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MYOPATHY AND NEUROPATHY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality in countries where tobacco consumption is high. Myopathy and neuropathy are known to accompany frequently and usually complicate COPD, worsening the quality of life and possibly the prognosis of patients. The exact impact of myopathy and neuropathy on respiratory muscle functions, lung function tests, arterial blood gases and survival of patients is still unknown.

Several studies have been conducted to determine the factors that are responsible for neuropathy and myopathy in COPD patients. Smoking, hypoxia, malnutrition, age, drugs and metabolic derangements have been blamed for causing neuropathy (1-13). And cardiac failure, a sedentary life style, malnutrition, hypoxia, hypercapnia, acidosis, ethanol and drugs were blamed to cause muscle weakness (14,15,16). Also papers have been published which examine the epidemiological properties, pulmonary functions and arterial blood gases of myopathic COPD patients who used steroids and who did not (16,17,18). Other studies examined the histological features and electrophysiologic properties of the myopathy and neuropathy seen in COPD patients (19-24).

It has been suggested that the myopathy in COPD patients, especially when related to steroid usage is a generalized one, and affects not only the peripheral muscles, but also the respiratory muscles (25). It was also suggested that myopathy may be a factor predictive of survival in COPD patients (16) .

The purpose of this study was to determine the ratio of myopathy and neuropathy in our COPD patients, the clinical characteristics of our neuropathic and myopathic patients and to determine the importance of detecting the presence of myopathy and neuropathy by determining their influence on the progression of COPD. This study was conducted to examine epidemiological properties, nutritional status, pulmonary functions, respiratory muscle functions, arterial blood gases, steroid usage and survival of myopathic and neuropathic COPD patients and compare them to electrophysiologically normal COPD patients. The findings about the survival of patients will be reported after five years of follow- up.

MATERIALS AND METHODS

Subjects

Chronic obstructive pulmonary disease patients followed in our outpatient clinic who had severe disease according to ERS criteria (26) and who applied to our outpatient clinic for routine controls were considered for the study.

Patients who had pathologies other than COPD which could cause neuropathy and myopathy were excluded. Then, patients who were included had no history or evidence of endocrinological disorders, hereditary muscular diseases, collagen vascular diseases, diabetes, uremia, porphyria, vitamin B12 deficiencies, primary biliary cirrhosis, malabsorption, malignity, macroglobulinemia, cryoglobulinemia or hereditary neuropathies. None of the patients used alcohol or drugs known to cause neuropathy and myopathy except for those used routinely in the treatment of COPD. All of the patients were using theophylline, inhaled Beta 2 mimetics, anticholinergics and steroids.

Physical examination, complete blood count, and biochemical analysis were performed.

None of the patients were on a regular training program. Electrolytes, total protein and albumin levels and body mass indexes (weight/height^2) were considered for nutritional studies. Either oral or parenteral studies (methylprednisolon) were administered to most of the patients for short courses during acute exacerbations. The total dose of methylprednisolon used during the previous six

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months were recovered from hospital records. The total dose was added and divided by the number of days to find the average daily dose.

Thirty patients fulfilling these criteria and who gave informed consent were included in the study. Neurologic examinations, electrophysiological studies, lung function tests, respiratory muscle function tests and arterial blood gases measurements were performed.

Neurologic and Electrodiagnostic Examination

All of the thirty patients were evaluated by the same neurologist who was not informed about the patients' clinical findings and laboratory results. The electrophysiological measurements were made by another neurologist, using Nikon Kohden Neuropack 2 MEB-702 A/K EMG device. Both motor and sensory conduction studies and electromyography were performed. All patients were examined while they were laying in a room with a stable temperature of 25°C. The neutral electrode NM 522S was fastened around the forearm in the upper extremity and the ankle in the lower extremity. In the first part the motor latencies , muscle action potential amplitudes (amplitudes of evoked potentials) and motor conduction velocities were determined on the wrist and elbow for median and ulnar nerves and on the ankle and knee for fibular and tibial nerves. Sensory latencies and amplitudes of the median nerve were measured on the wrist and second digit, of the ulnar nerve on the wrist and fifth digit and of the sural nerve on the ankle level orthodromically. In the second part, the deltoid, biceps, first dorsal, rectus femaris and anterior tibialis muscles were assessed during rest, slight contraction and maximal contraction.

Lung Function Tests

Lung function tests were performed using a constant-volume body plethysmograph and spirometer (Sensor Medics Vimax 22 series) while patients were in stable clinical conditions. The tests were performed by the same technician to all patients. The best measurement out of three was taken into consideration. FVC, FEV_1, FEV/FVC, $FEF_{25-75\%}$, PEF, DLCO and DLCO/VA were measured. Results were expressed as % of predicted values calculated according to Kory-Polgar references (19).

Respiratory Muscle Function Tests

Maximum inspiratory pressure (PImax) and maximum expiratory pressure (PEmax) as cmH2O were measured by the same technician using the same device as lung function tests. PImax was measured during a maximal inspiratory effort against an occluded airway residual volume and PEmax was measured during a maximal expiratory effort against the closed airway at total lung volume using the technique of Black and Hyatt (27). The best effort of three trials was taken into consideration.

Arterial Blood Gases

PaO2, PaCO2 and pH were determined by an automated blood gas analyzer (novo Biomedical Stal Profile 7 G07891050) during the stable period of the three patients.

Statistical Analysis

The analysis was performed using statistical package for social sciences (SPSS) for Windows, version 5.0. Patients were grouped according to the electromyography results as myopathic (Grp1), neuropathic (Grp2) and electromyographically normal COPD patients. The age, sex, body mass index, duration of illness, average daily dose of steroid used during the last six months, lung function tests, and arterial blood gas parameters of the patients were compared. Because the number of patients in each group was small, a non-parametric test, Kruskor Wallis variance analysis test was used for this comparison. If significance was detected ($p<0.05$), then subgroup analysis was done using Mann-Whitney U test. Bonferroni's adjustment (0.05/n tests) for multiple testing was used to prevent a type I error. Data were expressed as mean ± SD.

When the average daily doses of steroids were being compared, those patients who did not receive steroids during the last six months were not taken into consideration. The number of patients who did not receive methylprodnisolon was 1 in the myopathic group, 4 in the neuropathic group and 3 in the electromyographically normal group.

The patients will be followed for five years, or as long as they survived if less than five years for comparing the survival rates in each group.

RESULTS

Clinical Characteristics

30 severe (according to ERS criteria) COPD patients were included in the study. Their average age was 66±7.2, and the average duration of illness was 12.2±6,0 years. Their average BME was 26,0±7.6 kg/m^2, and the average daily dose of methylprednisolon

the patients used during the last six months was 2.81.9 mg. Steroids were used for short periods during acute exacerbations.

Table 1: Anthropometric characteristics

	Patients	Female/ Male	Age	Duration of illness (years)	BME, kg/m2	ADD of methylpre dinisolon (mg)
Total	30	8/22	66±7.2	12.2±6.0	26.0±7.6	2.8±1.9
Group 1 mean±SD	8	05.Mar	67.8±4.6	13.6±5.3	23.7±5.8	2.7±1.9
Group 2 mean±SD	14	Oca.13	65.4±4.6	10.9±6.8	24.7±3.4	2.7±2.0
Group 3 mean±SD	8	02.Haz	65.3±8.4	12.9±5.6	30.8±12.2	3.1±2.0

According to the results of electrodiagnostic assessment the patients were grouped into three: There were eight patients in the group with myopathy (Group 1), fourteen patients in the group with neuropathy (Group 2) and eight patients in the electrophysiologically normal group (Group 3). The three groups were well-matched for age, sex and duration of illness.

The body mass indexes of patients in each group were also similar and within normal limits. The electrolytes, total protein and albumin levels, which were considered as an indicator of nutritional status of all patients, were within normal limits.

Average daily dose of methylprednisolon used during the last six months showed no statistically significant difference among the patients who used methylprednisolon. However, there is an important difference between the number of patients in each group who did not use methylprednisolon during the last six months. Only one patient out of eight (12.5%) did not use steroid in the myopathic group whereas this number is four out of fourteen (28.6%) in the neuropathic group and three out of eight (37.5%) in the electromyographically normal group.

Neurologic Examination and Electrophysiological Studies

In the myopathic group, three of the patients had no symptoms or signs of muscle weakness. Their neurological examinations were normal. Five patients complained about difficulty in sitting down, raising up and climbing stairs. They had proximal muscle weakness in neurological examinations. Two of the patients had decreased deep tendon reflexes.

The eight patients in this group showed myogenous involvement in the proximal muscles. Shortening of the duration of the motor unit potentials, decrease in the amplitudes, increasing of polyphasic potentials were detected.

In the neuropathic group, three of the fourteen patients complained about weakness in sitting down, standing up and climbing stairs. On neurologic examination, two of the three patients showed a slight weakness in lower extremity muscles.

In the third group, two of the patients complained about easy fatigability, but the neurological and electrophysiological examination were within normal limits.

The fourteen patients had peripheral neuropathy. Eleven patients had reduction in amplitude measurements suggesting degeneration. In the eleven of these patients sensory fibers and in seven of these both sensory and motor fibers were affected. Three patients showed prolonged conduction times suggesting demyelinization. In two of these patients motor fibers and in one of these patients sensory fibers were affected.

Lung Function Tests

The lung function test parameters of the patients in each group are represented as means ± SD (Standard Deviations) in table two. FEV1/FVC , FEF 25-75% and PEF values are lower in Group 1 and 2 when compared to Group 3, but the difference is not statistically significant. The only statistically significant parameter among lung function tests in D_{LCO} (p=0.017) which is significantly low in Group 1, the myopathic group.

Table 2: Functional characteristics

	Total	Group 1 mean+SD	Group 2 mean+SD	Group 3 mean+SD
FUC, %	59.4+18.4	58.8+23.5	58.4+17.0	61.8+17.2
FEU, %	41.2+16.6	39.13+18.0	39.5+13.8	46.4+20.4
FEU, / FUC, %	56.8+13.1	53.4+10.9	52.2+7.4	68.1+17.0
FEF 25-75%, %	22.4+12.3	16.8+7.2	20.1+7.8	32.1+17.6
PEF, %	38.2+17.5	29.9+15.8	37.1+11.8	48.3+23.8
DLCO, %	62+22.58	42.5+23.9*	65.6+20.4**	75.3+10.3
DLCO / VA	4.28+1.34	3.46+1.43	4.58+1.48	4.60+0.5
pH	7.4+0.1	7.4+0.0	7.4+0.1	7.4+0.0
Pa O_2,mmHg	75.2+11.8	7.15+16.2	74.4+5.8	80.5+14.3
Pa CO_2,mmHg	43.4+6.6	47.6+8.1	41.1+3.8	43.1+7.5

** p<0.017 when compared to group 1

Respiratory Muscle Function Tests

The PImax value is significantly lower (p<0.017) in the myopathic patients when compared to electrophysiologically normal patients. The difference in PImax value is not significant between myopathic and neuropathic patients. The PEmax is also lower in the myopathic group when compared to both groups,

and in the neuropathic group PEmax is lower than the electrophysiologically normal group. However, these results are not statistically significant.

Table 3: Respiratory muscle functions

		PImax, cmH_2O	PEmax, cmH_2O	PImax, %	PEmax, %
Total		64.7+25.8	69.5+35.9	65.9+20.6	64.1+33.7
Group 1	mean+SD	47.4+23.9*	48.1+20.7	55.3+21.3	41.3+22.4
Group 2	mean+SD	64.1+24.1	66.1+19.1	64.9+19.8	63.0+20.5
Group 3	mean+SD	83.3+19.5	96.8+53.4	78.5+16.2	85.0+45.5

* $p<0.017$ when compared to group 3

Arterial Blood Gases

The myopathic patients are more hypoxic and hypercarbic than neuropathic and electrophysiologically normal COPD patients. Plus, neuropathic patients are more hypoxic than electrophysiologically normal COPD patients. However, none of these differences are statistically significant.

DISCUSSION

The present study yielded these major findings: (1) The frequency of myopathy is 27%, and neuropathy is 47 % in severe COPD patients chosen disregarding complaints about muscle weakness; (2) The incidence of subclinical myopathy and neuropathy is quite high, three of the eight myopathic patients and eleven of the fourteen neuropathic patients had no symptoms or clinical signs suggesting these pathologies; (3) The percentage of steroid usage is higher in the myopathic group, but steroid usage is not obligatory for the development of myopathy, (4) D_{LCO} and PImax is significantly low in myopathics and PImax is significantly low in neuropathics; (5) Myopathic patients are more hypercarbic and hypoxic and neuropathic patients are more hypoxic, but they are not significantly so. Several case reports have described acute myopathy following the administration of high doses of steroids (28-32). A retrospective cohort study on 86 acute ,severe asthma patients admitted to intensive care units showed that 30% of patients recieving corticosteroids and neuromuscular blockade developed myopathy (33). Animal studies showed alterations in diaphragm histopathology, biochemistry and respiratory muscle endurance after steroid administration (20-24,34). There is one previous study on healthy individuals (17) and another one on patients recieving steroids for non-respiratory diseases (18) examinig the effect of steroids on respiratory muscles. A significant deteriorating effect of steroids was observed on both inspiratory muscle strength and endurance which is reversible while tapering steroid dosage. Studies examining the effect of inhaled and oral steroids in asthma and COPD patients were published (35,36,14). Inhaled steroids have been observed not to cause myopathy while there are contradictory results about oral steroids. Decramer and colleagues observed a reduced survival in myopathic patients with two years of follow-up and suggested that muscle weakness may be an important determinant of survival in patients with COPD (16). Neuropathy has been well discussed in COPD patients, especially in relation with almitrine bimesylate therapy (6,11). A high incidence of neuropathy has also been described in COPD patients without almitrine usage. A wide percentage range of (between 44 and 87 %) neuropathy was reported by various authors (1-3,5,7-10), depending on the diagnostic criteria and electrophysiological study method, including the nerves that are studied. Smoking, age and hypoxia and malnutrition were blamed for causing neuropathy. The neuropathy was distally predominant, mainly sensory and characterized pathologically by axonal loss, accompanied in some cases by demyelination (1,2,7,8). Most of the patients were asymptomatic (1,2,5). In our study only three of the fourteen neuropathic patients were symptomatic. This high incidence of subclinical neuropathy points out the need for a higher degree of suspicion for neuropathy in COPD patients. Eleven of our neuropathic patients had degenerative type of neuropathy which is thougt to be caused by toxic and metabolic effects. Certain toxins in cigarette smoke were thought to be related to neuropathy. Determination of other metabolic and toxic factors which cause neuropathy needs further research. The frequency of myopathy is higher than what we had expected. Eight patients (27%) were myopathic and three of them were asymptomatic although they had myopathy. More careful evaluation of COPD patients for subclinical myopathy as well as neuropathy is needed since myopathy will affect their pulmonary functions.The presence of hypercarbia was found correlated to myopathy in previous studies (16). Hypoxia could also be a factor causing myopathy, but the presence of myopathy worsens the hypoxia by causing respiratory muscle dysfunction. Early detection of myopathy and slowing its progression if possible, could break this vicious circle.

The presence of a patient who did not recieve steroids during the last six months in the myopathic group points out to the presence of other factors that cause myopathy

in COPD patients. Hyperinflation and malnutrition have been implicated to cause muscle weakness in previous studies (16,17,18). Examining their role in causing overt myopathy needs further research.

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