism. The situation of organism anytime reflects also the time dependent rhythmic fluctuations of physiologic and behavioral functions that are ordered endogenously, besides the physical and biotic factors affect the organism directly. 24 hour cyclic variations of these functions indicate diurnal changes. Circadian, diel, solar day and nycthemeral terms have the some meaning. The other biorhythmic oscillations are circaseptan, circamounthly and circannual rhythms. Organisms shows annual variations due to annual oscillations of geophysical factors. Annual period is significant since it reflects seasonal variations.

The interaction of endogenous and exogenous rhythms with diseases is affective on stroke incidence. The determination of the rhythmicity of ischemic stroke is important in evaluating the patients with stroke risk. This study was carried out to investigate circadian, circaseptan, circannual rhythms in occurrence of cerebral infarct and their relations with some risk factors.

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## MATERIALS AND METHODS

The study was carried out prospectively in patients with acute ischemic stroke admitted into our clinic between May, 28,1992 and May, 28, 1993. Patients with a history of a previous stroke were excluded from the study. The patient group included 106 women (49.5%) and 108 men (50.5%). Cerebral infarcts of patients were identified by CT scanning. Information related to the onset of stroke was obtained from the patients or

their relatives. Their situation and physical activity during the onset of stroke was informed. If any stroke had been noticed after a patient was awarken, the onset of stroke was accepted as the time of awakening. The risk factors such as hypertension, diabetes mellitus, atrial fibrillation and obesity were registered.

Data were evaluated by one hour, two hour, four hour, daily, seasonal and annual intervals. Patients were divided into subgroups in terms of the risk factors, and their relations with time intervals were studied. The effect of the type and degree of activity during the occurrence of stroke of rhythmicity was Investigated. Chi square test was used for statistical analyses.

## RESULTS

The patients age were in the range of 17 and 95, their mean age was 62.41 ±14.71. 153 patients (71.5%) were smoking, 115 patients (53.7%) were obese. There were 108 hypertensive patients (50.5%) and 31 of them had never been treated with any antihypertensives. 26 of them regularly and 51 of them irregularly were taking antihipertensives. There were 34 patients with atrial fibrillation (15.9%), and 42 with diabetes mellitus (19.6%).

The one hour, two hour, four hour, weekly, mounthly and seasonal distributions of onset of stroke

Table 1. The distribution of time of onset of cerebral infarct according to one hour intervals

| Hour | Number of Patients | % |
|---|---|---|
| 00-01 | 3 | 1.4 |
| 01-02 | 2 | 1.0 |
| 02-03 | 7 | 3.3 |
| 03-04 | 4 | 1.9 |
| 04-05 | 6 | 2.9 |
| 05-06 | 12 | 5.7 |
| 06-07 | 15 | 7.2 |
| 07-08 | 10 | 4.8 |
| 08-09 | 16 | 7.7 |
| 10-11 | 17 | 8.1 |
| 11-12 | 15 | 7.2 |
| 12-13 | 8 | 3.8 |
| 13-14 | 8 | 3.8 |
| 14-15 | 6 | 2.9 |
| 15-16 | 10 | 4.8 |
| 16-17 | 18 | 8.6 |
| 17-18 | 12 | 5.7 |
| 18-19 | 9 | 4.3 |
| 19-20 | 6 | 2.9 |
| 20-21 | 3 | 1.4 |
| 21-22 | 5 | 2.4 |
| 22-23 | 4 | 1.9 |
| 23-24 | 2 | 1.0 |
| Total | 209 | 100.0 |

(Chi square-63.91 p<0.001)

Table 2. The distribution of time of onset of cerebral infarct according to two hour intervals

| Hour | Number of Patients | % |
|---|---|---|
| 00-02 | 5 | 2.4 |
| 02-04 | 11 | 5.3 |
| 04-06 | 18 | 8.6 |
| 06-08 | 25 | 12.0 |
| 08-10 | 27 | 12.9 |
| 10-12 | 32 | 15.3 |
| 12-14 | 16 | 7.7 |
| 14-16 | 16 | 7.7 |
| 16-18 | 30 | 14.4 |
| 18-20 | 15 | 7.2 |
| 20-22 | 8 | 3.8 |
| 22-24 | 6 | 2.9 |
| Total | 209 | 100.0 |

(Chi square=54.36 p<0.001)

Table 3. The distribution of time of onset of cerebral infarct according to four hour intervals

| Hour | Number of patients | % |
|---|---|---|
| 00-04 | 16 | 7.7 |
| 04-08 | 43 | 20.6 |
| 08-12 | 59 | 28.2 |
| 12-16 | 32 | 5.3 |
| 16-20 | 45 | 21.5 |
| 20-24 | 14 | 6.7 |
| Total | 209 | 100.0 |



Table 4. The distribution of time of onset of cerebral infarct according to daily frequency

| Days | Number of Datients | % |
|---|---|---|
| Monday | 37 | 17.3 |
| Tuesday | 36 | 16.8 |
| Wednesday | 33 | 15.4 |
| Thursday | 35 | 16.4 |
| Friday | 23 | 10.7 |
| Saturday | 23 | 10.7 |
| Sunday | 27 | 12.6 |
| Total | 214 | 100.0 |

(Chi-square=7.37 p>0.05)

were indicated in tables (Table 1,2,3,4,5,6). We observed peaks at 09°°-11°°, and 17°° in terms of one hour evaluation; between 06°°-08°°, 10°°-12°°, and 16°°-18°° hours in terms of two hour evaluation; between 08°°-12°°, and 16°°-20°° hours in terms of four hour evaluation (Figure 1). There were peaks on Monday, in April and in Spring in terms of daily, monthly

**Table 5.** The distribution of time of onset of cerebral infarct according to monthly frequency

| Month | Number of patients | % |
|---|---|---|
| January | 20 | 9.3 |
| February | 24 | 11.2 |
| March | 25 | 11.7 |
| April | 31 | 14.5 |
| May | 21 | 9.8 |
| June | 15 | 7.0 |
| July | 24 | 11.2 |
| August | 16 | 7.5 |
| September | 10 | 4.7 |
| October | 6 | 2.8 |
| November | 11 | 5.1 |
| December | 11 | 5.1 |
| Total | 214 | 100.0 |

(Chi-square=34.87 p<0.001)

**Table 6.** The distribution of time of onset of cerebral infarct according to one seasonal frequency

| Season | Number of patients | % |
|---|---|---|
| Winter | 55 | 25.7 |
| Spring | 77 | 35.9 |
| Summer | 55 | 25.7 |
| Fall | 27 | 12.6 |
| Total | 214 | 100.0 |

(Chi-square-23.38 p<0.001)

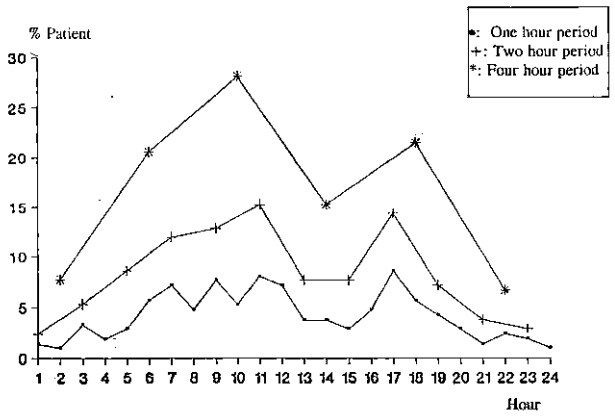


**Figure 1.** Distribution of time of onset of cerebral infarct according to one, two and four hour intervals

and seasonal evaluation, respectively. Strokes occured during sitting in 66 patients (29.4%), during walking in 31 patients (14.5%), during eating in 13 patients (6.1%), in water closet in 13 patients (6.1%), and during another activity in 27 patients (12.6%). In evaluation of 37.9% of mild and 3.3% of hard activity ac the time of stroke onset. The activity degree of a patient was unknown. Five patients whom we could not learn the time of stroke onset were evaluated just in terms of weekly, monthly and seasonal distributions.

There was no correlation between time of onset of stroke and sex, age, smoking, history of hypertension, antihypertensive therapy or atrial fibrillation. When diabetic patients were investigated according to one hour interval, it showed prominent peaks at 09°°, 11°°, and 17°° hours (p<0.05).

The frequency of onset of stroke was significantly high during walking, sitting and in water closet, and showed peaks between the time intervals of 08°°-14°°; 10°°-12°° and Iô°°-^°° hours respectively (p<0.001).

There was no relation between the stroke distribution according to daily frequency and sex, age, smoking, obesity, history of hypertension, antihypertensive therapy, atrial fibrillation or diabetes mellitus. The statistical significance between activity type and the distribution according to daily frequency was low (p-0.0508).

There was no relation between the stroke distribution according to monthly frequency and sex, age, smoking, history of hypertension, antihypertensive therapy, atrial fibrillation, diabetes mellitus or activity type. Significant increases of onset of stroke were observed in 3rd, 4th and 7th months in obese patients (p<0.01).

There was no relation between the stroke distribution according to seasonal frequency and sex, age, smoking, history of hypertensiyon, antihypertensive therapy, atrial fibrillation, diabetes mellitus or activity type. The incidence stroke was high in Spring in obese patients (p<0.01).

## DISCUSSION

Our data showed peaks of stroke incidence at 06°°-08°°, 08°°-10°°, 10°°-12°° and 16°°-18°° hours in terms of 2-hour evaluation. In earlier studies Agnoli (1), Tsementzis (2), Marier (3), Marsh (4), Oxfordshire Group (5),. Argentino (6), Gallerani (7), Pasqualetti (8), Hossman (9), Windt (10), ince (11) and Kaps (12) reported the peak of onset of stroke at O6°°-14°°, $_{10}$OO.$_{12}$OO $_{10}$OO.$_{12}$O$_{O)}$ $_{06}$OO_$_{12}$O$_{O|}$ $_{06}$OO_$_{12}$O$_{O)}$ $_{06}$OO_$_{12}$O$_{O)}$ O6°°-14°°, 02°°-08°°, 01°°-05°°, O6°°-18°°, O6°°-18°°, and O7°°-19°° hours, respectively.

The second peaks were reported at 14°°-16°° hours in Oxfordshire Group's study and at 20°° hour in Cugini's study (5,13). In this study we found the second peak between 16°° and 20°° hours.

The incidence of ischemic stroke was higher in weekdays than weekends in our study, the peak was observed on Monday. In some other studies the incidence of stroke was found high in weekdays which it was considered starting work again after weekend was the reason of this peak (1,13). Pasqualetti found the incidence of stroke was higher in weekends than

weekdays and concluded the reason might be the changes in life style and the **low** fibrinolytic activity in weekend (8).

The peaks of onset of cerebral infarct were reported in Spring and Winter in Japan, USA, England, Canada, Denmark, and Australia. No relation was found between stroke incidence and seasons in some studies in Yugoslavia, Mexico and Brazil (14,15). Our data showed the peak in Spring (35.9%) and the lowest incidence in fall (12.6%). The highest incidence was in April (14.5%) according to monthly distribution. Sobel reported bimodal peaks in 2nd and 4th months in patients with cerebral infarct (15).

It was reported that, the **factors** important in the pathogenesis of stroke showed diurnal rhythmicity. Those factors were blood pressure (2-4,6,8,9,13,16), myocardial ischemia (17), atrial and ventricular arrhythmia (18,19), plasma catecholamines (17), TSH **release** (17,20), **Cortisol** secretion (3,17), **glomerular filtration** rate (21), Na and K excretions (20), fibrinolytic activity (4,6,22), thrombin time (23), activated partial thromboplastin time (23), prothrombin time and platelet aggregation (24), blood viscoelasticity (25), hematocrit (21), protein concentrations (20), inhibition of **factor** Xa (23), tissue plasminogen activity (tPA) and fast acting inhibitory (PAI) levels (6,22,26), central dopamin activity (27) and antithrombin III (8,28). The levels of hematocrit, protein concentration, platelet aggregability, hypertension, blood viscoelasticity, serum Cortisol and central dopamin activity increase in the morning. Some of these factors show seasonal variation (15). Annual rhythmicity in basal metabolic rate, blood pressure, pulse rate, body temperature, and serum cholesterol concentration was identified (17,29,30-32). Factor VII, antithrombin III and cholesterol show positive correlation with temperature but negative correlation with fibrinolytic activity (28,30,32). Platelet and red blood cell counts, blood viscosity, cathecolamin secretion Increase at low degree temperatures (14,33). Fibrinolytic activity and antithrombin III level decreases in morning. So there is a tendency to thrombosis in morning. It can be considered that diurnal variation effecting the normal equilibrium between thrombosis and thrombolysis is the identifying factor of onset of stroke. The physiological factors like physical and mental stress, increase in symphatetic tension and intradiurnal temperature variation after getting up in the morning may effect onset of stroke. It was reported that there are peaks of fatal pulmonary embolism in the morning hours (34). Besides, myocardial infarction (MI) (3,6,13,17,19,22,24,34,39), angina pectoris (13,17,19,39), ischemic ST depression (6,39,40) and sudden cardiac death (3,17,19,22,24,34,39,40,41) showed peaks in morning.

Several studies reported second peaks of MI and sudden cardiac death in the evening hours (13,42). Although some studies claim that aspirin, warfarin and dipyridamole have no effect on diurnal rhythmicity of MI and cerebral infarct (1,4,43), some other studies report that aspirin and beta blockers decrease the peak in morning (19,35-38,44,45).

The rhythmicity in stroke is a significant epidemiological factor. Besides, the presence of periodic risk and the prediction of recurrence will provide important information in understanding of the physiopathological mechanism and controlling the causative factors. Those may help in the evaluation of patients having stroke risk.

Akut iskemik strokta circadian, circaseptan ve circannual ritimler

*Organizmadaki biyolojik aktivitelerin önemli bir kısmı periodik değişim gösterir. Strok insidansındaki periodisitede endojen ritimler, ekzojen ritimler ve hastalıklar arasındaki interaksiyonun etkili olduğu düşünülmektedir. Strok oluşumunda uzun süreli risk faktörlerinin yanında, presipitan faktörlerin de etkili olduğu bilinmektedir. Bu çalışma strokun circadian, circaseptan ve circannual ritimlerini ve bunların bazı risk faktörleri ile etkileşimlerini incelemek amacı ile planlandı. Çalışma 28 Mayıs 1992-28 Mayıs 1993 tarihleri arasında kliniğimizde yatan akut iskemik stroklu hastalar ile yapıldı. Daha önce geçirilmiş strok anamnezi olan hastalar çalışma dışı bırakıldı. Çalışma grubu 106 kadın-108 erkek, 214 hastadan oluştu. Yaş ortalaması 62.47±14.71 idi. Saatlik, iki saatlik ve dört saatlik zaman dilimlerine göre istatistiksel değerlendirme yapıldı. İnfarkt başlangıcının en yoğun olduğu saatler 06-08, 08-10, 10-12 ve 16-18 arasında idi Günlere göre yoğunluğunun hafta içi günlerde daha fazla olduğu, en sık da Pazartesi günü meydana geldiği tespit edildi. Aylara göre dağılımda yoğunluk Nisan ayında idi. Mevsimlere göre en çok ilkbaharda, en az sonbaharda yoğunluk bulundu. Circadian, circaseptan ve sircannual ritimler ile sigara, obezite, hipertansiyon, antihipertansif tedavi, atrial fibrilasyon, diabetes mellitus, yaş, cins, aktivite derecesi, aktivite cinsi arasındaki ilişkiler incelendi. Strok başlama zamanındaki periodisitenin bilinmesi strok profilaksisinde faydalı olabilir ve strokun patofizyolojik mekanizmalarının belirlenmesinde değişik perspektifler sağlayabilir.*
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