Subclinical peripheral neuropathy in stable middle-aged patients with chronic obstructive pulmonary disease

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ABSTRACT

Introduction: Presently, there are few studies addressing the subject of peripheral neuropathy in patients with chronic obstructive pulmonary disease (COPD). Consequently, there is a dearth of evidence and awareness of subclinical neuropathy in stable COPD patients with no significant hypoxaemia, particularly in the age group of 40-60 years. The present study was designed to evaluate the subclinical peripheral neuropathy in this study group.

Methods: 60 subjects were included in the study. The COPD group comprised 30 male smokers with stable COPD, aged between 40 and 60 years and with no clinical neuropathy; and 30 age-matched healthy male volunteers served as the control group. The following nerves were evaluated for latency, amplitude and conduction velocity: for motor nerve conduction – median nerve, ulnar nerve, and common peroneal nerves; and for sensory nerve conduction – median nerve, ulnar nerve, and sural nerves.

Results: Five out of 30 COPD patients had peripheral nerve impairment on electrophysiological evaluation. In these patients, we found decreased amplitude and conduction velocity in all examined sensory nerves; however, the conduction velocity was found to be more than 70 percent of the predicted value. These findings were suggestive of predominantly sensory (with milder involvement of motor nerves) axonal polyneuropathy.

Conclusion: We observed five out of 30 COPD patients to have predominantly sensory axonal peripheral neuropathy. These five COPD patients had significantly higher consumption of cigarettes, longer duration of illness and advanced airflow obstruction when compared to COPD patients with no peripheral neuropathy.

Keywords: chronic obstructive pulmonary disease, electrophysiological study, nerve conduction, peripheral neuropathy, subclinical neuropathy

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major public health problem and, currently, the fourth leading cause of death worldwide.[1] A further increase in prevalence, as well as mortality of the disease, is predicted for the coming decades. Peripheral neuropathy is a failure of the nerves that carry information to and from the brain and spinal cord. There are numerous reasons for peripheral neuropathy; chronic respiratory insufficiency has been implicated as one of the factors in previous studies.[2-10] However, there has been non-uniformity in the characteristics of the study subjects included by these studies. As observed in general clinical practice, the majority of patients experience a stable course of COPD and it is of practical interest to study the prevalence of peripheral neuropathy in such patients. In our present study, stable COPD patients belonging to the age group of 40–60 years, and having no clinical evidence of peripheral neuropathy, were included and evaluated for nerve conduction to detect subclinical peripheral neuropathy.

METHODS

The study was conducted at the Departments of Physiology and Respiratory Medicine at our Institute. The study was approved by Institutional Board of studies and by the ethical committee. We included 60 male subjects between 40 and 60 years of age, involving 30 patients with COPD and 30 age-matched healthy volunteers. All subjects gave their explicit written consent.

The diagnosis of COPD was based on modified criteria defined in the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines.[11] All COPD patients were smokers and had post-bronchodilator FEV_1 less than 80% of the predicted value, along with an FEV_1/FVC not more than 70%. They had an increase in FEV_1 less than 200 ml or less than 12% of baseline value, 20 minutes after two puffs of inhaled salbutamol that was given via a metered-dose inhaler using a spacer. All patients with COPD had experienced of symptoms for five years or more. All patients had a stable course of their disease with regular follow-up for one year preceding this study and no hospitalisation for COPD-related illness for six months prior to the commencement. There was no clinical evidence of any peripheral neurological deficit / neuropathy in any patient. All subjects were also evaluated for the presence of any known cause of peripheral neuropathy (Table I). Patients having concomitant diabetes mellitus, chronic alcoholism, uraemia, cystic fibrosis, sarcoidosis, leprosy, malignancy, any hereditary disorders involving peripheral nerves, history of intake of any neurotoxic drug, or history of any traumatic lesion possibly affecting peripheral nerve functions, were excluded from the study. All healthy volunteers were non-smokers. They were selected from medical/paramedical staff of our Institute; some healthy attendants of the patients were also included in the control group. All subjects underwent pulmonary function testing, pulse oximetry and electrophysiological studies.

The pulmonary function tests were carried out on Vitalograph-Compact (Vitalograph Inc, Kansas, USA). Spirometric – indices were calculated using best out of three technically-satisfactory performances in accordance to the recommendations of the American Thoracic Society.[12] The following parameters were recorded: peak expiratory flow rate (PEFR), forced vital capacity (FVC), forced expiratory volume in first second (FEV_1),

Table I. Evaluation for known causes of neuropathy.

Disease/disorder	Clinical evaluation	Relevant investigations	Another consultation
Diabetes mellitus	Polyuria, polydipsia	Fasting & postprandial plasma glucose, glucose tolerance test	Diabetic clinic
Chronic alcoholism	Clinical history	Liver function tests, mean corpuscular volume, serum uric acid, serum triglycerides	Internal medicine & psychiatry
Uraemia	Clinical symptoms	Blood urea nitrogen, serum creatinine, ultrasonography of kidneys	Nephrology clinic
Cystic fibrosis	Clinical presentation, family history	Chest radiographs, sweat chloride test	–
Sarcoidosis	Clinical features	Chest radiographs, HRCT thorax, serum & urine calcium, serum angiotensin-converting enzyme levels	Internal medicine, skin
Leprosy	Skin lesions, nerve thickenings	Biopsy of skin / nerve	Skin & neurological
Malignancy	Clinical history	Relevant radiological evaluation, histopathological examination of FNAC specimen	Internal medicine, surgery, suggestive specialty on history
Hereditary disorder involving peripheral nerves	Clinical features	Histopathological examination wherever indicated	Neurological
Neurotoxic drug	Clinical history	Drug toxicity evaluation as per history	Internal medicine
Traumatic lesion possibly affecting peripheral nerve	History of trauma	Radiological evaluation	Orthopaedic, surgery
Clinical peripheral neuropathy	Symptoms & signs	–	Neurological

HRCT: high-resolution computed tomography; FNAC: fine-needle aspiration cytology.

and FEV_1/FVC %. The pulse oximetry test was carried out on a pulse oximeter (Model MP-110, MEK Company, Korea).

Electrophysiological studies were carried out on a computerised nerve conduction testing equipment (RMS EMG EP MARK II, Recorders & Medicare Systems, Chandigarh, India). The various settings were as shown below:

1. Filter: for motor nerve conduction, low cut: 2–5 Hz, high cut:10 KHz and for sensory nerve conduction, low cut: 5–10 Hz, high cut: 2–3 KHz.
2. Amplification between 20,000 and 100,000 times.
3. Electrode impedance was kept below 5 kΩ.
4. Sweep speed for sensory nerve conduction: 1–2 ms/division.
5. Sweep speed for motor nerve conduction: 2–5 ms/division.
6. Stimulator: stimulus duration of 50 μs to 1000 μs and current 0–100 mA are required for effective nerve stimulation. Supramaximal stimulation (10%–30% more than the current required for maximal action potential) was used.

We adopted the established methodology described by Mishra and Kalita.[13] Patients were made to relax on a couch in a soundproof and air-conditioned examination room to avoid muscle artifacts. The following nerves were evaluated for latency, amplitude and conduction velocity: for motor nerve conduction – median nerve, ulnar nerve, and common peroneal nerves; and for sensory nerve conduction – median nerve, ulnar nerve, and sural nerves.

The motor nerve was stimulated at two points along its course and action potential was recorded with a pair of surface electrodes: an active electrode was placed on the belly of the muscle and an indifferent (reference) electrode was placed on the tendon. A ground electrode was placed between the stimulating and recording electrodes. The amplitude of compound muscle action potential (CMAP) was measured from baseline to negative peak. Motor nerve conduction velocity was calculated by the distance between points of two stimulations by latency of that segment. For median motor nerve conduction evaluation, the recording electrode was placed close to the motor point of abductor pollices brevis and the indifferent (reference) electrode was placed 3 cm distal at the first metacarpophalangeal joint. The stimulation was given at the wrist (3 cm proximal to the distal wrist crease) and at the volar crease of the brachial pulse. During ulnar motor nerve conduction evaluation, the nerve was stimulated at two sites – at the wrist and at a point below the elbow. The CMAP was recorded from hypothenar muscles. The active electrode was placed over the belly of abductor digiti minimi and the reference electrode was placed over the tendon 3 cm distal to the active electrode. For common peroneal nerve motor nerve conduction evaluation, the surface recordings were obtained from extensor digitorum brevis and the stimulation was given at the ankle and 2 cm distal to the fibular neck (below knee).

The sensory nerve conduction was measured antidromically. Sensory nerve action potential (SNAP) amplitude was measured from the baseline to the negative peak. Latency was the time from the stimulus artifact to the first negative deflection of SNAP. Sensory nerve conduction velocity was measured by stimulating at a single site. The sensory conduction velocity was calculated by dividing the distance between the stimulating and the recording sites by latency. Median sensory nerve conduction recording was made from the ring electrode at the interphalangeal joint of the index finger and stimulation was given at the wrist. For the ulnar sensory nerve conduction study, stimulation was carried out by a cathode placed 3 cm proximal to the distal crease at the wrist and SNAP was recorded from the fifth digit. The sural sensory nerve was stimulated 14 cm proximal to the recording electrode distal to the lower border of gastrocnemius at the junction of the middle and the lower third of the leg, the nerve was recorded by surface electrode between the lateral malleolus and the tendoachillis.

For statistical analyses, the data of healthy volunteers and COPD patients was analysed by incorporating the same in two different groups. The group means and the standard deviations for each variable were calculated in

Table II. Characteristics of healthy volunteers and COPD patients.

Parameters	Healthy volunteers	COPD patients
n	30	30
Gender	Male: 30 Female: nil	Male: 30 Female: nil
Age (mean ± SD) (years)	55.20 ± 5.92	55.20 ± 5.92
Height (mean ± SD) (cm)	168.60 ± 3.34	163.20 ± 6.09
Smoking (mean ± SD) (pack years)	Nil	39.97 ± 14.12
Duration of illness (mean ± SD) (years)	Nil	11.17 ± 4.56
FVC* (L)	4.136 ± 0.347	2.497 ± 0.402
FEV_1* (L)	3.525 ± 0.338	1.162 ± 0.299
PEFR* (L/min)	523.27 ± 30.24	146.79 ± 53.11
FEV_1/FVC %*	85.2 ± 3.2	46.7 ± 10.4
SaO_2 (%)*	97.8 ± 0.4	95.6 ± 1.8

* The difference between the two groups was statistically highly significant.

the healthy volunteers group and COPD group separately. The statistical significance of difference between group means of various parameters between healthy volunteers group and COPD group was analysed by using independent sample *t*-test – *t*-test and a p-value < 0.05 was taken as being statistically significant. Individual patients in the COPD group having abnormal amplitude and/or conduction velocity in any one or more nerves beyond the range of mean ± 2 standard deviations were selected as having the significant peripheral neuropathy. The characteristics of these patients were compared with those of COPD patients showing no peripheral neuropathy. All statistical analyses were carried out with the help of the Statistical Package for Social Sciences software version 10.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

The comparative analyses revealed that the height in the COPD group was statistically less than that in the healthy volunteers group ($p < 0.01$) (Table II); however, no confounding effect of height over impairment of nerve function was noted. The difference between the healthy volunteers group and COPD patients group with respect to FVC, FEV_1, PEFR, FEV_1/FVC %, and oxygen saturation (SaO_2) was significant statistically ($p < 0.001$) as was expected. The amplitude, latency and conduction velocity of median motor nerve, ulnar motor nerve and common peroneal motor nerve in the COPD group and healthy volunteers group were not significantly different (Table III). The amplitude of median sensory nerve in the COPD group was decreased. The latency of the median sensory nerve in the COPD group was significantly increased. There was no statistically significant difference between the conduction velocity of the median sensory nerve in healthy volunteers group and that in the COPD patients group. Although the amplitude of the ulnar sensory nerve was decreased and the latency of ulnar sensory nerve in the COPD patients group was increased when compared to the respective parameters in the healthy volunteers, these changes were not statistically significant ($p > 0.05$). Both the amplitude and conduction velocity of the sural sensory nerve in the COPD group were decreased, These findings were statistically highly significant. The latency of the sural

Table III. Nerve conduction parameters of healthy volunteers and COPD patients.

Nerve	Amplitude	Latency (ms)	Conduction velocity (m/s)
Median motor (mV)			
COPD patients	6.920 ± 2.325	4.149 ± 0.484	56.557 ± 4.929
Healthy volunteers	6.943 ± 2.325	3.906 ± 0.612	57.703 ± 5.848
p-value	**0.972**	**0.093**	**0.415**
Ulnar motor (mV)			
COPD patients	7.161 ± 1.887	3.789 ± 0.546	59.556 ± 5.695
Healthy volunteers	7.930 ± 2.230	3.531 ± 0.589	61.346 ± 6.807
p-value	**0.155**	**0.084**	**0.274**
Median sensory (μV)			
COPD patients	30.160 ± 11.893	3.059 ± 0.369	55.763 ± 6.150
Healthy volunteers	38.063 ± 17.344	2.842 ± 0.423	57.087 ± 5.833
p-value	**0.044**	**0.047**	**0.396**
Ulnar sensory (μV)			
COPD patients	27.590 ± 12.276	2.738 ± 0.376	54.127 ± 5.471
Healthy volunteers	34.710 ± 17.075	2.554 ± 0.431	54.990 ± 5.690
p-value	**0.069**	**0.084**	**0.551**
Common peroneal motor (mV)			
COPD patients	4.108 ± 2.035	7.437 ± 0.958	46.612 ± 4.503
Healthy volunteers	4.942 ± 2.270	7.002 ± 1.050	48.495 ± 4.610
p-value	**0.140**	**0.099**	**0.115**
Sural sensory (μV)			
COPD patients	10.973 ± 5.763	3.043 ± 0.360	46.883 ± 5.678
Healthy volunteers	17.927 ± 8.207	2.775 ± 0.426	51.253 ± 5.945
p-value	**0.001**	**0.011**	**0.005**

Table IV. Comparison of parameters in five COPD patients showing significant peripheral neuropathy with COPD patients having no peripheral neuropathy

Parameters	COPD patients with no peripheral neuropathy (n = 25) Mean ± SD	Individual patients with peripheral neuropathy				
		1	5	17	23	24
Age (years)	54.80 ± 6.21	59	55	60	58	59
Height (cm)	162.84 ± 5.81	166	163	159	170	168
Smoking (pack years)	35.64 ± 10.96	60	45	70	45	60
Duration of illness	9.84 ± 3.58	20	15	18	20	18
FEV_1 (L)	1.2324 ± 0.2710	0.80	0.95	1.02	1.01	0.85
PEFR (L/min)	159.98 ± 47.69	58	88	97	101	94
Amplitude, median motor nerve (mV)	7.160 ± 2.169	3.0	2.9	5.2	3.7	5.4
Conduction velocity, median motor nerve (m/s)	57.004 ± 4.282	46.7	49.7	54.1	49.0	53.8
Amplitude, ulnar motor nerve (mV)	7.2640 ± 1.660	3.5	4.2	6.1	4.4	6.1
Conduction velocity, ulnar motor nerve (m/s)	60.039 + 4.873	47.7	51.6	56.9	50.8	56.6
Amplitude, median sensory nerve (μV)	32.563 ± 9.524	7.8	10.8	8.6	12.1	8.7
Conduction velocity, median sensory nerve (m/s)	57.018 ± 4.310	42.8	49.9	44.6	49.2	43.2
Amplitude, ulnar sensory nerve (μV)	29.893 ± 10.217	6.5	7.3	6.7	8.0	6.9
Conduction velocity, ulnar sensory nerve (m/s)	55.062 ± 4.198	44.8	47.6	45.8	48.9	43.9
Amplitude, common peroneal motor nerve (mV)	4.3176 ± 1.7090	1.22	1.20	1.20	1.36	3.12
Conduction velocity, common peroneal motor nerve (m/s)	47.290 ± 3.530	40.1	40.6	40.2	40.7	44.8
Amplitude, sural sensory nerve (μV)	12.752 ± 4.512	2.0	3.2	2.1	3.5	2.1
Conduction velocity, sural sensory nerve (m/s)	48.948 ± 3.479	35.9	41.3	36.2	42.8	38.5

sensory nerve in the COPD group was significantly higher when compared to the healthy volunteers.

Five COPD patients had abnormalities in nerve conduction beyond the mean range of ± 2 standard deviations (Table IV). These five patients consumed more cigarettes (45 pack years or more) when compared to the mean of COPD patients with no peripheral neuropathy (35.64 ± 10.96 pack years). A significantly longer duration of illness was observed in each of these five patients compared to the COPD patients without any peripheral neuropathy. Moreover, these five COPD patients with peripheral neuropathy had severe airflow obstruction (a decrease in FEV_1 and PEFR) when compared to COPD patients with no peripheral neuropathy (Table IV). Median motor, ulnar motor and common peroneal motor nerve impairments were not significant in five COPD patients with peripheral neuropathy (Table IV). We found decreased amplitude and conduction velocity of median sensory nerve, ulnar sensory nerve, sural sensory nerve in each of these five COPD patients.

Table V. Previous studies on COPD patients.

Study	Clinical peripheral neuropathy	Patients with hypoxaemia	Prevalence	Type of peripheral neuropathy	Factors correlated
Faden et al[2]	Yes	–	20/23	Predominantly sensory, sural most common	Cigarette consumption
Kiessling et al[3]	Yes	Yes	10/59 in those with PaO_2 > 60 Torr	Sensory, distal, leg accentuated	Hypoxaemia
Pfeiffer et al[4]	Yes	Yes	3/20 with mild hypoxaemia	Sensorimotor, distal	PaO_2 and age
Nowak et al[5]	Yes	Yes	20% clinical & 4% subclinical	Lower limbs	Age, degree of hypoxaemia
Jarratt et al[6]	Yes	–	5%–18% had peripheral neuropathy	Sensory, axonal	Age
Poza and Martí-Massó[7]	Yes	Yes	87% abnormal neurophysiologic study	Predominantly sensory, axonal	Age, duration, smoking Not related to PaO_2 or $PaCO_2$
Jann et al[8]	Yes	Yes	19/30	Motor and sensory, axonal	Hypercapnia, severity of COPD
Ozge et al[9]	Yes	Yes	44.8% had polyneuropathy	–	Degree of hypoxaemia
Kayacan et al[10]	Yes	Yes	93.8%	Sensory	Cigarette consumption, PEFR, $PaCO_2$

The conduction velocity of these sensory nerves was also decreased, but it was still more than 70% of the normal value. The electrophysiological data of the five COPD patients with subclinical peripheral neuropathy revealed that they had a predominantly sensory (with milder involvement of motor nerves) and not exclusively sensory, axonal polyneuropathy. The pooled analysis in Table III gives the false impression of the absence of motor nerve impairment as the slight motor abnormalities in the five patients were masked by the normal values of the remaining 25 patients.

DISCUSSION

At first glance, this study appears similar to the many studies[2-10] conducted on this subject; only when we analyse the various characteristics of the study subjects, did the differences become obvious (Table V). In the present study, all COPD patients were smokers and had irreversible/partially reversible airflow limitation. Patients experiencing poorly-reversible airflow limitation observable in bronchiectasis, cystic fibrosis, tuberculosis, or asthma were not included. In previous studies, there were many variations in the patient characteristics of the study population included in their research. The various studies[2-5] carried out before 1990 were not expected to have clearly-defined criteria of COPD patients because no consensus over the definition of COPD was available during that time period. Many studies selected patients with respiratory insufficiency without considering defining criteria. Other studies did not conform to the reversibility criteria as recommended in the GOLD guidelines.[14] This was taken into consideration in the present study.

The patients selected for the present study had a stable course of their disease. None of them had any respiratory distress or significant hypoxaemia. The majority of studies in the past[2-5,7-10] included the COPD patients with hypoxaemia/severe hypoxaemia. Our objective was to assess the prevalence of peripheral neuropathy in stable COPD patients that are usually seen at the general clinical practice level. The age group of the COPD patients included in present study was between 40–60 years; the rationale being our desire to include subjects

going through their initial course of disease. None of the previous studies had excluded elderly patients above 60 years. Many studies had observed age to be a significant cofactor related to peripheral neuropathy[4-7] and we have tried to exclude this cofactor associated peripheral neuropathy by excluding the patients above 60 years.

All previous studies have suggested the existence of impaired peripheral nerve functions in patients with COPD, though the prevalence of peripheral neuropathy have varied markedly from one study to another (Table V). One possible explanation could be the non-uniformity between study subjects from different studies. Studies that included patients having clinical evidence of peripheral neuropathy, reported a higher prevalence of peripheral neuropathy upon neurophysiological investigation. Similarly, studies involving patients with severe hypoxaemia and/or hypercapnia, observed a higher prevalence of peripheral neuropathy upon neurophysiological analysis. We observed that five out of 30 COPD patients had significant impairment in nerve conduction parameters. A prevalence of subclinical peripheral neuropathy in 16.7% of the stable COPD patients is within expectation. It is not justifiable to compare the prevalence of peripheral neuropathy observed in our study with other previous studies due to significant differences in the characteristics of subjects included in these studies.

In our study, the group data analysis of COPD patients revealed no motor nerve impairment. However, individual data analysis of the five patients with electrophysiological evidence of peripheral neuropathy suggests a predominantly sensory (with milder involvement of motor nerves), and not exclusively sensory, axonal polyneuropathy. A possible explanation may be that the slight motor abnormalities in the five patients are masked by the normal values of the remaining 25 patients. All previous studies[2-10] observed peripheral neuropathy involving the sensory nerves in these patients. In addition, Jann et al had also found the involvement of motor nerves.[8] On neurophysiologic investigation, they found low amplitude compound muscle action potential, and sensory nerve action potential, with only slight reduction of nerve conduction velocity in affected patients. The data confirmed an axonal polyneuropathy.

In COPD, changes occur in peripheral nerves that are chronically subjected to hypoxaemia resulting from less than normal blood oxygen concentration.[1] Both hypoxic and diabetic neuropathies are associated with nerve capillary endothelial cell hyperplasia and hypertrophy, predisposing to luminal occlusion. When combined with the thickening of the nerve perineurium, this phenomenon may impede the transport of nutrients and oxygen. These mechanisms seem to be applicable to peripheral nerve dysfunction and lesions, resulting from impaired axonal transport (an energy-requiring process) and causing axonal degeneration.[15] Stoebner et al also observed that the microangiopathy in peripheral nerves in patients with COPD appears to be diffuse and essentially related to hypoxia.[16] Others have suggested that a substance or substances in cigarette smoke, such as nicotine, when taken on a long-term basis, may be toxic to the peripheral nerves.[2] Although none of our patients had significant hypoxaemia, they had a long duration of illness and more advanced airflow obstruction. Therefore, the issue of whether the severity of hypoxaemia alone, or the chronicity, as well as severity of hypoxaemia, contributes to the development of peripheral neuropathy, needs to be evaluated in future studies. As all five patients with electrophysiological evidence of peripheral neuropathy were heavy smokers, the possibility of the contents of cigarette smoke leading to peripheral nerves is valid.

In the present study, we found that five 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. The previous studies and the present one are suggestive of the various cofactors in COPD patients associated with peripheral neuropathy. These cofactors include smoking[2,7,10] and duration of illness.[7] The studies[2-10] carried out earlier have also observed age, severity of hypoxia, and hypercapnia as the possible cofactors. These cofactors could not be studied in this study because we have included stable COPD patients in the age group of 40–60 years in the design of our present study. In summary, we included 30 stable COPD patients and 30 healthy volunteers (as controls) in the age group of 40–60 years, with no clinical peripheral neuropathy. We observed that five out of the 30 COPD patients were found to have subclinical, predominantly sensory (with mild motor) axonal type of peripheral neuropathy. These five COPD patients had significantly heavier habits of smoking, longer duration of illness and advanced airflow obstruction, when compared to COPD patients with no peripheral neuropathy.

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