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. The clinical onset of both myocardial infarction and stroke occurs more frequently in the early morning than at other times of day. 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 ischemic stroke occurs much more often in the morning hours. This observation of higher morning incidence of ischemic stroke has been confirmed by meta-analysis. Chronobiological variations such as circannual (annual) variation, circaseptan (weekly) variation and circadian (diurnal) variation have also been reported.

Although a well-defined pattern of ischemic stroke onset has been proved, there is insufficient information about circadian pattern amongst subtypes of stroke. 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.

The aim of study is to determine whether the circadian pattern exists in ischemic and hemorrhagic 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 categorized 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).

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 1: Distribution of cases according to age and sex, (n= 800)](image)

Total of 640 males and 160 female patients included.

![Figure 2: Timings of individual stroke subgroups.](image)

![Table 1: Time of Stroke Onset.](table)

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

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.

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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. Elliot and Omama et al found that all subgroups of stroke show diurnal variation with respect to time of onset. The lack of circadian variation in SAH cases in our study may be because of relatively smaller number of cases. Elliot, Marshall and Argentino et al 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. Omama et al 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. 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. 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 later noon to early evening peak with smaller numbers in the morning. A study from Hong Kong showed the peak time of SAH onset between noon to 6 pm. 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. 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. Similar variation was found among ICB patients with respect to waking 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.

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. 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. 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. In this study 248 (74.3%) cases of ICB occurred during the day time when blood pressure is high following its circadian variation. SAH has generally been noted to occur during sports and sexual activity and in lavatory; aneurysmal SAH is even strongly correlated with rise in blood pressure. 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.

Acknowledgement

We acknowledge the work of Mr Bilal for his valuable assistance in statistical analysis.

References

Prevalence of human malaria infection in bordering areas of East Balochistan, adjoining with Punjab: Loralai and Musakhel
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Abstract

Objective: To study the prevalence of malarial infections in human population of districts Loralai and Musakhel areas of Pakistan.

Methods: Malarial parasites were identified in the blood slides of suspected patients of the disease from July, 2004 to June, 2006, and encompassed 7899 subjects.

Results: Out of 7899 suspected cases of malaria, 2275 (28.8%) were found to be positive for malarial parasite in blood smear slides. Out of positive cases, 1633 (71.7%) were identified as Plasmodium falciparum infection, 642 (28.2%) cases with P. vivax. However, seasonal variation was also noted with the highest (83.9%:30/39) in October and lowest (3/9) in February in Musa Khel area. There was no case of Plasmodium infection of P. falciparum in September and lowest (65.3 %: 34/52) in January in Loralai area whereas highest rate of infection (11.6%) was recorded in August while the lowest rate of infection (3.9%) was noted in March. Malaria in general population of district Buner and highest prevalence rate (71.7%:1633/2275) is noted in P. falciparum poses a significant health hazard but 28.2% of P. vivax (642/2275) also may lead to serious complications like cerebral malaria. No association was found between types of infection and age groups (JPMA 59:132; 2009).

Introduction

Malaria is one of the most devastating diseases in the World. Over 3 billion people live under the threat of malaria in 24 endemic countries and it kills over a million each year - majority being children.

According to a conservative estimate, about 500,000 malaria cases occur per annum (About 40% of cases are due to Plasmadium falciparum which is significantly more common in the Sindh Province (64%). P. falciparum has developed resistance to chloroquin. The two main malaria vectors- An. culicifacies and An. stephensi are both resistant to organochlorines and the latter has also developed resistance to organophosphate (Malathion). In Pakistan, Akbar reported malaria at a children hospital Baqai Medical University and observed high incidence of falciparum as compared to vivax (65% vs 35%). Mohammad and Hussain studied prevalence of malaria in general population of district Buner and highest rate of infection (11.6%) was recorded in August while the lowest rate of infection (3.9%) was noted in March. Malaria in