Restless Legs Syndrome in Chronic Obstructive Pulmonary Disease

Abstract:

Restless Legs Syndrome (RLS) is a common chronic sensory motor disorder that prevents initiation and/or sleep staying. This syndrome has uncomfortable sensations in their legs (and sometimes arms or other parts of the body), with moving their legs to relieve this sensations. The symptoms of RLS are usually worse in the evening and at night. The diagnosis of RLS is clinical and based primarily on the patient's history. International Restless leg Syndrome Group Study (IRLSGS) evaluates symptoms and severity of RLS.

RLS can be divided into two groups: primary and secondary. Iron deficiency, Parkinson’s disease, kidney failure, diabetes, peripheral neuropathy, pregnancy may cause RLS.

Antinausea, antipsychotic drugs, some antidepressants, and antihistamines, may worsen symptoms. RLS was seen in Chronic obstructive pulmonary disease (COPD), which makes it worse outcome. COPD is a main preventable health problem leads to morbidity and mortality. Thus, RLS in COPD causes excessive daytime hyper somnolence, fatigue, poor quality of life, disability and neuropsychological complications, such as social isolation, frequent daytime headaches, anxiety and depression.

Key words: Restless legs syndrome, Chronic obstructive pulmonary disease, Sleep.

Introduction:

Restless leg syndrome also called Willis-Ekbom disease (WED) is a sensory motor disorder leads an urge to move the limbs (1-6). This syndrome has uncomfortable sensations in their legs (and sometimes arms or other parts of the body), so with moving their Limbs these sensations were relieved (4-10). The symptoms of RLS are usually worse in the evening and at night than at the day time (6,8). The diagnosis of RLS is clinical and based essentially on the patient’s history. The clinical criteria for the diagnosis of RLS are based on those developed by the International Restless Legs Syndrome Study Group. The International Restless Legs Study...
Group introduced the following four features as minimal criteria for the diagnosis of RLS: 1-desire to move the extremities, often associated with discomfort and restlessness, 2- occurrence or worsening of symptoms at rest, 3- relief of symptoms completely or partly during activity, 4- occurrence or worsening of symptoms only in the evening or at night (10,11). Also, International Restless leg Syndrome Group Study (IRLSGS) describes symptoms and severity of RLS (11). RLS was classified in to primary (idiopathic) and secondary (12,1). People with RLS usually have hard to fall asleep and stay asleep. In addition, they often don’t get enough sleep may feel tired and sleepy during the day. RLS can make it difficult to concentration, daily and social activities performance. Not getting enough sleep can also make you feel depressed or have mood swings (7-10). It should be noted, COPD characterized by airflow obstruction that is not fully reversible (13-17).

COPD is a preventable and debilitating disease in the worldwide till 2030 would be the third causes for mortality (17,18). Shortness of breathing and chronic productive cough are the cardinal manifestation in COPD (22-28). Cigarette smoking is a main risk factor for COPD. Although occupational exposure, biomass inhalation, genetic predisposition were documented for pathogenesis of COPD( 29-38). Sleep disorder breathing such as OSA, Restless leg syndrome are co morbidities in COPD (39).

**Literature Review**:  
We conducted a narrative review of restless legs syndrome in Chronic obstructive pulmonary disease in the Pubmed and google scholar database. If an article that satisfied the study was identified. A full-text article was excluded if it was not related to restless legs in COPD. One hundred and eighty-nine articles were selected for full text review. It should be noted, we excluded psychiatric and neurologic disorders, liver disease, hepatitis encephalopathy and another metabolic disorders in this article.

**Restless legs Syndrome, COPD**:  
Restless legs syndrome of any severity occurs in 5 to 15 percent of adults. This syndrome can be seen at any ages and sexes, but slightly more common in women. To this point, RLS is
common in COPD patients (3-6). The incidence of COPD is over 10%-15% in adults 40 years of age or older, (13,14). Although, the prevalence of COPD is increasing, so the morbidity and mortality are health problems in the all of the world (21-24). Up to now, the accurate cause of RLS is unknown. Nearly half of people with RLS also have a family member. Idiopathic RLS was observed in younger age and had a genetic predisposition. Inversely, the secondary RLS had more severe progression in symptoms and observed in late onset (2-3,6-7). The effective treatment with dopaminergic drugs in RLS, support that malfunction in central nervous system (CNS) is responsible for pathogenesis rather than peripheral nervous system (2-12). In secondary RLS, predisposing factor include: iron deficiency, Parkinson’s disease, kidney failure, diabetes, and peripheral neuropathy often include symptoms of RLS. Antinausea drugs, antipsychotic drugs, some antidepressants, cold and allergy medications containing sedating antihistamines, may worsen symptoms. Pregnancy, alcohol use and sleep deprivation, may trigger symptoms or make them worsen (3-7). Low central nervous system (CNS) iron is a persistent finding in RLS/WED. Diminished serum ferritin levels (<50 mcg/L) relate with RLS. Decreased serum ferritin is the important indicator of low iron stores and the only serum measure to consistently correlate with RLS (10-12). Although the association between RLS and COPD remain unclear, but the hypoxemia may be predisposing factor for RLS (39-40). Several studies have been reported that sleep quality is worse in COPD patients compared to healthy people (39). So, daytime fatigue and poor sleep quality are considerable complications in COPD patients. Apart from symptoms, there are nocturnal desaturation, decrease in ventilation and gas exchange abnormalities in patients with COPD (31-39). As a result, in COPD patients, this alteration may be lead to significant daytime hypoxemia and hypercapnea (33). Besides, nocturnal cough, dyspnea and wheezing, restless leg syndrome can result in difficulty initiating and maintaining sleep, so it leads to poor sleep and quality of life (39-42). Furthermore, Restless leg syndrome frequency leads to insomnia (1-12). Hypercapnea and hypoxemia may be associated to RLS in COPD patients as an initiation or trigger factor. Therefore patients with idiopathic RLS have been found to have fragmented sleep with prolonged sleep latencies, small duration of total sleep time and higher
arousal index (4-11). The severity of RLS symptoms was higher in COPD compared in idiopathic form (4,10). In addition, RLS was higher in the late stages of COPD, severe obstruction, more hypercapnea and hypoxemia (4). High frequency of depression and arterial hypertension were found in COPD with RLS (2,4,8-12). There is an extreme incidence of sleep disorders (such as RLS, periodic limb movement and obstructive sleep apnea) in COPD patients (4,8). RLS was seen more in OSA. Although RLS can be associated with sleep disordered breathing, mostly OSA, but the relationship between the two disorders are still unclear (43). Coexistence OSA and COPD named sleep overlap syndrome (44-47). While the mechanism of RLS in COPD is yet unclear, but hypoxemia and/or hypercapnea may be related to the pathogenesis of RLS (34-39). Hypoxemia can lead to an increase in vascular endothelial growth factor (VEGF). VEGF expression is increased in the substantia nigra and in the anterior tibialis muscle of the RLS patients (1-12). RLS was seen in 8.3% of OSA patients, then clinicians recommend RLS screening by a questionnaire and by an interviewer using the criteria described by the International Restless leg syndrome study group (48,49,50,11). Briefly, anxiety, depression, cardiovascular events were found in RLS, COPD, OSA that exaggerated together (22,51-53).

**Obstructive sleep Apnea:**

Obstructive sleep apnea is a common disorder defined by repeated closure upper airway during sleep that leads to a significant functional disability and end organ damage and mortality (54-57). Essential manifestations of OSA in adults include: apneas, hypopneas, loud snoring, morning headache, daytime sleepiness, fatigue, low concentration, poor cognitive, and restlessness (58-62). The prevalence of OSA was 2% in female and 4% in male. The most important predisposing factors for OSA are aging, male gender, obesity, and craniofacial or upper airway soft tissue abnormalities. Additional risk factors include smoking, nasal congestion, menopause, and family history, but the best documented risk factor for OSA is obesity (60-68). OSA was diagnosed when apnea hypopnea index (AHI)
was ≥5 per hour. Apnea is defined as the complete stop in respiratory flow over a period of ten seconds or more. Polysomnography measures the apnea–hypopnea index (AHI), a measure of the number of apnea or hypopnea events per hour during sleep (69-71). The AHI is used to diagnose and assess the severity of OSA (54, 70). OSA patients are at risk for profound hypoventilation, respiratory failure, more chronic hypoxemia and cardiovascular complications (72-77). Patients with OSA, especially in untreated cases, are at risk for a major range of cardiovascular impairment, including systemic hypertension, pulmonary arterial hypertension, coronary artery disease, cardiac arrhythmias, heart failure, and stroke (72). OSA is a prone for diabetic mellitus and resistance to insulin (78). Sleep overlap syndrome (concomitant COPD and OSA in an individual) leads to more severe nocturnal desaturations, increases risk for pulmonary hypertension, cardiac morbidity and mortality (79-88).

**Periodic Limb Movements (PLM):**

Periodic Limb Movements are short involuntary movements are occurring during sleep at about 20-40 second intervals (5, 88). They are characterized by a rhythmic and repetitive extension of the big toe and dorsiflexion of the ankle with occasion flexion at the knee and hip (89). The majority of patients of RLS have PLMS. Approximately, 80%-90% RLS have PLMS (3-10). In addition, PLMS was seen in OSA (50, 61). Although, several studies have documented a high incidence of PLMS in healthy people over the age of 40 years (88).

**Diagnosis:**

There is no specific diagnostic test for RLS, so its diagnosis is clinical. The International Restless Legs Syndrome Study Group (IRLSSG) formulated four criteria defining RLS: (1) there is an urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs; (2) the urge to move the legs begins or worsens during inactivity such as lying or sitting; (3) the urge to move is partially or totally relieved by movements; and (4) the urge to move is worse in the evening or at night. Thus, diagnosis of RLS is based on a history and does not need a polysomnography recording (1-4), although polysomnography
confirmation would be considered when sleep disordered breathing was seen. OSA was diagnosed with polysomnography. Additionally, PLMS are recorded at night during sleep in polysomnography (80-88).

**Treatment:**

RLS treatment is based on the severity of RLS and degree of disability. In mild and intermittent symptoms, lifestyle improvement was recommended. Mild exercise, limited caffeine intake, leg message, hot baths may be benefit. Up to 90% patients with RLS relieve with dopaminergic agents. Benzodiazepines treat RLS symptoms, but when RLS concomitants OSA, benzodiazepines aggregate apneas and hypoventilations, and the sleep disordered breathing make worsen (1-12). Some studies have been shown that CPAP treated OSA as well as RLS and PLMS. Weight reduction, oral device, nasal congestion relieve are the proper treatment for OSA (70-78).

**Conclusion:**

RLS is a common neurological sensory motor disorder, so serious to interfere in sleep quality. Its prevalence is higher in COPD patients than in healthy controls due to importance, screening of RLS in patients with COPD strongly recommended.

**Acknowledgement:**

This study was supported by a grant from the Vice Chancellor for Research of the Mashhad University of Medical Sciences (Grant number:921045)

**Conflict of Interest:**

The authors declare no conflict of interest.

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