The incidence of polyneuropthy and its relation with disease parameters in chronic obstructive pulmonary disease

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ABSTRACT

Objective: Chronic Obstructive Pulmonary Disease (COPD) is accompanied by several concomitant conditions due to its systemic effects. Hypoxia and oxidative stress associated with COPD are also believed to contribute to the disease course through the effects of several inflammatory mediators. Major causative agents causing of peripheral neuropathy are age, hypoxia, duration and severity of COPD, hypercapnia and smoking. The present study aimed to investigate the incidence of polyneuropathy and its relation with disease parameters in COPD patients.

Methods: Of a total number of 45 patients who had been followed up between January 1, 2015 and December 31, 2016 with a diagnosis of COPD at Ufuk University School of Medicine were enrolled retrospectively. All patients underwent electroneuromyography, arterial blood gas measurements and pulmonary function tests. Patients were divided as those with or without neuropathy, and factors contributing to the development of neuropathy were investigated based on clinical and laboratory findings.

Results: Eleven (24.4%) patients were women and 34 (74.6%) were men, and the mean age was 73.2 years. Mean PaO_2 was 58.2 mmHg, pCO_2 was 41.2 mmHg, and FEV1 was 45.3%. Neuropathy was diagnosed in twenty (44.4%) patients. Significant differences were found in pO_2, pCO_2, SO_2, mMRC, smoking status and number of exacerbations per year ($p < 0.05$).

Conclusions: Patients who experience frequent exacerbations and those with hypoxemia or hypercapnia as demonstrated should be taken into more careful clinical assessments with respect to polyneuropathy.

Keywords: chronic obstructive pulmonary disease, neuropathy, hypoxemia, hypercapnia, modified Medical Research Council

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [1]. COPD has several systemic effectsand the concurrent systemic inflammation was shown to be associated withdifferent concomitant diseases.Polyneuropathy is a clinical manifestation resulting from concomitant and common impairment of peripheral nerves due to the same causes and physiopathological processes.

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Causes of peripheral neuropathy include but not limited to diabetes mellitus, malignancy, Sjögrensyndrome, dysproteinemia, AIDS, Vitamin B12 deficiency, polyneuropathies due pyridoxine intoxication and hereditary or idiopathic sensorial polyneuropathies [2]. COPD is one of these causes (3). However, in patients who are diagnosed with peripheral neuropathy, COPD is usually ignored while the other potential causes are prioritized. This process that follows a chronic and deteriorating course eventually results in tissue hypoxemia and affects not only the lungs but the whole body. Previous studies investigated how the peripheral nerves and muscles are affected from this process. The objectives of the present study were to evaluate the neurophysiological changes in peripheral and central nervous systems in hypoxemic and/or hypercapnic COPD cases and to investigate the correlations of these changes with disease stage and the severity of dyspnea.

METHODS

Of a total number of 45 patients who had been followed up between January 1, 2015 and December 31, 2016 with a diagnosis of COPD at Ufuk University Faculty of Medicine were enrolled retrospectively. Complete blood count, biochemistry, Vitamin B_{12}, folic acid and thyroid function test (TFT) results of all patients were evaluated. Patients with a history of cancer that might have caused peripheral neuropathy and those with a diagnosis of diabetes mellitus, vitamin B_{12} deficiency, renal failure or hypothyroidism were excluded from the study. The study was conducted after approval was obtained from the ethics committee of our hospital.

Pulmonary Function Tests

Pulmonary function tests (PFTs) were performed by 'VMAX'; ''Encore system (Germany)'' device. During PFTs, post-bronchodilator force vital capacity in one second (FEV1), force vital capacity (FVC)and FEV1/FVC values were recorded based on GOLD criteria. For COPD staging, patients with FEV1 values > 80% were considered to have mild, FEV1: 80-50% were considered to have moderate, FEV1: 50-30% were considered to have severe and FEV1 <30% were considered to have very severe COPD.

Arterial Blood Gas Analyses

Analyses were performed by 2001 version of the "Instrumentation Laboratory-Synthesis 25" device. pH, partial arterial oxygen pressure (PaO_2), partial arterial carbon dioxide pressure ($PaCO_2$) and arterial oxygen saturation (SaO_2) values were recorded.

Electrophysiological Examination

The examinations were performed using Medelec Synergy EMG device. In accordance with clinical definition of peripheral neuropathy (nerve conduction studies of at least 2 extremities); median nerve sensorial and motor conduction, ulnar nerve sensorial and motor conduction of the upper extremities and peronealnerve motor conduction, tibialnerve motor conduction and suralnerve sensorial conduction of the lower extremities, as well as all motor and sensorial nerve conduction studies were performed. A diagnosis of carpal tunnel syndrome (CTS) was made in the presence of a deceleration in median sensorial conduction velocity, prolongation of median motor nerve distal latency, a decrease in motor action potentials and the presence of at least 0.3 ms latency difference or latencies longer than 0.5 msec when the ulnar-median nerve peak latency difference was compared to the other extremity. CTS was classified as mild, moderate and severe. Moreover; during each nerve conduction study, F wave (in at least one nerve for both an upper and a lower extremity) as one of the late latencies was investigated irrespective to the presence of findingssupporting polyneuropathy criteria. Most frequently, the right upper and lower extremities of the patients were studied. In patients who were found to have carpal tunnel syndrome, upper extremity nerve conductions were also evaluated.

Statistical Analysis

Statistical analysis was performed by SPSS 12 (Statistical Program for Social Sciences) software. Data were evaluated by using descriptive statistics (mean, standarddeviation). Independent sample test was used to compare the two groups andchi-square test was used to compare qualitative data. Data that were not normally distributed were compared between the two groups by Mann Whitney U test. A p value < 0.05 were considered significant in all statistical analyses of study data.

RESULTS

Eleven (24.4%) patients were women and 34 (75.6%) were men and their mean age was 73.22 ± 9.42 years. (Table 1) Never-smokers constituted 17.8% (n = 8) of the study population, while 71.1% (n = 32) were ex-smokers and 11.1% (n = 5) were active smokers. Mean smoking history was 43.13 ± 28.3 pack-years. Body mass index (BMI) in neuropathy present group was 25.67 ± 6.69 kg/m². Mean values of arterial blood gases (ABG) were as follows: pH: 7.41, PaO_2: 58.28 mmHg, $PaCO_2$: 41.27 mmHg, SO_2: 89.68%. Mean PFT results were as follows: FEV1:46.71% (1.19 lt), FVC:63.82% (2.18 lt), FEV1/FVC:55.93. Of all patients, 4 (8.9%) had electrophysiological changes while no change was noted in remaining 41 (91.1%) patients (see Table 1). Patients were divided into two groups as those with or without neuropathy. Of the patients with neuropathy, one had motor neuropathy, 8 had sensorimotor neuropathy and 11 patients had sensorial neuropathy based on electrophysiological findings. In total, 7 patients had findings of carpal tunnel syndrome. Neuropathy was diagnosed in 44.4% (n = 20) of the patients, while the remaining 55.6% (n = 25) did not have neuropathy (Table 1).

In total, 7 (63.64%) women and 13 (38.24%) men had neuropathy and their mean age was 75.30±9.07 years. Of 25 patients without neuropathy, 21 (61.76%) were men and 4 (36.36%) were women and their mean age was 71.56 ± 9.55 years. Mean age and gender distribution were not significantly different between the two groups ($p = 0.204$ and $p = 0.145$, respectively). In terms of ABG findings, mean pH of patients with neuropathy was 7.39 ± 0.05 (Table 2). There were significantly different between the two groups in term of pO_2 ($p = 0.012$), pCO_2 ($p = 0.003$), SO_2 ($p = 0.001$) and number of exacerbations per year ($p < 0.001$). Moreover, the percentage of smoking (pack-year) and mean modified Medical Research Council (mMRC) scores were also significantly different ($p = 0.040$ and $p = 0.001$, respectively). Mean age, smoking history, pH, FEV1 (%), FEV1 liters (lt), FVC (%), FVC lt, FEV1/FVC (%), BMI and time since diagnosis of COPD (years) and co-morbidities (Coronary heart disease, Congestive heart disease, Alzheimer disease)

Table 1. Overall demographical characteristics

Parameter	Data
Gender	
Women	11 (24.4%)
Men	34 (75.6%)
Age (mean)	73.22 ± 9.42
Smoking	
Never-smoker	8 (17.8%)
Ex-smoker	32 (71.1%)
Active-smoker	5 (11.1%)
Smoking (packet-year)	43.13 ± 28.30
Concomitant diseases	
Present	32 (71.1%)
Absent	13 (28.9%)
pH	7.41 ± 0.044
pO2, mmHg	58.28 ± 9.95
pCO2, mmHg	41.27 ± 9.70
SO2, %	89.68 ± 5.79
FEV1, %	46.71 ± 16.15
FEV1, lt	1.19 ± 0.51
FVC, %	63.82 ± 14.65
FVC, lt	2.18 ± 0.70
FEV1/FVC, %	55.932 ± 11.37
Electrophysiological Changes	
Present	4 (8.9%)
Absent	41 (91.1%)
Neuropathy	
Present	20 (44.4%)
Absent	25 (55.6%)

Data are shown as mean ± standart deviation or number (%). FVC = force vital capacity, FEV_1 = force vital capacity in one second, pO_2 = partial oxygen pressure, pCO_2 = partial carbon dioxide pressure, SO_2 = oxygen saturation

were not significantly different between the two groups ($p > 0.05$) (Table 2). According to GOLD 2017 guideline, twenty-six (57.8%) patients were GOLD-Stage C, 19 (42.2%) were GOLD-Stage D. There were 5 (19.2%) patients in GOLD-Stage C and 11 (57.9%) patients in GOLD-Stage D, and this difference was statistically significant ($p = 0.001$).

Nerve conduction studies demonstrated significant differences in both median nerve distal latencies, right sural conduction velocity, right tibial nerve distal latency, both median nerve sensorial conduction velocity, right peroneal and tibial nerve motor conduction velocities between the two groups are shown in Table 3 ($p < 0.05$).

Table 2. Comparison of the parameters between study groups

	Neuropathy present (n = 20)	Neuropathy absent (n = 25)	p value
Age (years)	75.30 ± 9.07	71.56 ± 9.55	0.204
Smoking	39.05 ± 31.92	46.40 ± 25.22	0.605
pH	7.39 ± 0.05	7.41 ± 0.03	0.224
pO$_2$, mmHg	54.81 ± 10.18	61.75 ± 7.76	**0.012**
pCO$_2$, mmHg	46.67 ± 11.16	36.95 ± 5.48	**0.003**
SO2, %	86.67 ± 5.86	92.09 ± 4.56	**0.001**
FEV1 (%)	44.60 ± 14.17	48.40 ± 17.68	0.444
FEV1 (lt)	1.15 ± 0.46	1.23 ± 0.56	0.775
FVC (%)	62.35 ± 14.20	64.70 ± 14.60	0.631
FVC (lt)	2.00 ± 0.62	2.33 ± 0.74	0.132
BMI, kg/m^2	25.67 ± 6.69	25.39 ± 5.75	0.486
Time since COPD diagnosis (years)	9.40 ± 7.57	7.32 ± 6.27	0.313
Number of exacerbations per year	2.00 ± 0.85	1.04 ± 1.31	**< 0.001**
mMRC			**0.001**
1	0 (0%)	10 (40%)	
2	10 (50%)	13 (52%)	
3	9 (45%)	2 (8%)	
4	1 (5%)	0 (0%)	
Smoking, (packet-year)			**0.040**
Non-smoker	6 (30%)	2 (8%)	
Ex-smoker	13 (65%)	19 (76%)	
Active-smoker	1 (5%)	4 (16%)	

Data are shown as mean ± standart deviation or number (%). BMI = body mass index, COPD = Chronic Obstructive Pulmonary Disease, FEV$_1$ = force vital capacity in one second, FVC = force vital capacity, mMRC = modified medical research council, pO$_2$ = partial oxygen pressure, pCO$_2$ = partial carbon dioxide pressure, SO$_2$ = oxygen saturation

Table 3. Comparison of neurophysiological changes in electroneuromyography between groups

	Neuropathy present	Neuropathy absent	p value
RMNSL	2.14 ± 1.87	2.89 ± 0.94	0.679
LMNSL	2.78 ± 1.30	2.92 ± 0.71	0.671
RUNSL	2.31 ± 1.44	2.71 ± 0.33	0.739
RSNV	19.36 ± 18.13	36.33 ± 8.18	**< 0.001**
RMNML	3.84 ± 0.69	3.34 ± 0.50	**0.012**
LMNML:	3.49 ± 0.59	3.12 ± 0.43	**0.032**
RUNML	2.54 ± 0.53	2.47 ± 0.57	0.449
RCPNL	4.15 ± 2.40	4.49 ± 1.19	0.575
PTNL	4.79 ± 0.99	4.23 ± 0.55	**0.047**
RMNSV	21.60 ± 18.80	38.28 ± 11.85	**< 0.001**
LMNSV	31.42 ± 14.43	39.38 ± 8.59	**0.001**
RUNMV	27.66 ± 16.68	40.84 ± 4.12	**< 0.001**
RCPNV	36.34 ± 19.39	46.17 ± 11.51	**0.037**
RPTNV	42.29 ± 5.03	45.93 ± 5.48	**0.022**

Data are shown as mean ± standart deviation. RMNSL = Right median nerve sensory latency, LMNSL = Left median nerve sensory latency, RUNSL = Right ulnar nerve sensory latency, RSNV = Right sural nerve velocity, RMNML = Right median nerve motor latency, LMNML = Left median nerve motor latency, RUNML = Right ulnar nerve motor latency; RCPNL: Right common peroneal nerve latency, RPTNL = Right posterior tibial nerve latency, RMNSV = Right median nerve sensory velocity, LMNSV = Left median nerve sensory velocity, RUNMV = Right ulnar nerve motor velocity, RCPNV = Right common peroneal nerve velocity, RPTNV: Right posterior tibial nerve velocity

DISCUSSION

The neuropathic patients are more hypoxic and hypercarbic than neuropathic and electrophysiologically normal COPD patients in our study. pO_2, pCO_2, SO_2 and number of exacerbations per year were significantly different between the two groups. Moreover, mean modified Medical Research Council (mMRC) scores were also significantly different. The relation between chronic hypoxemia and peripheral neuropathy (PN) in COPD has been known for a long time [4, 5]. Hypoxia blocks energy metabolism of peripheral nerve tissue [6]. The severity of hypoxia may increase due to endothelial cell hyperplasia which results in luminal occlusion in capillary veins [4]. In rats with induced chronic hypoxemia, a reduction in nerve conduction velocity was observed as a result of axonal degeneration [7]. Stoebner *et al*. [8] observed microangiopathy caused by hypoxemia in peripheral nerves. While several studies reported a relation of hypoxemia and its severity with PNP, Jann *et al*. [9] found such a relation with the severity of COPD and hypercapnia.

Systemic inflammation is the key for linking COPD and most of its dependent comorbidities. In addition to inflammation, imbalance of proteinases and antiproteinases and the oxidative stress are important in the pathogenesis of COPD. In advanced COPD, the lung capacity reduces for gas exchange, producing hypoxemia and, later on, hypercapnia [10]. In the present study, significant associations were noted both with hypoxemia and hypercapnia. Also, frequent hospitalizations and therapies like systemic corticosteroids might contribute this situation [11].

Hypoxia and/or hypercapnia may occur or will get worse in COPD patients, especially during exacerbation. The inflammation also increases. Accordingly, we found a significant relationship between annual attack rate and frequency of neuropathy in our study. In addition mMRC dyspnea and frequency of neuropathy was directly correlated. The reason for this may be the probability of increased damage of neurons innervating diaphragm and other respiratory muscles by neuropathy.

The most important external source of oxidants is tobacco smoke and its constituents. Tobacco smoke damages the lungs, both by triggering inflammation and by direct effects of the inhaled particles and gases [12, 13]. Tobacco smoke causes protease-antiprotease imbalance by suppressing antiprotease activity. Resultant tissue damage may lead to local and systemic inflammation. In a previous study, Faden and Agrawal reported a correlation between smoking habits and sensorial nerve functions [14, 15]. Kayacan *et al*. [16] highlighted the concomitant relation between the brainstem auditory evoked potentials (BAER). According to that study, smoking affects the ponto-medullary brain region potentially by altering $PaCO_2$, HCO_3 and pH levels. On the contrary, Ulubay *et al*. [17] did not demonstrate such a relation in their study. The significant relation noted between smoking habits and neuropathy incidence in the present study can be explained by the high proportion of smokers in the study group.

In the present study peripheral neuropathy has occurred at an incidence of 44.4% in patients with COPD. The prevalence of PN among COPD patients showed wide variety in previous studies (5% to 100%) [4, 5, 16, 18, 20-26]. In line with the previous studies, the distribution and types of neuropathic parameters mostly indicated involvement of lower extremities and manifestation as sensorial NP [4, 20, 23, 24]. Neuropathy incidence varies depending on the clinical and electrophysiological criteria used to define the abnormalities.

CONCLUSION

In conclusion, chronic obstructive pulmonary disease is a systemic disorder that does not only involve the lungs, but also affects non-pulmonary organs through inflammation. This is important in terms of quality of life. Electroneurophysiological changes are rather common among patients who experience frequent hospitalizations, who are severely hypoxemic and/or hypercapnic. Nowadays, better identification of the comorbidities accompanying COPD may be beneficial for the patients in terms of early initiation of specific medical or supportive therapies.
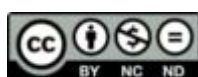
Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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