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RESEARCH ARTICLE

VARIATION OF COGNITION AND CEREBRAL ACTIVITY WITH SEVERITY OF AIRFLOW OBSTRUCTION IN COPD

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Abstract

Introduction: Cognitive dysfunction is one of the important systemic effect of Chronic Obstructive Pulmonary Disease that affects various cognitive domains in these patients.

Aim: Assessment of cognitive function in specific cognitive domains in COPD with various stages of severity as observed by airflow obstruction.

Methods: N=68 COPD patients and N=20 controls were matched for age and education. EEG changes, SpO2 and rSO2 were compared between COPD and control group. Cognitive scores and EEG wave patterncompared among different stages of severity in COPD group.

Statistical analysis: Was done using SPSS version 18. Two independent t test was used for bivariate testing between COPD and control group. Chi square test applied to assess the frequency distribution of variables among each group. One way analysis of variance (ANOVA) was used to compare mean values of cognitive scores and Chi square test for number(%) of patients with abnormal scores in cognition and slow waves in EEG across groups with different severity of airflow obstruction (FEV1% Predicted).

ResultsOncomparison of EEG slow wave, (rSO2) and (SpO2) among COPD and age matched control group, electroencephalographic(EEG) study in COPD group showed slower wave pattern than their age matched healthy counterpart which was statistically significant at $p<0.001$, so was true about rSO2 of right frontal region in the study group. Among the COPD groups with different severity ("moderate", "severe", and "very severe" grades), patients with "severe" and "very severe" airflow obstruction performed poorly with Folstein MMSE (statistically significant at $p<0.001$), more than 50 % of patients had abnormal scoring with CDT in all the three groups and with TMT-A in "severe" and "very severe" group.

Conclusions: We found relative frontal hypoxemia and EEG slow wave in COPD group compared to healthy control. With severegrades of disease risk of cognitive impairment was noted. Thus, suggesting that low lung functioning may contribute to cognitive disorders by decreasing the oxygen delivery to brain neurons.

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Introduction:-

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease with impairment of airflow. It has systemic impact with a progressive behaviour.It is noted to be the third leading cause of death by 2020 (GOLD initiative 2011)

COPD is defined as a preventable and treatable disease with significant extra-pulmonary effects that may contribute to its severity in individuals, as per the Global Initiative for Lung Disease (GOLD)guideline (Global Strategy for Diagnosis, Management, and Prevention of COPD). As pulmonary function deteriorates, and as the disease progresses, the risk of alveolar hypoxia and consequent hypoxemia increases.

COPD is a multisystem diseasewith extrapulmonary manifestation (Agusti A, 2007).It can cause multiple comorbidities, such as heart disease, osteoporosis, type 2 diabetes mellitus, lung and cancer (Sin DD et al, 2004) (Wasswa-Kintu S, et al 2005).

One of the potential systemic manifestation is functional impairment of brain, that may explain the increasingly reported cognitive deficits in the disease (Dodd JW et al, 2010). Cognition can be defined as a collective form for high-order neural processes that affects information handling. Cognitive abilities are mainly inferred from behaviour, which is determined by neurological, psychological, and emotional factors (Lezak MD et al, 2004)**.** The cognitive ability is usually broken up into discrete domains, although it is rarely possible to study single domains in isolation. Performance within each domain depends on one or more of the main classes of cognitive function.

Cognitive impairment has been observed in77% of patients with COPD and hypoxemia (Grant Iet al, 1987). Several studies have presented that cognitive dysfunction in COPD has been associated with higher mortality and disability (Hynninen KM et al,2005). Patient leads a handicapped life being dependentthroughout. Fear of exaggeration of symptoms is the cause for anxiety and dependency. As the disease progresses, COPD patients goes into depression, which is quite challenging as the symptoms of depression and anxiety overlaps (Abebaw M et al, 2014).

There are several studies done in COPD and cognitive dysfunction. Hung et al, observed from his study that cognitive impairment was common among patients with COPD than those without COPD (Hung WW et al, 2009). The hypoxemia because of COPDled to cognitive impairment, this being detrimental to oxygen-dependent enzymes in the synthesis of neurotransmitters such as acetylcholine (Heaton RK et al, 1983)**.** There are very many studies in this area, that had shown the association of cognitive dysfunction with hypoxemia. One study had showed that cognitive impairment has a prevalence of 77% in patients with COPD and hypoxemia (Grant I, et al, 1982).

Inspite of several evidence, COPD effects on cognition are still poorly understood and there are many studies done in this area to delineate possible mechanisms that leads to cognitive dysfunction in these patients and the cognitive domains most affected in COPD. Certain number of earlier studies pertaining to cognitive impairment in COPD had limitations due to absence of control groups and use of limited neuropsychological measurements (Orth M et al, 2006, PrigatanoGPet al, 1983)**.** Wehypothesised in our earlier study that there is a relationship between level of hypoxemia and disease severity with risk of cognitive impairment (John J, et al, 2015, John J et al 2015). Our present study is aimed at characterizingthe relationships between the various cognitive domains in COPD patients with various stages of disease severity as assessed by FEV1 in COPD and its relationship with electroencephalographic changes (EEG) and cerebral oxygenation.

Methods:-

A cross sectional analytical study performed at department of respiratory medicine in Govt. T D Medical College Hospital, Alappuzha during January 2015 to July 2015. A sample size of (N=100) patients with COPD, as per (GOLD-2014) guidelines, were recruited.

A previous study done in Turkey found that 64% of COPD patients showed cognitive impairment. Assuming 50% cognitive impairment in our setting, with a 95% confidence and 80% power of the study, Sample size= 4PQ/d2=100. Out of the 100 cases of COPD that had visited at the outpatient clinic of Chest and TB,only (N=68) patients attended the Neurology clinic for cerebrovascular tests, like EEG and cerebral oximetry. Selection of controls was in such

that they match with respect to age and education level with that of the COPD cases. Age and education matched healthy subjects (N=20), were selected as control group. The purpose of the study was explained before obtaining written consent.The study was granted Institutional ethical clearance of Govt. T D M C Alappuzha.

Inclusion Criteria for the study are:
Cases selected were COPD patients aged >40yrs, non-smokers with at least high school education.

Exclusion Criteria
All patients with any neurological illness, history of depression (ruled out by Hamilton depression rating scale, HAM-D-21 > 8, not included in the study) (Hamilton M, 1967). Patients withcomorbidities like, hypertension, diabetes mellitus, severe anaemia, electrolyte imbalances and with visual or hearing impairment.

Pulmonary function tests (PFT) was done using spiropalm 6MWTthat comply with ATS/ERS guidelines. COPD patients were subjected to post-bronchodilator therapy (2 puffs of salbutamol given via a metered dose inhaler through a spacer and waited for 20 minutes) FEV1 less than 80% of the predicted value along with an FEV1/FVC % not more than 70% were included in the study. COPD patients were grouped based on GOLD staging (**Table 1**). Patients were grouped into four stages based on FEV1% Predicted (>=80%, 50-79%, 30-49%, <30% normal).

Cognitive Assessment
A multiparametric assessment was done using four validated psychometric questionnaires:1) the Mini Mental Status test (Folstein MMSE)for spatial and time, orientation, attention, and calculation (overall normal score: >24) (Folstein M.F et al, 1975). 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, for memory, attention, and symbolic representation. A score of ≥3 represents a cognitive deficit, while a score of 1 or 2 is considered normal (Shulman KI et al, 2006). 3) The Trail Making test TMT-A,that assesses visual processing and reproduction of numeric sequences (cognitive impairment: ≥94 seconds)(Reitan RM 1958), and 4) the TMT- B, that assesses cognition flexibility and shifting capacity (cognitive impairment: ≥283 seconds) (Giovagnoli AR, 1996).

Cerebral Oximetry
Cerebrovascular oxygenation of frontal region of brain was assessed using SENSMART x 100, a six-channel machine with adult rSO2 sensor with pulse oximeter, based on NIRS technology. It assessed concentration changes of oxygenated, deoxygenated, and total haemoglobin (Hb). NIRS studies in humans is the ratio of oxygenated haemoglobin (Hb) to total haemoglobin (Hb), an index of changes in tissue O2 saturation (rSO2).We used disposable sensors to place over the forehead on both the sides. Patients were observed for 15 minutes in a calm and relaxed state, machine calculated average value of rSO2 at the end of 15 minutes.

Electroencephalographic Tests
Computerized EEG recordings were obtained using XLTEK EEG 32 U. Each subject was seated in a soundproof, light-controlled, well ventilated recording room. 30 minutes of resting EEG data was collected from the 14 monopolar electrode sites of the Inter-national 10/20 system, referred to as Cz. The electrode impedance was carefully kept below 5 kΩ. 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 was evaluated by a neurologist. The frequency range of EEG waves classified into delta rhythm (0.5 - 4Hz), theta rhythm (4 -7Hz), alpha rhythm (8 - 13Hz) and beta rhythm (14- 30Hz). Normally, the slow ranges (0.3 -7Hz) and the very fast range (>30Hz) are sparsely represented, medium (8 - 13Hz) and fast (14 - 30Hz) components predominate.

A visual assessment of slow wave pattern **(**≤7 Hz)was observed in the frontal leads and patients were grouped into three groups as follows- 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
Was done using SPSS version 18, statistical software (SPSS, Inc., Chicago, USA). Two independent t test was used for bivariate testing between COPD and control group. Chi square test applied to assess the frequency distribution of variables among each group (**Table-ll**)

One way analysis of variance (ANOVA) used for comparison of more than two groups that follow normal distribution. Chi square test used to assess number (%) of COPD patients with slow waves in EEG and number(%) of COPD patients with abnormal cognitive scores across different severity of airflow obstruction (FEV1 % Predicted) (**Table-lll**).

Results:-

Table-1 shows the grading of severity of airflow limitation in COPD (based on post bronchodilator FEV1into ("mild", "moderate", "severe", and "very severe" groups) as per GOLD guidelines.

Table-ll depicts the comparison of EEG slow wave pattern, rSO2 and peripheral oxygen saturation (SpO2) among COPD group and age matched control group. It was observed that with theelectroencephalographic(EEG) study, slow wave pattern was observed more in COPD group than their age matched healthy counterpart which was statistically significant at p<0.001. Also, rSO2 of right frontal region was seen significantly better in control group than in the study group (p<0.001). The mean values obtained with rSO2left frontal and SpO2 showed a decline in COPD compared to the control group, but not statistically significant.

Table-lll- Among the COPD groups with different severity of airflow obstruction (FEV1), it was observed that the mean scores obtained with FolsteinMMSE showed a decreasing trend from "moderate" to "severe" grades, withnumber of patients showing abnormal scoring was higher in "severe" and "very severe" groups which was statistically significant at p<0.001). The mean scores in CDT were better in "moderate" group than the other groups, similarly more than 50 % of patients had abnormal scoring with CDT in all the three groups and with TMT-A in "severe"and"very severe"group but not statistically significant(**Figure-1**). We did not find any relation of EEG slow wave pattern with any of the COPD groups.

Table l:- Classification of severity of airflow limitation in COPD (based on post bronchodilator FEV1).

Stage I	Mild COPD	FEV1/FVC<0.70	FEV1≥ 80% normal
Stage II	Moderate COPD	FEV1/FVC<0.70	FEV1 50-79% normal
Stage III	Severe COPD	FEV1/FVC<0.70	FEV1 30-49% normal
Stage IV	Very Severe COPD	FEV1/FVC<0.70	FEV1 <30% normal, or <50% normal with chronic respiratory failure present*

Table ll:- Comparison of selected variables based on group.

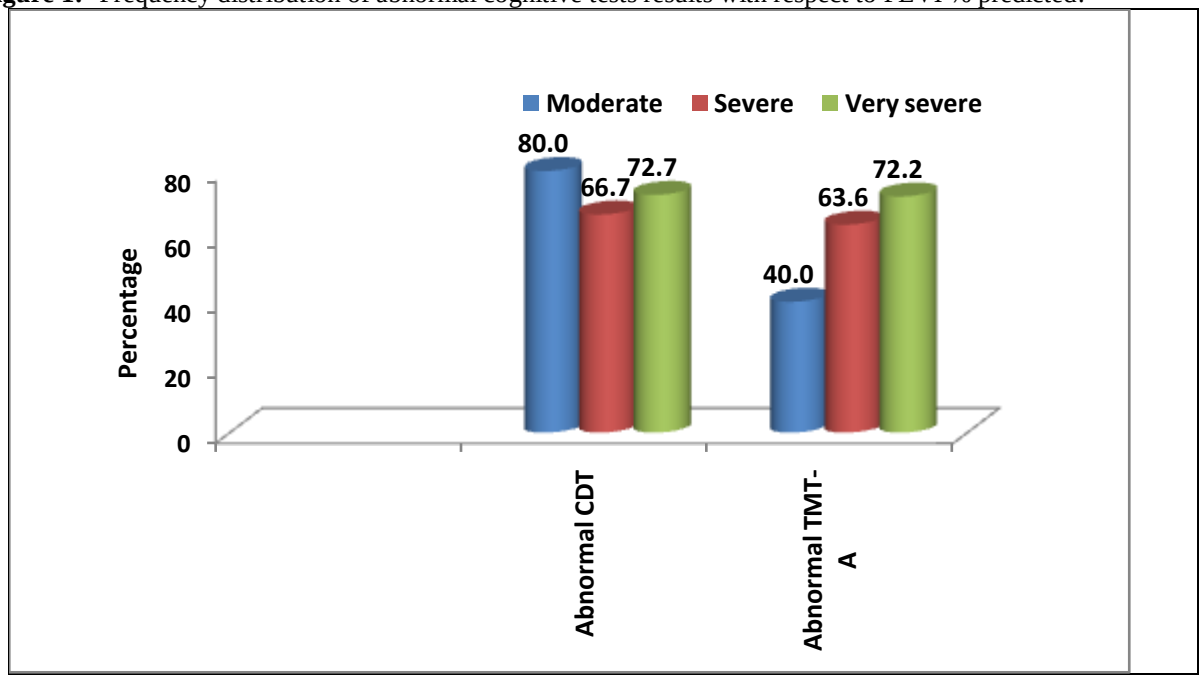
		Case (N=68)	**Control (N=20)**	**P value**
Age (Mean/SD) *		63.8 ± 7.4	59.4 ± 11.8	0.078
†EEG	With Nil slow wave pattern in the frontal leads	0 (0)	14 (70)	0.000**
	Left frontal only (>50% slow waves)	12 (30.8)	0 (0)	
	Right frontal only (>50% slow waves)	9 (23.1)	4 (20)	
	Both frontal (>50% slow waves)	18 (46.2)	2 (10)	
*Regional Cerebral oxygen saturation	RSO2- RF%*	67.3 ± 5.6	73.3 ± 5.1	0.000**
	RSO2-LF%*	71.8 ± 5.9	74 ± 2.9	0.109
*Peripheral oxygen saturation	SpO2 %*	94.5 ± 3.2	96 ± 2.2	0.076
*Independent t test; Data presented as Mean±SD, † Chi Square test data presented as Number (%), **Significant at p<0.05, ***Significant at p<0.001(2 tailed), (Normal reference values- FolsteinMMSE>24; CDT<3; TMT-A<94sec; TMT-B<283sec)				

Tablelll:- Cognition and changes in EEG with respect to FEVI % Predicted.

	FEVI %			**P value**
	Moderate	**Severe**	**Very severe**	
Copying †	0 (0)	1 (8.3)	0 (0)	0.315

MMSE*		25 ± 1	23.2 ± 4.3	23.1 ± 5.7	0.741
Abnormal MMSE†		0 (0)	8 (66.7)	8 (36.4)	0.031**
CDT*		3.8 ± 1.5	4 ± 1.9	4.1 ± 1.8	0.945
Abnormal CDT†		4 (80)	8 (66.7)	16 (72.7)	0.847
TMT-A*		97.2 ± 49.3	164.5 ± 99.4	149.1 ± 78.6	0.330
Abnormal TMT-A†		2 (40)	7 (63.6)	13 (72.2)	0.409
TMT-B*		131.8 ± 34.1	158.8 ± 57.4	160.7 ± 102.5	0.834
Abnormal TMT-B†		0 (0)	0 (0)	2 (20)	0.366
EEG >50 %†	Left	2 (40)	3 (25)	7 (31.8)	0.385
	Right	0 (0)	5 (41.7)	4 (18.2)	
	Both	3 (60)	4 (33.3)	11 (50)	
*ANOVA, Values are expressed as Means ± SD, †Chi square test, values expressed as Number (%),**Significant at p<0.05, (Normal reference values- Folstein MMSE>24; CDT<3; TMT-A<94sec; TMT-B<283sec.)					

Figure 1:- Frequency distribution of abnormal cognitive tests results with respect to FEVI % predicted.



Discussion:-

From the various studies done on COPD and various cognitive domains, there is a strong evidence of cognitive dysfunction in COPD patients. Few studies had even shown the prevalence of cognitive impairment in COPD to be higher than in healthy control subjects (Dodd JW et al, 2012; Thakur Net al, 2010). Antonelli-Incalziet al., in their studyfound, in COPD, prevalence of cognitive dysfunctionwas 32.8% and severe forms of cognitive impairment was around 10.4%. (Antonelli-Incalzi R, et al, 2006).

But it is also of concern that depending upon the diagnostic criteria adopted, the methods used for assessing the cognitive impairment and sample size of the studies, the incidence of cognitive impairment in patients with COPD varies in different studies from 12% to 88% (Hynninen KM, et al, 2005).

As per our previous study, cognitive function in COPD patients were significantly declined when compared to the normal healthy individuals (John J, et al, 2015). We used a multiparametric assessment that wasable to inform on several domains of cognition. Few other studies also resulted the same, as per whichin COPD, a general cognitive decline especially in cognitive functions of learning, visuospatial and constructional abilities, executive functions, and language skills, were seen (Antonelli-IncalziR et al, 2007; Hung WW et al, 2009).

In our present study, presence of frontal EEG slow wave pattern in comparison to their age matched healthy controls is suggestive of signs of brain dysfunctions in these patients. This was supported by a similar study showing impairment of pulmonary function correlating with the degree of alpha frequency slowing, and the slowest alpha frequencies occurred in those COPD patients with the lowest FEV1/FVC ratios (Reeves RR, et al, 2000). These can be attributed to frontal hypoperfusion in COPD (Hung WW et al, 2009). Latter parallels with our results, where we observed a relative decrease in frontal regional oxygen saturation (rSO2) and relative decrease in peripheral oxygen saturation in COPD than controls even though within normal limits.

We also found in our study that severity of airflow obstruction, as observed by FEV1% predicted, had greater effects on cognitive domains than the milder form of disease. Again, cognitive domains like global cognitive functions (FolsteinMMSE), visuospatial, motor constructional abilities and executive functions(CDT and TMT-A) were impaired with severity of airflow obstruction.

CDT performance is attributed to prefrontal cortex, especially to the time taken to complete the task, as it requires more planning(Shoyama M, et al, 2008).Functional magnetic resonance imaging have shown that bilateral frontal lobe activation occurs during performing CDT, along with other regions (Ino T, et al, 2003). Certain studies had observed that patients with focal lesions, circumscribed to the frontal lobes, have reported CDT impairment (Freedman M et al, 1994).

The trail making test (TMT) is known to be a good estimator of frontal lobe function and a sensitive indicator of executive function. (Soury S et al, 2005). From previous studies, lesions to the frontal cortex and its basal ganglia–thalamic connections, was attributed to impairment of executive control functions (ECF)(Donald R, et al, 2002). The results acquired from our study points to the association of COPD and impairment of cognitive functions pertaining to frontal lobe.

Our study matched with few other studies in which prevalence of cognitive impairment was associated with severity of COPD disease, being 3.9% among patients with mild grades of COPD, 5.7% among patients with moderate and 7.7% among patients with severe grades (Thakur N, et al, 2010). In fact, a relationship has been found between the Mini-Mental State Examination score and the severity of COPD (Lima OMet al, 2007).

But there are studies that had showed patients with mild hypoxemia did not show much difference in cognition than their healthy counterparts, cognitive function is affected by hypoxemia only when the latter is severe (Salik Yet al, 2007).

In our previous study, we observed that a significant impairment in orientation and registration was seen along with loss of attention, verbal language and recall in severely (<90%) and moderately hypoxemic (90-95%) patients.And, with increasing duration of the disease there were impairmentof cognitive flexibility, visual search, motor performance, and executive function (John J, et al, 2015). Grant et al, in their study demonstrated that there is 77% prevalence of cognitive impairment in patients with hypoxemic COPD (Grant I, et al, 1982).

The term "executive functions", wascoined by Lezak, refers to skills involved in formulating goals, planning their achievement, and effectively performing behaviors (LezakMD, et al, 2004). COPD patients were seen to be showing a slow processing speed when assessed for executive functions (Dodd JW et al, 2013). It was found that twenty percent of patients with exacerbated COPD exhibit a loss in processing speed which is significantly enough to be considered pathological.

Archana C Dogra et al, in their study found, all the domains of cognition were variably affected, among which most affected cognitive functionswere visuospatial and motor constructional abilities.Early stages of COPD affected attention problems and information processing speed but as disease progresses the impairments become more severe and diffuse (Archana C Dogra et al, 2015). Some studies have also observed involvement of memory and language in these patients especially in the early stages of the disease. (Archana C Dogra et al, 2015).

According to Villeneuve et al.,verbal memory and learning was also affected in patients with COPD (Villeneuve S, et al, 2012). In such patientsprevalence of impairment in visuospatial memory and intermediate visual memory was 26.9% and 19.2%, respectively (Antonelli-Incalzi R, et al, 2008). It is observed that even when the data are adjusted

for age, gender, smoking history, and level of education, there is an increased association of COPD with an increased risk of impaired cognitive function (Thakur N, et al, 2010).

As it is already stated in several studies, low peripheral oxygen saturation (≤ 88%) has been strongly associated with a risk of cognitive impairment in patients with COPD, it is seen that home oxygen therapy has been seen to have lessened the burden of hypoxemia and reduced the risk of developing cognitive impairment (Thakur N, et al, 2010).

Thus, it is quite indicative from our findings that, with increasing airflow obstruction, chronic hypoxemia ensues which could affect the cerebral hypoxemia attributing to cognitive dysfunction.

Several studies had expressed various results in terms of cognitive dysfunction and its association to various parameters of the disease. The reasons for this variation across studies could be because age of the patients included in the studies, as well as the use of different cognitive tests.

Thus, we suggest that a cognitive scoring should be a routine component of the evaluation of COPD patients to improve the quality of life in these patients by early diagnosis and intervention.

Limitations of the Study

Our study consisted ofsmall sample size that had accounted for weak outcomes for certain measures.We did not conduct neuroimaging studies in our study population to identify the cerebral perfusion. It was costlyand is not usually recommended for COPD patients.

Conclusions:-

From lot of previous evidence, it is quite indicative that there is a strong link between chronic obstructive pulmonary disease and cognitive dysfunction. Although various mechanisms have been put forward for the development of same, still, of which hypoxemia stands the most unshaken cause for cerebral dysfunction.

In the present study, we found a relative frontal hypoxemia, decreased peripheral oxygen saturation and presence of EEG slow wave pattern in COPD group in comparison to their healthy control group. We also observed that with progressive severity in airway obstruction risk of cognitive impairment were more, especially involving global cognitive functions, visuospatial, motor constructional abilities and executive functions. Thus, suggesting that low lung functioning may contribute to cognitive disorders by decreasing the oxygen delivery to brain neurons leading to cognitive dysfunction. Based on ourobservation, we would like to suggest that a routine inclusion of the neuropsychological battery of test in COPD patients to assess cognitive impairment.

Future concerns would be to do a follow up study in the patients with COPD of same sociodemographic profile and investigate thoroughly both in terms of lung function and neuropsychological assessment along with neuro imaging for blood flow in various areas of brain. Also, it is imperative to understand from which stage of disease, the cognitive dysfunction if present, can be reverted.

Conflicts of Interest:

The authors report no conflicts of interest in this work.

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