Sleep Apnea

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ABSTRACT

Background: Sleep apnea is a condition that interrupts breathing while sleeping, usually caused by an obstruction blocking the back of the throat so that the air cannot reach the lungs. The brief cessation in breath automatically forces individuals to wake up and restart breathing. This can happen many times during the night, making it hard for the body to get enough oxygen, and impacts the sleep quality. It is the most common type of sleep disorder breathing.

Objectives: The present study was designed to investigate the effects of obstructive sleep apnea (OSA) on different mental, physical and nervous disorders which are manifested in such patients. This study would not only benefit in ascertaining the causes of OSA through assessment of higher mental functions of autonomic and peripheral nervous systems but also in the development of algorithm for estimation of degree of damage to the nervous system with severity of OSA.

Methods: A total of 1365 consecutive participants participated in this study at the Department of Pulmonary Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana State, India for suspected sleep disordered breathing (SDB) between October 2012 and February 2016. In this cohort, 1140 participants were deemed ineligible, as per the inclusion criteria. Therefore, 225 patients were considered in the study along with 75 control subjects, who were healthy individuals. The cohort was diagnosed by an experienced pulmonologist for the symptoms of snoring and daytime somnolence. The data included documentation of age, gender, weight, height, BMI, waist and neck circumference, and clinical data such as history of apnea, insomnia, dyslipidemia, hypertension, and coronary heart disease. All participants underwent overnight polysomnography (PSG) in sleep laboratory. The cognitive function tests consisted of mini-mental state examination and by employing the depression questionnaire (Using Zung self report depression scale). The autonomic function tests were performed. Variabilities in heart rate were determined. Brain natriuretic peptide (BNP) levels in the blood were measured.

Results: The study group had an AHI ≥5 per hour of sleep while the control group had AHI <5 per hour of sleep. Overall, patients in the OSA cohort were older compared to those in the Control cohort. The overnight polysomnography values indicated distinct differences

Keywords

Apnea, hypoxia, Obstructive sleep apnea, Polysomnography, Sleep.

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among the parameters of the analysis depending upon the category of the patient (i.e., mild, moderate and severe). Oxygen saturation in blood during both REM and NREM sleep stages clearly indicated lower oxygen in patient cohort than the control group. The cognitive function tests revealed that in comparison to the control group, OSA patients had significantly impaired cognition. OSA patients had significantly higher ($p \leq 0.05$) depression. Motor action, muscle action potential and nerve action potential was significantly lower ($p \leq 0.05$) than that of the control group of healthy patients. The plasma BNP in OSA patients was significantly higher ($p \leq 0.05$) than control subjects. RR intervals in the patient group were significantly shorter than in the control group. The blood pressure of the OSA patients in general was relatively higher than the control group, both during the postural response and in handgrip test.

Conclusions: Among the enrolled individuals, those with severe OSA were affected in all faculties, namely, cognitive abilities and health attributes; and had high BNP levels in their blood. In aggregate, OSA patients can be alleviated from the syndrome, if accurate diagnosis is made on time. This study developed an algorithm which would aid the clinicians in early detection of OSA symptoms and mitigate the prognosis of the syndrome.

INTRODUCTION

Definition

Sleep is an integral part of a healthy life. Pathological disruption of sleep results in adverse effects on health. Apnea is the transient pause in breathing during sleep (for about 10 sec) and causes decreased oxygen levels in blood.

Sleep apnea is a condition that interrupts breathing while sleeping. This is usually caused by an obstruction blocking the back of the throat so that the air cannot reach the lungs. The brief cessation in breath automatically forces individuals to wake up and restart breathing. This can happen many times during the night, making it hard for the body to get enough oxygen, and impacts the sleep quality[1]. It is the most common type of sleep disorder breathing (SDB) worldwide as reported in different epidemiological studies[2].

Obstructive sleep apnea (OSA) is a sleep disorder involving repeated episodes of complete or partial obstruction of the upper airway, which cause transient cessations of breathing during sleep. These breathing disruptions cause intermittent hypoxia and sleep disturbances which are associated with daytime sleepiness and fatigue[3]. The recurrent complete or partial obstruction of the upper airway causing intermittent hypoxia (IH) results in complete or partial airflow interruptions[4]. These episodes of oxygen denaturation are followed by alternate reoxygenation. This airflow impairment is a significant health problem with neurocognitive and cardiovascular morbidities.

The disruption in the airway relates to the upper respiratory tract consisting of nasal and oral cavities, pharynx, larynx and the extra thoracic trachea[5]. The airway closure during sleep is the main cause of the apnea. OSA also reportedly affects brain function through intermittent hypoxemia and sleep fragmentation owing to repeated apneas[6]. The mechanisms responsible for these cognitive deficits still remain elusive, with researchers hypothesizing the same to be a result of daytime sleepiness[7].

Unlike central sleep apnea, OSA is associated with snoring and daytime somnolence[8]. OSA is described as apnea and/or hypopnea in accordance with the sleep hours. Common symptoms include daytime sleepiness, recurrent apneas during sleep, fatigue and repeated awakenings during sleep, morning headache, daytime fatigue and impaired concentration. OSA is usually diagnosed when apnea-hypopnea index (AHI) is ≥5, an index to indicate the extent of sleep apnea, represented by the number of apnea-hypopnea events per hour of sleep. The normal AHI score is between 0 - 4. A recent study conducted on

south Indian patients revealed that OSA was clinically manifested in patients in age group of 55 years and older, and BMI >25 kg/m^2. These patients also showed symptoms of hypertension, dyslipidemia, duration of apnea >20 seconds and oxygen desaturation index >10/h[9]. In another study conducted on a cohort from north India, OSA was found to be prevalent in 9.3% individuals, with high BMI and abdominal fat and the males having more propensities to acquire the disease. Also OSA was linearly associated with the socio-economic strata of the patients[10].

Epidemiology and etiology of OSA

OSA affects cognitive functions in 1 - 4% of adults, with increased risk among men than women (24% vs. 9%). The risk factors mainly affect old and obese males[11].

OSA is also known to diminish physical, emotional and intellectual capabilities, in addition to affecting functional quality of life. OSA patients suffer from attention deficits, impaired concentration, memory and cognition loss, and reduced executive functioning[12,13,14]. Executive functions are a group of neuropsychological processes that enable individuals to behave flexibly in a goal-directed manner as well as adapt to task and environmental demands[15]. OSA also severely affects public health by impairing socio-economic productivity and cultural behavior causing severe functional impairments such as impaired driving, increased risk for accidents, increased maintenance and healthcare cost and decreased quality of life[16,17].

The evidence on impairment and difficulties in normal life functioning has been further elaborated by several meta-analyses based on systematic reviews conducted by researchers on OSA. Recent meta-analyses on OSA provided evidence on impairments in attention or vigilance, motor conduction, delayed verbal and visual long-term memory, visuo-spatial or constructional abilities, and executive function. OSA not only affects the health state but also the socio-economic condition, productivity and quality of life[17-19]. Another meta-analysis on OSA patients further confirmed that attention and memory impairment was prevalent in 60% of OSA patients; while in 80% of OSA patients, visuo-construction and psychomotor functioning has been reported to be been impaired[20].

Co-morbidities

Multiple co-morbidities are reported to be associated with OSA which increased the burden of this malady on patients. Associated with OSA are also ailments of cardiovascular diseases, obesity, hypertension, dyslipidemia, insulin resistance and diabetes. Cardiovascular diseases are the most prevalent co-morbidity among OSA subjects. OSA patients reportedly suffer from myocardial infarction caused by brain natriuretic peptide (BNP) released by cardiac ventricles in response to volume and pressure overload due to apnea[2,21,22]. Therefore, OSA holistically affects patients overall nervous system (including the autonomic and peripheral nervous systems).

Mechanism

The precise mechanism responsible for cognitive and psychological consequences is still unknown. The principal mechanism has been attributed to recurrent collapse of pharyngeal airway during sleep, causing intermittent blood-gas disturbance (hypercapnia and hypoxemia) and surges of sympathetic activation[11]. Owing to the correlation of plasma concentration of BNP with severity of OSA, preventing myocardial infarction in such patients by monitoring the symptoms of apnea could be possible. One proposed mechanism outlines the adverse effects on prefrontal complex (the area of brain responsible for executive functions, being affected by intermittent hypoxia, since it is metabolically active. As a result, several metabolic disorders have also been manifested in OSA patients[23]. The chronic repeated hypoxia from OSA could also lead to peripheral neuropathy, which has not been investigated yet.

Therefore, the present study was designed to investigate the effects of OSA on different mental, physical and nervous disorders which are manifested in such patients. This study would not only benefit in ascertaining the causes of OSA through assessment of higher mental functions of autonomic and peripheral nervous systems but also in the development of algorithm for estimation of degree of damage to the nervous system with severity of OSA.

OBJECTIVES

The present study was undertaken with the following specific objectives.

- To investigate the functioning of nervous system viz., higher mental function, peripheral nervous system and autonomic nervous system in OSA patients.

- For Estimation of sensory and motor nerve conduction velocities in normal patients and compare with OSA patients
- To assess the plasma BNP levels and its correlation with severity of disturbance in respiration during sleep.
- To assess and compare the effects of OSA on higher mental functions, nerve conduction velocities, autonomic functions, changes in these attributes with the severity among patients with OSA versus normal individuals
- For ascertaining whether effect on higher mental functions, nerve conduction velocities, autonomic functions could be employed as a prognostic marker for early detection of OSA.
- For estimation of plasma BNP levels in OSA patients.
- For Development of an algorithm for early detection of the syndrome in the patients.

METHODS

Sample Size

A total of 1365 consecutive participants participated in this study at the Department of Pulmonary Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana State, India for suspected sleep disordered breathing (SDB) between October 2012 and February 2016. In this cohort, 1140 participants were deemed ineligible, as they were not appropriate as per the inclusion criteria. Therefore, 225 patients were considered in the study along with 75 control subjects, who were healthy individuals. The study group had an AHI ≥5 per hour of sleep while the control group had AHI <5 per hour of sleep. The cohort was diagnosed by an experienced pulmonologist for the symptoms of snoring and daytime somnolence.

Inclusion criteria

Patients who met the following inclusion criteria were selected in this study.

- Adults (21 - 65 years) having symptoms of sleep apnea (Loud snoring, witnessed apneas or history of OSA based on laboratory PSG within three months of screening).
- Patients not using continuous positive airway pressure (CPAP) therapy, oral appliances or any other treatment for OSA.

Exclusion criteria

Patients meeting any of the following criteria were excluded from the study.

- History of treatment for OSA, diabetes, other disorders such as Parkinson's disease which are known to affect peripheral neuropathy which cannot be stopped safely for 48 hrs, no peripheral neuropathy (B_{12}, thyroid stimulating hormone, serum protein electrophoresis), patients unable to stop hypertensive medicine for 48 h, inability to cooperate with testing/ undergo testing, smokers, pregnant and lactating females.
- Not willing to sign informed consent form

Regulatory Approval

- The study protocol was approved by the institutional ethics committee and informed consent was obtained from the participants by the modified questionnaire by trained professionals before overnight polysomnography.

Study Variables/Outcomes

Variables

These data included documentation of age, gender, weight, height, BMI, waist and neck circumference, and clinical data such as history of apnea, insomnia, dyslipidemia, hypertension, and coronary heart disease. These data provided a basis of classification of patients besides the apnea-hyponea index (AHI), and a means to correlate OSA with associated physical and clinical symptoms. The study protocol was approved by the institutional ethics committee and informed consent was obtained from the participants by the modified questionnaire by trained professionals before overnight polysomnography. These results were verified by the physician before the test. The data were recorded in accordance with the reported method[24]. The patients' age, height and weight, body mass index (BMI), daytime sleepiness (The Epworth sleepiness scale) and self-reported habitual snoring (by spouse/ attendee with the patient).

Outcomes

Polysomnography

All participants underwent overnight polysomnography (PSG) in sleep laboratory of Owaisi Hospital and Research Centre, Hyderabad, Telangana, India under the supervision of trained personnel. Standard protocol for the study was followed and was in accordance with the

literature. Arousal and stages of sleep were ascertained employing standard experimental criteria in accordance with literature[25]. Based on the severity of apnea, patients were categorized into mild, moderate and severe groups, prior to inclusion into the study. The control subjects were those without any disturbance in breathing during sleep. For homogenous experimental design, the patient population of each category was kept the same, along with number of control (healthy) individuals. Philips' Alice 5 computerized system product number 1043941 was employed to analyze the PSG results.

Cognitive function tests

The cognitive function tests consisted of mini-mental mental state examination and by employing the depression questionnaire (Using Zung self report depression scale). Mini-mental mental state examination aimed at measuring the degree of alertness and cognition among OSA subjects' vis-à-vis control subjects using the attributes such as language, memory and recall, and calculation skills. The depression questionnaire scaled the depression level of the subjects on the basis of scores such as scores lower than 50 indicating no depression, 50-59 mild depression, 60 and higher showing moderate to higher depression. The protocol for these studies was in accordance with literature[26,27].

Nerve conduction studies

The nerve conduction studies for the patient population and the control group was conducted on the left leg of the patients and the control group. ALERON 201, RMS India was employed for this work. The research aimed at ascertaining attributes of motor conduction, conduction velocity, muscle action potential, nerve action potential using standard procedures which have been reported previously[28].

Autonomic function test

The autonomic function tests were performed to determine the changes in responses pertaining to attributes of heart to the syndrome on the basis of valsalva maneuver, deep breathing, blood pressure and blood pressure response to handgrip. These tests would provide insight into the changes in various functions of heart and its behavior in the patient population (On the basis of severity of the syndrome) and the control group. The investigation would be carried out in accordance with literature reports[29,30].

Heart rate variability test

The present research also envisages working the variabilities in heart rate of the cohort under study, by measuring values of mean, standard deviation, square root of mean squared difference for R-R intervals, using polyrite-D (Recorders and medicare systems, Chandigarh, India. The study protocol adapted the methods reported by previous study[31].

Measurement of brain natriuretic peptide (BNP) levels in the cohort

In order to further assess the physical state of the population under study, BNP levels in the blood were measured for patients and the control group, using Triage meter plus device (Biosite Diagnostics, San Diego, CA, USA), immediately after blood collection. The examination was conducted between 8-10 AM, using fluorescent immunoassay. The quantity (%) of blood BNP was correlated to its concentration, for comparative analysis between patient and control group. The assay was carried out as per the method reported in the literature[32].

Algorithm for OSA diagnosis

Based on the clinical findings from this study, an algorithm would be developed to assess the severity of the syndrome based on diagnostic symptoms of the patients. This would aid early detection of the syndrome allowing suitable intervention or measures to take effect.

RESULTS & DISCUSSION

Overall, patients in the OSA cohort were older compared to those in the control cohort (Mean age: 56.0 years vs. 53.0 years) and had higher proportion of males than females (79:11) (Table 1). The BMI value of the patient group was significantly higher than control group, suggestion role of high BMI in conceiving of OSA. Also, behavioral parameters such as alcohol intake, hypertension and habitual snoring were found to be significantly different in the two groups, again with significant difference. A significantly high lipid content in patients group over control group further attested to the occurrence of the syndrome in individuals with higher lipids in blood. Further, high BMI was well correlated with higher lipids in blood of patient group ($r = 0.90$), strongly indicative of a relation between BMI values, lipid content in blood and risk of conceiving the syndrome.

Table 1: Baseline demographic and clinical characteristics of OSA patients and controls

Characteristic	Patient (n=225)	Controls (n=75)	Level of significance
Age (21 - 65 years)	56 ±11	53 ±8	p = 0.000
Gender (Male : female)	79 : 11	71 : 29	NA
Body mass index (BMI)	36 ±6	23 ±4	p = 0.000
Alcohol intake (%)	12 ±3	6 ±2	p = 0.000
Hypertension (%)	86 ±8	31 ±4	p = 0.000
Hyperlipidemia (%)	31 ±5	23 ±3	p = 0.000
Habitual snoring (%)	92 ±10	43 ±8	p = 0.000

NA: not applicable

Significant difference among means was considered at p ≤0.05.

Overnight polysomnography of patients and control group

The overnight polysomnography values indicated distinct differences among the parameters of the analysis depending upon the category of the patient (i.e., mild, moderate and severe) (Table 2). From the analysis it was quite evident that patients with severe OSA required maximum time to go to sleep. The patient group required significantly higher time to achieve rapid eye movement (REM) sleep stage, indicative of intermissions. Accordingly, during the entire sleep time, the REM sage was comparatively lower for OSA patients than the control group. The patient group had comparatively lower sleep efficiency than the control group, along with higher arousal index and lower oxygen in blood both when asleep and upon waking.

Furthermore, oxygen saturation in blood during both REM and NREM sleep stages clearly indicated lower oxygen in patient cohort than the control group. Even among OSA patients, there is a strong indication of differences in the values of PSG indicative of differences in the sleep patterns and efficiency, depending upon the stage of the syndrome in the individual (Table 2). These findings strongly indicate substantial loss of nocturnal sleep in OSA patients which leads to commonly reported daytime somnolence, lack of alertness, headache and other associated sleep related morbidities.

Table 2: Changes in polysomnographic parameters in the study groups

Characteristic	OSA Patient type				Level of significance
	Mild (n=75)	Moderate (n=75)	Severe (n=75)	Control (n=75)	
Sleep onset	12.38 ±7.40	18.50 ±10.43	20.05 ±12.40	4.22 ±3.81	p = 0.000
REM onset	152.60 ±48.42	172.22 ±58.45	184.29 ±61.62	7.52 ±64.15	p = 0.000
Sleep efficiency (%)	63.85 ±3.72	73.82 ±4.93	85.87 ±6.19	90.56 ±7.44	p = 0.000
REM stage (%)	12.45 ±5.45	14.84 ±8.21	17.43 ±8.96	20.71 ±9.04	p = 0.000
Apnea-hyponea index	26.20 ±13.12	31.20 ±16.32	39.90 ±18.32	1.25 ±0.7	p = 0.000
Apnea index	6.63 ±3.14	8.83 ±4.24	12.83 ±6.24	0.77 ±0.22	p = 0.000
Mean arousal index	14.45 ±2.52	17.45 ±3.11	21.45 ±5.53	4.63 ±1.43	p = 0.000
Lowest level of oxygen saturation (%)	86.10 ±4.32	81.30 ±4.45	67.25 ±3.81	92.45 ±5.10	p = 0.000
Saturation during wake	96.22 ±3.64	96.10 ±3.82	92.15 ±2.22	97.53 ±4.32	p = 0.000
Saturation during REM sleep	93.28 ±2.68	91.9 ±3.89	81.94 ±2.10	96.64 ±3.10	p = 0.000
Saturation during NREM sleep	94.24 ±3.60	92.55 ±3.30	85.13 ±2.20	96.91 ±3.90	p = 0.000

Participants were in the age group of 21 – 75 years, with equal number of individuals in each category of patients (mild, moderate and severe) and control individuals (n=75 in each group).

Significant difference among means was considered at p ≤0.05.

Cognitive function tests of patients and control group

The cognitive function tests revealed that in comparison to the control group, OSA patients had significantly impaired cognition and their scores were significantly lower than the control group. The participants were unable to recognize the alphabets and had short memory, difficulty in carrying out simple calculations. These results strongly indicate lack of sleep affecting the overall alertness, cognition, and verbal and non verbal ability and memory.

Furthermore, OSA patients had significantly higher ($p \leq 0.05$) depression on Zung's self reporting depression scale. Insomnia, poor daily routine performance possibly led to increase in depression in OSA subjects. The patients with severe OSA recorded a score >60, moderate 55 - 60 and mild 50 - 55. The control subjects on an average had a score <50, indicative of no depression. The correlation between cognitive impairment and depression was found to be high ($r = 0.94$), indicative of a co-morbid cumulative effect of OSA on overall cognition, intelligence, memory and depression. These findings also suggest societal difficulties of OSA patients, especially those with moderate to severe OSA.

Nerve conduction study in patient and control group

The nerve conduction study revealed a significant decrease in OSA patients. Motor action, muscle action potential and nerve action potential was significantly lower ($p \leq 0.05$) than that of the control group of healthy patients. OSA patients had significantly higher distal latency and lower measured velocity ($p \leq 0.05$), indicative of lower impulse of nerve conduction owing to the syndrome. The sural sensory conduction velocity and sural sensory nerve action potential were also comparatively lower in OSA patients than the control group; with the least conduction in the OSA patients in the severe category.

Autonomic function testing of the cohort

The autonomic function tests showed clear effect of OSA on the heart and its functions. The values established on negative effects of OSA on breathing of the OSA patients in comparison with the control group. The subjects had difficulty in breathing and the heart rate was significantly higher than that of the normal subjects, during deep breathing, standing up and valsalva manoeuvre, indicative of detrimental effect of OSA on heart. The blood pressure of the OSA patients in general was relatively higher than the control group, both during the postural response and in handgrip test. Measurement of heart rate during handgrip and Valsalva manoeuvre challenges revealed significant heart rate differences among OSA patients and between OSA and control group ($p \leq 0.05$). The 30 : 15 ratio was significantly higher in the control group than in the patient population, indicating cardiovascular issues in the latter population ($p \leq 0.05$). AHI was well related to valsalva and 30 : 15 ratios, higher the severity higher the value, with concomitant higher health hazard.

Analysis of heart rate variability in the subjects

The examination of heart rate variability in the population marked a strong relationship between OSA and heart rate variability. The 24 hour Hotler scale readings also corroborated this fact and revealed that RR intervals in the patient group were significantly shorter than in the control group. Even within the patients group, the RR interval for the patients with severe OSA was the shortest. The SDNN, SDANN, RMSSD, VLF, LF, HF values were significantly higher in the control group than in the patient population. This finding indicates that the OSA patients had lower RR intervals, inducing a pressure on the heart for pumping of blood resulting in difficulty in breathing.

Analysis of plasma BNP levels

The plasma BNP in OSA patients was significantly higher ($p \leq 0.05$) than control subjects. Among OSA patients also, highest BNP was observed in patients in the sever category with values in the range of 184 ±15 pg/mL while that for the moderate patients was 130 ±12 pg/mL, mild was 82 ±10 pg/mL, while control subjects had BNP at 6 ±3 pg/mL.

Algorithm for diagnosis of OSA syndrome

A first of its kind of algorithm was developed for sequential assessment of the symptoms and the tests data for a clinician to ascertain the characteristic of the disease in the patient and its severity. This algorithm is based on the findings made in this study in various experiments. This algorithm would possibly aid early detection of the syndrome and alleviation of the patients from this condition.

CONCLUSIONS

OSA is a serious sleep disorder that affects millions of individuals across the globe. The present study which included South Indian patients specifically residing in and around Hyderabad, Telangana State, India, highlights the effects of OSA in higher mental functions and in heart diseases. The study encompassed a categorized patient population comprising of individuals with mild, moderate and severe OSA based on AHI scores. Among the enrolled individuals, those with severe OSA were affected in all faculties, namely, cognitive abilities and health attributes; and had high BNP levels in their blood. In aggregate, OSA patients can be alleviated from the syndrome, if accurate diagnosis is made on time. For achieving this, this study developed an algorithm which would aid the clinicians in early detection of OSA symptoms and mitigate the prognosis of the syndrome.

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