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Subclinical peripheral neuropathy in patients with chronic obstructive pulmonary disease without hypoxemia

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Abstract:

AIM: The aim of the study was to determine the prevalence of subclinical peripheral neuropathy (PNP) in stable chronic obstructive pulmonary disease (COPD) patients without severe hypoxemia.

MATERIALS AND METHODS: Fifty-six (52 men and 4 women) patients with COPD without severe hypoxemia, 25 healthy smokers, and 24 healthy nonsmokers were included in the study. The latency, amplitude, and velocity measurements of right and left median motor nerve, tibial motor nerve, peroneal motor nerve, median sensory nerve, sural sensory nerve, right ulnar motor nerve, and right ulnar sensory nerve were performed.

RESULTS: A high proportion of PNP was detected in the COPD group compared to the smoker and nonsmoker control groups (41.1%, 36.0%, and 33.3%, respectively). However, the difference between the groups was not statistically significant ($P = 0.784$). However, some of the electrophysiological measurements were statistically significantly worse in the COPD group ($P < 0.05$). In the COPD group, a correlation was not detected between PNP and duration of COPD, age, body mass index, smoking status (pack/year), forced vital capacity %, forced expiratory volume in 1 s %, SO_2, and C-reactive protein values ($P > 0.05$).

CONCLUSION: The present study demonstrates that the PNP may be an extrapulmonary manifestation of COPD. The physician should be aware of the possibility of PNP in COPD patients without severe hypoxemia.

Keywords:

Chronic obstructive pulmonary disease, electromyelography, peripheral neuropathy

Introduction

Chronic obstructive pulmonary disease (COPD) is primarily characterized by the presence of irreversible airflow limitation resulting from airway inflammation and remodeling often associated with the development of parenchymal destruction and emphysema.[1] Increasing evidence indicates that COPD is a complex disease involving more than airflow obstruction. Patients with COPD can have multiple coexisting systemic effects and comorbidities that extend beyond the lung.[2] Comorbidities including coronary artery disease, diabetes mellitus, osteoporosis, muscle weakness, anemia, depression, and anxiety are frequent in COPD.[3]

Peripheral neuropathy (PNP) could occur in patients with COPD, but the actual prevalence and clinical importance of PNP is still unclear in COPD.[4-6] Therefore, PNP is not included in the list of COPD

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comorbidities. Although the adverse effects of chronic respiratory failure on the central nervous system are well known, its effects on the peripheral nervous system have not been emphasized adequately. Smoking, chronic hypoxia, and older age could be contributing factors for the development of PNP in COPD. We aimed to determine the prevalence of subclinical PNP in stable COPD patients without the diagnosis of PNP and severe hypoxemia.

Materials and Methods

Study design

The study was approved by the ethics committee, and informed consent was obtained from the participants (July 15th, 2011; 2012/203). Eighty stable patients with COPD patients and eighty healthy volunteers were enrolled. Healthy volunteers constituted forty nonsmokers and forty smokers. The diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease.[1] All patients had at least a 10 pack-year history of cigarette smoking or exposure to biomass and postbronchodilator (400 μg salbutamol) forced expiratory volume in 1 s and forced vital capacity (FEV_1/FVC) ratio of <70% predicted. The Vitamin B12, folic acid, and thyroid hormone concentrations were measured in addition to routine hemogram and biochemical tests in COPD patients and healthy control group in order to exclude risk factors for PNP.

There was no clinical evidence of neuropathy in any patient. None of the patients was using systemic steroids and neurotoxic drugs.

Exclusion criteria

1. Patients with the disease that can cause polyneuropathy (diabetes mellitus, alcoholism, malignancies, lung surgery, and renal and thyroid diseases)
2. Low Vitamin B12 and folic acid levels
3. Oxygen saturation <90%
4. Patients who had an exacerbation of the disease in the past 6-month period and present smokers.

A total of 24 patients with abnormal thyroid function test results (n = 14) or Vitamin B12 and folate values (n = 10) were excluded from the study. In healthy nonsmoker group, patients with abnormal thyroid function test results (n = 10) and Vitamin B12 and folate values (n = 6), and in the healthy smoker group, patients with abnormal thyroid function test results (n = 5) and Vitamin B12 and folate values (n = 10) were excluded from the study. Fifty-six (52 men and 4 women) patients with COPD, 25 (23 men and 2 women) healthy smokers, and 24 (22 men and 2 women) healthy nonsmokers were included in the study.

Respiratory function tests

Respiratory function tests were performed in patients with COPD and smokers in the control group. V_{max} (Viasys-Healthcare®-2007 GmbH, Hoechberg, Germany) was used for the measurement of respiratory function tests. Each participant performed a maximal expiratory flow maneuver in the sitting position until three acceptable measurements were obtained, and the best result was recorded. Respiratory function tests such as FEV_1, FVC, and FEV_1/FVC were evaluated. After three measurements, the best values were taken into consideration.

Electrophysiologic study

Electrophysiologic study was performed using Nihonkohden MEB-9002K VMA EP/EMG Measuring System 2005 USA brand electromyograph in the electromyography laboratory. The measurements of conventional motor and sensory nerve conduction latencies, amplitudes, and velocities were performed bilaterally from the upper and lower extremities. The latency, amplitude, and velocity measurements of the right and left median motor nerve, tibial motor nerve, peroneal motor nerve, median sensory nerve, sural sensory nerve, right ulnar motor nerve, and right ulnar sensory nerve were performed.

Statistical analysis

Data were analyzed using the IBM Statistical Package for the Social Sciences version 11.5 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using the Shapiro–Wilk test. Parametric tests were applied to data of normal distribution (independent *t*-test and one-way analysis of variance). The distribution of categorical variables in both groups was compared using the Pearson's Chi-square test. Continuous data were presented as mean ± standard deviation. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

Results

Age, body weight, height, and body mass indices (BMIs) of the three study groups did not differ statistically significantly [Table 1]. The mean duration of illness in COPD patients was 7.55 ± 5.28 years, and the mean number of exacerbations was 0.88 ± 0.99. The mean SaO_2% in the COPD group was 94.92 ± 1.31.

Table 1: Intergroup comparisons of age, body weight, height, and body mass indices of the patients

	COPD	Healthy smokers	Healthy nonsmokers	*P*-
Age (years)	61.37±6.55	58.16±3.91	61.17±6.92	0.069
Weight (kg)	78.04±14.09	79.68±14.66	79.83±10.83	0.739
Height (cm)	167.16±7.78	167.36±11.61	167.50±6.37	0.590
BMI (kg/m^2)	27.94±4.87	28.26±3.61	28.46±3.62	0.799

Values are expressed as mean±SD (one-way ANOVA). COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, SD: Standard deviation

A statistically significant difference was not detected between COPD group and the smokers in the control group as for smoking (43.82 ± 22.89 vs. 46.20 ± 17.87 pack-years, respectively) ($P = 0.431$). Spirometric values were statistically significantly lower in the COPD group (FVC, FEV_1, and FEV_1/FVC) when compared with smokers in the control group [Table 2].

The latency, amplitude, and velocity of the right and left median motor nerve, tibial motor nerve, peroneal motor nerve, and right ulnar motor nerve are shown in Table 3. A statistically significant difference was seen between groups as for left tibial motor nerve latencies and velocities, right tibial motor nerve velocities, and left and right peroneal nerve velocities. Significantly prolonged left tibial nerve latencies and left peroneal nerve latencies were observed in the COPD group. The latency, amplitude, and velocity of the right and left median sensory nerve, sural sensory nerve, and right ulnar sensory nerve are shown in Table 4. A statistically significant difference was seen as for right sural sensory nerve latencies, amplitudes, and velocities and right ulnar nerve velocities. A significant prolongation of right sural sensory nerve latencies was observed in the COPD group. The percentage of PNP was 41.1% (23/56) in the COPD group, 36% (9/25) in healthy smokers, and 33.3% (8/24) in healthy nonsmokers. A statistically significant difference was not found between distributions of the cases with established PNP ($P = 0.784$). In the COPD group, a correlation was not detected between PNP and duration of COPD, age, BMI, smoking status (pack/year), FVC%, FEV_1%, and SaO_2.

Discussion

We have found higher rates of PNP in patients with COPD compared to healthy smokers and healthy nonsmokers (41.1%, 36.0%, and 33.3%, respectively). Although the higher rate of PNP observed in COPD patients was not statistically significant, a significant retardation of lower extremity nerve conduction velocities was detected in the COPD group, and some latency values were significantly higher than that in the control group. In the COPD group, no correlation was found between PNP and age, duration of illness, number of exacerbations, BMI, smoking, and levels of FEV_1, FVC, and SaO_2.

Fifty-two of 56 COPD patients composing the study group are male because COPD is seen more frequently in the male population in our country. In our country, COPD is much more common in men because the smoking rates are much higher in males compared to females, and occupational exposure poses a significant risk to men. In an epidemiological study conducted in our country in 2008, only 80 of 1160 COPD patients were women.[7]

Table 2: Spirometric values of the group with chronic obstructive pulmonary disease and smokers in the control group

	COPD	Healthy smokers	*P*
FVC (%)	83.68±17.96	101.04±17.83	<0.001
FEV_1 (%)	57.73±14.45	102.60±17.41	<0.001
FEV_1/FVC (%)	54.91±8.97	81.64±8.90	<0.001

Values are expressed as mean±SD (independent *t*-test). COPD: Chronic obstructive pulmonary disease, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 s, SD: Standard deviation

Table 3: Latency, amplitude, and velocity of the right and left median motor nerve, tibial motor nerve, peroneal motor nerve, and right ulnar motor nerve in chronic obstructive pulmonary disease and control groups

	COPD	Healthy smokers	Healthy nonsmokers	*P*
Median motor nerve				
Left				
Latency (ms)	3.33±0.37	3.47±0.45	3.47±0.46	0.221
Amplitude (mV)	6.36±2.14	6.78±2.75	6.72±2.62	0.773
Velocity (m/s)	51.07±6.35	54.06±5.09	53.01±3.88	0.136
Right				
Latency (ms)	3.42±0.40	3.49±0.61	3.60±0.66	0.723
Amplitude (mV)	6.44±2.36	7.19±2.80	6.89±2.78	0.466
Velocity (m/s)	51.79±3.34	51.86±3.83	50.87±4.65	0.612
Tibial motor nerve				
Left				
Latency (ms)	5.01±0.56	4.60±0.65	4.82±0.58	0.035
Amplitude (mV)	4.51±2.08	4.57±1.64	4.36±1.66	0.858
Velocity (m/s)	46.59±4.68	48.28±4.74	48.44±2.88	0.050
Right				
Latency (ms)	4.87±0.57	4.59±0.60	4.84±0.63	0.139
Amplitude (mV)	4.03±1.85	3.95±1.74	4.03±2.06	0.987
Velocity (m/s)	45.26±3.45	46.95±3.85	47.87±3.27	0.006
Peroneal motor nerve				
Left				
Latency (ms)	4.75±0.82	4.16±0.58	4.42±0.77	0.005
Amplitude (mV)	2.25±0.81	2.46±0.90	2.31±1.01	0.577
Velocity (m/s)	46.38±4.40	48.37±5.72	48.01±4.38	0.065
Right				
Latency (ms)	4.54±0.76	4.05±0.60	4.38±0.98	0.059
Amplitude (mV)	2.39±1.21	2.53±0.87	2.39±1.17	0.250
Velocity (m/s)	47.38±5.51	49.39±4.57	49.65±4.55	0.013
Ulnar motor nerve				
Right				
Latency (ms)	2.63±0.28	2.58±0.30	2.67±0.36	0.656
Amplitude (mV)	6.20±1.82	6.45±1.95	6.35±1.89	0.866
Velocity (m/s)	53.91±5.43	52.56±5.60	52.98±4.54	0.274

Values are expressed as mean±SD (one-way ANOVA). COPD: Chronic obstructive pulmonary disease, SD: Standard deviation

Visser *et al*. found no significant difference in electrophysiological measurements between smokers and nonsmokers in their study.[8] Similarly, in our study, there was no significant difference between the

Table 4: Latency, amplitude, and velocity of the right and left median sensory nerve, sural sensory nerve, and right ulnar sensory nerve in chronic obstructive pulmonary disease and control groups

	COPD	Healthy smokers	Healthy nonsmokers	*P*
Median sensory nerve				
Left				
Latency (ms)	2.90±0.24	2.88±0.39	2.85±0.35	0.453
Amplitude (mV)	6.57±2.43	8.53±4.72	7.19±4.16	0.145
Velocity (m/s)	50.49±4.27	52.10±5.48	52.40±5.44	0.176
Right				
Latency (ms)	2.92±0.29	2.87±0.45	2.98±0.37	0.553
Amplitude (mV)	6.60±3.27	7.71±3.96	6.79±3.62	0.335
Velocity (m/s)	50.26±4.91	52.49±6.38	49.59±4.27	0.152
Sural sensory nerve				
Left				
Latency (ms)	3.56±0.39	3.48±0.41	3.45±039	0.403
Amplitude (mV)	5.05±2.60	5.37±3.79	4.60±2.13	0.821
Velocity (m/s)	51.97±4.10	53.25±5.82	54.23±4.12	0.109
Right				
Latency (ms)	3.61±0.40	3.36±0.52	3.36±0.36	0.015
Amplitude (mV)	5.29±2.98	7.34±4.98	7.32±4.54	0.032
Velocity (m/s)	51.56±4.17	55.32±6.84	53.64±4.65	0.024
Ulnar sensory nerve				
Right				
Latency (ms)	2.33±0.21	2.25±0.17	2.32±0.20	0.257
Amplitude (mV)	4.61±2.20	5.67±3.23	4.95±2.24	0.348
Velocity (m/s)	50.03±4.00	52.49±3.50	50.54±3.66	0.026

Values are expressed as mean±SD (one-way ANOVA). COPD: Chronic obstructive pulmonary disease, SD: Standard deviation

electrophysiologic measurements of the smoker and nonsmoker control groups.

The association of COPD and PNP was first reported by Appenzeller *et al*. in 1968.[9] Investigations about the frequency of PNP in COPD continued in the subsequent years. Studies usually have shown that peripheral nerve functions may deteriorate in patients with COPD. Faden *et al*. performed the first serious clinical study in this area in 1981.[4] They compared the neurophysiological and clinical findings of 23 COPD patients who are active smokers with an age-matched control group with normal pulmonary function tests. They demonstrated subclinical motor and sensory conduction slowdown in 87% of the patients in the COPD group. Agrawal *et al*. found PNP in 17% of the thirty COPD patients who are active smokers.[6] Nowak *et al*. reported clinically significant PNP in 20% and subclinical PNP in 4% of the patients.[10] Poza and Martí-Massó detected electrophysiologic abnormalities in 87% of COPD patients.[11] Jann *et al*. reported PNP in 63%, whereas Ozge *et al*. reported PNP in 55% of the patients.[12,13] In our study, PNP was present in 41.1% of the COPD group. Significant differences between the ratios of clinically significant or subclinical PNP have been reported in studies in COPD patients. In general, the frequency of PNP appears to be higher in cases of hypoxemia and/or hypercapnia. On the other hand, in all of the studies in the literature, case numbers are not high enough to generate a general idea of the incidence of PNP in COPD because they generally involve small groups.

Conclusion

COPD is a chronic disease that affects a large number of extrapulmonary organs and systems and therefore has significant systemic effects. Previous studies and our findings show that PNP, with its sensory and motor components, can be regarded as one of the systemic effects of COPD. As the shortcomings of our work, the number of patients was low, and we did not investigate the markers of systemic inflammation and did not question the quality of life. In order to obtain stronger results, it is possible to work with larger categorized groups in terms of sociodemographic and clinical characteristics. Both the effects of PNP on the clinic and prognosis of COPD and the effect of PNP treatment on the clinic and natural course of the disease should be the subject of further studies.

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Conflicts of interest

There are no conflicts of interest.

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