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Restless legs syndrome in lung chemical warfare patients

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Original Article

Abstract

BACKGROUND: Restless legs syndrome (RLS) has been associated with a variety of diseases, including chronic obstructive pulmonary disease (COPD), which can worsen the symptoms of underlying disease and correlates with co-morbidities. We aimed to investigate RLS in patients with chemical warfare-induced lung diseases.

METHODS: This cross-sectional study recruited patients with sulfur mustard (SM) lung injury, their healthy family members, and patients with COPD from August 2018 to August 2019. COPD was confirmed by medical history, physical examination, and spirometry according to GOLD COPD guidelines. RLS diagnosis was recognized by the International Restless Legs Syndrome Study Group (IRLSSG) and severity was assessed using the International Restless Legs Scale (IRLS) rating scale. Other research measures were COPD Assessment Test (CAT), modified Medical Research Council (mMRC) scale for dyspnoea severity, and Epworth Sleepiness Scale (ESS) for daytime somnolence. Laboratory values included hemoglobin, ferritin, creatinine, and fibrinogen.

RESULTS: This study was conducted on 143 men in three groups: 40 (30.0%) SM-exposed veterans, 73 (55.3%) patients with COPD, and 30 (20.9%) healthy cases. Due to the high prevalence of COPD and better comparison with the control group, more patients with COPD were selected. 20 cases (50%) of the veterans group had RLS, while 25 (32.9%) cases of COPD were affected by this disorder. One normal case (3.33%) suffered from RLS. The chemical veterans who suffered from cough, sputum production, chest pain, and hemoptysis had a higher incidence in proportion to patients with COPD ($P < 0.001$). The CAT score was significantly higher in SM-exposed veterans with RLS ($P = 0.004$).

CONCLUSION: RLS is more common in SM lung injuries with higher CAT scores; therefore, evaluation and treatment of RLS are recommended in mustard lung victims.

KEYWORDS: Lung; Chemical Warfare; Chronic Obstructive Pulmonary Disease; Restless Legs Syndrome

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Introduction

Restless legs syndrome (RLS) is a sensor motor disorder characterized by non-stopped desire or an urge to move the limbs, especially legs, which worsens during rest times and is relieved by movement. Thus, RLS makes it difficult to get comfortable enough to fall asleep and interferes with sleep. The diagnosis

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of RLS is clinical and there is no specific diagnostic test for RLS.[1-3] The prevalence rate of RLS among the adult general population ranges from 3.9% to 15% based on the target population of the studies. Nevertheless, RLS is a common yet frequently under-diagnosed illness.[4] It is divided into two groups of idiopathic or familial and secondary type. Iron deficiency, megaloblastic anemia, kidney failure, dialysis, hypothyroidism, diabetes mellitus (DM), peripheral neuropathy, multiple sclerosis (MS), fibromyalgia, rheumatoid arthritis (RA), Sjogren disease, systemic lupus erythematosus (SLE), and pregnancy are predisposing factors for RLS. Antinausea and antipsychotic drugs, some antidepressants, antihistamine and caffeine, nicotine, and alcohol may also worsen the RLS symptoms.[5] What should be mentioned is that co-morbidity of RLS can worsen the symptoms of the underlying disorders and it is associated with poor quality of life and increased morbidity rate.[6] Clinical criteria for the diagnosis of RLS are based on those expressed by the International Restless Legs Syndrome Study Group (IRLSSG).[7] Moreover, war is always a terrible and unfortunate event. During the Iraq-Iran War between 1980 and 1988, more than 50000 Iranians have been injured by sulfur mustard (SM) gas, an alkylating irreversible toxic potent agent.[8] Lung, eye, skin, and central and peripheral nervous systems are the most commonly affected organs in victims exposed to mustard gas. Of these, the pulmonary system is an important target for SM injury which leads to various diseases from acute tracheal inflammation to chronic obstructive pulmonary disease (COPD).[9] The main symptoms of delayed COPD mustard injury are chronic cough, dyspnea, and sputum.[10] COPD is a common progressive disease characterized by not completely reversible airflow restriction.[11] Patients with COPD have many serious comorbidities that lead to morbidities. It is mentioned that COPD increases the risk of developing RLS.[12] Thi Truong et al. reported that RLS prevalence in patients with COPD was 2.2 times higher than in non-COPD patients.[12] Although studies have reported chemical lung injuries, there is still much uncertainty about the chemical gases' complications. However, numerous comorbidities have been denoted in patients with chemical lung injury, considering the higher rate of RLS among veterans especially military veterans who were exposed to SM.[13] Rezaeitalab et al. study showed that RLS and obstructive sleep apnea (OSA) were higher in male military veterans and mustard lung injury victims with post-traumatic stress disorder (PTSD).[13] It is important to evaluate RLS in the chemical warfare victims with COPD. The main purpose of the present study was to evaluate RLS in Iranian patients with mustard lung injuries with COPD.

Methods

Study design and participants: This observational cross-sectional study included 40 confirmed mustard lung injuries, 73 clinically stable patients with COPD, and 30 healthy individuals from August 2018 to August 2019. Inclusion criterion was being male and cases were recruited from Imam Reza and Ibn-e-Sina Hospitals, Mashhad University of Medical Sciences, Mashhad, Iran. Healthy cases were selected from the first-degree families of patients with mustard lung injuries in order to rule out familial causes of RLS. All chemical warfare patients had validated documents demonstrating SM exposure and suffered from important late pulmonary complications. According to GOLD guidelines definitions,[14] patients with mustard lung injury and COPD with a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) < 0.7 after inhalation of 400 µg of a bronchodilator (albuterol) were included in the study. Current or ex-smokers of mustard lung victims were

excluded for any of the following conditions: FEV1 increase of more than 12% and 200 ml after short-acting bronchodilator inhalation (salbutamol spray), hospitalization or exacerbation in the past 2 months, difficulty in walking, or diagnosis of asthma, bronchiectasis, tuberculosis, and malignancies. All cases with acute and chronic kidney injury, iron deficiency and megaloblastic anemia, DM, hypothyroidism, neuropathies, Parkinson's disease, MS, RA, Sjogren disease, SLE, alcohol, tricyclic antidepressant (TCA) drugs and benzodiazepine, cigarette smoking, and opioids utilization, or those who were not competent to give informed consent were excluded from the study.

Examinations and tests: Spirometry test was taken from all patients with COPD and mustard lung injuries by one professional technician. Specific questionnaires were answered concurrently in a face-to-face interview by three medical researchers. History and physical examinations were taken from all patients and healthy subjects. COPD Assessment Test (CAT) was fulfilled by all mustard lung victims and patients with COPD. CAT is a self-administered questionnaire that provides a simple scoring system for evaluating the effect of COPD on the patient`s health status. The CAT contains eight items, that concentrate on respiratory symptoms, such as cough, sputum production, chest tightness, and dyspnoea, as well as on non-respiratory symptoms, such as lack of energy or sleep disturbance as well as additional indicators, like limitations in doing activities or confidence leaving home. The GOLD guidelines recommended a CAT score of 10 points or higher to classify high symptomatic COPD.[14,15] The severity of dyspnoea was assessed by the modified Medical Research Council (mMRC) Dyspnoea Scale, with scores ranging from 0 (only getting breathless with strenuous exercise) to 4 (too breathless to leave the house or getting breathless when dressing or undressing).[15] RLS was recognized by the criteria of the IRLSSG, and its severity was diagnosed by the International Restless Legs Scale (IRLS) rating scale.[1] Laboratory parameters measured included serum fasting blood sugar (FBS), serum levels of hemoglobin, ferritin, urea, creatinine, and fibrinogen.

Ethics approval: The study protocol was approved by the local Research Ethics Committee (registered number: IR.MUMS.Fm.Rec1394.575) and written informed consent was obtained from all cases.

Statistical analysis: The variables were presented as frequency (%), percentage and mean ± standard deviation (SD). Descriptive analysis was used to summarize the demographic characteristics of the cases. Evaluation of correlation of qualitative variables was performed by chi-square test. The normality of quantitative variables was evaluated by the Kolmogorov-Smirnov test. In order to compare pulmonary indexes and quality of life due to CAT, chi-square test and Mann-Whitney test were used. Statistical analysis was carried out using SPSS software (version 16, SPSS Inc., Chicago, IL, USA) and the significant description was P-value < 0.05.

Results

The mean age of mustard lung injury group, patients with COPD, and healthy cases was 55.9 ± 5.9, 64.4 ± 8.6, and 59.0 ± 9.8, respectively. 50% of mustard lung victims, 32.9% of patients with COPD, and one normal case had RLS (P = 0.074). Although RLS in chemical veterans was more frequent than patients with COPD, it was not statistically significant. Among pulmonary symptoms, cough, expectoration, chest pain, and hemoptysis were statistically higher in SM lung victims than COPD cases (Table 1). In spirometry indexes, remarkable differences in FEV1 and FEV1/FVC variables were seen in the two groups (mustard lung injury and COPD) (P < 0.001) (Table 1). Outstandingly, our study notably reported a CAT score of over 10 in all mustard lung-injured patients.

Table 1. Demographic variables, clinical manifestation, and spirometric parameters between mustard lung injury cases and patients with chronic obstructive pulmonary disease (COPD)

Variables	Sulfur mustard lung injuries (n = 40)	Patients with COPD (n = 73)	P
Age (year) (mean ± SD)	55.9 ± 5.9	64.4 ± 8.6	NS
RLS [n (%)]	20 (50.0)	24 (32.9)	0.074
BMI (kg/m2) (mean ± SD)	25.1 ± 3.2	26.2 ± 4.6	0.290
MMRC scale (mean ± SD)	2.3 ± 1.0	2.1 ± 1.0	0.090
Cough [n (%)]	63 (86.3)	23 (57.5)	0.990
Expectoration [n (%)]	65 (89.0)	40 (100)	0.100*
Hemoptysis [n (%)]	1 (2.0)	12 (16.4)	< 0.001*
Chest pain [n (%)]	14 (19.1)	11 (27.5)	0.002**
Wheezing [n (%)]	32 (80.0)	46 (63.0)	0.060
Rhonchi [n (%)]	28 (70.0)	13 (17.8)	< 0.001
Crackle [n (%)]	25 (62.5)	32 (45.2)	0.070
FEV1 (%) [median (IQR)]	39.1 (16.7)	51.3 (16.0)	< 0.001
FVC (%) [median (IQR)]	72.0 (11.2)	76.1 (10.8)	0.140
FEV1/FVC [median (IQR)]	60.1 (16.1)	70.7 (13.7)	< 0.001
MMEF (%) [median (IQR)]	25.5 (26.2)	33.3 (19.2)	0.100
Hemoglobin (g/dl) (mean ± SD)	14.1 ± 0.8	14.4 ± 1.0	0.730
Ferritin (ng/dl) (mean ± SD)	187.0 ± 1.2	156.0 ± 1.3	0.120
Creatinine (mg/dl) (mean ± SD)	0.8 ± 0.3	0.8 ± 0.1	0.880
Fibrinogen(mg/dl) (mean ± SD)	432.2 ± 0.2	426.0 ± 0.5	0.830

*Fisher's exact test; **Chi-square test

COPD: Chronic obstructive pulmonary disease; RLS: Restless legs syndrome; BMI: Body mass index; MMRC: Modified Medical Research Council; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; MMEF: Maximal mid-expiratory flow; IQR: Interquartile range; SD: Standard deviation; NS: Not significant

Mustard lung injury and COPD groups had CAT scores of 28.90 ± 8.06 and 25.30 ± 7.54, respectively, and there was a statistically significant difference between the two groups (P = 0.042) (Table 2).

Discussion

The main aim of the present study was RLS assessment in lung chemical warfare victims. COPD is the latest pulmonary complication of chemical weapons in Iranian victims.[16] We do not have enough knowledge regarding the association between RLS and COPD and mustard lung injury. According to the databases, this research was applied for the first time and the results are the first presentation. The findings of the present study indicated that half of 40 (50.0%) confirmed patients with mustard lung injuries had RLS and 34.24% of patients with COPD had this disorder. Although the prevalence of RLS was higher in SM-exposed veterans, the difference was not statistically significant (P = 0.074).

Prevalence of cough and expectoration, chest pain, and hemoptysis in mustard lung injuries was much more than COPDs. In mustard lung injuries, rhonchi and chest pain were considerably more common than patients with COPD. Indeed, FEV1 and FEV1/FVC in COPD cases decreased more than patients with mustard lung injuries.

Table 2. Comparison of COPD Assessment Test (CAT) scores in mustard lung injuries and chronic obstructive pulmonary disease (COPD) groups with or without restless legs syndrome (RLS)

CAT score	Mustard lung injuries (mean ± SD)	Patients with COPD (mean ± SD)	P*
With RLS	32.25 ± 7.08	27.40 ± 7.68	0.004
Without RLS	25.55 ± 7.71	24.20 ± 7.32	0.072

*Mann-Whitney test

COPD: Chronic obstructive pulmonary disease; RLS: Restless legs syndrome; CAT: COPD Assessment Test; SD: Standard deviation

The important point in our study is related to the higher CAT scores in SM victims with RLS. Khazdair and Boskabady reported inflammatory cytokine roles, while increased inflammatory cytokines and lung function declined in SM-induced lung injury.[17] Although several co-morbidities had been reported in SM victims leading to poor health status, as indicated in Rezaeetalab and Rezaeitalab study, there was an association between COPD and RLS.[18] But according to research on scientific databases, there are no studies that have assessed the CAT scores and mMRC in mustard lung injury with or without RLS. This issue suggests that the practitioners should be aware of the role of RLS in the progression of co-morbid medical illnesses such as COPD.[18] In addition, in a qualitative study by Rezaeitalab et al. which was accomplished on Iranian chemical warfare victims, it was reported that their muscles became restless as they played ping pong or tried to fix their limbs.[13] Moreover, Rezaeitalab et al. study expressed that veterans with mustard-induced lung disease had some sleep disorders concurrent with restless legs at night; in addition, OSA was accompanied by periodic leg movements syndrome. This complication might be related to OSA which is presented in about one-fourth of SM victims.[19] Besides, the findings of the present study showed that the prevalence rate of RLS among chemically-injured veterans was higher significantly compared to the general population (50% vs. 5%-10%) which emphasizes the more attention to RLS among this special population. This issue is concordant with a study conducted by Rezaeitalab et al., which showed the high presence of RLS in male veterans (22.5%) with PTSD. All of the victims had OSA, while they did not have a history of diabetes, renal failure, and Parkinson's disease or other definitive secondary risk factors for RLS.[19]

Based on Ding et al. study which assessed 2745 adult women, the prevalence rate of RLS was reported at 37.4% and 23.8% among women with or without COPD, respectively ($P < 0.001$). The findings indicated that COPD could increase the risk of RLS by 30%.[20] However, the prevalence of RLS varies in different societies. Wijemanne and Ondo study reported approximately 7% prevalence for RLS, but clinically significant symptomatic RLS in about 2.7%. The RLS incidence increases with age. The prevalence is typically proposed lower in Asian countries. Early-onset RLS has a peak incidence at 20-40 years of age, is often familial, and has a slow disease evolution. Late-onset RLS may quickly progress and is likely familial, and concomitant with comorbidities.[21] The present study assessed the veterans, who were exposed to SM and compared them with patients with COPD and healthy cases. The veterans had a higher rate of pulmonary symptoms such as cough, wheezing, expectoration, and rhonchi than patients with COPD. Shahriary et al. study showed high serum levels of inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), immunoglobulins, and signs of oxidant-antioxidant imbalance system compared to patients with COPD.[16] This study discussed the role of systemic inflammation in chemical lung injury veterans. Khazdair and Boskabady studied the respiratory symptoms, total and differential white blood cells (WBCs), hematological values, and pulmonary function tests (PFTs) in cases with chemical lung injuries.[22] 46 chemical war victims and 42 healthy cases matched by age and sex were evaluated by questionnaire. PFTs were measured before and after inhalation of 200 µg of salbutamol. Moreover, the basic measures were taken in the healthy control group. All chemical lung injury victims reported respiratory symptoms, including night and exercised cough; wheezing was higher in the veterans compared to the control group ($P < 0.001$). All PFT parameters were also

lower in mustard lung veterans compared to control subjects ($P < 0.001$).[22] This study is concordant with the findings of our research, but it had two groups and patients with COPD were not entered into the study.

In the end, our research has some limitations, such as the lack of a follow-up period to assess the impact of RLS on respiratory conditions in long term. Further, regarding curable nature of RLS, the effect of before and after treatment can be considered in patients with mustard lung injury in future studies.

Conclusion

Cough and sputum, chest pain, and hemoptysis are more common in chemically injured victims than in patients with COPD. Our data confirm that RLS is more common in veterans with mustard lung injuries and these chemical warfare victims have higher scores compared to diagnosed patients with COPD. Therefore, it is recommended to evaluate RLS in chemical warfare victims and lung involvement.

Conflict of Interests

Authors have no conflict of interests.

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