ORIGINAL ARTICLE

PERIPHERAL NEUROPATHY AND ABNORMAL VISUAL EVOKED POTENTIALS IN STABLE PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Objective: To know the frequency and predictors of peripheral neuropathy and the abnormal visual evoked potentials in stable patients with chronic obstructive pulmonary disease.

Material & Methods: All consecutive patients of stable COPD of age ≥ 40 years were screened for peripheral neuropathy. Total 57 patients of stable COPD of age ≥ 40 Years were selected. Spirometric examination was done in all the patients using an electronic portable based spirometer with printer. Neurophysiological evaluation (neurological disability score-NDS), Mini Mental State Examination-questionnaire (MMSE), Visual analogue scale (VAS) were done on all subjects. The following nerves were evaluated for latency, amplitude, and conduction velocity. For motor nerve conduction: - median, ulnar, common peroneal and tibial nerves were evaluated. For sensory nerve conduction: - median, ulnar and sural nerves were evaluated. VEP was evaluated in all the 57 subjects. The continuous variables were described using means and analysis was done using independent t test.

Results: Sub-clinical neuropathy was seen in 28 (49%) out of 57 stable COPD patients. Sensory neuropathy was seen in majority of patients. Sural nerve was the most commonly involved nerve. Neuropathy was predominantly axonal in nature. Abnormal VEP was found in 18 (32%) patients in whom P100 latency was more than 107.

Conclusions: Electro-physiological testing showed the presence of peripheral neuropathy in 49% patients and abnormal VEP in 32% patients with stable COPD, who had no neurological symptoms. Maximum number of stable COPD patients with severe obstruction, heavy smoking index and bio-mass exposure had peripheral neuropathy, but statistically this was not found significant.

Key words: COPD, Spirometry, VEP, Peripheral neuropathy.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has been a major public health problem worldwide. It is one of the leading causes of morbidity and mortality in the world and is associated with significant economic burden and poor quality of life in the patient. According to the Global Initiative for Obstructive Lung Disease (GOLD).[1], COPD is a common preventable and treatable disease and is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the lungs and airways to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. According to the World Health Organization (WHO), an estimated 3 million people die due to COPD every year, making it the fourth leading cause of death in the world.[2] Co-morbidity refers to a disease that co-exists with another primary disease. Co-morbidities associated with COPD can contribute to the ill-effects of the primary disease and further complicate its management. Co-morbidities

associated with COPD patients include cardiovascular diseases, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, lung cancer and peripheral neuropathy. Peripheral neuropathy is an important co-morbidity in COPD patients. About one-third of COPD patients show clinical evidence of peripheral neuropathy and two-thirds have subclinical neuropathy. [5]

Therefore, the presence of subclinical neuropathy is much higher than clinical neuropathy.

Visual evoked potentials are also affected in these patients. Visual evoked potentials provide a quantitative and qualitative measure of the optical pathway. The present study was designed to assess the prevalence, characteristics, and predictors of peripheral nerve involvement and visual evoked potentials abnormalities in stable COPD patients.

MATERIAL AND METHODS

This study was cross sectional in nature and was conducted in the Department of Pulmonary Medicine and Neurology at Indira Gandhi Medical College, Shimla. All consecutive patients of stable COPD of age ≥ 40 years were screened for peripheral neuropathy. Only stable COPD patients of age ≥ 40 Years with no history of exacerbation in preceding six weeks were selected. Exclusion criteria: COPD patient with acute exacerbation within last six weeks, patients with impaired vision and patients with other associated diseases causing peripheral neuropathies for example: Diabetes, Alcoholism, Uremia, Leprosy, Malignancy and use of neurotoxic drugs. All the eligible patients fulfilling the inclusion and exclusion criteria were then subjected to detailed personal history and history pertaining to the disease. COPD was diagnosed on the basis of risk factors, symptoms, physical examination and post-bronchodilator (grading of COPD was done as per GOLD criteria) spirometry. The demographic features of patient included namely age, sex, occupation, demography, smoking habits, smoking index and bio-mass exposure. Oxygen Saturation (SpO_2) was measured in all the patients by using Pulse Oximeter (Model: CMS50D). Complete blood count, Erythrocyte sedimentation rate (ESR), Urinalysis, Chest X-ray, Blood sugar, Serum protein levels, Renal Function Test (RFT)/ Liver Function Test (LFT)/ Thyroid Function Test (TFT), Human Immunodeficiency virus test were done to exclude patients with other associated diseases causing peripheral neuropathies.

Spirometric examination was done in all the patients using an electronic portable based spirometer with printer (MODEL-VITALGRAPH-COMPACT-BUCKINGHAM, ENGLAND). It fulfilled the accuracy and precision criteria as laid down by American Thoracic Society/European Respiratory Society. Spirometric data was recorded as absolute measures and percent of predicted for age, sex, height and weight. Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 Second (FEV_1) and ratio of FEV_1/FVC were measured. At least three measurements were made for each lung function variable to ensure reproducibility and best measurement was accepted for final analysis. Grading of COPD was done as per GOLD guidelines.

The following right sided nerves were evaluated for latency, amplitude, and conduction velocity. For motor nerve conduction: - median, ulnar, common peroneal and tibial nerves were evaluated. For sensory nerve conduction: - median, ulnar and sural nerves were evaluated. MODEL: A4 channel EMG machine of sigma enterprises from Germany was used for the nerve conduction study.

For visual evoked potentials A 4 channel EMG machine of sigma enterpriser from Germany was used for VEP studies. Electrodes were attached at the Fz and Oz. The ground electrode was placed at FPz. The input impedance was kept below 5 kΩ. Each subject was seated comfortably on a chair in a quiet darkened room 140 cm away from the screen and instructed to fix his one eye on a small red cross at the centre of the screen while the other eye was fully covered with eye patch. A black and white chequered board was generated by an electronic pattern generator of the 4 channel EMG machine of sigma enterpriser from Germany evoked potential recorder. The rate of pattern reversal was 2 Hz and an average of 100 responses was recorded. At least two trials were always obtained to ensure reproducibility of the VEP pattern. The absolute latencies and amplitude of positive and negative waves were recorded. Neurophysiological evaluation (neurological disability score-NDS) was done on all subjects. The mental status was also assessed using a questionnaire (Mini Mental State Examination-questionnaire). Normal cutoff value was 19 for uneducated patient, 23 for elementary or junior high school pass, 27 for high school pass and 29 for college graduate.[6] Visual Ana-

logue Scale (VAS) was done for neurological symptoms, for example, tingling sensations, numbness and loss of perception. It had markings from 0 to 100. The zero mark was used for absence of symptoms and 100 marks for the maximum symptoms.

The continuous variables were described using means and statistical analysis was done using independent t test. The categorical variables distributed in the study population were described in percentages and analyzed using chi square test, whichever applicable. Two tailed significance $p<0.05$ was taken to be statistically significant. Statistical analysis was done using Epi Info Version 7 software.

RESULTS

Total 57 patients were included in the study. Patients were divided into two age groups, 40 to 60 years and 60 to 80 years. Mean age of the patients was 61 years. Mean age among male patients was 62 years and, among females, it was 60 years. Men constitute 77% of the total patients and female constitutes 23%. Electro-physiological testing showed presence of peripheral neuropathy in patients of stable COPD, who had no neurological symptoms. Subclinical neuropathy was seen in 28 (49%) patients of stable COPD patients. Sensory neuropathy was seen in majority of patients. Sural nerve was most commonly involved. Neuropathy was predominantly axonal in nature. Maximum number of stable COPD patients with severe obstruction, heavy smoking index and bio-mass exposure had peripheral neuropathy. However, the correlation was not statistically significant, that may be due to small sample size. Abnormal VEP was found in 18 (32%) patients and it was found mainly in patients with severe obstruction, heavy smoking index and bio-mass exposure. However, the correlation was not statistically significant, that may be due to small sample size. A study with larger sample size may help in determining the predictors of peripheral neuropathy in stable COPD patients in future.

It was found that 6 patients in the age group 40-60 years and 12 patients in the age group 60-80 years had neuropathy, with p-value 0.20 (NS) whereas abnormal VEP was found only in 2 patients in the age group 40-60 years and 10 patients in the age group 60-80 years with p-value 0.06 (NS).

Table 1: Prevalence of risk factors among total 57 patients in the present study

Smokers	Percentage
Current smokers	69%
Non smokers	5%
Ex smokers	26%
Smoking Index (Mean±SD)	666.66±351.59
Biomass exposure (percentage)	49 (86%)
Duration of COPD	
<5 years	40 (70%)
>5 years	17 (30%)

Table 2: Age group-wise Neuropathy & Abnormal Visual Evoked Potential in the present study

Age (years)	Neuropathy	No Neuropathy	P value
40-60	6	9	0.20
60-80	12	7	
	VEP (Abnormal)	VEP (Normal)	
40-60	2	13	0.06
60-80	10	9	

Table 3: Gender-wise Neuropathy & Abnormal Visual Evoked Potential in the present study

Gender	Neuropathy	No Neuropathy	p-value
Male	16	12	0.33
Female	2	4	
	VEP (Abnormal)	VEP (Normal)	p-value
Male	10	18	0.93
Female	2	4	

Table 4: Grading of Smoking Index-wise Neuropathy & Abnormal Visual Evoked Potential in the present study.

Smoking Index	Neuropathy	No Neuropathy	p-value
Mild <100	0	0	
Moderate 100-300	5	3	0.44
Heavy >300	23	26	
	VEP (Abnormal)	VEP (Normal)	
Mild <100	0	0	
Moderate 100-300	6	4	0.06
Heavy >300	12	35	

It was found that 16 male patients and 2 female patients had neuropathy and p-value was 0.33 (NS), whereas abnormal VEP was found in 10 male patients and 2 female patients with p-value 0.93 (NS).

Different grades of smoking index were found among various patients. It was found that out of total 28 patients with neuropathy, 23 patients (82%) has smoking index more than 300 and 5 patients (18%) has smoking index 100-300 with p-value 0.44 (NS), whereas abnormal VEP was found in 12 (67%) patients with smoking index more than 300 and 6 (33%) patients with smoking index 100-300 with p-value 0.06 (NS).

DISCUSSION

We planned to evaluate the frequency and predictors of peripheral neuropathy and VEP in stable patients with COPD. Neuro-physiological evaluation was done in all subjects by neurological disability score (NDS). The mental status was assessed using a questionnaire (MMSE-questionnaire). Visual analogue scale (VAS) was used for neurological symptoms for example tingling sensations, numbness and loss of perception. Mini mental statement score, neurological disability score and visual analogue score were found normal in all the patients.

Total 57 patients were included in the study. Total numbers of patients with sub-clinical peripheral neuropathy were 28. The predominant type of neuropathy in the present study was axonal neuropathy noted in 21 (75%) patients, whereas; demyelinating neuropathy was found in 3 (11%) patients and mixed axonal and demyelinating neuropathy in 4 (14%) patients. Predominant sensory involvement was observed in the present study and isolated sural neuropathy was found in 12 patients (42%). Similar results were found in other studies,[7,8,9] although the contributing causative factor in all these studies were different. Faden *et al.*[8] found higher incidence of sensory neuropathy affecting the sural nerve (20 subjects), ulnar nerve (11), radial nerve (8), and median nerve (7).

Among 21 patients with axonal neuropathy, 13 (62%) patients had severe obstruction, 5 (24%) patients had moderate obstruction and 3 (14%) patient had mild obstruction. Eight (38%) patients with axonal neuropathy were in the age group 40-60 years and other 13 (62%) patients were in the age group 60-80 years. Fifteen (71%) patients with axonal neuropathy were smokers with smoking index more than 300 and 6 (29%) patients were ex-smokers with smoking index more than 300. Similarly cigarette smoking as a contributing causative factor was found in other studies.[8,10] Nineteen (90%) patients with axonal neuropathy had bio-mass exposure whereas 2 (10%) patients had no bio-mass exposure. Among 3 patients with demyelinating neuropathy, 2 (67%) patients had severe obstruction and one (33%) patient had moderate obstruction. All the 3 patients with demyelinating neuropathy were in the age group 60-80 years. All of them were smokers and had biomass exposure. It was observed in the present study that neuropathy was more common in patients who had severe obstruction in spirometry, those who were smokers with smoking index more than 300 and those who were exposed to bio-mass fuel, although, statistically it was non-significant. In another study, Agarwal Dipti et al.[4] observed 5 out of 30 COPD patients to have predominantly sensory axonal peripheral neuropathy. But this study was different from our study because they compared these 30 COPD patients with healthy volunteers.

Abnormal VEP was found in 18 (31%) patients out of total 57 patients. Out of these 18 patients, severe obstruction was found in 12 (66%) patients, moderate obstruction in 3 (17%) patients and mild obstruction in 3 (17%) patients. Thirteen (72%) patients were smokers and 5 (28%) patients were ex-smokers. Fourteen (78%) patients had bio-mass exposure and 4 (22%) patients had no bio-mass exposure. The majority of patients with abnormal VEP had higher smoking index of >300 and biomass fuel exposure. Manal et al. and sezer et al. also demonstrated presence of abnormal VEP in COPD patients.[11,12] In another study by P P Gupta et al.[3] found 23 of the 40 stable COPD patients having significant VEP abnormality detected on electrophysiologic evaluation when they compared with healthy volunteers.

We also compared the smoking habits and corresponding smoking index, bio-mass exposure and duration of COPD with neuropathy and VEP. Total 28 patients were diagnosed with neuropathy which comprises of 20 (71%) smokers and 8 (29%) ex-smokers. Abnormal VEP was found in total 18 patients, among these 13 (72%) patients were smokers and 5 (28%) were ex-smokers. Among 28 patients with neuropathy, 23 (82%) had smoking index >300 and 5 (18%) had smoking index of 100 to 300. Similarly, out of 18 patients with abnormal VEP, 12 (67%) patients had smoking index >300 and 6 (33%) patients had smoking index of 100 to 300. Agrawal D *et al.* [4] observed that 5 COPD patients with peripheral neuropathy had significantly heavier habits of

smoking, as well as the duration of illness compared to COPD patients with no peripheral neuropathy.

Bio-mass exposure was reported in 49 patients and 8 patients had no biomass exposure. Among the 49 patients with biomass exposure, 26 (53%) patients had neuropathy and 23 (47%) patients had no neuropathy. Abnormal VEP was found in 14 (29%) patients out of the total 49 patients. Among 28 patients with neuropathy, 16 (57%) patients had duration of COPD less than 5 years and 12 (43%) patients had duration of COPD more than 5 years. Out of 18 patients with abnormal VEP, 10 (56%) patients had duration of COPD less than 5 years and 8 (44%) patients had duration of COPD more than 5 years.

The presumed etiopathogenic factors reported in previous studies were chronic hypoxia, tobacco smoke, malnutrition and toxic substances. But in our study the main contributing factor could be severity of obstruction, smoking and bio-mass exposure. Previous study done by Faden *et al.*[8] found that a substance or substances in cigarette smoke, such as nicotine, taken on a long-term basis, may be toxic to peripheral nerves. In the present study, the same could be contributing factor for peripheral neuropathy. However, these factors were not found significant due to small sample size in our study.

To conclude, in the present study of 57 patients of stable COPD, Electro-physiological testing showed presence of peripheral neuropathy, who had no neurological symptoms. Sub-clinical neuropathy was seen in 28 (49%) patients of stable COPD patients. Sensory neuropathy was seen in majority of patients. Sural nerve was most commonly involved. Neuropathy was predominantly axonal in nature. Maximum number of stable COPD patients with severe obstruction, heavy smoking index and bio-mass exposure had peripheral neuropathy. However, the correlation was not statistically significant, that may be due to small sample size. Abnormal VEP was found in 18 (32%) patients and it was found mainly in patients with severe obstruction, heavy smoking index and bio-mass exposure. However, the correlation was not statistically significant, that may be due to small sample size. The major limitation was small sample size in our study; therefore, we recommend a comparatively larger sample size in future studies to find out the statistically significant correlation.

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