Original Article

Circadian pattern of onset of ischaemic and haemorrhagic strokes, and their relation to sleep/wake cycle

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Abstract

Objective: To determine whether there is a circadian pattern of onset of ischaemic and haemorrhagic strokes, and their relation to sleep/wake cycle.

Methods: A descriptive study with prospective data was conducted at the Combined Military Hospital Lahore from Jan 2004 to Dec 2007. Eight hundred patients above 26 years of age who had their first ever stroke were included in the study. Strokes were classified into cerebral infarction (CIF), intra-cerebral bleed (ICB) and subarachnoid haemorrhage (SAH). Diagnosis was confirmed either by CT or MRI scan of brain.

Results: Out of 800 patients, 80% were males and 20% were females. There were 438 (55%) cases of CIF, 329 (41%) of ICB and 33 (4%) of SAH. The age of the patients ranged from 26 to 84 years. Of all stroke cases, 592 (74%) occurred when the patients were awake and 208 (26%) occurred during sleep ($p<0.001$). ICB cases showed significant variation with respect to wake/sleep cycle ($p<0.001$). In CIF and SAH cases there was insignificant association with wake/sleep state of the patient, ($p<0.180$ and 0.792 respectively). Of all strokes 22.5% occurred between 4 am - 8 am, followed by 20.7% between 4 pm - 8 pm, 20.1% between 8 am - 12 noon, 19.5% between 12 noon to 4 PM, 12.7% between 12 midnight and 4 am while 4.3% cases occurred between 8 pm and 12 midnight. The maximum number of CIF (28.5%) occurred between 4 am- 8 am, maximum ICB (29.8%) between 8 am to 12 noon and maximum SAH (30.3%) between 4 pm - 8 pm. The CIF and SAH cases showed smaller peaks between 4 pm to 8 pm and 8 am to 12 noon respectively. The lowest number of ICB cases (4.9%) were around mid night. Significant circadian variation was found in CIF and ICB patients ($p<0.001$), however it was insignificant for SAH cases ($p=0.391$).

Conclusion: The findings of this study confirm the presence of circadian variation among cases of ischaemic stroke and intra cerebral bleed while no circadian variation was found in subarachnoid haemorrhage. CIF, ICB and SAH predominantly occur in early morning hours, late morning hours and in late afternoon to early evening respectively. Only intracerebral bleed was affected by wake/sleep state (JPMA 59:129; 2009).

Introduction

Recent data indicates that major unfavorable cerebrovascular events are not randomly distributed over time, but show a peculiar distribution along the day, the week, and the months of the year.[1] The clinical onset of both myocardial infarction and stroke occurs more frequently in the early morning than at other times of day.[2] Data in the literature suggest the existence of a particular pattern in circadian variation of cardiovascular and cerebrovascular diseases. Several studies have demonstrated that the onset of acute ischaemic stroke occurs much more often in the morning hours.[3] This observation of higher morning incidence of ischaemic stroke has been confirmed by meta-analysis.[4] Chronobiological variations such as circannual (annual) variation, circaseptan (weekly) variation and circadian (diurnal) variation have also been reported.[5] Although a well-defined pattern of ischaemic stroke onset has been proved, there is insufficient information about circadian pattern amongst subtypes of stroke.[6] Circadian periodicity of stroke onset suggests that the timing of its occurrence is not a random event and it may depend on underlying precipitating factors. The identification of triggering and associated factors of stroke onset could provide clues to the mechanisms involved and thereby help towards specifically targeting the risk factors through appropriate pharmacological interventions.[3]

The aim of study is to determine whether the circadian pattern exists in ischaemic and haemorrhagic stroke, and to find relationship of wake/sleep state of patient with the stroke onset. There has been no study reported in local literature about the circadian variation in subtypes of stroke in our population.

Patients and Methods

The study was carried out at combined military hospital Lahore from Jan 2004 till Dec 2007. Patients of

both gender, 26 years or above of age with their first stroke were included in the study. Patients with previous history of stroke were excluded. Diagnosis was made by a neurologist and the subtypes were confirmed on neuroimaging (CT Scan/MRI brain). Strokes were classified into cerebral infarction (CIF), intracerebral bleed (ICB), and subarachnoid haemorrhage (SAH).

Each day was divided into six sections of four hours duration each. Time calculation was started from 0000 hrs (12 midnight). Time of stroke onset was noted and each patient was bracketed in a particular four hour time period. Exact time was noted for patients who were awake at the time of stroke onset. Information about onset of stroke in patients who were asleep, was collected from their attendants. Patients were further catagorized into wake/sleep state at stroke onset.

Results

Eight hundred patients fulfilled the inclusion criteria. Amongst them 640 (80%) were males and 160 (20%) females. Out of 800 patients, 438 (55%) were cases of CIF, 329 (41%) of ICB and 33 (4%) of SAH. Out of 438 CIF cases 374 (85.4%) were males while 64 (14.6%) were females. Among ICB cases 249 (75.7%) were males and 80 (48.5%) were females. There were total of 33 SAH cases and out of them 17 (51.5%) were males, while 16 (48.5%) were females. Age of the patients ranged from 26 to 84 years. Age groups in both genders is shown in Fig 1. Of all types of strokes, 74% (n=592) occurred in both the genders when the patients were awake while 26% (n=208) occurred during sleep, (p= 0.001). Out of 438 CIF cases 273 (62.3%) occurred during awake state while 165 (37.7%) developed stroke during sleep, (p=0.180). Among ICB cases, 296 (89.9%) and 33(10%) developed stroke while awake and sleep states respectively, (p<0.001). Out of 33 SAH cases 23 (69.7%) and 10 (30.3%) developed it while awake and sleep respectively, (p=0.792).

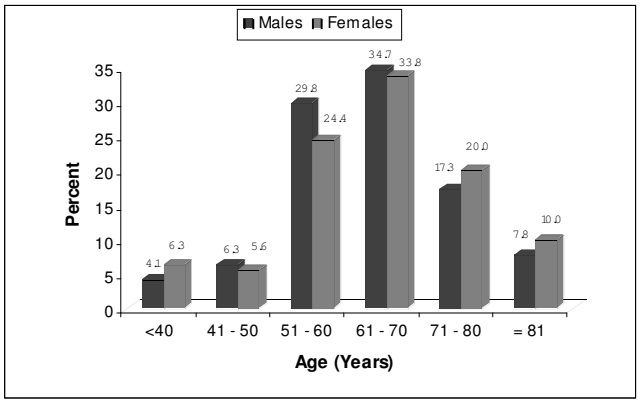

Figure 1: Distribution of cases according to age and sex, (n= 800)
Total of 640 males and 160 female patients included.

Among all stroke cases 180 (22.5%) occurred between 4 am and 8 am, followed by 166 (20.7%) between 4 pm to 8 pm, 161 (20.1%) between 8 am and 12 pm, 156 (19.5%) between 12 pm and 4 pm, 102 (12.7%) between 12 midnight and 4 am while only 35 (4.3%) were between 8 pm and 12 midnight.

The maximum number of CIF (28.5%), ICB (29.8%) and SAH (30.3%) occurred between 4 am to 8 am, 8 am to 12 noon, 4 pm to 8 pm respectively (Figure-2). There was significant circadian variation noted for CIF (p<0.001) and ICB (p<0.001), however no significant circadian variation was found in SAH cases (p=0.391). (Table -1)

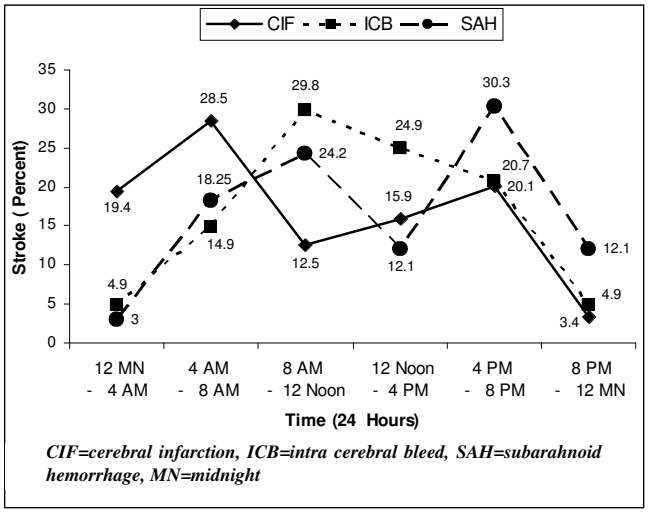

Figure 2: Timings of individual stroke subgroups.

Table 1: Time of Stroke Onset.

TYPE OF STROKE	0000-0400 HRS n (%age)	0400-0800 HRS n (%age)	0800-1200 HRS n (%age)	1200-1600 HRS n (%age)	1600-2000 HRS n (%age)	2000-0000 HRS n (%age)	p value (df)
CIF	85 (19.4)	125 (28.5%)	55(12.6%)	70(16%)	88(20.0%)	15 (3.4%)	<0.001 (5)
ICB	16 (4.9%)	49 (14.9%)	98(29.8%)	82(24.9%)	68(20.7%)	16 (4.9%)	<0.001 (5)
SAH	1 (3.0%)	6 (18.2%)	8 (24.2%)	4 (12.1%)	10(30.3%)	4 (12.1%)	0.391 (5)

Whole 24 hours of a day has been divided into 6 equal time periods each of 4 hours duration.
df is degrees of freedom
Chi-sq test has been applied for statistical analysis.

Discussion

This study confirms circadian variation in cases with cerebral infarction and intra cerebral bleed ($p<0.001$) while it was non significant in subarachnoid haemorrhage ($p=0.391$). The circadian variation observed in the incidence of myocardial infarction and stroke may be due to the effect of molecular clock or the time dependent exposure to environmental stresses.[2] Elliot[4] and Omama et al[7] found that all subgroups of stroke show diurnal variation with respect to time of onset.[4,7] The lack of circadian variation in SAH cases in our study may be because of relatively smaller number of cases. Elliot,[4] Marshall[8] and Argentino et al[9] found CIF to have a single peak in the morning, while in our study maximum patients developed stroke between 4 am and 8 am, followed by another smaller peak between 4 pm to 8 pm. Similar observations have been made by others.[7,10,11] Omama et al[7] found that 20% of all CIF occurred during sleep. In our study, 37.7% ischaemic cases developed stroke during sleep or at the time of awakening. Others have noted that over 50% of ischaemic stroke were either present on awakening or developed during earlier hours of the morning.[3,12] A smaller peak in late after-noon in our patients is probably attributed to the habit of afternoon nap (siesta) common in this part of world.

ICB and SAH have been reported to have double peaks with respect to time of onset.[7,13-16] In this study it was found that maximum number of patients developed ICB between 8 am to 12 noon. The number gradually declined till 8 pm without a double peak and it was lowest around mid night. Two statistically insignificant peaks were observed in SAH cases with respect to its occurrence, $p=0.391$, with maximum cases occurring between 4 to 8 pm. Subarachnoid haemorrhage cases have shown late after noon to early evening peak with smaller numbers in the morning.[7,17] A study from Hong Kong showed the peak time of SAH onset between noon to 6 pm.[18] Our data coincides with the findings of these studies.

In Japanese population two peaks were observed among cerebral bleed cases. Peak was observed in the morning in patients less than 65 years of age. Whereas late after noon peak was seen in all age groups. However in our study we did not see any such variation.[13] This difference may be due to afternoon nap common in this region but further studies are needed.

Studies have shown that nearly 10% of ICB and SAH cases occurred during sleep.[7,17,19] Similar variation was found among ICB patients with respect to wake/sleep state, $p<0.001$; in contrast 30.3% cases of SAH occurred during sleep state, though this difference was statistically insignificant ($p=0.792$). Cerebral bleeds that developed during sleep had the worst prognosis and measures to prevent them are needed to be identified.[19]

Previous studies have reported that there is increase in haematocrit, platelet aggregation and coagulability in morning hours which increase the chances of ischaemic stroke, while the chances of haemorrhage are reduced.[20,21] This study showed that over 47% of ischaemic strokes occurred between 12 midnight and 8 am, while intracerebral bleed occurred in only 19% of the cases. Arterial blood pressure has been noted to be the trigger for haemorrhagic and ischaemic stroke.[7] Physical activity, low external temperature and other triggerers of sympathetic tone raises the arterial blood pressure which has been strongly correlated with ICB and SAH.[15,22,23] In this study 248 (74.3%) cases of ICB occurred during the day time when blood pressure is high following its circadian variation.[13] SAH has generally been noted to occur during sports and sexual activity and in lavatory;[24] aneurysmal SAH is even strongly correlated with rise in blood pressure.[25] This favours the notion that high blood pressure is a strong trigger for haemorrhagic stroke. The main limitations of this study are that the seasonal variation, and exact activity level of the individuals at the time of stroke onset were not recorded. Other limitation of the study was that the female gender was under represented (20%). Future studies need to address these issues as well.

Conclusion

The study confirms the circadian variation in cases of cerebral infarction and intra cerebral bleed. The findings of this study conclude that the incidence of ischaemic stroke is significantly increased in the morning while maximum cases of intra cerebral bleed occur between 8 am and 4 pm. Attempts to prevent their occurrence must take into account this circadian variation. Appropriate preventive measures like control of blood pressure and coagulation may be needed during these vulnerable periods.

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