ORIGINAL ARTICLE

Study of Sleep Disordered (SDB) and Sleep Architecture in Stroke Patients in India

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Abstract

Introduction: Sleep disordered breathing (SDB) is being recognized as a risk factor for stroke. OSA is easily modifiable; the diagnosis is simple, and the treatment straight-forward. These characteristics make OSA an ideal target for interventions aimed to reduce cerebro-vascular disease burden. However, data from India is lacking.

Methodology: Fifty subjects with a history of recent onset stroke, and hundred matched controls were recruited. A comprehensive history and other relevant features were recorded. After the acute phase of the stroke was over, the patients underwent an overnight polysomnography (PSG). The sleep architecture was also analyzed.

Results and Conclusions: SDB was seen in 78% stroke patients but in only 28% of controls (OR 9.1169 (95 % CI 4.1009 to 20.2684) P < 0.0001). Mixed apnea was seen in 53.85% of the cases and was the predominant type of sleep apnea observed. The prevalence of SDB was high in stroke patients with obesity and congestive cardiac failure. We found a reduction in total sleep time, sleep efficiency and REM sleep in stroke patients and an increased stage 2 sleep. Also, stroke topography affected sleep architecture with patients with multiple sites involved having decreased REM sleep.

Keywords: Stroke, Cerebro-vascular accident (CVA), Sleep disordered breathing (SDB), polysomnography (PSG), sleep architecture.

Introduction

Epidemiological studies point to stroke as the leading cause of high mortality or permanent disability in the aging population[1-2]. Health organizations put emphasis on primary prevention of stroke through the determination of risk factors of cardiovascular diseases. The risk factors for stroke can be classified as modifiable and non-modifiable. Non-modifiable stroke risk factors include age, race, sex, and a family history of cardiovascular disorders, whereas the most important modifiable risk factors include arterial hypertension, diabetes mellitus, obesity, dyslipidemia, carotid stenosis, current smoking, established cardiovascular disease, and atrial fibrillation. Aggressive treatment of risk factors in stroke patients, including hypertension, atrial fibrillation, and carotid stenosis, is widely accepted. During the past few years, efforts have been made to determine new preventable and treatable stroke risk factors in the hope that byaddressing these risk factors we may prevent strokes and its associated morbidities[3].

Sleep disordered breathing (SDB) is increasingly being regarded as a risk factor for stroke[3]. Seminal

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studies in the 1990s exhibited a link between habitual snoring and stroke and further prompted studies assessing the role of SDB in stroke patients. A meta-analysis of 29 studies found that 72% of stroke patients had SDB, as defined by an apnea-hypopnea index (AHI) ≥ 5[4]. Some studies have demonstrated that patients with stroke and OSA have an increased risk of poor functional outcome and mortality compared to patients of stroke without SDB[5-7]. SDB is easily modifiable; the diagnosis is simple, and the treatment straight-forward. These characteristics make OSAS an ideal target for interventions aimed to reduce cerebrovascular disease burden.

Also, changes in sleep architecture have been observed in stroke patients[8]. Sleep architecture is defined as the structure and pattern of the different sleep stages experienced by the patient. Infratentorial and supratentorial strokes have been associated with changes in the duration of REM and NREM sleep and with changes in sleep efficiency[8].

We conducted this study to see the prevalence of SDB in stroke patients in India and to identify risk factors which will help in recognizing those stroke patients who should be offered screening for SDB. We also wanted to look for changes insleep architecture in such patients.

Methodology

The present observational study was conducted in the Department of Pulmonary, Critical Care & Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital (VMMC & SJH), New Delhi. Fifty subjects with a history of recent onset stroke were recruited on the basis of the following inclusion and exclusion criteria:

Inclusion criteria were:

1. Acute stroke, confirmed by neuro-imaging and
2. Age between 20 and 85 years.

Exclusion criteria were:

1. Coma
2. Previous stroke (asymptomatic infarcts discovered at imaging were included)
3. Another cerebral pathology
4. Serious medical or psychiatric diseases
5. A known pre-existing sleep disorder (patients who were under treatment or had a diagnosis of a sleep disorder, at the time of admission)
6. Increased psychomotor agitation and
7. Use of medication with a primary effect on the central nervous system (CNS; benzodiazepines, antidepressants, antipsychotics etc.) during the time of the study.
8. History of chronic respiratory disease or any acute cardiac or respiratory conditions that might lead to hypoxia.
9. Those in a terminal stage of the disease at the moment of the evaluation (Glasgow Coma Scale score less than[8])

In addition, one hundred age-sex and BMI matched controls were recruited from the medical OPD and berlins questionnaire[9] to assess sleep apnea was filled by the participants. According to the questionnaires, the controls were classified as high risk or low risk for sleep apnea. Those patients, who were high risk for sleep apnea, underwent an overnight polysomnographic study to confirm the presence of SDB.

Experimental Design

Written informed consent was taken from all the subjects. Those patients who passed the acute phase of the neurological event (alive for more than a week from the onset of the stroke) were included in the study. The diagnosis and location of acute ischemic stroke was determined following international guidelines[10-11] and was based on an evaluation of the existing neurological defects and brain-computed tomography scans. The patients were classified based on the type of stroke as either belonging to the ischemic stroke group or the hemorrhagic stroke group. The patients were also classified according to the stroke topography into the following groups:

1. Cortical stroke,
2. Sub-cortical stroke,
3. Brainstem stroke,
4. Cerebellar stroke and
5. Multiple sites involved.

Data was collected from all patients on demographic, clinical, (age, sex, sleep-history and Epworth Sleepiness Scale self-reports of their status before the acute stroke), anthropometric (body mass index in kg/m^2) and other

risk factors, including arterial hypertension, hypercholesterolemia, diabetes mellitus, congestive cardiac failure (CCF) (defined according to international guidelines or through the current use of drugs); smoking status (current [more than 10 cigarettes/d] or past/never smoker) and alcohol consumption (current/ reformed and never).

After the acute phase of the stroke was over, the patients underwent an overnight polysomnography (PSG). This is because according to a review of Sleep-related breathing and sleep-wake disturbances in ischemic stroke, in the sub-acute stroke phase SDB improves[12], which suggests that breathing abnormalities are exacerbated by stroke and hence a PSG done during acute stage may not reflect the preexisting sleep disorder nor the sleep disorder prevalent in the long term. The patients underwent an overnight, in-lab supervised polysomnography (PSG) (Alice 5, Respironics, Murrysville, PA). The following parameters were measured: 2 channels each for electroencephalography (EEG); electromyography (EMG); and electro-oculography; airflow recording through nose and mouth by thermistor and nasal pressure cannula; thoracic and abdominal efforts by plethsmography; oxygen saturation through pulse oximetery; and tracheal sound recording by using a microphone attached to the neck. SDB was diagnosed when a patient with symptoms suggesting SDB had a Respiratory Disturbance Index (apneas + hypopneas + RERAs) > 5 per hour. They were further classified as mild, moderate and severe based on RDI. The diagnosis was based on the criteria laid down in the AASM Manual for the Scoring of Sleep and Associated Events[13]. Sleep architecture was assessed by studying the total sleep time (TST); time spent in different sleep stages and time spent awake; the sleep latency; REM stage latency and sleep efficiency. In the analysis, all sleep stages were expressed as a percentage of the sleep episode (time from sleep onset to final awakening).

All the data obtained thereby, was recorded systematically and analyzed using standardized statistical methods. Categorical variables were compared using the ã2 test, and numerical variables using the t test for independent samples. Statistical significance was set at 5% (corresponding to p value less than 0.05). Univariate analysis was done to identify variables independently correlated with SDB.

Observation and Results

The study population consisted of thirty cases of ischemic stroke (60%) and twenty cases (40%) hemorrhagic strokes. No cases of transient ischemic attack could be enrolled due to non-availability of such cases. Both the subjects and control groups were comparable with regards to age, sex, anthropometric characteristics, presence of associated diseases and habits (Table 1).SDB was seen in 78% stroke patients but in only 28% of controls and this difference was found to be statistically very highly significant (OR 9.1169 (95 % CI 4.1009 to 20.2684) P < 0.0001). It was observed that sleep disordered breathing (SDB) was seen in 78% of the stroke patients while hypertension was present in 58% of the patients and other associated diseases were far less prevalent in the stroke patients. In the stroke patients with SDB, mixed apnea was seen in 53.85% of the cases and was the predominant type of sleep apnea was observed. Central apnea was seen in 28.21% of the cases while obstructive apnea was seen in 17.95% of the cases. When the sleep architecture in the stroke patient was compared with controls with sleep disordered breathing, it was seen that stroke patients had decreased total sleep time, decreased sleep efficiency, decreased REM sleep and increased stage II sleep.

The stroke patients were divided into two groups based on the absence or presence of SDB and their characteristics and sleep architecture was assessed (Table 2). Only BMI was found to be significantly different. There were no significant differences in the sleep architecture of the stroke patient with or without SDB.

Subgroup analysis of type of stroke (Table 3) and stroke topography (Table 4) with the clinical characteristics and parameters studied to assess sleep architecture was also done. It was seen that hypercholesterolemia was significantly higher in the ischemic stroke group. The duration of REM sleep was significantly different in the different stroke topographies.

Discussion

An increasing body of evidence is being published in the literature concerning the effect of stroke on the development, occurrence, and course of sleep-disordered breathing (SDB). In many studies in stroke patients, SDB was diagnosed in a significant proportion of the

Table 1: Characteristics in the stroke patients and control groups.

Characteristics		Stroke patients (N=50)	Control Group (N=100)	P value
Age		54.66 ± 12.49	52.12 ± 10.03	0.1808
Sex	Male	31 (62%)	67 (67%)	0.6711
	Female	19 (38%)	33 (33%)	
BMI (kg/m^2)		28.81 ± 5.12	28.95 ± 5.65	0.8829
Associated Diseases :				
Hypertension		29 (58%)	53 (53%)	0.6848
Diabetes Mellitus		21 (42%)	44 (44%)	0.9535
Hypercholesterolemia		20 (40%)	35 (35%)	0.6750
CCF		7 (14%)	15 (15%)	0.8704
Habits and Addictions:				
Smoking	Never Smoked Smoked in the past / continues to smoke	16 (32%) 34 (68%)	37 (37%) 63 (63%)	0.6725
Alcohol consumption	Never consumed alcohol	17 (34%)	35 (35%)	0.9034
	Consumed alcohol in the past / continues to consume alcohol	33 (66%)	65 (65%)	
Sleep Disordered Breathing				
SDB Present		39 (78%)	28 (28%)	<0.001
Obstructive		7	23	
Central		11	2	
Mixed		21	3	
Sleep architecture			(N*=28)	
Total sleep time (min)		246.78 ± 7.15	260.89 ±12.11	<0.001
Sleep efficiency (%)		74.78 ± 14.15	81.81 ± 7.73	0.0175
Stage I (%)		5.25 ± 3.52	4.12 ± 2.38	0.1342
Stage II (%)		57.89 ± 8.10	52.58 ± 6.42	0.0039
Stage III/SWS (%)		7.88 ± 4.03	8.36 ± 4.10	0.6175
REM (%)		9.77 ± 5.15	13.94 ± 5.43	0.0012
Wakefulness (%)		19.21 ± 7.32	20.99 ± 10.25	0.3765
Sleep Latency (min)		45.33 ± 23.14	43.06 ± 20.43	0.6663
REM latency (min)		124.49 ± 41.87	116.00 ± 36.09	0.3703

Data expressed as mean ± SD and number (Percentage)

Table 2: Characteristics in stroke patients (with or without SDB).

Characteristics		SDB Absent (n=11)	SDB Present (n=39)	P value
Age		57.72 ± 13.38	53.79 ± 12.28	0.362
Sex	Male	6	25	0.564
	Female	5	14	
BMI (kg/m^2)		23.28 ± 1.47	30.36 ± 4.68	< 0.001
Associated diseases:				
Hypertension		9 (81.81%)	20 (51.28%)	0.092
Diabetes Mellitus		3 (27.27%)	21 (53.84%)	0.175
Hypercholesterolemia		4 (36.36%)	23 (58.97%)	0.305
CCF		0 (0%)	7 (17.94%)	0.324
Habits and Addictions:				
Smoking	Never smoked	1	15	0.080
	Smoked	10	24	
Alcohol consumption	Never consumed alcohol	3	14	0.728
	Consumed alcohol	8	25	
RDI		2.40 ± 1.72	21.52 ± 15.87	0.0002
ODI		4.75 ± 1.50	25.78 ± 17.27	0.0002
Sleep architecture				
Total sleep time (min)		255.23 ± 76.94	244.39 ± 71.61	0.665
Sleep efficiency (%)		71.97 ± 16.15	75.57 ± 13.66	0.461
Stage I (%)		5.46 ± 3.87	5.20 ± 3.46	0.831
Stage II (%)		57.35 ± 6.44	58.04 ± 8.58	0.806
Stage III/SWS (%)		8.33 ± 2.87	7.75 ± 4.33	0.678
REM (%)		9.31 ± 5.62	9.90 ± 5.08	0.741
Wakefulness (%)		19.55 ± 7.16	19.11 ± 7.45	0.862
Sleep Latency (min)		48.96 ± 24.74	44.30 ± 22.90	0.561
REM latency (min)		127.74 ± 43.11	123.57 ± 42.04	0.774

Data expressed as mean ± SD and number (percentage)

Table 3: Characteristics in the different groups based on the type of CVA.

Characteristics		Hemorrhagic Stroke (n =20)	Ischemic Stroke (n=30)	P value
Age		55.30 ± 13.93	54.23 ± 11.68	0.7702
Sex	Male	13 (65%)	18 (60%)	0.9526
	Female	7 (35%)	12 (40%)	
BMI (kg/m^2)		29.70 ± 4.47	28.21 ± 5.51	0.3188
Associated diseases:				
Hypertension		11 (0%)	18 (0%)	0.9534
Diabetes Mellitus		8 (0%)	13 (0%)	0.8150
Hypercholesterolemia		4 (0%)	16 (0%)	0.0392
CCF		3 (0%)	4 (0%)	0.8679
Habits and Addictions:				
Smoking	Never smoked	7	9	0.9507
	Smoked	13	21	
Alcohol	Never consumed alcohol	9	8	0.3002
consumption	Consumed alcohol	11	22	
Respiratory Disturbance Index		16.52±14.80	17.84±17.17	0.6272
ODI		21.06 ± 17.00	21.22 ± 18.24	0.9752
Sleep architecture				
Total sleep time (min)		258.17 ± 74.01	239.18 ± 71.1	0.3672
Sleep efficiency (%)		73.95 ± 10.67	75.33 ± 16.22	0.7393
Stage I (%)		5.61 ± 3.49	5.02 ± 3.57	0.5662
Stage II (%)		56.55 ± 9.24	58.77 ± 7.27	0.3476
Stage III/SWS (%)		8.93 ± 3.92	7.18 ± 4.02	0.1343
REM (%)		8.84 ± 5.57	10.39 ± 4.85	0.3021
Wakefulness (%)		20.06 ± 8.51	18.64 ± 6.50	0.5072
Sleep latency (min)		41.13 ± 20.98	48.12 ± 24.41	0.3001
REM latency (min)		123.98 ± 40.99	124.82 ± 43.14	0.9454

Data expressed as mean ± SD and number (percentage)

Table 4: Characteristics in the Different Groups Based in the Topography of CVA.

Characteristics		Cortical (n=17)	Sub-cortical (n=16)	Brainstem (n=8)	Cerebellar (n=4)	Multiple (n=5)	P value
Age		56.00 ± 13.99	54.44 ± 11.91	55.37 ± 10.99	43.75 ± 8.06	58.40 ± 13.87	0.485
Sex	Male	8	9	6	3	5	0.2177
	Female	9	7	2	1	0	
BMI (kg/m^2)		29.67 ± 4.76	27.11 ± 3.72	30.29 ± 6.16	32.69 ± 6.16	25.85± 6.26	0.139
Associated Diseases:							
Hypertension		12	8	1	3	5	0.0144
Diabetes Mellitus		5	6	6	1	3	0.2025
Hypercholesterolemia		4	7	5	1	3	0.2965
CCF		1	3	1	1	1	0.7730
Habits and addictions:							
Smoking	Never Smoked	3	7	3	1	2	0.5431
	Smoked in the past / continues to smoke	14	9	5	3	3	
Alcohol consumption	Never consumed alcohol	7	5	1	1	3	0.4733
	Consumed alcohol in the past / continues to consume alcohol	10	11	7	3	2	
Respiratory Disturbance Index		16.82±15.28	16.76±13.38	18.15±21.10	22.06±24.03	15.66±18.39	0.980
Oxygen Desaturation Index		21.90 ± 17.78	18.74 ± 13.47	23.41 ± 23.45	23.32 ± 24.06	21.02 ± 20.13	0.974
Sleep Architecture							
Total sleep time (min)		247.46 ± 61.27	250.74 ± 84.63	228.65 ± 68.87	204.09 ± 64.02	249.89 ± 71.29	0.776
Sleep efficiency (%)		74.83 ± 12.09	75.361± 4.91	80.13 ± 10.11	78.72 ± 11.94	61.03 ± 20.97	0.183
Stage I (%)		6.08 ± 3.55	4.55 ± 3.45	4.37± 4.07	6.32 ± 4.35	5.27 ± 2.40	0.670
Stage II (%)		55.76 ± 6.59	60.51 ± 9.75	58.29 ± 6.03	54.23 ± 11.68	59.00 ± 6.77	0.450
Stage III/SWS (%)		7.08 ± 4.24	8.58 ± 4.51	8.95 ± 3.70	5.41 ± 2.48	8.59 ± 2.95	0.513
REM (%)		11.65 ± 5.53	7.573± 0.54	10.24 ± 5.22	14.41 ± 5.72	5.98 ± 3.14	0.018
Wakefulness (%)		19.43 ± 6.32	18.79 ± 7.67	18.15 ± 7.95	19.63 ± 12.57	21.17 ± 6.19	0.966
Sleep latency (min)		47.53 ± 21.59	45.26 ± 26.77	47.85 ± 23.75	34.16 ± 20.87	42.93 ± 22.97	0.882
REM latency (min)		134.93 ± 47.94	120.65 ± 40.78	117.72 ± 45.57	115.15 ± 39.07	119.57 ± 23.18	0.810

Data expressed as mean ± SD and number (percentage)

subjects compared to the control group of patients without a history of stroke[14-15]. While , the reported incidence in the general population is reported to be to be around 2% in women and 4% in men, a meta-analysis by Johnson et al[4], reported that SDB is present in up to 72% of ischemic and hemorrhagic stroke and TIA patients. A recent study from Israel reported that in an unselected sample of patients with acute ischemic stroke, almost 90% had sleep-disordered breathing with third having severe form of the disorder[16].

Our results concur with the published data, as we found that SDB was present in 78% of stroke patients while only 28% of the age-sex matched controls without a history of stroke were afflicted by it. The study demonstrates that SDB was a frequent accompaniment of stroke. In fact, the reported frequency likely underestimates the actual prevalence of SDB in stroke patients. Most of the studies excluded patients if they had severe medical conditions, died prior to sleep study, or were unable to consent. We also excluded patients with previous strokes, those patients having a GCS score of less than 8 and those with a serious medical or psychiatric disease. Hence in all probability, the actual prevalence of SDB in stroke patients may be even higher than estimated.

However, daily clinical practice shows that physicians pay much less attention to SDB than to other associated diseases like hypertension and diabetes. This is presumably because SDB is still frequently not considered a serious disorder, but depreciated as a benign loud snoring. This disregard for SDB is rather shocking in view of the common occurrence of sleep disordered breathing in stroke patients which is almost as frequent as generalized atherosclerosis and arterial hypertension and is commoner than diabetes, cardiac arrhythmias, and coagulation disturbances. In our study, while 78% of stroke patients had SDB, only 58% were suffering from hypertension, and 42% had diabetes mellitus. Hence, it is essential that neurologists and physicians realize the importance of SDB in stroke patients and are trained in its identification.

In multiple studies[14-15] it was observed that the incidence of OSA in stroke patients was much higher than central apneas, which accounted for less than 10%. In a meta-analysis of 29 studies[4] SDB was primarily obstructive in nature, with only 7% of patients having primarily central apneas. In contrast, we noticed that mixed apneas were the predominant type (53.85%) of sleep apnea and obstructive apneas was seen only in 17.95% of the cases. Central apnea was seen in 28.21% of the cases.

A Korean study[17] had shown that BMI and systolic bloodpressure (SBP) were significantly higher in patients withSDB than in patients without SDB. Our results have also shown that BMI is an independent predictor of SDB. When these groups based on RDI were analyzed, it was observed that increased CCF was very significantly associated with severity of sleep-disordered breathing. We propose that all stroke patients who are obese should be screened for presence of SDB and especially those with CCF.

The high frequency of SDB in stroke patients raises the question of whether SDB precedes stroke, being a risk factor for it; or whether it arises as a consequence of stroke. This seemingly simple question has defied a simple solution. Both the disorders share many common risk factors including increasing age, obesity, and alcohol abuse. If the driving force behind the association between stroke and SDB were that stroke caused the SDB, then the prevalence of SDB would have been low in the control group. In our study, we meticulously selected the controls to account for the confounding factors, and found that the prevalence of SDB was comparatively low in the control group. This hints that SDB may be an outcome of stroke. If this is true, then we also expect the stroke typography to have an impact on SDB.

However, most studies[18-20] have failed to identify a link between SDB and the type of stroke or stroke typography. A recent study tried to examine the relationship between stroke location and the prevalence of OSA and found that stroke location cannot be used to identify a group with higher risk of OSA[21]. In concordance with these studies, in our study, when the respiratory disturbance index (RDI) was compared between the groups based on type of stroke and stroke typography, there was no statistically significant difference. This suggests that the type of stroke and stroke typography did not have a significant impact on SDB. Also, some studies[22-23] report that the frequency of SDB was similar in patients with TIA and stroke. (In our study, we were unable to study this aspect due to non-availability of TIA patients.) This has beeninterpreted that in some of the cases, the SDB preceded the occurrence of stroke. It is still an open question whether SDB is a cause or a consequence of stroke. The resolution of this enigma requires further studies to disentangle

the various factors associated with the disease and to ultimately define the true relationship between SDB and stroke.

A number of studies have also analyzed the effect of stroke on sleep architecture. There have been contradictory reports regarding the alterations in the sleep architecture. Most studies, comparing stroke patients to controls, report a reduction in sleep efficiency and increased wakefulness after sleep onset[24-27], with[25] or without[28] a reduction in total sleep time. Stage II is found to be reduced[25], or even increased[28-29], and similar results are reported for slow wave sleep (SWS)[25,29-32]. Also, rapid eye movement (REM) sleep reduction is found in some studies[28], but not confirmed by others[25]. A recent meta-analysis showed that patients with stroke have poorer sleep than controls; with lower sleep efficiency, shorter total-sleep-time and lesser time in stage II[33]. In our study, when we evaluated the sleep architecture, we observed that patients were awake 19.21% of the TST. The average sleep efficiency of stroke patients was 74.78%. We report a reduction in total sleep time, sleep efficiency and REM sleep in stroke patients compared to controls with sleep disordered breathimg.

In the present study, we observed that though the presence of SDB and the type of stroke (hemorrhagic stroke or ischemic stroke) had no influence in the sleep architecture, sleep architecture was affected by the stroke topography. Percentage of REM sleep was low in those patients with stroke at multiple sites but was higher in those strokes, which involved the cerebellum. One of the limitations of our study was that polysomnographic evaluation was not done in all the controls. We were not able to compare the sleep architecture of controls without SDB with stroke patients. Also, when stroke topography was being analyzed, the smallest group only comprised 4 patients. A study with a larger number of subjects is required for a better and thorough evaluation.

In conclusion, given the high frequency of SDB in stroke patients, screening for OSA in all stroke and TIA patients may be warranted. If not possible in all patients, at least those patients with high BMI (especially those with cardiac failure) should be offered testing for SDB.

Suggestions for further studies:

1. In hospitalized and particularly bed-bound patients, circadian rhythms are often disturbed. Therefore, 24-hour studies will probably provide more data on total sleep time and sleep architecture in these patients.
2. To evaluate impact of stroke on sleep architecture, stroke patients without SDB should be compared to in-patient controls without SDB (to eliminate the effect of confounding variables like the presence of SDB and factors associated with hospitalization).

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