Original article:

Cognitive decline in patients of chronic obstructive pulmonary disease

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Abstract:

Background: Cognitive dysfunction is an important systemic effect of COPD affecting various cognitive domains in these patients. The purpose of the present study was to assess type cognitive skills affected in COPD patients and to compare the cognitive skills between hypoxemic and non hypoxemic subgroups of COPD with healthy volunteers.

Material &method: In a hospital based prospective case control study, we examined fifty consecutive COPD patients and age, IQ and education matched fifty healthy controls. COPD group was further subdivided into hypoxemic and non hypoxemic patients based on baseline oxygen saturation (hypoxemic COPD were defined with resting oxygen saturation<90%)

All the subjects were then assessed for cognitive skills of orientation, attention, memory, visuo perceptual abilities and executive functions by neuropsychological battery of tests.

Result: We found that COPD patients showed impairment in trial making B, Digital substitution, stroop color test ($p<0.001$) compared to the controls. The non hypoxemic performed poorly than controls on MOCA, MMSE and Trial making B($p<0.001$)

Conclusion: Cognitive skills of executive functioning are mostly affected while memory are spared in patients of COPD .The impairment of cognition is also observed in non hypoxemic COPD patients supporting multifactorial aetiology of cognitive decline in COPD.

Keywords: COPD , Cognitive dysfunction

Introduction:

Cognitive impairment has been demonstrated in 77% of patients with COPD and hypoxemia[1] and is an important predictor of mortality and disability in them[2,3]. Earlier studies [4-10], were limited due to sample sizes, absence of control groups, and use of limited neuropsychological measurements. We employed neuropsychological battery of tests to evaluate spectrum of cognitive domains involving orientation, attention, memory, visuo perceptual abilities and executive functions.

We aimed to

-to assess frequency of cognitive dysfunction in COPD patients

-to determine differences in cognitive impairments amongst subgroups in COPD (patients with and without hypoxemia) and with controls.

Material and Methods:

A hospital based prospective study was conducted from June 2013 to December 2013. Institutional ethical clearance was obtained for the study by institutional review board.

Fifty consecutive patients aged 30-60 years with atleast Primary School Education COPD diagnosed and staged as per GOLD (2013) guidelines[11] were included in the study. All patients were clinically stable for≥8 weeks and were treated only with necessary medications for COPD.

We also enrolled fifty controls during the same study period as COPD patients, who weren't diagnosed of any lung disease (present or any time in past) and with normal spirometric pulmonary functions. Controls were matched with COPD patients for age, level of education, IQ and socioeconomic background.

The clinical examination and detailed examination was same as for patients with COPD. The purpose of the study was explained to both the groups and explicit written consent was obtained thereof

The exclusion criteria were applicable to both cases and controls.

1. Diagnosis of major neurologic or psychotic disorders (Parkinson's disease, dementia, clinical stroke or depression).
2. Taking medication that affects central nervous system (sedative or anti-psychotics).
3. Any visual and hearing impairment.
4. Major clinical medical illness that could affect cognitive functioning(cancer, diabetes, renal disease, chronic heart failure)

Both the groups underwent a through clinical examination to rule out psychopathology, chronic debilitating medical disorders, endocrinal disorders, history of alcohol or drug abuse and medication known to affect cognition.

All the patients were then screened for the study by a thorough medical examination and biochemical investigations such as complete blood count, lipid profile, blood sugar, serum protein, blood urea, serum creatinine, serum electrolyte profile, serum assays for vitamin B12, folic acid and thyroid hormones assay. Plain chest radiograph, resting electrocardiogram and echocardiography were also performed to rule out any co morbidity and complications of COPD

All the patients performed post-bronchodilatior spirometry with an electronic portable PC based spirometer with printer.

Neuro-psychological evaluation was carried out by submitting to the individuated groups the following tests in order to appraise their global cognitive functions and some neurological functions such as short and long term verbal memory, short and long term visuo-spatial memory, attention, executive functions (cognitive flexibility and planning) and praxis. Cognitive status was assessed with a battery of five neuropsychological tests which taps the cognitive domains of memory, verbal tasks, attention, executive functioning and mental flexibility. A Psychometric Test Battery were performed in a fixed sequence and lasted for approximately 50 minutes.

- Monteral Cognitive Assessment Test (M O C A) [12] -memory, visuo-spatial function, abstraction, language, fluency, orientation, copying.
- Standardized Mini Mental Status Examination (MMSE)[13] - a summed score ranging from 0- 30, evaluates various dimensions of cognition (memory, calculation, orientation in space and time, language, and word recognition).
- Digit Symbol Substitution Test of Wesher Adult Intelligence Scale[14]-memory, perceptual organization, visuomotor coordination, and selective attention.
- Trail Making Test B of Haldstead Reirtan Battery[15]-mental flexibility, motor executive function and planning.

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- Stroop Color Interference Test[16]- focused attention by making use of response interference.

COPD group was further sub divided into hypoxemic and non hypoxemic based on baseline oxygen saturation (hypoxemic being defined as SpO_2>90%). Fifty patients of COPD were further classified into hypoxemic and non hypoxemic depending on resting oxygen saturation level .Hypoxemic group being defined as those COPD patients with baseline oxygen saturation of <90%. Out of fifty COPD patients twenty eight (56%) were in hypoxemic subgroup while twenty two (44%) formed non hypoxemic subgroup of COPD patients.

Statistical Analysis:

Statistical analysis was done using SPSS version 18, statistical software (SPSS, Inc., Chicago, USA). Two independent t test and chi square test was used for Bivariate testing between COPD and control group. All measures of cognition were subjected to one way ANOVA with appropriate post hoc analysis for comparing COPD and non hypoxemic COPD and hypoxemic COPD with non hypoxemic COPD patients. Correlation of cognitive parameters with oxygen saturation in hypoxemic and non hypoxemic group of COPD was evaluated by Spearman rho and Pearson's coefficient. Probability values of p values <0.05 were considered to be statistically significant.

Result:

The mean age of the study population was 62±1.14 year with majority (n=63/100) of them being males. Out of total of fifty patients with COPD: 15 were in stage 1, 26 with stage 2, 7 were with stage 3 and 2 were in stage 4 of COPD. The baseline scores of COPD patients and controls were well matched for age, education level and body mass index. However there was statistical significant difference in smoking index of patients with COPD and the controls (p<0.001).

The spirometric data showed that COPD patients exhibited higher degree of obstructive airflow than the controls. It was observed that there were statistically significant differences between COPD patients and controls for all subgroup of pulmonary function tests namely FVC, FEV_1, FEV_1/FVC, PEFR (p<0.001) as summarized in table 1.The distribution of cognitive test correctly performed in COPD and control group is depicted in table 2. It was observed that COPD group performed poorly on neuropsychological test battery than the controls, with statistical difference between the two groups were attention(calculation) p<0.01, executive subtests of copying landmark(p<0.001), trial making B(p<0.001) and drawing clock(p<0.001). There was no significant differences in COPD and control group on tests for memory(immediate recall, delayed recall and visual recall) and verbal tasks(language, vocabulary, fluency, word generation).It was also observed that visuo spatial subtest of digital substitution(p<0.001) ,color stroop interference test(p<0.001)differed significantly in COPD and controls.

Out of fifty COPD patients, twenty eight (56%) were in hypoxemic subgroup while twenty two (44%) formed non hypoxemic subgroup of COPD patients. To study the impact of hypoxemia on cognitive dysfunction ANOVA was done between controls and two subgroups of COPD (hypoxemic COPD and non hypoxemic COPD). The results between the hypoxemic(n=28/50) and non hypoxemic (22/50) subgroups of COPD revealed that in hypoxemic group there was significant impairment in cognitive function as evidenced by statistically significant differences in trial making B(p<0.001), and ,digital substitution test(p<0.001) stroop colour test (p<0.001),MMSE(p<0.001).

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It was also observed that COPD patients of non hypoxemic group had a poorer performance of subtests of cognitive test when compared with control group suggesting that factors other than hypoxia in COPD patients also contribute to cognitive dysfunction. We found that cognitive skills of trial making B test ($p<0.01$), MOCA and MMSE score ($p<0.001$) significantly affected in non hypoxemic in comparison to healthy control group (table 3).

The mean score of MMSE AND MOCA in controls, hypoxemic and non hypoxemic patients with COPD revealed that the score were within normal range for controls however, in hypoxemic MMSE score of 19.58±2.94 suggests moderate cognitive dysfunction and suggests Mild cognitive dysfunction in non hypoxemic with MMSE score 24.53±3.17. Similarly, a score on MOCA of hypoxemic 21.70±3.46 was lower than MOCA score of 24.41±3.52 of non hypoxemic COPD (table 3).Since hypoxemia is major factor of cognitive dysfunction, its role was further explored by correlating cognitive tests and oxygen saturation and in both the subgroups of COPD patients. The results revealed a statistically significant strong positive correlation between baseline oxygen saturation and executive visuospatial motor tasks moderately with MMSE, MOCA and inverse weakly with color stroop test and attention in hypoxemic group of COPD patients. Trial making B test had a strong inverse correlation with baseline oxygen saturation in hypoxemics, however, no correlation was found with orientation, language (verbal task) and memory tests as summarized in table 4.Non hypoxemic patients of COPD correlated weakly with scores of MMSE and MOCA.

Discussion :

COPD and cognitive impairment are highly prevalent chronic diseases and are associated with multi morbidity and mortality in elderly population. Cognitive dysfunction reduces the level of functioning assessed by activities of daily living and is associated with poor compliance with both medication and oxygen therapy and this poor compliance increases the risk of acute exacerbation[17].

In the early stages of COPD cognitive impairment is often limited to attention problems and information processing speed. As COPD progresses to a more advanced stage the impairments become more severe and diffuse. Orientation, executive functions and memory seem to be most affected[8, 18]. Several studies have confirmed [5-9] declines in a number of cognitive functions, such as memory reaction, time, memory, abstract reasoning skills, and complex visual-motor processes in COPD patients. The main goal of our study was to find which parameters of cognition are most affected in COPD and to compare how the cognitive functions differ between the hypoxemic COPD patients and non hypoxemic COPD patients and the control group.

In the current study, we tested for cognitive functions of attention, language, memory (short term and long term), and executive functions (conceptual and visual-spatial construction).In our study executive tests and attention test were more affected than thought related processes (abstraction, thinking, learning and language skills) in COPD patients as summarized in table 2.

COPD patients in the study performed poorly on the executive task which involves attention, planning, and praxis. In stroop color interference test it was observed that there was slower overall reaction time in the COPD group and they made significantly more mistakes in their response behaviour and were less accurate than the controls. This slower reaction time could be possibly due to time taken to filter contradictory and conflicting

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stimulus information in interference patterns of the test.

A significant impairment was seen in the COPD patients in executive task involving visuospatial perception such as copying clock, drawing landmark test, trial B making test. All these tests used to assess visuo-constructive abilities require verbal understanding, memory and spatially coded knowledge in addition to constructive skills. Stuss[19] et al. reported that hypoxia in COPD results in a relatively focused pattern of impairment in measures of memory function and tasks requiring attention allocation.

A poor performance on these tasks can be explained due to frontal hypoperfusion in patients with COPD. Earlier studies [20,21,22] suggested that frontal-dominant perfusion decrease in COPD patients occurs due to the greater sensitivity of the frontal regions to hypoxia than the other cerebral regions. Since, frontal lobes are considered as seat of intelligence, a hypoperfusion to this cerebral regions result in deficit in planning, programming, logical thinking, arithmetic calculations and attention. Further, an impairment of executive motor constructive tasks (copying and trial making) can also be attributed to the muscle weakness which frequently seen in COPD patients[23,24] .

Memory is reported to be impaired in patients with COPD [5,25,18] most often in the more very severe stages of COPD. This severity of disease causes condition of chronic hypoxemia which leads to structural alteration in hippocampus and other regions of brain, such as transentorhinal, parahippocampal gyrus and entorhinal cortexes, which play a critical role in the memory [4,5,20,21,22].

In our study we did not find any significant impairments on verbal memory, implicit memory (procedural) and explicit memory (semantic and episodic)in patients with COPD. A possible explanation can be that out of fifty COPD patients in our study population we had only nine patients with severe and were severe disease while majority (n=41/50) of COPD patients had mild -moderate disease. To determine possible factors that play a role in causing cognitive impairment in patients with COPD, the differences between two subgroups of COPD(hypoxemic and non hypoxemic) patients were evaluated. We found that hypoxemic had moderate cognitive impairment while non hypoxemic had mild cognitive impairment as per MMSE scores.

While in all the subtests, scores were significantly lower in hypoxemic COPD group of patients than Non hypoxemic COPD patients. These results are more consistent with the data previously reported, in which, hypoxemic patients showed more deterioration in cognitive functions than non hypoxemic[26,27] .

Cognitive impairments are both more severe and diffuse in patients with hypoxemia because of more diffuse damage in cortical and subcortical regions of brain, compared to non hypoxemic.

It was also observed that non hypoxemic COPD patients scored significantly lower than controls on trial making, MOCA and MMSE.A lower cognitive performance by non hypoxemic can be attributed to factors other than hypoxia which affects cognition in non hypoxemic COPD patients. Current evidence suggests that hypoxemia alone is not enough to entirely account for the cognitive deficits which occur in COPD it includes various contributing factors such as tissue hypoxia, systemic inflammation, and oxidative stress [28,29].

It can also be hypothesised that oxidative stress can be the result of nicotine released during cigarette smoking which over a period of time causes oxidative stress by generation of free radical, that leads to damage of neuronal cells [29].This could be one of the cause of cognitive deficit in non hypoxemic who have normal baseline oxygen

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saturation.However, non-hypoxemic patients with resting oxygen saturation ≥ 90%, may have had nocturnal desaturation and frequent episodes of oxygen desaturation during daily activities are known to cause hypoxic damage to brain tissue[30].

Our study had several limitations that should be acknowledged. First, our sample size was small, which may partially account for weak association between some measures in our study.

Although participants were stringently selected to avoid the influence of possible confounding variables, such as diabetes, cerebro vascular disease, and major chronic diseases, there is a possibility that other chronic or subclinical diseases which were not included in the analysis may also have contributed to cognitive decline.

We did not perform MRI /CT perfusion study to identify certain brain regions especially hippocampus, entorhinal cortex, transentorhinal and parahippocampal gyrus which play a critical role in the neural control of cognitive function need to be examined. However, it was costly and usually not recommended for COPD patients.We did not evaluate the inflammatory markers like cytokines which can also contribute to brain tissue damage in especially non hypoxemic patients.

Conclusion:

We found significant impairment in cognitive performance in COPD patients compared to healthy controls. Furthermore this cognitive impairment was also observed in non hypoxemic patients supporting a multifactorial` aetiology of cognitive decline. In conclusion, exact neuropsychological diagnosis and cognitive training should be included into the clinical routine when treating COPD patients especially in long term rehabilitation programs.We also suggest that cross sectional study design presented here requires to be tested in prospective research designs to evaluate longitudinal decline in COPD. This would help to provide a more clear insight into the underlying mechanisms to cognitive impairments in patients with COPD.

Table 1: Baseline characterstics of COPD patients and healthy controls group

VARIABLE	COPD PATIENTS (N=50)	CONTROL (N=50)
Age (Years)	64.8±2.42	62±1.18
Sex(M/F)	28/22	35/15
Education (1-6)	4	4
Smoking (Packs/Year)*	39.95±18.46	16.45±14.48
Ex Smokers(Number, Percent)	34(68%)	44(88%)
Current Smokers(Number, Percent)	16(32%)	6(12%)
BMI (Kg/M2)	19.68±1.28	20.13±0.74

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FEV1(Liters)*	1.09±0.78	2.84±0.46
PEFR(Liters/Sec)	3.46±1.67	6.84±1.24
FVC(Liters)*	1.75±0.11	3.64±0.38
FEV1/FVC Ratio %*	60.52±6.35	73.04±4.28
Baseline Oxygen Saturation ,Percent	98.1±1.25	96±1.26
FFMI (Kg/M2)	13.36±0.37	20.18±0.21

*P value <0.05 is statistical significant. BMI=Body Mass Index, COPD =Chronic Obstructive Pulmonary Disease, Data Are Expressed In Mean±SD, Education (0-6) score 4=primary school ;6=university

	Control(N=50)	**COPD Patients (N=50)**
	Correct response number, percent	Correct response number,percent
ORIENTATION	50(100%)	48(96%)
ATTENTION		
Digital span backward	46(92%)	39(78%)
Digital span forward	49(96%)	42(84%)
Serial calculation	46(88%)	38(76%)
LANGUAGE		
Naming	46(92%)	46(92%)
Word Generation	44(88%)	38(76%)
Phrase Construction	49(98%)	46(92%)
Verbal fluency Phonetic fluency	44(88%)	40(80%)
Semantic Fluency	45(90%)	40(80%)
MEMORY		
Spontaneous memory	48(96%)	44(88%)
Delayed Recall	46(92%)	34(68%)
Visual memory(recall copy of landmark)	48(96%)	44(88%)
EXECUTIVE FUNCTION		
Conceptual		
Abstraction -similarities	48(96%)	42(84%)

Sequencing	48(96%)	46(92%)
Calculation	44(88%)	38(76%)
Motor-visuospatial construction		
Clock drawing test *	44(88%)	32(64%)
Copying pentagon*	41(82%)	31(62%)
Trial B Making *	42(84%)	26(52%)
Color Stroop Test *	44(88%)	26(52%)
Digital Substitution Test*	44(88%)	36(72%)

TABLE 2: Frequency distribution in controls and COPD, who correctly performed neuropsychological battery of test *p<0.05 on chi square test between controls and COPD patients

	CONTROL N=50	**HYPOXEMIC COPD PATIENTS (N=22/50)**	**NON HYPOXEMIC COPD PATIENTS (N=28/50)**
Color Stroop			
Time In Sec	22.5±0.76	29.7±0.42**	24.5±1.12
Error	2.2±0.96	4.10±0.34	3.23±0.30
Trial B sec	94±52.24	184.54±146.69**	142.24±73.56*
Digital Symbol Substitution Test n/time	47.14±1.12	28.42±2.24**	32.44±1.68
MOCA SCORE	28.54±1.58	21.70±3.46	24.41±3.52*
MMSE SCORE	28.78±0.98	19.58±2.94**	24.53±3.17*

Table 3: analysis of controls and hypoxemic and non hypoxemic groups of COPD patients on neuropsychological tests

All comparison by one way ANOVA with post-hoc test; p<0.05 are significant. Data Are Expressed In Mean ± SD, sec=second, Trial B = n/TIME=number in 75 sec, Digital Symbol Substitution Test Time is n/TIME=number in 90 sec

***p<0.01 is significant compared to control,**p<0.01 is significant compared to non hypoxemic**

Cognitive parameters	**Hypoxemic-Group Correlation Coefficient**	**Non-Hypoxemic Group Correlation Coefficient**
Orientation	**0.012**	**0.45**
Attention	**O.210***	**0.164**
Language	**0.001**	**0.012**
Memory	**0.162**	**0.124**
Executive function, conceptual	**0.186**	**-0.202**

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Executive function, visuo perceptual	**0.724***	**0.312**
MOCA score	**0.448****	**0.283****
MMSE score	**0.423****	**0.265****
Digital Symbol Test	**0.268**	**0.000**
Trial Making B Test	**-0.674****	**-0.374**
Stroop color Test time	**-0.250****	**-0.137**
Stroop color Test error	**-0.126****	**-0.022**

Table 4: Correlation between cognitive parameters and baseline oxygen saturation in hypoxemic and non hypoxemic COPD patients*. Spearman Rho Correlation is significant at the 0.05 level (2-tailed).Pearson correlation is significant at p<0.001(2 tailed)**

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