Original Research Article

The proportion of cognitive impairment in patients with obstructive sleep apnoea

Nagabhushan D[1], A K Badrinath[2*], Sujitha Gurram[3], K Vinoth[4]

{[1]Post Graduate, [2]Professor, Department of General Medicine} {[4]Assistant Professor, Department of Psychiatry}
Sri Manakula Vinayagar Medical College and Hospital, Kalitheerthalkuppam, Puducherry, INDIA.
[3]Post Graduate, Department of Psychiatry, Mamata Medical College, Khammam, Telangana, INDIA.
Email: akbsts@yahoo.co.in

Abstract

Forty one patients with obstructive sleep apnoea had neuropsychologic testing prior to nocturnal sleep study in a sleep disorders clinic. The patients who had obstructive sleep apnoea with hypoxemia had more severe cognitive impairment than normal control subjects. Obstructive sleep apnoea had significantly poorer cognitive functioning on four of eight tests ($p<0.005$) In addition, the patients who had obstructive sleep apnoea had mean performance scores in the impaired range on measures of attention, concentration, complex problem-solving, and short-term recall of verbal and spatial information. In contrast, the normal healthy subjects had no mean performance score in the impaired range. The degree obstructive sleep apnoea during sleep and wakefulness significantly correlated with the degree of overall cognitive impairment t; however, measures of sleep fragmentation did not significantly correlate with overall cognitive impairment in patients with obstructive sleep apnoea. We conclude that patients who have obstructive sleep apnoea have cognitive impairment which is more severe than those normal healthy subjects.

Key Words: Obstructive sleep apnea; cognitive impairment; Mini mental scale.

[*]**Address for Correspondence:**
Dr. A.K. Badrinath, Professor, Department of General Medicine, Sri Manakula Vinayagar Medical College and Hospital, Kalitheerthalkuppam, Puducherry, INDIA.
Email: akbsts@yahoo.co.in

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INTRODUCTION

Obstructive sleep apnoea (OSA) is a common sleep disorder affecting about 2–4% of the adult population, with the highest prevalence reported among middle-aged men[1]. OSA is a very common disorder among obese individuals. OSA is characterized by repetitive episodes of complete or partial collapse of the upper airway (mainly the oropharyngeal tract) during sleep, by temporarily blocking the inflow of air[2]. These episodes lead to intermittent hypoxemia and fragmentation of sleep, which can give rise to variable cognitive impairments in OSA[3]. OSA is characterized by periodic complete or partial cessation of breathing while sleeping. These recurrent events of breathing result in fragmented sleep and recurrent hypoxemia (reductions in hemoglobin oxygen levels)[4]. It has been documented that OSA causes excessive daytime sleepiness, mood changes and dysfunctions in several cognitive domains[5,6]. However, there are different opinions on which cognitive abilities are affected mostly by OSA and on the exact nature of cognitive decline. The comparison of the findings of research studies is difficult because of differences in severity of disease, criteria that are used to assess the severity of syndromes and different sample sizes[7]. Other variables such as the sensitivity of neuropsychological battery chosen[7] and different group ages are also confounding factors[8]. OSA is an increasingly common disorder in India with very high prevalence rate of 7.5%, associated with metabolic syndrome, upper body obesity with significant morbidity and mortality[9]. Patients with OSA show deficits across a wide range of cognitive functions including attention, memory, psychomotor speed and visuospatial abilities, constructional abilities, executive functions and language abilities[10,11]. The

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etiology of OSA is multifactorial, consisting of a complex interplay between anatomic, neuromuscular factors and an underlying genetic predisposition toward the disease. Cognitive changes in OSAS can be multiple and varied, including cognitive processing, memory, attention deficit, and executive functions[7]. Cognition is defined as all mental processes involved in acquisition, processing, storage and retrieval of information.[12]. Studies conducted previously to assess cognitive functions in OSA have shown variable results[13]. Attention and memory have been consistently shown to be affected in OSA. Hence, it becomes very important to assess effect of OSA on various cognitive domains in the Indian population. The present study was conducted to study the proportion of cognitive impairment in patients with obstructive sleep apnea.

MATERIALS AND METHODS

The present cross sectional study was conducted among the patients coming to the OPD and admitted at Department of General Medicine**,** Sri Manakula Vinayagar Medical College and Hospital, Kalitheerthalkuppam, with symptoms of obstructive sleep apnea. This study was carried with the prior approval from the Institutional Ethics Committee. Mini mental scale, a 30-point questionnaire is used in the present study to assess the prevalence of cognitive impairment in patients with obstructive sleep apnea.[14] A total number of 41 individuals with recently diagnosed cases of OSA were selected as study group. Whereas, forty one healthy age, sex and education matched individuals in the age group of 18–59 years were selected as control group. All cases and controls were selected according to the inclusion/exclusion criteria. Cases and controls were explained in detail about the procedure to be performed in their vernacular language to their satisfaction. Written informed consent was obtained. Inclusion criteria for cases were as follows: (i) Apnea– hypopnea index > 5; (ii) ESS > 10. Inclusion criteria in controls to rule out OSA were as follows: (i) ESS < 10; (ii) Body mass index (BMI) < 30 kg/sq. m; (iii) Neck circumference < 40 cm; (iv) No history of snoring and tiredness; (v) No history of partners observation of apnea, choking and gasping during sleep; (vi) Systolic BP < 120 mm Hg, Diastolic BP < 80 mm Hg.

Statistical Analysis: Intergroup differences between OSA subjects and normal control were assessed using chi-square test and independent t-test. The generalized linear model for repeated measure analysis of variance (ANOVA) test adjusted for age and education years was used to analyze cognitive function measures. The statistical significance criterion was defined as a p value < 0.05 for two-tailed test. The level of significance for comparison of multiple neuropsychological tests was set at $p < 0.0063$ (= 0.05/8) according to Bonferroni correction. SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

RESULT

Baseline Clinical Characteristics between OSA subjects and normal control: Table 1 shows OSA subjects (n = 13) were older (t = 2.787, p = 0.008) and had lower education years (t = -2.419, p = 0.020) than normal control subjects (n = 28). The present also evaluated the parameters like Total sleep time, present results have clearly showed that, the total sleep time in control was 352 (43.8) whereas, the OSA subjects have showed 375 (54.8) which was not statistically no difference difference (p=0.389). The observations from Mean global AHI showed that the normal subjects have shown 51.7 (18.0) and OSA subjects have shown 46.8 (9.5) which is statistically insignificant (p=0.267). ESS score showed no difference between groups at baseline (t = 0.548, p = 0.588). After treatment, ESS score within OSA groups showed no significant difference, as compared to normal control (t = 0.482, p = 0.421).

Table 1: Baseline clinical characteristics between OSA subjects and normal control

	Normal control	OSA subjects	p-value
Age (years)	65.1 (4.5)	69.6 (5.5)	0.008*
Gender (male)	20 (71.4%)	8 (61.5%)	0.818
Education (years)	14.8 (4.0)	11.2 (5.5)	0.020*
Total sleep time (min)	352 (43.8)	375 (54.8)	0.389
Mean global AHI (events/hr)	51.7 (18.0)	46.8 (9.5)	0.267
Epworth scale score	8.9 (6.0)	10.0 (4.5)	0.588
BMI (kg/m^2)	25.8 (3.6)	24.3 (2.8)	0.203

Data are presented as mean (standard deviation) for continuous variables and number (%) for categorical variables. *p < 0.05, t-test or chi square test.AHI: apnea-hypopnea index, BMI: body mass index, OSA: obstructive sleep apnea.

Demographic and Clinical Characteristics: A total of 82 subjects participated in the study. Participants were divided two groups, OSA groups (n = 41) and normal healthy control (n = 41) (Table 2). Both groups were age and gender matched. Table 2 showed clinical characteristics and neuropsychological parameters of the study subjects. In the present study, neurocognitive function tests showed no significant differences between the normal and OSA subjects (p = 0.533**).** OSA groups had a decline of memory performance (DSF; t = -3.647, p = 0.001, DSB; t = -7.925, p < 0.001) with Bonferroni correction. The significant decline in the memory was seen in the DSF and DSB when compare with other parameters.

Table 2: Clinical characteristics and neuropsychological parameters in OSA subjects and normal control subjects

	Normal control	OSA subjects	p-value
Age (years)	66.6 (5.1)	66.5 (5.2)	0.949
Gender (male)	28 (68.3%)	28 (68.3%)	1.000
Education (years)	13.4 (4.3)	13.7 (4.8)	0.810
BMI (kg/m^2)	352 (43.8)	25.3 (3.4)	0.002*
AHI (events/hr)	4.8 (3.9)	50.1 (15.9)	< 0.001*
Neurocognitive function tests			
MMSE-KC	27.4 (1.7)	27.0 (3.3)	0.533
Memory			
DSF	8.1 (2.3)	6.5 (1.3)	0.001
DSB	6.7 (1.3)	4.1 (1.6)	< 0.001
WLR	5.7 (1.7)	5.9 (2.2)	0.569
CR	7.1 (2.5)	7.2 (2.7)	0.865

Data are presented as mean (standard deviation) for continuous variables and number (%) for categorical variables. *p < 0.05, independent t-test or chi square test. BMI: body mass index, AHI: apnea-hypopnea index, MMSE-KC: mini-mental state examination packet, DSF: digit span forward, DSB: digit span backward, WLR: word list recall, CR: constructional recall, OSA: obstructive sleep apnea. The OSA subjects had greater cognitive impairment than those normal control subjects. The OSA subjects had significantly poorer scores on four of eight tests than the normal control subjects (Table 3). In addition, the OSA subjects had mean scores within the cognitively impaired range on four of eight neuropsychologic measures when adjusted for their mean age and education. This number of mean test scores in the brain-impaired range was significantly greater ($p<0.05$) than that of the normal control subjects, which had no mean score in the impaired range. Cognitive functions in the impaired range for the OSA subjects with obstructive sleep apnea were attention and concentration, complex problem solving, short-term recall of verbal information (delay stories), and short-term recall of visuospatial information (delay designs).

Table 3: Cognitive Function Testing in OSA subjects and normal control subjects

Cognitive Function	Normal control	OSA subjects
General intellectual	20±1	18±3
Attention and concentration	90±7	126±20
Vigilance and eye/hand coordination	0.70±0.02	0.86±0.10
Rapid, complex problem-solving	108±6	89±12
Memory		
Immediate recall/verbal	12±1	9±1
Delay recall/verbal	9±1	6±1
Immediate recall/visuospatial	14±1	10±2
Delay recall/visuospatial	10±2	6±2

Values are means± SE.

Participants' raw scores were converted to t scores for each domain of cognitive function (speed of information processing; verbal, learning, memory, executive function; and working memory) and t scores were calculated. All t scores were adjusted for gender, age, education, during calculations. In a healthy population, a neurocognitive deficit (t score, 640) would be expected in 15% of participants. In our sample, 31% were impaired, showing a higher rate of impairment in our group. Table 4 shows average t scores and percent impairment for each domain.

Table 4: Mean (standard deviation) t scores and percent of participants classified as impaired. Higher t score indicated better performance

	t score	% Impaired
Processing speed	48.2 (8.4)	16.3
Verbal fluency	48.6 (10.5)	20.4
Learning	44.2 (9.5)	36.7
Memory	45.9 (9.1)	24.5
Executive function	48.5 (9.5)	14.3
Working memory	50.1 (9.6)	14.3

DISCUSSION

The aim of this study was to assess cognitive function in moderate to severe OSA subjects. In comparison of characteristics, normal control presented older age and lower levels of education. At baseline, mild to severe OSA patients reported higher deficit of attention and working memory than normal healthy controls. Despite several inconsistent findings on the effect of OSA on memory functioning, delayed recall memory might be moderately impaired,6 and the domain of attention or executive functioning is substantially affected by OSA.[15] Previously reported study decline of delayed recall and executive function in 42 OSA patients, as compared to 21 normal healthy subjects, indicating that cognition impairments are associated with severe OSA in elderly adults.[16,17] However, present samples had higher education years and were younger in age. The cause of cognitive impairment in OSA patients is under discussion. Recent studies suggest that the decline of executive functions and visuospatial function might be related to severity of hypoxemia; whereas, the attention and memory deficit might be due to excessive daytime sleepiness resulting from sleep fragmentation.[18] Although correlation analysis in this study was not done among daytime somnolence, measures of nocturnal hypoxemia and results of cognitions, frequent sleep fragmentation might be more effective on attention functioning in OSA groups as comparison of AHI. Two previous studies have described cognitive impairment in patients with sleep apnea[19,20] One study reported significant relationships between cognitive performance and sleep-related respiratory disturbances in 41 elderly men.[19] Impairment of visuospacial reasoning, memory, and psychomotor speed were positively correlated with the numbers of disturbed breathing events during sleep. The second study

demonstrated cognitive impairment in 76 percent of patients with severe sleep apnea.[20] These patients had deficits in thinking, perception, memory, communication, and the ability to learn new information. The lack of significant linear correlation between variables reflecting sleep fragmentation and overall cognitive impairment does not exclude a role of sleep fragmentation in producing cognitive impairment. Both groups have marked sleep fragmentation, and a threshold effect could be present[21] Although this study shows statistically significant correlations between overall cognitive impairment and measures of both groups, no direct role of hypoxemia as a cause of cognitive dysfunction is proven. Further studies using either daytime or nocturnal oxygen supplementation may help to define the relative importance of awake and sleeping hypoxemia in maintaining cognitive functioning in patients with sleep apnea. In this context, the finding that cortisol levels are associated with neurocognitive function in patients with OSA may be related to the possible role of cortisol in hippocampal volume loss observed in the neuroimaging studies of individuals with OSA[22]. Interestingly, some studies found that it was nighttime levels that were important for neurocognitive function, rather than 24-h or daytime levels of cortisol. This finding in a sleep disorder setting is worthy of attention. The study of memory function has revealed the importance of sleep and nighttime HPA activity. Plihal and Born[23] experimentally manipulated cortisol levels during sleep and showed that elevated cortisol levels impaired declarative memory after only one single night. Given the evidence linking long-term elevated cortisol levels to atrophy in hippocampi and cerebral cortex, the examination of resting or nighttime cortisol levels on cognition is particularly informative[24-26]. The negative impact of cortisol on cognitive performance has been linked to elevated nightly nadir levels of this hormone[27]. Born and Wagner[28] showed that declarative memories, the formation of which involves the hippocampus, benefit from the inhibition of endogenous cortisol during early sleep, though an increased level of endogenous cortisol was associated with reduced emotional memory retention. The authors proposed that the effect of circulating cortisol on the glucocorticoid receptors in the hippocampus impacts memory formation during sleep[28]. Our study examined the associations between OSA, cognitive function. In addition to the expected finding that increasing severity of OSA was associated with reductions in neurocognitive functioning. Importantly, even after controlling for potential confounding factors, night time sleep duration were a significant predictor of neurocognitive functioning, though OSA severity was not related. Several specific domains of neurocognitive functioning were particularly related to nighttime sleep, with night time sleep duration accounting for up to 16% of the variance in the domains of learning, memory, and working memory. The finding that nighttime sleep duration was a significant predictor of neurocognitive function over and above indices of OSA severity is important, as it allows speculation that perhaps it not apnea per say, but rather the physiologic responses to apnea (in particular HPA activity) that provide the proximal association with neurocognitive impairment.

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