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Pattern & correlates of neurocognitive dysfunction in Asian Indian adults with severe obstructive sleep apnoea

Hanish Sharma, Surendra K. Sharma, Tamilarasu Kadhiravan, Manju Mehta*, Vishnubhatla Sreenivas**, Vinay Gulati & Sanjeev Sinha

*Departments of Medicine, *Psychiatry & **Biostatistics, All India Institute of Medical Sciences New Delhi, India*

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***Background & objectives*: No published data are available on neurocognitive dysfunction in Asian Indians with obstructive sleep apnoea (OSA). We therefore, studied the pattern and correlates of neurocognitive dysfunction in Indian adults with severe OSA.**

***Methods*: Fifty patients aged 25-65 yr with severe OSA (apnoea-hypopnoea index > 30) and 25 age, sex, and education level-matched normal controls were studied. Both groups were administered a standardized battery of neurocognitive tests.**

***Results*: Patients with severe OSA had significantly impaired performance on tests of alertness, working memory, response inhibition, problem solving, and executive function. However, the difference in executive function between the groups disappeared after adjusting for delayed information processing. The test scores did not correlate with apnoea-hypopnoea index, arousal index, or Epworth sleepiness score. However, the percentage of time spent at < 90 per cent oxygen saturation had a weak correlation with the number of stroop errors (Spearman's rho = 0.64; *P* = 0.033), number of trials required (rho = 0.05; *P* = 0.02), and perseverative errors on Wisconsin card sorting test (rho = 0.36; *P* = 0.02).**

***Interpretation & conclusions*: Our results suggested that delayed information processing rather than impaired abstract thinking was probably the cause of impaired performance on composite tests of neurocognitive function in patients with severe OSA.**

Key words Executive function - Indians - neurocognitive function - obstructive sleep apnoea - working memory

Obstructive sleep apnoea (OSA) is characterized by recurrent sleep disruption and hypoxaemia due to collapse of the upper airway during sleep. It is known to be associated with various cognitive defects since its first description. Cognition comprises of the ability to register, remember, develop abstract concepts, plan, decide and foresee. Cognitive areas most frequently reported to be affected by OSA are general intelligence, attention, memory, executive function, and motor functioning[1]. Subjects with OSA suffer from fragmented sleep due to recurrent effort related arousals (to overcome airway obstruction) and nocturnal hypoxaemia due to airway obstruction with consequent hypoventilation. These two factors are differentially related to the neurocognitive deficits observed in OSA[2]. Recent population-based studies have found the prevalence of OSA among Indians to be comparable to the Western populations[3,4]. However,

no data are available on the cognitive impairment in Indian subjects with OSA. Studies from Western populations had heterogenous subjects and used varied psychometric tests focused on different cognitive domains, making the results difficult to aggregate and analyse[5,6]. There are only a few studies focusing on impairment of "executive" or so-called "higher mental" functions in patients with OSA with differing conclusions[7-11]. We hypothesised that patients with OSA suffer from excessive sleepiness and slowed information processing, without any independent impairment in higher mental or 'executive functions'. A systematic study adjusting for the pervasive effects of slowed information processing on any sort of cognitive assessment is essential for proper profiling of cognitive impairment. Hence, we sought to study the various domains of cognitive function in a homogenous population of Asian Indian patients with OSA, to gain insight into the profile and correlates of cognitive impairment.

Material & Methods

Study population: The present study was conducted over a two-year period from November 2005 to November 2007. The study subjects (cases) were screened and consecutively selected from middle-aged adults (25-65 yr) of either gender referred for overnight polysomnographic study (PSG) to the Sleep Laboratory of All India Institute of Medical Sciences, New Delhi, India. Twenty five subjects from the community (as part of a community-based prevalence study[3] who were group matched for age, sex, and education-level and had a normal PSG were recruited as controls.

Screening: All subjects underwent peripheral venous blood sampling for a complete haemogram, renal function tests, and thyroid profile. Subjects suffering from any neurological or psychiatric illness, hypothyroidism, chronic alcohol use (>40 g/wk), drug abuse, chronic renal failure, history of major head injury, history of learning difficulty or those using antiepileptic, antipsychotic or antidepressant medications were excluded after a thorough history and chart review. Written informed consent was obtained from all study subjects before participation. The protocol of the study was reviewed and approved by the Institute Ethics Committee.

Polysomnography: Polysomnography studies were conducted on a Rembrandt 7.3 version PSG machine (Medcare Technologies, USA) according to methods described previously[12]. Apnoea and hypopnoea were scored as recommended by the American Academy of Sleep Medicine[13].

Arousals were scored as per standard guidelines[14]. An abnormal breathing event during objectively measured sleep was defined according to the common clinical criteria of either a complete cessation of airflow lasting 10 sec (apnoea) or a discernible reduction in airflow accompanied by a decrease of 4 per cent in oxyhaemoglobin saturation (hypopnoea).The average number of episodes of apnoea and hypopnoea per hour of sleep, the apnoea hypopnoea index (AHI) was calculated. The Epworth sleepiness scale (ESS) was used to score sleepiness and a score of more than 10 was considered to be suggestive of excessive daytime somnolence (EDS). OSA was defined as an AHI of ≥ 5. All the cases included in the study had an AHI>30 considered as severe OSA. Subjects diagnosed with co-existing sleep disorders were excluded from the study.

Neurocognitive testing: Both cases and controls underwent neurocognitive testing using a standardized battery of tests (Table I). The tests included in the battery were carefully selected with low inter-observer variability and compared with available normative data for Indian population[5,15]. Previously validated indigenised versions of the tests were used[16]. These tests can be administered in a limited time duration (Table I).

None of the cases were already on CPAP (continuous positive airway pressure) treatment. In order to eliminate any possible transient improvement in cognitive function brought about by the use of CPAP for titration purposes in split night studies, all subjects underwent neurocognitive testing after an interval of at least three days after the PSG.

Statistical analysis: Data were collected using a predesigned data collection instrument. Statistical analysis was performed using a statistical software package (SPSS 11 for Windows, SPSS Inc, Chicago, IL). After assessing for approximate normal distribution, continuous variables were summarized as mean ± standard deviation or median (interquartile range), and all categorical variables were expressed as numbers with proportions. Between-group comparisons were done by independent samples t-test for continuous variables with a normal distribution and Mann-Whitney U test when the distribution was skewed. Categorical variables were compared using the chi-square test. The results of the digit backwards recall were adjusted for performance on the digit forwards and compared by two-way ANOVA. Correlation of test

Table I. Neurocognitive test battery used in the present study

Test	Description	Cognitive domain assessed	Scoring
WAIS- R	Assessment of general aptitude, comprehension, and logic	General intellectual functioning	Each response numerically scored
Digit symbol substitution	Component of WAIS-R	Concentration/psychomotor slowing	Number of correct responses
Digit span	Recalling digits as told and in inverse order	*Forward recall*: working memory (six items) *Backward recall*: working memory and "executive function" (eight items)	Scored as 2,1 or 0 depending on whether both items, single or none of the articles in the set are recalled
Logical short stories	Immediate and delayed recall of a short story	Attention and long-term memory	Number of items recalled (total 21)
Porteus adult maze	Finding the way out of a test maze	Planning	Time taken in sec
Stroop test	*Reading*: names of various colours listed out *Interpretation*: reading out the same names, coloured incongruently	Response inhibition, mental flexibility	Time taken in sec Number of errors done
Wisconsin card sorting test	Sorting a group of cards as per varying sorting principles (colour, form, number) based on examiner's positive or negative feedback	Composite test of "executive function"	Number of trials, persevarative (inability to recognise set shifting) errors, correct responses, and sets completed

WAIS-R, Weschler's adult intelligence scale - revised (Indian adaptation)[16]

scores with polysomnographic variables was tested by Spearman's rank sum correlation. The actual scores of the Wisconsin card test were expressed as percentiles (based on normative data for Indians) and compared between cases and controls. All tests were two-sided, and a $P<0.05$ was considered statistically significant.

Results

A total of 514 subjects were referred for diagnostic PSG during the study period. Of these, 344 were in the age group of 25-55 yr and 95 of them had severe OSA (AHI > 30). These were screened and 50 cases and 25 controls were included for the assessment of neurocognitive impairment. The included subjects were similar in age and disease severity to the remaining subjects with OSA (Table II). The excluded cases were apparently less sleepy based on ESS and AHI, however, the difference was not significant. Forty five persons with severe OSA were excluded due to the presence of significant alcohol use in 36, hypothyroidism in 6, mental retardation in 1 and consent refusal in 2.

Patients with severe OSA took significantly more time in digit symbol substitution and finding the way out of a test maze (Table III). They also had comparatively low scores in digit forward recall, digit backward recall, stroop test and tests of logical memory. However, the difference in digit backwards scores was not significant ($P<0.08$) when adjusted for the score in digit forwards

Table II. Comparison of included and excluded cases and controls

Variable	Included cases (n=50)	Not included cases (n=45)	Controls (n=25)
Age (yr)	43 ± 7.5	40.6 ± 6.2	45.6 ± 6.2
Females	8 (16)	6 (13.3)	4 (16)
Education			
School level*,**	23 (46)	25 (55)	11 (44)
College level†	27 (54)	20 (44)	14 (56)
ESS	17.3 ± 3.1	13.6 ± 4.3	8.6 ± 1.3
AHI (events/h)	54.2 ± 7.1	42.6 ± 11.9	1.6 ± 0.9
Arousal (events/h)‡	33.2 ± 12.6	21.4 ± 5	3.4 ± 3
% REM sleep	11.2 ± 6.4	8.9 ± 4.5	17.2 ± 3.1
% Sleep time SO2 < 90	46.5 ± 16.5	48.9 ± 21.2	5.6 ± 3.2

ESS, Epworth sleepiness scale (maximum score=24); AHI, apnoea-hypopnoea index measured by polysomnography
*Up to 10 yr of education; †more than 10 yr of education; ‡number of arousals identified by EEG averaged per hour, assessed during PSG
Numbers in parentheses are percentages

Table III. Scores of neurocognitive assessment of cases and controls

Variable	Cases (n=50)	Controls (n=25)	*P* value
Digit symbol time for completion (sec)*	112 ± 8.1	91 ± 3.2	0.03
Digit forwards score	11 (7-12)	11 (10-12)	0.06
Digit backwards score	9 (7-11)	12 (10-14)	0.003
Stroop effect†	134.2 ± 20	96.5 ± 12	0.020
Stroop errors	9 (6-11)	3 (2-5)	0.022
Porteus maze:time for completion (sec)	188 ± 46.2	112 ± 56.8	0.001
Logical memory (school-educated)			
Immediate recall	13 (12-15)	16 (15-18)	0.090
Delayed recall	11 (10-15)	16 (15-18)	0.090
Logical memory (college-educated)			
Logical memory immediate recall	15 (14-17)	18 (15-20)	0.031
Logical memory delayed recall	14 (13-15)	20 (18-20)	0.002

Data presented as mean±SD or median (inter-quartile range)
*Standardized for age, sex, education level- specific Indian normative data; †Extra time in seconds required for stroop interpretation compared to naming
College educated (>10 yr of education)
School educated (Up to 10 yr of education)

recall. This was done to adjust for the effects of slowed information processing (reflected in forward digit recall) in assessment of higher mental functions (reflected in digit backwards recall: which involves working memory and processing)[17]. Their performance in the stroop test was significantly impaired even when controlled for the effects of generalized slowing measured by the "stroop effect" (difference of stroop reading and interpretation). In the Wisconsin card sorting test patients with severe OSA required significantly more trials (P<0.02) to complete the task and committed more persevarative errors (Table IV).

No significant correlation was present between the test scores of cases with OSA (n=50) and AHI, arousal index, percentage sleep time spent at less than 90 per cent oxygen saturation (T90) and duration of rapid-eye movement (REM) sleep or the subjective sleepiness score (Table V). The T90 had a weak but significant correlation with the number of stroop errors (rho=0.64, P<0.03), number of trials required (r=0.05, P<0.02) and persevarative errors (r=0.36, P<0.02) (Wisconsin card sorting test).

Discussion

We found that patients with severe OSA have delayed information processing resulting in reduced short term memory. They may not have any independent deficit in higher "executive" function for example, in digit recall backwards versus forwards.

We excluded likely possible confounding causes for cognitive impairment, and employed a battery of neurocognitive tests that measured complementary cognitive domains with low inter-observer variation. To ensure homogeneity, all the cases studied had severe OSA. This may partly explain the lack of a distinct correlation between test performance and AHI.

Previously reported cognitive deficits in patients with OSA are attentional capacity deficits (reduced

Table IV. Results of the Wisconsin card sorting test in cases and controls

Variable	Cases (n=50)	Percentiles*	Controls (n=25)	Percentiles*	Norm	*P* value
No. of trials**	92.6 ± 17.5	75	85.3 ± 12.1	81	110 ± 21.1	0.02
No. of errors	24.7 ± 13.9	63	20.1 ± 9.4	75	40.25 ± 23.4	0.06
Percent errors	25.2 ± 10.4	66	18.4 ± 8.6	81	34 ± 16	0.04
Perseverative errors+	10.2 ± 5.4	66	15.6 ± 6.2	56	22.7 ± 15.8	0.02
Conceptual responses++	60.8 ± 5.3	60	65.4 ± 9.4	60	56.6 ± 14.9	0.30
Per cent conceptual responses	68.1 ± 13.6	70	77.8 ± 7.4	80	48.32 ± 17.05	0.09

All values are mean ± standard deviation; Norm = the normative values of the 50th percentile for the Indian population; *P* value between cases and controls; *The scores of the in terms of percentiles for normal Indian population; **Number of trials required to produce 6 sets of 10 correct responses (maximum 128 attempts); +The number of times perseverative errors are made that is the choice reflects a principle that was previously in operation but which has been changed in the current trial; ++Conceptual response is defined when the subject makes 3 consecutive correct responses

Table V. Correlations between test performance and polysomnographic measures

Test scores	ESS	AHI	Arousal index	Percentage time SpO2 < 90	Percentage REM sleep
Digit symbol (sec)	0.42 (0.522)	0.54 (0.120)	0.32 (0.472)	0.36 (0.684)	0.12 (0.841)
Stroop effect (sec)	0.38 (0.711)	0.33 (0.600)	0.16 (0.922)	0.56 (0.500)	0.08 (0.930)
Stroop errors	0.08 (0.966)	0.28 (0.645)	0.40 (0.504)	0.64 (0.033)	0.10 (0.800)
Porteus maze (sec)	0.48 (0.292)	0.51 (0.084)	0.44 (0.680)	0.26 (0.640)	0.06 (0.980)
Logical story : immediate recall	-0.34(0.720)	-0.42 (0.520)	-0.10 (0.820)	-0.14 (0.674)	0.06 (0.982)
Logical story: delayed recall	-0.29(0.650)	-0.36 (0.505)	-0.20 (0.663)	-0.42 (0.640)	-0.10 (0.880)

Data presented as Spearman's rho (*P* value)
REM, rapid eye movement sleep; ESS, Epworth sleepiness scale

information processing speed and short-term memory span), decreased vigilance, and simulated driving decrements[7,18-22]. The nature of the neurocognitive deficits found in OSA is still debatable[6,19]. The results of the present study corroborated, the known slowness of information processing manifest in tests like digit symbol substitution, decreased working memory as in recalling items from a logical story, problem solving as in finding the way out of a temporary test maze and mental flexibility or response inhibition as demonstrated in the stroop test.

The executive functions (*e.g.*, mental set shifting, updating of working memory and monitoring, and inhibition of dominant responses) are responsible for integrating perception and action. It is unclear whether the effects of reduced alertness on higher cognitive functioning were taken into account in a previous study in which executive dysfunction was correlated to prefrontal lobe damage caused by chronic, intermittent hypoxaemia[23]. We adjusted for the effects of decreased alertness for example in test of digit recall[17]. The results from our study suggested a significantly decreased score in backward digit span test, however, when these were adjusted for the performance on forward digit span the results were comparable with normal controls. This implies that patients with OSA may fail on a digit span backward test, because they already have difficulties in retaining the digits in working memory[24].

Patients with OSA exhibited significant impairment in response inhibition or mental flexibility as measured in the stroop test. This comprises two subparts: firstly involving simply naming the coloured words, followed by a more complex task of interpreting the incongruently coloured words (*e.g.* the word blue coloured in yellow). It was significantly impaired even after adjusting for the effects of generalized slowing by measuring the net "stroop effect" (difference of stroop reading and interpretation). Similar results were obtained in earlier studies assessing performance in simulated driving tests, especially during lane change demonstrating considerably increased response time in patients with OSA[25].

The results from the Wisconsin card sorting test demonstrated the impairment in executive function in terms of increased number of attempts required and number of errors committed. In particular, patients with OSA exhibited a disproportionate increase in the frequency of perseverative errors or inability to recognize a "shift in sets". The scores in Wisconsin test correlated significantly with night-time hypoxia and not with AHI which is a marker of sleep fragmentation. This lends support to the hypothesis that night time hypoxia impairs cognitive function independent of sleep fragmentation.

Correlating cognitive performances with polysomnographic variables, fails to account for the effect of disease duration and chronic sleep deprivation, apparently due to the poor sensitivity of both the cognitive and polysomnographic measures. This might explain the lack of association observed in the present study. However, cognitive performance has been found to improve uniformly with CPAP, suggesting limitations in the sensitivity of polysomnographic variables of disease severity for correlation with cognitive dysfunction. We observed a significant correlation between stroop errors and T90. However, due to the large number of correlations tested the effect of chance cannot be ruled out. Specific tests to rule out the effect of chance due to multiple correlations tested were not done.

Cognitive impairment is the most common reason for decreased quality of life in patients with OSA. Evaluation of patients with mild and moderate OSA with neurocognitive tests may help in reassessing the present classification of disease severity based on AHI.

Also, routine neurocognitive evaluation in addition to polysomnography may help in guiding treatment decisions.

In conclusion, the results of this study suggest that patients with severe OSA have markedly delayed information processing without any independent impairment in other cognitive domains. No characteristic association between cognitive deficit and measures of night time hypoxia or sleep fragmentation was observed. However, the subject population in the present study was not representative of the population, as it is essentially a sample of convenience drawn from patients attending the medical outpatient department. Further focused population-based studies employing the specified statistically adjusted focused assessment techniques may help in uncovering the true magnitude of cognitive impairment attributable to obstructive sleep apnoea in the population.

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Reprint requests: Dr Surendra K. Sharma, Chief, Division of Pulmonary, Critical Care & Sleep Medicine, Head, Department of Medicine
All India Institute of Medical Sciences, New Delhi 110 029, India
e-mail: surensk@gmail.com, sksharma@aiims.ac.in