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Clinical Profile & Circadian Variation in Onset of CVA in Tertiary Care Hospital

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Abstract
Introduction: *Stroke or CVAs include some of the most common and devastating disorders. Most CVAs manifest by the abrupt onset of a focal neurologic deficit. Cerebral ischemia is caused by a reduction in blood flow that lasts longer than several seconds and has a peculiar distribution along the day , week & even months of the year. Various patterns of circadian onset variation have been reported in literature.*
Materials and Methods: *200 patients were taken for study from December 2016 to November 2018, study conducted prospectively in all patients with clinical diagnosis of stroke who fulfilled the eligibility criteria. The local ethics committee approved the trial protocol and verbal informed consent was obtained from all the patients or their relatives as applicable. The patients were subdivided into two groups based on the etiology of CVA: Group 1 (infarct) and Group 2 (hemorrhage). The time of presentation was divided into 6 sections of four hour interval starting from 00.01 hrs (12:01 am midnight).*
Result: *Mean age of the study subjects was 57.8 years. Male predominance was seen among study. Unilateral hemiplegia was the most common presenting complaint (94%). Out of the total 200 cases of stroke, 65.5% were ischemic stroke while remaining 34.5% were haemorrhagic stroke. Most common associated risk factors were hypertension (60.5%), alcohol (40.5%), smoking (45%). ECG changes were seen in 54% cases. Most common time of occurrence of stroke was early morning hours i.e. between 4am to 12 noon (57%). Only 11.5% stroke patients present during the night hours i.e. 8pm to 4am. No significant association was observed between type of stroke and diurnal variation (p-0.22). Most common time of occurrence of stroke was early morning hours in both hemorrhagic and ischemic stroke.*
Conclusion: *Our study confirms that stroke as many other cardiovascular diseases occurs preferentially during waking and in the morning irrespective of the stroke subtype.*
Keywords: *CVA (cerebro vascular accidents).*

Introduction

Some of the most common and devastating disorders of Stroke or Cerebrovascular diseases include: ischemic stroke, hemorrhagic stroke, and cerebrovascular anomalies such as intracranial aneurysms and arteriovenous malformations (AVMs). According to the Global Health Observatory (GHO), stroke is the second most common cause of death during last decade with a rising trend[1]. A stroke, or cerebrovascular accident, is defined by this abrupt onset of a neurologic deficit that is attributable to a focal

vascular cause[2]. Thus, the definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. Cerebral ischemia is caused by a reduction in blood flow that lasts longer than several seconds. Neurologic symptoms are manifest within seconds because neurons lack glycogen, so energy failure is rapid. If the cessation of flow lasts for more than few minutes, infarction or death of brain tissue results. When blood flow is quickly restored, brain tissue can recover fully and the patient's symptoms are only transient: This is called a transient ischemic attack (TIA. Focal ischemia or infarction, conversely, is usually caused by thrombosis of the cerebral vessels themselves or by emboli from a proximal arterial source or the heart. Intracranial hemorrhage is caused by bleeding directly into or around the brain; it produces neurologic symptoms by producing a mass effect on neural structures, from the toxic effects of blood itself, or by increasing intracranial pressure.

Clinical features vary from paralysis, communication difficulties, difficulties with mental processes, such as learning, concentration and memory. Some patients can present with visual disturbances, urinary incontinence, swallowing difficulties and emotional problems etc. It has physiological, economical and psychological impact on the patients[3].

There are available data from observational studies suggesting that cerebrovascular events are not randomly distributed over time, but have a peculiar distribution along the day (circadian variation with morning peak of occurrence), week (circaseptan variation with higher frequencies in the last and first days of the week) and even months of the year (circannual or seasonal variation with predilection for the cold months)[4].

Various patterns of circadian onset variation have been reported for cerebrovascular events. Regarding the ischemic stroke (IS), the earliest studies suggested a higher incidence in evening hours or during nocturnal sleep[5]. Starting with the 1980s the studies more strongly indicate the morning higher occurrence of stroke with the lowest incidence during nighttime[6–9], confirmed by the conclusions of the meta-analysis of Elliot et al[10]. In the last years there were reports that showed a second peak, not so striking but evident, in the late afternoon[11–13]. There is an obvious similarity between cardiovascular events and cerebrovascular events regarding their diurnal variation with an increase during the morning hours after awaking and a decrease during the nocturnal sleep. This pattern of diurnal variation is typical for myocardial infarction, angina and sudden death. This similarity suggests that cerebrovascular and cardiovascular events share common triggering factors[4,14,15].

For the hemorrhagic stroke (HS), the results of different studies show some differences, but the double-peak pattern is the most frequently reported. The highest peak seems to be in the morning for some authors and in the afternoon for others[10,11]. The most various patterns are reported regarding the subarachnoid hemorrhage (SAH), but all of them with the highest occurrence between 10.00 and 16.00 (with or without any peak) and the lowest during nighttime, suggesting the overlapping with the working hours.

Although the temporal pattern of stroke occurrence has been recognized, at least for the circadian variation of the stroke onset, the reason underlying the temporal nature of stroke is not completely understood. A constellation of exogenous cyclic factors such as temporal pattern in posture, physical activity, emotional stress and food behavior can influence the stroke occurrence. There are also data suggesting that endogenous factors, all having demonstrated a temporal variation, such as blood pressure (BP - with physiological nocturnal decrease and morning increase), autonomic system activity (with activation of the sympathetic nervous system after the wake-up moment) and hemostatic balance (with increased platelet aggregability, hypercoagulability and hypofibrinolysis in the

morning), can influence the susceptibility to stroke or can even have a triggering role. Their physiological diurnal rhythms (related to the central and peripheral internal clock activity) and moreover, the alterations of this rhythm, are the most important factors contributing to the stroke occurrence, even bigger than the trigger itself[4,6].

The majority of available studies concerning the aspects of chronological variation refer to Ischemic stroke, there are less reports available for SAH and even hemorrhagic stroke, and only a few treating the three major types of stroke simultaneously. The aims of our study are to investigate the existence of a circadian pattern in stroke occurrence and the possible differences in the circadian variation among stroke subtypes in cases presenting at a tertiary care centre.

Material and Methods

200 patients were taken for study, who were admitted in department of medicine in a tertiary care hospital from December 2016 to November 2018. A cross sectional observational study was conducted in all patients with clinical diagnosis of stroke who fulfilled the eligibility criteria. The local ethics committee approved the trial protocol and verbal informed consent was obtained from all the patients or their relatives as applicable.

Patients included in the study or their relatives were asked detailed history and detail physical examination of patients was done. All patients underwent CT scans and appropriate blood investigations like Lipid profile, random blood sugar, TLC, PT INR, renal function test, liver function test and an ECG as well.

Inclusion Criteria wasall adult patients presenting within 72 hours with a diagnosis of CVA based on: Sudden onset neurological deficit, Neuroimaging consistent with diagnosis of Infract or Hemorrhage, giving Informed consent.

Few patients excluded were the ones, who could not give proper history regarding onset or no responsible attendant was found, Transient ischemic events, Patients in whom stroke symptoms are caused by subdural hemorrhage, tumors, poisoning or trauma. All the patients were admitted to the intensive care unit initially and were given standard management as per the clinical condition. The control of blood pressure, glycemic status, and ventilator care was as per the standard management protocol of an acute stroke patient. The patients were subdivided into two groups based on the etiology of CVA: Group 1 (infarct) and Group 2 (hemorrhage).

The division into the groups was based on the findings of neuroimaging and patients with hemorrhagic transformation of an infarct were included in Group 1 only.

The time of presentation was divided into 6 sections of four hour interval starting from 00.01 hrs (12:01 am midnight). Statistically analysed, the quantitative data was represented as their mean ± SD. Categorical and nominal data was expressed in percentage. All analysis was carried out by using SPSS software version 21.

Results

Table 1 Distribution of cases as per Age group

Age group (yrs)	N	%
< /=40	21	10.5%
41-50	34	17.0%
51-60	64	32.0%
61-70	71	35.5%
> 70	10	5.0%
Total	200	100.0%
Mean age - 57.8 +/- 16.23 years		

Age range was 16 to 96 years with mean age of the study subjects was 57.8 years.. Youngest patient was 16 years of age and eldest being 96 years old. Elderly population constitutes about 40% cases i.e. over 60 years of age.

Table 2 Distribution of cases as per Gender

Gender	N	%
Female	79	39.5%
Male	121	60.5%
Total	200	100.0%

Male predominance was seen among study groups with 60.5% males to 39.5% females. The male to female ratio was 1.53:1.

Table 3 Distribution of cases as per Presenting Complaints

Presenting Symptoms	N	%
Unilateral Hemiplegia	188	94.0%
Monoparesis	12	6.0%
Cranial nerve involvement	191	95.5%
Convulsions	27	13.5%
Unconsciousness	24	12.0%
Speech disturbances	69	34.5%
Incontinence	73	36.5%
Cerebellar signs	2	1.0%
Headache	21	10.5%
Vomiting	23	11.5%

Unilateral hemiplegia was the most common presentation (94%) of which 50%had right sided and 44% had left sided involvement. Other complaints include: convulsions (13.5%), unconsciousness (12%), vomiting (11.5%), headache (10.5%), monoparesis (6%) and positive cerebellar signs (1%)

Table 4 Distribution of cases as per Type of Stroke

Type of Stroke (CT Diagnosis)	N	%
Ischemic stroke	131	65.5%
Hemorrhagic stroke	69	34.5%
Total	200	100.0%

Out of the total 200 cases of stroke, 65.5% were ischemic stroke while remaining 34.5% were haemorrhagic stroke. In the category of hemorrhagic stroke both intracerebral and subarachnoid hemorrhages were included. There were 6 patients of subarachnoid hemorrhage amongst 69 hemorrhagic stroke patients, rest all being intacerebral hemorrhage. Few patients with neurodeficits but indeterminate CT findings were not included in the study. Thus in present study, incidence of ischemic stroke was almost double than haemorrhagic stroke.

Table 5 Distribution of cases as per Risk Factors

Risk Factors for Stroke	N	%
Hypertension	121	60.5%
CVD	15	7.5%
DM	37	18.5%
Hypercholesterolemia	51	25.5%
Smoking	90	45.0%
Alcohol	81	40.5%

Amongst risk factors, most common was hypertension 121 (60.5%). Smoking was found to be most common risk factor amongst addictions constituting 90 cases (45%).

Table 6 Association of Risk factors with type of Stroke

Risk Factors for Stroke	Infraction (n-131)		Hemorrhagic (n-69)		Total	p- value
	N	%	N	%		
Hypertension	71	54.2%	50	72.5%	121	**<0.05**
CVD	13	9.9%	2	2.9%	15	**<0.05**
DM	22	16.8%	15	21.7%	37	**0.81**
Hypercholesterolemia	23	17.6%	28	40.6%	51	**0.09**
Smoking	60	45.8%	30	43.5%	90	**1.00**
Alcohol	52	39.7%	29	42.0%	81	**0.61**

As per the risk factor, a significant association was seen between presence of hypertension and hemorrhagic stroke (positive in 72.5% hemorrhagic stroke cases as compared to 54.2% infraction cases). A total of 9.9% cases of Ischemic stroke gave history of cardivascular disease as compared to 2.9% cases of hemorrhagic stroke ($p<0.05$). Distribution of other risk factors like diabetes, hypercholesterolemia, smoking and alcohol were comparable between both subtypes of stroke ($p>0.05$).

Table 7 Association of ECG changes with type of stroke

ECG Changes	Type of Stroke		Total
	Hemorrhagic	Ischemic	
None	28	64	92
	40.6%	48.9%	46.0%
Atrial/ Ventricular ectopies	15	9	24
	21.7%	6.9%	12.0%
ST depression	17	44	61
	24.6%	33.6%	30.5%
Bundle branch block	17	14	31
	24.6%	10.7%	15.5%
AV block	2	1	3
	2.9%	0.8%	1.5%
AF	0	1	1
	0.0%	0.8%	0.5%
p- value - 0.31			

ECG changes were seen in 54% cases with ST depression being the commonest finding (30.5%) followed by bundle branch blocks and AV ectopies (15.5% and 12%). AV block and atrial fibrillation was seen in 3 and 1 case each respectively. No difference was observed between the stroke subtypes related to ECG findings (p>0.05).

Table 9 Distribution of cases as per Time of occurrence

Time of Occurrence	N	%
12 am - 4 am	11	5.5%
4 am - 8 am	40	20.0%
8 am - 12 noon	74	37.0%
12 pm - 4 pm	33	16.5%
4 pm - 8 pm	30	15.0%
8 pm - 12 midnight	12	6.0%
Total	200	100.0%

Only those patients in whom the precise time of onset was known to the relatives were included in the study. 11(5.5%) cases happened in the window of 4 hours between 12 am to 4 am. 40(20%) cases happened between 4am to 8am and 74(37%) cases i. e. maximum number of cases happened between 8am to 12pm. Most common time of occurrence of stroke was morning hours i.e. between 4am to 12 noon (57%). while 31.5% of stroke cases occurred in afternoon and evening hours i.e. between 12 noon to 8pm. Only 11.5% stroke patients present during the night hours i.e. 8pm to 4am.

Table 10 Association of time of occurrence with type of stroke

Time of Occurrence	Type of Stroke		Total
	Hemorrhagic	Ischemic	
12 - 4 am	4	7	11
	5.8%	5.3%	5.5%
4- 8 am	14	26	40
	20.3%	19.8%	20.0%
8 am - 12 noon	23	51	74
	33.3%	38.9%	37.0%
12 -4 pm	10	23	33
	14.5%	17.6%	16.5%
4- 8 pm	12	18	30
	17.4%	13.7%	15.0%
8pm -12 midnight	6	6	12
	8.7%	4.6%	6.0%
Total	69	131	200
	100.0%	100.0%	100.0%
p- value - 0.22			

No significant association was observed between type of stroke and diurnal variation (p-0.22). Most common time of occurrence of stroke was early morning hours in both hemorrhagic and ischemic stroke.

Table 11 Mean NIHSS score among Infraction and Hemorrhagic stroke cases

NIHSS Score	Mean	SD
Hemorrhagic (n-69)	14.3	9.10
Ischemic (n-131)	8.7	5.60
p- value	**<0.01**	

NIHSS score is primarily a tool to objectively quantify the impairment caused by stroke.It is composed of 11 items each of which scores ability between a 0 to 4. The maximum possible score is 42 with minimum score being a 0. Mean NIHSSscore was significantly higher among hemorrhagic stroke cases as compared to ischemic stroke cases (14.3 vs 8.7; p<0.01). This shows that impairment caused by stroke is more in hemorrhagic stroke cases.

Table 12 Mortality rate among Infraction and Hemorrhagic stroke cases

Mortality	N	%
Infarction (n-131)	4	3.1%
Hemorrhage (n-69)	13	18.8%
Total (n-200)	17	8.5%

Among haemorrhagic stroke cases was 18.8% i. e. amongst the 69 patients of CT diagnosed hemorrhagic stroke 56 survived and 13 patients died. Whereas in ischemic stroke amongst 131 cases 4 patients died, constituting total of 3.1%. This shows that mortality rates among stroke cases is higher in hemorrhagic stroke cases.

Discussion

A hospital based observational study was conducted to evaluate the clinical profile of patients with cerebrovascular accidents in rural population and assess the circadian variation in onset of ischemic and haemorrhagic stroke. Consecutive type of non-probability sampling will be followed for the selection of study subjects. A total of 200 patients with clinical diagnosis of acute stroke, fulfilling the eligibility criteria came to us during the study period.

Demography: Mean age of the study subjects was 57.8 years with 40% cases being over 60 years of age. Male predominance was seen among study groups with 60.5% males to 39.5% females.sex ratio male to female being 1.53 to1.

Various studies have shown that prevalence of stroke increases with advancing age. However regarding gender differentiation, different studies showing varied results. In a study by Pavan MR et al. out of the total 100 patients, 50 were males and 50 were females. The mean age of stroke patients was 61.01±14.1 years. Somasundaran et al. in their study observed that out of the total 464 patients, 207(44.6%) were females and 257(55.4%) were males with mean age of 64.3 years. In another study by Chukwuonye et al, mean age of the subjects was 66.5±2.6 years with 58% females and 42% males.

Clinical Presentation- Unilateral hemiplegia was the most common presenting complaint (94%). Cranial nerve involvement was seen in 95.5% cases while incontinence and speech disturbances were reported in 36.5% and 34.5% cases respectively. predominant cases of unilateral hemiplegia was also seen in the studies by Patil B et al, Prasad C et al., Kaur I et al. and Vaidya et al. Vaidya et al. and Eapen, R et al. observed cranial nerve involvement in majority of the cases (88%, 94%).

***Type of Stroke-** Out of the total 200 cases of stroke, 65.5% were ischemic stroke while remaining 34.5% were haemorrhagic stroke. In a study by Somasundaran A et al, out of the total 108 cases, 72.2% were ischemic strokes and rest 27.8% were hemorrhagic strokes as confirmed by CT brain. Reviewing the Indian stroke epidemiological data, the Mumbai registry has recorded 80.2% ischemic strokes and 17.7% hemorrhagic strokes. Data from Kerala state were obtained from the Trivandrum Stroke registry where 83.6% were ischemic strokes and 16.4% were hemorrhagic stroke. Pavan et al. in a similar study observed 71% ischemic and 29% hemorrhagic stroke cases.

***Risk Factors-** Most common observed risk factors were hypertension (60.5%), alcohol (40.5%), smoking (45%), hypercholesterolemia (25.5%) and diabetes (18.5%). History of CVD was given by 7.5% cases. A significant association was seen between presence of hypertension and hemorrhagic stroke while history of CVD was associated with ischemic stroke. Vaidya et al. found that most common risk factor in stroke patients was Hypertension (34%) followed by diabetes (28%) and past h/o cerebrovascular stroke (15%). In a similar study by Eapen R et al. Hypertension, diabetes and dyslipidemia was observed in 40%, 28% and 19% subjects respectively. In a study conducted in South India conducted on 109 patients of stroke in age group of 15-45 years, there were 76 (69.7%) smokers, 53 (48.6%) alcoholics, 59 (54.1%) diabetics and 79 (72.5%) hypertensives. A retrospective review was done of the medical records of 177 patients seen in a tertiary referral centre in Thiruvananthapuram, Kerala. Hypertension, smoking, alcohol and hyperlipidemia were significantly more prevalent in the cases of stroke. Another study in Taiwan explored the etiology of stroke. The 4 most common risk factors were hyperlipidemia (53.1%), smoking (49.8%), hypertension (45.8%), and family history of stroke (29.3%). Strong et al. also estimated that hypertension was the most common risk factor for stroke, which was present in 54% of the cases in their study. In a similar study by Pavan et al, risk factors associated with stroke patients were Hypertension (37%), smoking (26%), diabetes (18%), alcohol (13%) and history of TIA (11%) and CVD (5%). Sridharan SE et al. observed that hypertension was the most frequent risk factor, seen in 83.2% patients. Half of the patients had diabetes mellitus and 26% had dyslipidemia.

A significant association between presence of hypertension and hemorrhagic stroke were also seen in the studies by Patil B et al., Prasad C et al., Kaur I et al., Strong et al. and Sridharan SE et al..

***ECG Findings-** ECG changes were seen in 54% cases with ST depression being the commonest finding (30.5%) followed by bundle branch blocks and AV ectopies (15.5% and 12%). In the study by Togha et al., the most common ECG abnormalities associated with stroke were T-wave abnormalities, prolonged QTc interval and arrhythmias, which were respectively found in 39.9%, 32.4%, and 27.1% of the stroke patients. In a study on patients with ischemic stroke but without history of primary heart disease, Dogan et al. found ischemia-like ECG changes in 65% of patients, QTc interval prolongation in 26%, and arrhythmias in 44% of them. In the study of Lindgren et al. transient ST-T changes were found in 54% of patients with ischemic stroke with no primary heart disease. Prominent U-wave, QT interval prolongation, and arrhythmia were observed in 17%, 13%, and 4% of them, respectively.

***Circadian Variation**- Our study showed that stroke onset is not random in 24 hour period but has a characteristic pattern of the circadian variation of both ischemic and haemorrhagic stroke. Most common time of occurrence of stroke was

early morning hours i.e. between 4am to 12 noon (57%). Only 11.5% stroke patients present during the night hours i.e. 8pm to 4am. No significant association was observed between type of stroke and diurnal variation (p-0.22). Most common time of occurrence of stroke was early morning hours in both hemorrhagic and ischemic stroke.

The results of our study are in accordance with the findings of the majority of previous reports available in literature, with the highest incidence of stroke occurrence during the morning and the minimum occurrence during the night for all stroke types (IS, HS and SAH).

Fodor DM et al., in the spectral Fourier analysis of the time of stroke onset has shown the existence of two cycles: one of 12-hours and one of 24-hours. They suggest the possibility that initially the two cycles antagonize each other and after 12-hours they synchronize with a synergic effect. The 24 cosinor curve analysis shows a hall-mark of the 12-hours cycle in their first part. Therefore they speculate the existence of a protective mechanism against stroke in the 00.01–04.00 interval. The nocturnal sleep seems "to protect" against stroke despite the old traditional teaching that strokes are more likely to occur at night, but further studies are needed to confirm this hypothesis, maybe including persons working on night shifts and changing their sleep cycle.

The same circadian pattern for Ischemic and hemorrhagic stroke suggests common triggers for all two types of stroke, the endogenous factors also having a known circadian variation. The best studied triggers are the blood pressure (BP) and the coagulation status. The BP has a well-known circadian variation with a nocturnal dip and a morning increase. The loss of the physiological circadian pattern of BP (non-dipper and reverse-dipper profile) and the excessive morning BP surge at wake-up are accompanied by an increased risk of cerebrovascular events. Both aspects are characterized by high morning BP. The same situation is suggested for the other vascular risk factors (DM, hypercholesterolemia, smoking status, AF and CAD) with the same circadian variation in their presence or absence. During the morning hours, physiologically the hemostatic balance is inclined to a temporal prothrombotic status, with increased levels of the hematocrit, increased platelet aggregability, hypercoagulability and hypofibrinolytic activity.

The highest occurrence of stroke during morning hours has a sociological dimension as information, with practical implication for the admission, evaluation and treatment of stroke in Emergencies Departments/Stroke Units, requiring an increased level of awareness and availability during the morning interval. Another wide implication may be the prevention of stroke by treating the risk factors concerning their circadian variation. In order to address this problem further studies with long-term investigations are needed.

Conclusion

Our study confirms that stroke as many other cardiovascular diseases occurs preferentially during waking and in the morning irrespective of the stroke subtype. In this context, strategies considering the specific treatment of risk factors during the circadian period of their major influence on stroke onset may ameliorate preventive and therapeutic interventions. Further efforts to study the specific aspects of circadian rhythms on cerebrovascular disease areneeded to better understand the pathophysiological features and to obtain beneficial effects in terms of prevention and treatment.

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