Peripheral Nervous System Involvement Associated with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is a main cause of mortality in developed and under-developed countries. Along with cardiovascular complications of COPD, there are some subclinical complications such as polyneuropathy due to hypoxia. Peripheral muscle weakness is a crucial problem in COPD. Current study evaluates correlation between peripheral nervous system and muscular system involvement parallel with severity of COPD. Methods: In present study, 40 patients with COPD were selected between January of 2013 to January of 2014 who attends in Tabriz Imam Reza Hospital. Patients underwent electro diagnostic study. Nerves were studied as sensory and motor peroneal, tibial and sural in lower limb and sensory and motor median and ulnar nerves in upper limb. These results compared with 40 healthy subjects. Results: Patients mean age was 58.85±12.60 years. There was significant relation between hypoxia and right peroneal nerve NCV (p=0.006) and between smoking and right peroneal amplitude (p=0.001). There were significant differences between sensory left median nerve amplitude (p=0.02) and sensory left ulnar nerve amplitude with COPD severity. Radiculopathy was seen in 52.5%, carpal tunnel syndrome was seen in 7.5%, restless leg syndrome in 5% and Myopathy was seen in 2.5% of subjects. Conclusion: Neuropathy observed in patients with chronic obstructive pulmonary disease is mostly in sensory nerves, which intensifies with increase in chronic obstructive pulmonary disease severity.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has been a major public health problem worldwide which is a respiratory disease characterized by progressive, partially reversible airflow limitation, which results from an emphysematous destruction of the lung parenchyma and increased airway resistance due to inflammation, bronchospasm and increased mucus production [1]. Nowadays, there is an increased recognition for the need to create awareness regarding COPD and to help the thousands of people who suffer from the disease and die prematurely from COPD or its associated complication(s). As a result, a committed group of scientists encouraged the US National Heart, Lung, and Blood Institute and the World Health Organization to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The initial step in the GOLD program was to prepare a consensus Workshop Report, Global Strategy for the Diagnosis, Management, and Prevention of COPD [2]. Cardiovascular problems (e.g., coronary heart disease), neurological impairments (e.g., polyneuropathy), and metabolic disorders (e.g., osteoporosis) are also commonly associated with COPD as are psychological alterations such as depression and anxiety [3]. While the presentation, development and manifestations of COPD are highly variable from patient to patient, the severity of the disease typically progresses as the patient ages. Neuropathy may be associated with varying combinations of weakness, autonomic and sensory changes, loss of muscle bulk or fasciculation [4]. Peripheral muscle weakness is a crucial problem in COPD. Functionally, skeletal muscle dysfunction in COPD patients is characterized by significant reduction in muscle strength and endurance [5]. It is structurally characterized by loss of muscle mass and cross-sectional area (muscle atrophy), fiber type distribution (reduction in the proportion of oxidative fibers and increases in the proportion of glycolytic fibers), oxidative metabolic capacity (attenuation of...
mitochondrial enzyme activities and expression) and capillary distribution (significant loss of capillary density). Although disuse and inactivity are important contributors to the pathogenesis of skeletal muscle dysfunction in COPD patients, several other systemic and local factors are also involved [6-8]. These include systemic inflammation, malnutrition, corticosteroid usage, hypoxemia, aging, smoking and local factors such as the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and enhanced protein degradation inside muscle fibers, a result of increased activities of the proteasomal and lysosomal pathways and activation of calpains and caspasases. Jarratt et al. [9] reported electrophysiological evidence of neuropathy was three times as common as clinical evidence in COPD patients. In their study patients with peripheral neuropathy, the changes were distally predominant, affected mainly sensory fibers, and were consistent with an axonal type of neuropathy. There was a significant correlation between age and the incidence of peripheral neuropathy. Ozge and co-workers [10] studied 49 patients with COPD in whom other causes of PNP had been excluded. The rate of axonal neuropathy was significantly higher in the hypoxemic group and the severity of neuropathy was correlated with the degree of hypoxemia. Kayacan et al. [11] enrolled 32 patients (30 Male, 2 Female) with COPD. They detected PNP in 93.8% of the study subjects. Sensory nerve conduction velocity of median nerve was reduced as PaCO₂ was elevated and pH was lowered.

The objective of this study was to assess the correlation between peripheral nervous system and muscular system involvements parallel with the severity of COPD.

MATERIALS AND METHODS

The study was conducted at the department of neuroscience research center and Tuberculosis and Lung Disease Research Center of Tabriz University of medical science. This study was approved by institutional board of studies and by the ethical committee (ID: 5515). Forty patients with COPD were recruited for this study. The diagnosis of COPD was based on the smoking history and on pulmonary function tests showing irreversible bronchial obstruction. The range of age of the participants was between 32 to 82 years (mean: 58.85±12.60 years). Forty healthy and nonsmoking volunteers of similar age were recruited and served as control subjects. All patients and healthy volunteers gave their written consents. Patients having diabetes mellitus, chronic alcoholism, uremia, cystic fibrosis, anemia, sarcoidosis, leprosy, any type of malignancy, heredity disorders involving peripheral nerves, history of intake of any usage of neurotoxic drugs or history of any traumatic lesion possibly affecting peripheral nerve functions were excluded from the study [10, 11]. All subjects underwent pulmonary function tests, pulse oximetry and electrophysiological studies. Electrophysiological studies carried out on a computerized nerve conduction testing equipment (Neuroscreen plus TOENNIES, 4 canals, Germany). 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 were examined. 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 positive peak to negative peak (peak to 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 pollicis 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 velar crease of the brachial pulse. During ulnar motor nerve conduction evaluation, the nerve was stimulated at two sites. The compound muscle action potential (CMAP) was recorded from hypothenar muscle. 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. 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 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 carried out by a cathode placed 3 cm proximal to the distal crease at the wrist and SNAP recorded from the fifth digit. The sural sensory nerve 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.

Settings of the electromyography equipment were made to the following description:
1. Filter: for motor nerve conduction (low pass: 5 Hz, high pass: 5000 Hz and for sensory nerve conduction, low pass: 5Hz, high pass: 2000 Hz.)
2. Amplification between 20,000 and 100,000 times.
3. Electrode impedance was kept below 5 kD.
5. Sweep speed for motor nerve conduction: 1 ms/division.
6. Stimulator: stimulus duration of 50 Ds to 1000 Ds and current 0-100 mA are required for effective nerve stimulation.

RESULTS AND DISCUSSION

Results:
The study included 80 subjects comprising of 40 COPD patients containing 33 male and 7 female and 40 aged matched healthy volunteers. The mean age of the patients was 58.85±12.60 years (Range 32 to 82 years of age).

The duration of symptoms in all COPD patients was at least 6 years or more. All healthy volunteers were nonsmokers and had no symptoms suggestive of any pulmonary disease. The amplitude of sural nerve in COPD group was decreased in 7 subjects. The NCV of sural nerve in COPD group was decreased in 4 subjects. The amplitude and NCV of sensory right median nerve were decreased respectively in 15 and 24 subjects. The amplitude and NCV of motor right median nerve was decreased respectively in 1 and 6 subjects. The amplitude and NCV of sensory right median nerve was decreased respectively in 8 and 31 subjects. The amplitude and NCV of motor left median nerve was decreased respectively in 0 and 7 subjects. The amplitude and NCV of sensory right ulnar nerve were decreased respectively in 16 and 15 patients. The amplitude and NCV of motor right ulnar nerve were decreased respectively in 2 and 2 subjects. The amplitude and NCV of sensory left ulnar nerve were decreased respectively in 9 and 17 subjects. The amplitude and NCV of motor left ulnar nerve were decreased respectively in 1 and 3 subjects. The amplitude and NCV of right and left peroneal nerve were decreased respectively in 10 and 18 subjects. The amplitude and NCV of right and left tibial nerve were decreased respectively in 7 and 11 subjects. As shown in this study, in sensory nerves the abnormal criteria increased parallel with the severity of COPD. There was a statistically significant difference between the amplitude of left sensory median (p = 0.02) and left sensory ulnar nerve with the severity of COPD (P = 0.03) (Table 1).

Table 1: Decreasing of amplitude and NCV factors in groups.

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There was a statistically significant correlation between hypoxemia and NCV of right peroneal nerve (0.006). Radiculopathy was seen in 21 patients. Six subjects were hypoxic and 15 cases were without hypoxemia. This shows that the radiculopathy had more incidences in hypoxic group. In all categories of COPD, radiculopathy had a high incidence. Tunnel carpal syndrome had been seen in 3 subjects. Restless legs syndrome had been seen in 2 subjects. Myopathy was seen in only one patient.

Discussion:
Chronic obstructive pulmonary disease (COPD) is the term used to describe slowly progressive airways obstruction, usually associated with smoking [12]. The incidence and type of neuropathy in patients with chronic obstructive pulmonary disease (COPD) were assessed [13-15]. Skeletal muscle weakness is a prominent problem in many patients with chronic obstructive pulmonary diseases [16-19]. Muscle wasting is one of the factors that can be considered in the pathogenesis of skeletal muscle weakness in COPD. Several factors are associated with peripheral neuropathy such as cigarette smoking and duration of COPD. Other studies suggest that age, severity of hypoxemia and hypercapnea can be relative causes of peripheral neuropathy [20-22].

Nowak et al [19] found that age and the degree of hypoxemia of the patient can be predictors to differentiate between COPD patients with and without PNP. Although the cause of PNP in COPD patients remains unknown, their obstructions suggest that chronic hypoxemia may contribute to PNP. In a multicentric study [21], 43 of 151 patients with COPD showed a clinically manifested PNP, whereas in a comparative group comprising of 32 asthmatics there were only 2 clinical PNP cases. Patients with known risk factors for
PNP were not included in this study. The PNP observed was usually mild, mainly sensorial, distal and leg-accentuated. Out of 52 COPD patients with a PaO₂ up to 55 Torr, polyneuropathy was seen in 21 (40%); and of 59 COPD patients with a PaO₂ above 60 Torr, 10 (17%) had polyneuropathy.

A study highlighted that the microangiopathy in peripheral nerves in patients with COPD may be diffuse and essentially due to hypoxia and reduction in blood flow, as in diabetic neuropathy [23]. A prospective study [24] enrolled 30 COPD patients (28 men and 2 women) with no known causes of PNP. Six patients reported slight paresthesiae. Clinical examination revealed signs that clearly suggested PNP in 8 patients (27%) whereas signs were nonspecific in 14. The neurophysiological study was abnormal in 26 patients (87%), suggesting axonal polyneuropathy that was predominantly sensory. The presence of PNP was related to age, duration of disease and smoking, but not with sex or pO₂ or pCO₂ on the date of examination. The motor and sensory conduction studies showed only reduced mean amplitude of the ulnar nerve SNAP and of the compound muscle action potential of the abductor pollicis brevis muscle. The EMG was abnormal in 94.7% of the cases. From this study support the hypothesis of an involvement of peripheral nerves in COPD [21-25]. A study reported the presence of PNP in 19 out of 30 COPD patients [25]: 7 patients had clinical signs of a symmetric motor and sensory polyneuropathy, patients had only subclinical evidence of peripheral nervous system involvement. Neurophysiological studies showed low amplitude CMAP and SNAP with only slight reduction of nerve conduction velocity in affected patients: these data confirm an axonal polyneuropathy. The severity of PNP in COPD patients correlated with hypercapnia, the degree of disability and thus with the severity of COPD. Hypoxia, age and duration of the disease were not related with the presence of PNP. Improvement of respiratory function produced slight but progressive improvement of neurological symptoms.

A study [26] investigated 43 patients with COPD. PNP was found in 74% patients, it was mild in 39%, and severe in 35%. The authors concluded that neuropathies were mixed but predominantly of the axonal type. Axonal degeneration and demyelination were confirmed by nerve biopsy; muscles presented neurogenic atrophy. Statistical analysis showed that the duration of hypoxemia was related to neuropathy. In a prospective study [27], 43 COPD patients having no known risk factor causing PNP were included. Electrophysiological recordings showed slight or significant signs of PNP in 17 and 15 patients respectively, thus indicating that the condition was frequent. Clinically, it was often silent or manifested only by sensory disorders predominant in the lower limbs. Electrophysiology suggested axonal degeneration associated with some degree of demyelination, and these lesions were found at histology to be present in sensory nerves. Age, alcoholism and the other respiratory function values did not correlate with lesions of the peripheral nervous system, though the duration of hypoxia correlated with polyneuropathy. The prevalence of clinical and electrophysiological signs of PNP was evaluated in 151 COPD patients with no concomitant disorders affecting the peripheral nervous system. Thirty patients had clinical signs of a mild sensorimotor and distal neuropathy and 13 additional patients had only electrophysiological abnormalities. The rate and the severity of the neuropathy correlated with the severity of chronic hypoxaemia. Three out of 20 patients with mild hypoxaemia (PaO₂ less than 15 mm Hg below normal) had polyneuropathy as compared with 15 out of 36 with severe hypoxaemia (PaO₂ more than 30 mm Hg below normal (rates different at the 10% level). PaO₂ and age were the only variables discriminating between patients with and without peripheral neuropathy.

The previous studies have suggested the existence of impaired peripheral nerve functions in patients with COPD. Many of COPD patients have clinical evidence of peripheral neuropathy and have electrophysiological abnormalities. The appearance consists of a polyneuropathy often subclinical or with primarily sensory signs, which has the neurophysiological and pathological features of mainly axonal neuropathy. Hypoxia probably plays an important role, either by direct action on nerves fibers or by enhancing the effects of other neurotoxic factors or deficiencies. In this study, we consider the increase of abnormalities in sensory than motor nerves in cases with severe COPD. Our results showed that in patients with COPD, the amplitude of mentioned peripheral motor and sensory nerves were decreased .these findings revealed mild mixed type axonal demyelinating polyneuropathy occurs in this status.

Conclusion:

The individuals with COPD had functional and neurophysiological alterations in comparison with the healthy individuals. The findings of our study showed that neuropathy is more in sensory nerves and correlates with severity of COPD, although more investigations are needed to confirm these findings.

REFERENCES


