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ASSESSMENT OF COGNITIVE FUNCTION USING NEUROPSYCHOLOGICAL TEST BATTERY IN MILD TO MODERATE COPD PATIENTS

Physiology

Namita — Senior resident, Department of Physiology,Lady Hardinge Medical College, New Delhi – 110001, India

Rajiv Bandhu* — Professor, Department of Physiology, Lady Hardinge Medical College, New Delhi – 110001, India*Corresponding Author

SujataGautam — Professor, Department of Physiology, Lady Hardinge Medical College, New Delhi – 110001, India

Debasish Chaudhury — Professor, Department of Medicine, Lady Hardinge Medical College, New Delhi – 110001, India

Sunita Mondal — Director Professor and Head, Department of Physiology,Lady Hardinge Medical College, New Delhi – 110001, India

ABSTRACT

COPD is associated with several co-morbidities which substantially affect the clinical progression of the disease and patient's survival. Studies have shown that lower pulmonary function increases the likelihood of cognitive impairment. In our study, the cognitive function was assessed by neuropsychological test battery using the Letter cancellation test, Trail making test A, Trail making test B, Digit span forward test and Digit span reverse test in the mild to moderate non-hypoxemic COPD patients. These tests are used for studying cognitive functions like executive function, immediate verbal memory, sustained attention, auditory attention and response speed. In Letter cancellation test greater time was taken by COPD cases to perform the same task than the healthy control group (p=0.003). Errors of omission was also more for the COPD cases (p= 0.025). The COPD cases took more time in Trail making test A and Trail making test B such that Significant difference was seen in the Trail making test A score (p=0.0395) and Trail making test B score (p= 0.0176).In the Reverse digit span test COPD case performed poorly in comparison to the control group (p= 0.002). Therefore it can be concluded from our study that even mild to moderate non-hypoxemic COPD is associated with cognitive decline apparent in different domains like attention, alertness, executive function and working memory.

KEYWORDS

COPD, Cognitive function, Letter cancellation test, Trail making test, Digit span test.

INTRODUCTION

COPD is known to be associated with co-morbidities. Overall clinical picture of the disease and patient care is possible only after identification, understanding and assessment of the relevant co-morbidities in COPD1,2. The extrapulmonary effects of COPD are considered to be due to interconnected mechanisms involving systemic inflammation, tissue hypoxia and oxidative stress [3].

Cognition involves a range of brain functions that include the processes by which an individual perceives, registers, stores, retrieves and uses information so that our behavior can be adapted to new situations 4. Studies have shown that poor lung function is related to impaired cognition. Lower pulmonary function is a predictor of lowering of cognitive function with higher likelihood of dementia in the near future 5,6.Systemic inflammation and hypoxic damage to brain seen in these patients can result in various neurological manifestations according to regions of brain involved [7,8,9].

In our study, cognition was assessed using the following neuropsychological tests- Letter cancellation test (LCT), Trail making test A (TMT-A), Trail making test B (TMT-B), Forward digit span test (FDS) and Reverse digit span test (RDS). Letter cancellation test depends on subject's vigilance, motivation, and arousal as they visually scan the array and select appropriate responses. These tasks are assigned as measures of the capacity for sustained attention, concentration, visual scanning, and rapid response activation and inhibition10,11. Forward and backward digit span tests the short-term verbal memory; additionally backward digit span is also a sensitive test for executive function 10. The Trail Making Test (TMT) is one of the most widely used instruments in neuropsychological assessment is an indicator of speed of cognitive processing and executive functioning. Additionally visual search, motor speed, speed of processing, working memory and general intelligence can also be measured by this test[10].

Our study focuses on assessing cognitive functioning in mild to moderate non-hypoxemic COPD patients. Most of the studies done in the past have focused on hypoxemic severe COPD patients. Studying cognitive function in mild to moderate severity COPD patients will help us to better understand the effect of the disease and the associated factors. The strength of our study is that it explores the relationship between COPD and cognitive impairment in the various cognitive domains through different neuropsychological tests. Additionally, our study aims at identifying correlation if any between the cognitive performance and the pulmonary function in COPD.

MATERIALS AND METHODS

The study was carried out in the Department of Physiology and the Department of Medicine, Lady Hardinge Medical College and S.S.K. Hospital, New Delhi. The study was approved by Institutional Ethics Committee for Human Research.

A convenient sample size of 35 COPD patients and 35 apparently healthy volunteers fulfilling the inclusion and exclusion criteria were enrolled in the study. Their informed written consent was taken.

Both the groups underwent a detailed history and thorough clinical examination. The smoking pack year was assessed in all smokers of case and control group.

Inclusion criteria required the participants to be of 40 to 60 years of age, with at least primary school education or equivalent. Patients with altered sensorium and confusion, taking sedative or anti-psychotics medication, history of alcohol or substance abuse, morbidly obese or diagnosed with any known major clinical medical illness that affects cognitive function like diabetes, renal disease, hepatic disease, cancer and obstructive sleep apnea were excluded from the study. Before spirometry and cognitive function assessment oxygen saturation was measured by pulse oxymetry and the participants with oxygen saturation SaO2>90% were included in the study.

Age, sex, BMI, socioeconomic status (by modified Kuppuswamy's socioeconomic status scale)12 and number of years of education were matched for the two groups. Spirometry and neuro-cognitive test was performed according to standard protocol.

ASSESSMENT OF PULMONARY FUNCTION [13]

Standardized spirometry was performed in both cases and controls using the GanshornMediegin Electronics System, Germany. For the

COPD patients the Short-acting bronchodilators were withheld for the previous 6 hours, long-acting bronchodilators for 12 hours, and sustained release theophylline for 24 hours. The forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), the ratio of FEV1 and FVC, Mid-expiratory flow25-75% (MEF25-75%) and Peak expiratory flow (PEF)were obtained.

Spirometry volumes were presented in liters and flow rates in liters per second, as well as percentage of predicted values on basis of age, height, weight, ethnicity and sex according to ERS 1993 by Zapletal for Indian population.

The reversibility was tested after inhalation of 400 µg of salbutamol through metered dose inhaler, connected to a spacer. The criteria for diagnosis of COPD included altered spirometric profile (FEV1 / FVC < 0.7) with reduced reversibility (less than 12% reversal, as well as not more than 200 ml of increase in FEV1 post-bronchodilatation with salbutamol). The classification of airflow limitation severity in COPD patients was based on post-bronchodilator FEV1, as defined in GOLD guidelines13.

NEURO-COGNITIVE TESTS [10,11]

The Neurocognitive tests were presented to all the subjects in the following order:

LETTER CANCELLATION TEST: The task sheet consists of six 52 characters row in which the target character is randomly interspersed approximately 18 times in each row. The subject was instructed to cancel out all target letters. The score was the time taken by subject to actually perform this task. In addition, the numbers of different errors (omissions and commissions) done by the subject was also counted.

Trail Making Test: It involves a series of skills related to attention including complex scanning, coordination, visuo-motor tracking, speed of information processing, and motivation.

Part A: Assesses visuo-motor speed and attention. The circles are numbered 1 – 25. The subject is instructed to draw a line to connect the numbers in ascending order. The score is the time taken by the subject to complete the task.

Part B: In addition to visuo-motor speed and attention, it requires the subject to shift strategy and hence, is a sensitive measure of executive functions as well. In Part B, the circles include both numbers (1 – 13) and letters (A – L). As in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.).The score is the total time taken by the subject to complete the task.

DIGIT SPAN TEST:

Digit Span Forward Test: The sheet consists of Lists for random sequence of digits arranged in sets and it begins with 3 digit sequences. The list becomes progressively longer as we work down the page and the maximum digit sequence is of 8 numbers. The number sequence was orally presented to the patient at the rate of one number per second. The subject was asked to repeat the digits in the exact sequences in which they were presented. The score was maximum number of digits that the patient recalled in the exact order.

Digits Span Backward Test: The list begins with 2 digit sequence and the last digit sequence is of 7 numbers. The subject was asked to repeat the sequences of numbers of increasing digit length in reverse order to what was said by the examiner. The score was the maximum number of digits that the patient was able to recall in reverse order.

Statistical analysis - The data was subjected to statistical evaluation using Graph Pad Prism Version 6 software. Mean and standard error of mean (Mean± SEM) of all the variables for both groups were calculated according to accepted statistical methods.

RESULTS

No statistically significant difference was seen in the age, height, weight, BMI, years of education and socioeconomic status (Table 1,2).

Table 1: The Basic Demographic Profile Of Case Group (copd) And Control Group (healthy Volunteer)

Parameters	COPD Group (N = 35)	Control Group (N = 35)	P Value
Age (Years)	52.5 ± 1.14	49.7 ± 1.07	0.084
Sex (Male/female)	20/15	20/15	0.416
Height (Cm.)	161.0 ± 1.33	162.7 ± 1.66	0.434
Weight (Kg.)	57.6 ± 1.64	59.5 ± 1.75	0.815
B.M.I. (Kg/m2)	22.2 ± 0.59	22.4 ± 0.57	0.660
Years Of Education (Years)	9.2 ± 0.54	9.6 ± 0.56	0.084

*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant Analysis by unpaired 't' test and chi square test.

Table 2: Shows the socioeconomic distribution of Case Group (COPD) and Control Group (healthy volunteer)

Parameters	Case Group (n = 35)	Control Group (n = 35)	p value
UPPER	1	1	0.8875
MIDDLE (Upper and Lower)	18	20	
LOWER (Upper and Lower)	16	14	

*p<0.05-significant **p<0.01- highly significant ***p<0.001-very highly significant Analysis by Chi square test Significant difference was present in the smoking history between the case and the control group (Table3)

Table 3: Smoking history among Case (COPD) and Control Group (healthy volunteer)

Parameter	COPD Group (N=35)	Control Group (N=35)	P Value
Smoker	15	5	0.0082**
Non-Smoker	20	30	
Packyears	14.13 ± 2.03	2.67 ± 0.092	0.0002***

*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant Smoking history analysed by chi square test, packyears analysis by unpaired 't' test

Table 4 shows the comparison of pulmonary function test (PFT) indices IVC, FEV1, FEV1/IVC, MEF25-75% and PEF between COPD cases and controls. Significant difference was present in the IVC (p=0.043) and very highly significant difference was seen in FEV1, FEV1/IVC, MEF25-75% and PEF (p< 0.0001).

Table 4: Pulmonary function test indices among Case (COPD) and Control Group (healthy volunteer)

Parameter	COPD Group (N=35)	Control Group (N=35)	P Value
IVC (Liters)	2.22 ± 0.11	2.73 ± 0.14	0.043*
FEV1(Liters)	1.330 ± 0.06	2.246 ± 0.09	< 0.0001****
FEV1/IVC (%)	61.09 ± 1.50	83.54 ± 1.18	< 0.0001****
MEF25-75% (Liters/Sec.)	1.008 ± 0.06	2.637 ± 0.12	< 0.0001****
PEF (Liters/Sec.)	2.711 ± 0.20	4.840 ± 0.31	< 0.0001****

*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant Analysis by unpaired 't' test

Table 5 shows the comparison between Neurocognitive tests scores. In Letter cancellation test greater time was taken by COPD cases to perform the same task than the healthy control group (p=0.003). Errors of omission was also more for the COPD cases (p= 0.025). No significant difference was found in the errors of commission. Significant difference was seen in the Trail making test A score (p=0.0395) and Trail making test B score (p= 0.0176) between the two groups. In the Reverse digit span test COPD case performed poorly in comparison to the control group (p= 0.002). No significant difference was seen in the Forward digit span test score.

TABLE 5: Neurocognitive test scores of Case (COPD) and Control Group (healthy volunteer)

Parameter		COPD Group (N=35)	Control Group (N=35)	p Value
LCT	Time Taken (Sec.)	169.5 ± 7.030	138.5 ± 7.941	0.0032**
	Errors of omission	7.571 ± 0.4421	6.000 ± 0.4201	0.0259*
	Errors of commission	0.8286 ± 0.1560	0.4857 ±0.1255	0.1063

	TMT-A (Sec)	131.5 ± 7.542	114.2 ± 7.912	0.0395*
	TMT-B (Sec)	188.9 ± 8.437	158.3 ± 9.340	0.0176*
FDS		5.086 ± 0.1442	5.486 ± 0.1659	0.0732
RDS		3.143 ± 0.1368	3.771 ± 0.1365	0.0018**

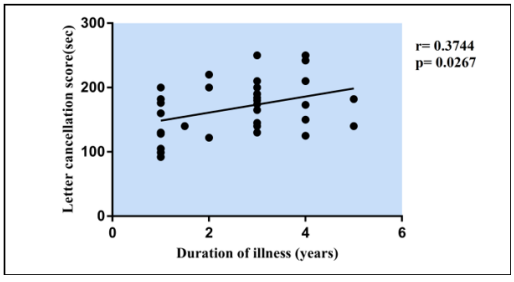
*p<0.05-significant, **p<0.01-highly significant, ***p<0.001-very highly significant Analysis by unpaired 't' test.

Table 6: Basic demographic profile and Neurocognitive test scores of Non-smoker Case (COPD) and Non-smoker Control Group (healthy volunteer)

parameters	Non- smoker cases (n=20)	Non- smoker Controls (n=30)	'p' value
Age	53.00	50.50	0.6532
Sex (male/female)	5/15	5/25	0.4705
Height	156.0	158.5	0.1009
Weight	55.00	57.50	0.3211
BMI	22.0	22.0	0.6322
Years of education	3.0	3.0	0.9600
LCT	178.0	133.5	0.006**
TMT	TMT-A	141.0	95.50,
	TMT-B	191.5	141.5
FDS	5.0	6.0	0.0222*
RDS	3.0	4.0	0.0023*

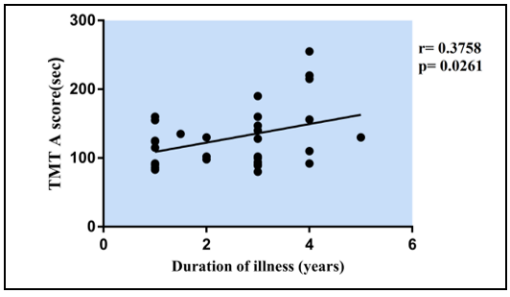
*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant Analysis by Mann-Whitney test

Fig 1: Association between duration of illness and LCT score



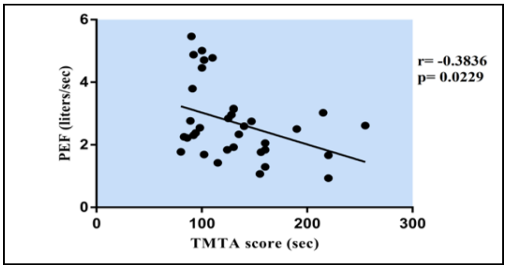
*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant Analysis by Pearson correlation coefficient

Fig 2: Association between duration of illness and TMT-A score



*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant Analysis by Pearson correlation coefficient

Fig 3: Association between PEF and TMT-A score



*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant Analysis by Pearson correlation coefficient

DISCUSSION

The present study sought to assess cognitive functions in COPD cases and control group by battery of neuropsychological tests which included Letter cancellation test, Trail making test A, Trail making test B, Digit span forward test and Digit span reverse test. Significant reduction in the performance was observed in the COPD cases in almost all the tests in comparison to the control group.

Our findings are in concordance with the findings of previous studies that suggest that COPD is a significant risk factor for cognitive decline in older persons 8,9,10. We found that even in mild to moderate non-hypoxemic COPD cases cognitive domains like executive function, immediate verbal memory, sustained attention, auditory attention and response speed are affected.

Many previous studies in India have used these set of tests for assessing the cognitive function 11,14,15. In our study in the Letter cancellation task the time taken to perform (p=0.003) and also the omission error committed (p=0.026) was significantly more in the COPD patients. This indicates an overall reduction in cognitive abilities like response speed and sustained attention, visual search and scanning. Also it suggests impaired ability of activation and inhibition of rapid responses with increased distraction.

The COPD cases took more time in Trail making test A and Trail making test B such that Significant difference was seen between the COPD cases and the control subjects in the Trail making test A score (p=0.0395) and Trail making test B score (p= 0.0176) . This indicates an overall reduction in cognitive abilities like attention, visual search and scanning, sequencing and shifting, psychomotor speed, abstraction, flexibility, execution and modification of a plan of action, and additionally to maintain two trains of thought simultaneously[16].

In COPD cases a significantly lower score was observed in the Reverse Digit span test (p=0.002) which is suggestive of impairment in not just auditory attention and working memory but also in executive function. Reverse Digit span test assesses the ability to manipulate information in the verbal working memory and hence it is a sensitive measure of executive function [10].

We found a positive correlation between the spirometry parameters and TMT scores. Duration of illness was also found to be positively correlated with the cognitive decline. These positive associations obtained suggest that deterioration of lung function in COPDleads to significant decline in the cognitive functioning of brain.

Attention tasks depends on parietal cortex functioning. Left inferior parietal cortex plays an important role in immediate verbal memory and prefrontal association area is responsible for the executive function 17. Decline in the Letter cancellation test and Digit span tests scores indicates towards involvement of this brain area. Previous studies also suggests that poor performance of COPD patients in the neurocognitive tests is attributed by the involvement of frontal lobe, parietal lobe, hippocampus, para-hippocampal gyrus [9,18].

In previous studies on COPD patients the pathogenesis linked to damage in the brain areas were factors like tissue hypoxia, systemic inflammation, oxidative stress, and ventilation perfusion mismatch[7,8,9,19,20].

In our study non-hypoxemic COPD cases were enrolled and results showed significant cognitive decline in them. Although previous studies have shown relation between cognitive decline and hypoxemia, but the correlation between cognitive function and hypoxia is weak, also few studies are available showing cognitive decline being present even in non-hypoxemic individuals21. However, in this study the effect of intermittent hypoxia and episodes of oxygen desaturation during daily activity cannot be ignored as oxygen saturation was measured only during the rest. Previous studies have shown that intermittent hypoxia, episodes of oxygen desaturation during daily activity, nocturnal desaturation and obstructive sleep apnoea can cause brain damage[22,23].

Smoking can also be considered as an important contributor in the cognitive decline process obtained in our study. A growing body of evidence suggests a decrease in grey matter volume in several regions of the brain because of chronic smoking and this can be a reason for the cognitive decline 24,25,26. In our study significant difference was

present in the smoking history between the case and control group. There were 20 non-smokers in the case group and 30 non-smokers in the control group respectively. When we compared the neurocognitive tests scores among the non-smokers in the two groups we found a significant difference between them. The performance of the COPD cases was significantly lower than the healthy controls. This signifies that factors other than smoking are playing a key role in the process of cognitive decline.

Many previous studies have shown similar impairment in cognitive function in COPD patients but most of them were done on hypoxemic patients or with advanced stage of severity 27,28. Our study results are especially important because it indicate significant cognitive function decline in mild to moderate non-hypoxemic cases who were of relatively younger age group. Hence, we can say that impairment in cognition probably starts earlier in the disease course. Also unlike many previous studies which just studied global cognitive functioning, we explored the relationship between COPD and cognitive impairment in the various cognitive domains through different neuropsychological tests29. We can conclude from our study that cognitive functioning like executive function, immediate verbal memory, sustained attention, auditory attention and response speed are declining even in the initial stages of non-hypoxemic COPD patients.

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