A Study of Electro Encephalo Graphic Changes and Cognitive Functions in Patients with Chronic Obstructive Pulmonary Disease with Different Grades of BODE Severity

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ABSTRACT

Introduction: Cognitive dysfunction is an important systemic effect of COPD affecting various cognitive domains. The objective of this study was to examine the association of disease severity and neurological abnormalities in COPD patients.

Material and methods: Out of hundred patients sixty eight patients with COPD of different severity reported to the neurologic clinic for EEG evaluation and assessment of cerebral perfusion (rSO2), in a cross sectional study. All patients were graded into groups based on severity of disease by a multidimensional staging (BODE) index, then assessed for cognitive skills by neuropsychological battery of tests, EEG evaluation and frontal cerebral perfusion (rSO2).

Results: With increasing disease severity the percentage of patients with abnormal cognitive scores were increasing and so were true with the presence of slow waves in frontal EEG leads, but not statistically significant.

Conclusion: Executive function like visuospatial and motor constructional abilities (TMT), symbolic representation and visual processing (CDT), predominantly a function of frontal lobe was seen to be affected more among the cognitive skills which invariably were projected in the frontal leads of EEG in the form of presence of slow wave pattern.

Keywords: Chronic obstructive pulmonary disease, cognitive impairment, functional impairment, hypoxemia, hypercarbia, severity index.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) has been considered as a disease primarily affecting the lungs however its extrapulmonary effects have been increasingly recognized with diverse manifestations involving various body systems causing different co morbidities of various severities. The airflow limitation in COPD is usually non-reversible and associated with an abnormal inflammatory response of the lungs which leads to hypercarbia and hypoxemia.[1] There are studies showing that cognitive dysfunction is one among the systemic manifestations of COPD.[2-3]

Cognition is a collective term for higher level neural processing. Cognitive ability is broken down into discrete domains. It is difficult to study single domains in isolation. Hence an attempt was made to assessing most of the cognitive functions in the form of questionnaires and tasks.

Cognitive dysfunction appears to be relatively common in COPD populations, and appears to increase in prevalence with impairment in gas exchange. Cognitive impairment was associated with severe pulmonary dysfunction from a previous study[4], although its prevalence varied from study to study.[5-6] However, cognitive impairment in COPD is not always reported. COPD effects on cognition are still poorly understood.

Our objective was to assess the effect of disease severity on cognition and its relation with electroencephalographic changes (EEG) and cerebral oxygenation.

MATERIAL AND METHODS

A cross sectional study was performed in collaboration with the Departments of pulmonary medicine and Neurology at Govt. T D Medical College Hospital, Alappuzha during January 2015 to July 2015. A sample size of the study population (N=100) with COPD, as defined in the Global Initiative for obstructive lung disease (GOLD-2014) guidelines[7], were recruited at the Chest and TB outpatient clinic, out of which only (N=68) patients attended the Neurology clinic for cerebro vascular tests, like EEG and cerebral oximetry. Written consent was obtained from the participants after explaining the purpose of the study to them. And Institutional ethical clearance was obtained for the study by institutional review board of Govt. T D M C Alappuzha.

Inclusion criteria for the study are - COPD patients of age >40 yrs, as per the GOLD guidelines and patients with at least high school education as low educational levels would cause miscategorizing normal subjects as cognitively impaired.

Exclusion criteria - Patients with neurological disorders, history of depression (Hamilton depression rating scale HAM-D-21 > 8, not included in the study[8], Patients on continuous oxygen therapy, or with other comorbidities like, hypertension, diabetes mellitus, severe anaemia, electrolyte imbalances and patients with visual or hearing impairment

Pulmonary function tests (PFT) done using *spiropalm 6MWT* comply with *ATS/ERS guidelines*). COPD patients with post-bronchodilator (20 min after inhalation of 2 puffs of salbutamol given via a metered dose inhaler through a spacer) FEV_1< 80% of the predicted value along with an FEV_1/FVC% not more than 70% were included in the study.

Measurement of COPD severity - We used (BODE) Index, which is a multi-modal measure of disease severity, the BODE

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components includes the validated BMI (Body Mass Index), Obstruction, Dyspnea, Exercise Capacity.[9] The BODE Index is based on the body-mass index (B), the degree of airflow obstruction (O) measured by Forced Expiratory Volume in one second (FEV1), grade of dyspnea (D) assessed by the modified Medical Research Council (mMRC) Dyspnea Scale;16 (≥ 2 as an indicator of more symptoms) and exercise capacity (E) measured by the six-minute-walk test. Each component is assigned a specific score and the total score ranges from 0 to 10 points (higher scores indicate greater severity). It has been validated in patients with a mean age of 66 years and with an average FEV1% predicted of 45%.[9]

Cognitive assessment- Cognition impairment was evaluated using four validated psychometric questionnaires: 1) the Mini Mental Status test (MMSE)[10], which assesses spatial and time orientation, attention, and calculation (normal score: >24 points); In present study, MMSE was administered in their native language [Malayalam] by exact conversion of the questions of MMSE International Version in English. 2) the Clock Drawing test, which assesses memory, attention, and symbolic representation A score of ≥3 represents a cognitive deficit, while a score of 1 or 2 is considered normal[11] 3) The Trail Making test TMT-A[12], which assesses visual processing and reproduction of numeric sequences (cognitive impairment: ≥94 seconds);37 and 4) the TMT- B[13], which assesses cognition flexibility and shifting capacity (cognitive impairment: ≥283 seconds).

Cerebral oximetry for regional oxygen saturation was measured using a six channel machine SENSMART x 100 along with adult rSO2 sensor with pulse oximeter, based on NIRS technology. Disposable sensors were placed on the forehead on both the sides. Patient was observed for 15 minutes in a calm and relaxed state, machine calculated average value of rSO2 was observed at the end of 15 minutes, value was recorded.

Electroencephalographic (EEG) tests - Each subject was seated in a soundproof, light-controlled, well ventilated recording room, while 30 minutes of resting EEG data were being collected from the 14 monopolar electrode sites of the Inter-national 10/20 system, referred to as Cz. Computerized EEG recordings were obtained using XLTEK EEG 32 U. The electrode impedance was carefully kept below 5 kΩ. Hyperventilation was employed as standardized activation method. The filtering interval, frequency and amplitude of the device were adjusted to 10 to 59 Hz, 30 mm/sec, and 100 μV, respectively. The EEG results were evaluated visually by a neurologist. The frequency range is generally classified into several frequency components, or delta rhythm (0.5 - 4Hz), theta rhythm (4 -7Hz), alpha rhythm (8 - 13Hz) and beta rhythm (14-30Hz).[14]

A visual assessment of slow wave pattern (≤7 Hz) was observed in the frontal leads and patients with more than 50% of slow wave pattern in frontal leads were grouped as those with >50% slow waves in right frontal leads only, >50% slow waves in left frontal leads only and >50% slow waves in frontal leads of both sides.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS version 18, statistical software (SPSS, Inc., Chicago, USA). Neuropsychometric scores, EEG slow waves (≤7 Hz) and cerebral oxygen saturation (rSO2) were compared among different BODE groups using parametric ANOVA test and non-parametric (Kruskal Wallis test), as appropriate (P<0.05 indicated statistical significance. Chi square test was used to assess the frequency of abnormal cognitive test scores among each BODE group.

RESULTS

The mean age of the COPD patients of this study was 64.47 ±8.01 year. Table 1 - depicts the comparison of neuro psychometric scores, EEG and rSO2 among various BODE group. BODE index scores were categorized into four quartiles, quartile 1 to 4 with scores of 0-2, 3-4, 5-6 and 7-10, respectively. It was observed that, more than 50% of patients had abnormal cognitive tests scores with CDT (all the BODE groups) and TMT-A (BODE1, 3, 4 groups). Mean TMT-A scores were seen to be more with increasing BODE quartiles suggestive of taking more time to complete the test with higher quartile COPD groups but not statistically significant. We also observed a trend in the MMSE mean scores, which was decreasing with

		BODE 1	BODE 2	BODE 3	BODE 4	P value
rSO2 †	Left Frontal	72.2 ± 3.6	75.1 ± 15.7	65.4 ± 15	69.6 ± 7.1	0.379
	Right Frontal	66.7 ± 3.4	79.7 ± 14.4	69.2 ± 7.8	61.5 ± 12.8	0.014
MMSE †		25 ± 1	25 ± 2.8	24.2 ± 5.5	22.1 ± 5.2	0.467
Abnormal MMSE ‡ [N (%)]		0 (0)	2 (33.3)	4 (33.3)	10 (55.6)	0.251
CDT √		4.7 ± 1.2	3.2 ± 1.5	4.5 ± 1.9	3.9 ± 1.7	0.416
Abnormal CDT ‡ [N (%)]		3 (100)	4 (66.7)	8 (66.7)	13 (72.2)	0.702
TMT-A †		121 ± 52.4	88.5 ± 52.9	153.4 ± 107.2	168.9 ± 76.3	0.224
Abnormal TMT-A ‡ [N (%)]		2 (66.7)	2 (33.3)	5 (55.6)	13 (81.3)	0.184
TMT-B †		150 ± 42.4	124.8 ± 21.6	119.8 ± 32.2	214.2 ± 119.9	0.151
Abnormal TMT-B ‡ [N (%)]		0 (0)	0 (0)	0 (0)	2 (33.3)	0.184
EEG ‡ >50 %	Left ‡ [N (%)]	2 (66.7)	2 (33.3)	2 (16.7)	6 (33.3)	0.729
	Right ‡ [N (%)]	0 (0)	1 (16.7)	4 (33.3)	4 (22.2)	
	Both ‡ [N (%)]	1 (33.3)	3 (50)	6 (50)	8 (44.4)	

Values are expressed as Means ± SD; † ANOVA, ‡ Chi square test, √ Kruskal Wallis test; BODE-1 is defined by a score of 0-2, BODE-2, score of 3 to 4, BODE-3, score of 5 to 6, and BODE-4, score of 7 to 10, with higher scores indicating a greater risk of death; Abbreviations- MMSE, Mini Mental Status test; CDT, clock drawing test; TMT A, Trail Making test A; TMT B, Trail Making test B. (Normal reference values- MMSE>24; CDT<3; TMT-A<94sec; TMT-B<283sec.)

Table-1: Variation of cognition, cerebral oxygenation and EEG changes with BODE severity

higher BODE groups, but not statistically significant. We could not find any noticeable association of disease severity with that of cerebral oxygen saturation (rS02). Whereas we observed a trend of higher BODE quartile groups having more number of patients with >50% of slow wave pattern in EEG, but not statistically significant.

DISCUSSION

Cognitive dysfunction may interfere with COPD patients' ability to self manage their medication, adjust their doses in response to respiratory symptoms, and perform necessary functions in life without any aid. In other words cognitive impairment may create difficulties with performing daily activities, especially those that involve memory or complex reasoning.[15]

Our main objective was to observe whether cognitive impairment in COPD was related to EEG changes and frontal cerebral oxygen saturation (rSo2). We have already hypothesized in our earlier study that cognitive function in COPD patients were significantly declined when compared to the normal healthy individuals.[16]

And we also observed in our previous study that with increasing severity of disease as assessed by various severity parameters in lung, most of the domains of cognition were involved in which memory, attention, symbolic representation and visual processing (CDT), reproduction of numeric sequences, cognition flexibility, and shifting capacity (TMT-A and TMT-B) were the most affected cognitive functions.[17]

From various literatures it is known that TMT is a sensitive indicator of executive function[18] and therefore a good estimator of frontal lobe function.The executive functions is a broad term and comprises a set of cognitive skills that are responsible for the planning, initiation, sequencing, and monitoring of complex goal-directed behavior. Executive control depends on the integrity of frontal systems. It is understood from previous studies that the Executive control function (ECF) impairment has been associated with lesions to the frontal cortex and its basal ganglia–thalamic connections.[19] And clock-drawing test (CDT), has been traditionally viewed as a visuospatial task, that is sensitive to right hemisphere pathology.[20] From the study conducted by Black D N et al, Frontal leukotomy selectively affects CDT performance relative to age, disease, and education-matched control subjects.[21]

We hence focused primarily on frontal EEG leads and prefrontral cerebral oxygen saturation. And extended our aforementioned study[17] from assessing cognitive functions to EEG changes and cerebral oxygen saturations (rSO2).

In the present study also we noticed BODE-4 COPD group comprising maximum number of patients with abnormal cognitive scores especially with MMSE, CDT and TMT-A, clearly indicating that there is a risk of cognitive impairment with severity of COPD. MMSE[10] that assess global cognitive functions, CDT for memory, attention, symbolic representation and visual processing and the Trail Making Test (TMT-A)[12] that investigate sub-cortical dysfunction such as sequence alternation, cognitive flexibility, visual search, motor performance, and executive function[22] were seen to be most affected in this study, but not statistically significant may be due to small sample size. COPD patients with presence of slow wave EEG pattern in both the frontal regions were increasing through various stages of disease severity, suggesting, COPD affects the brain function to some extent.

Earlier studies[23-24] suggested that frontal dominant perfusion decrease in COPD patients, it occurs due to the greater sensitivity of the frontal regions to hypoxia than the other cerebral regions. From our study we could not explain any decrease in frontal oxygen saturation. A detailed cerebral perfusion study would be helpful.

There are few limitations in our study, like less sample size, sampling of patients only hospital based rather than planned sample collection from community and lack of arterial blood gas analysis to quantify hypoxemia and hypercarbia, cerebral imaging for perfusion and spectral analysis of EEG to assess the power band of each EEG waves.

Future concern- A more detailed study on cerebral perfusion using imaging techniques and arterial blood gas analysis with respect to different stages of COPD disease.

CONCLUSION

In conclusion, from our study we could observe that, with the disease severity executive motor control predominantly visuospatial and motor constructional abilities (TMT), symbolic representation and visual processing (CDT) and global cognitive functions (MMSE) were affected, former being exclusively a function of frontal lobe, invariably projected well with the presence of slow waves in the frontal EEG leads.

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