Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Restless legs syndrome in chronic obstructive pulmonary disease

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ARTICLE INFO

Article type
Review article

Article history
Received: 20 May 2016
Revised: 27 Sep 2016
Accepted: 10 Oct 2016

Keywords
Chronic obstructive pulmonary disease
Restless legs syndrome
Sleep

ABSTRACT

Restless legs syndrome (RLS) is a common chronic sensory motor disorder that prevents initiation and/or sleep staying. Patients with this syndrome have 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 primarily based on clinical evaluation and clinical history of the patient. International restless leg syndrome group study (IRLSSG) evaluates the symptoms and severity of RLS. RLS can be divided into two groups of primary and secondary. Iron deficiency, Parkinson's disease, kidney failure, diabetes, peripheral neuropathy, and pregnancy may cause RLS. Antinausea, antipsychotic drugs, some antidepressants, and antihistamines may also worsen the symptoms. RLS is also observed in chronic obstructive pulmonary disease (COPD), which makes the outcomes worse. COPD is a main preventable health problem that can lead to morbidity and mortality. Thus, RLS in COPD causes excessive daytime hypersomnolence, fatigue, poor quality of life, disability and neuropsychological complications such as social isolation, frequent daytime headaches, anxiety and depression.

Please cite this paper as:
Rezaeetalab F, RezaeiTalab F. Restless legs syndrome in chronic obstructive pulmonary disease. Rev Clin Med. 2017;4(2):73-77.

Introduction

Restless leg syndrome (RLS) also called Willis-Ekbom disease (WED) is a sensory motor disorder that leads to an urge to move the limbs (1,2). Patients with this syndrome have uncomfortable sensations in their legs (and sometimes arms or other parts of the body), so with moving their limbs these sensations are relieved (3-5). 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 based on clinical evaluation and the patient's history. Clinical criteria for the diagnosis of RLS are based on those developed by the international restless legs syndrome study group (IRLSSG). The IRLSSG suggested 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(9-11). Also, IRLSSG described the symptoms and severity of RLS (11). RLS is classified into primary (idiopathic) and secondary (1,12). People with RLS usually have problem to fall asleep and stay asleep. In addition, since they do not get enough sleep, they may feel tired and sleepy during the day. RLS can make it difficult to concentrate, and daily and social activities performance may also be affected by RLS. Lack of enough sleep can also make patients feel de-

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pressed or have mood swings (7-10). It should be noted that chronic obstructive pulmonary disease (COPD) characterized by airflow obstruction is not fully reversible (13). COPD is a preventable and debilitating disease worldwide and till 2030 it would be the third cause for mortality (14,15). Shortness of breathing and chronic productive cough are the cardinal manifestation in COPD (16,17) Cigarette smoking is a main risk factor for COPD. Also occupational exposure to toxicants, biomass inhalation, and genetic predisposition were documented for pathogenesis of COPD (18-22) Sleep disordered breathing such as obstructive sleep apnea (OSA), and RLS are comorbidities in COPD (23,24).

Literature Review

A narrative review was conducted on RLS in COPD through literature search in the PubMed and google scholar databases. One hundred and eighty nine articles were found for full text review.

Restless legs syndrome and COPD

RLS of any severity occurs in 5 to 15 percent of adults. This syndrome can be observed at any ages and sexes, but its frequency is 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 with 40 years of ages or older (13,14,25). Since, the prevalence of COPD is increasing worldwide, the related morbidity and mortality such as RLS are important health problems that needs further attention (26-28). However, the accurate cause of RLS is unknown. Idiopathic RLS is observed in younger age and had a genetic predisposition. Inversely, the secondary RLS had more severe progression in symptoms and is observed in late onset (2,3,6,7). The effective treatment with dopaminergic drugs in RLS supports that malfunction in central nervous system (CNS) is responsible for pathogenesis rather than peripheral nervous system (2-12). In secondary RLS, predisposing factor that often include symptoms of RLS are iron deficiency, Parkinson's disease, kidney failure, diabetes, and peripheral neuropathy. Antinausea drugs, antipsychotic drugs, some antidepressants, cold and allergy medications containing sedating antihistamines may worsen the symptoms. Pregnancy, alcohol use and sleep deprivation, may trigger symptoms or make them worsen (3-7). Low CNS iron is a persistent finding in RLS/WED. Therefore, decreased serum ferritin (<50 mcg/L), which is an important indicator of low iron stores, correlates with RLS (10-12). Although the association between RLS and COPD remains unclear, but the hypoxemia may be predisposing factor for RLS (29-32). Findings have shown that sleep quality is worse in COPD patients compared to healthy people (33-38). Therefore, 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 (39). As a result, in COPD patients, this alteration may lead to significant daytime hypoxemia and hypercapnea (33). Besides, nocturnal cough, dyspnea and wheezing, RLS can also result in difficulty in initiating and maintaining sleep; hence, RLS may lead to poor sleep and quality of life (39-42). Furthermore, frequent RLS leads to insomnia (1-12). Hypercapnea and hypoxemia, as an initiation or trigger factor, may be associated with RLS in COPD patients. 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(4-11,39). The severity of RLS symptoms is higher in COPD compared to idiopathic type (4,10). In addition, RLS is frequent in the late stages of COPD, severe obstruction, hypercapnea and hypoxemia (4). High frequency of depression and arterial hypertension were found in COPD with RLS (11,12). There is an extreme incidence of sleep disorders (such as RLS ,periodic limb movement (PLM) and OSA) in COPD patients (4,8). RLS is observed more in OSA. Although RLS can be associated with sleep disordered breathing, particularly OSA; however, the relationship between the two disorders are still unclear (39-41). Coexistence of OSA and COPD is commonly known as sleep overlap syndrome (42-47). While the mechanism of RLS in COPD is not yet clear; however, it is suggested that 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 is observed in 8.3% of OSA patients. Clinicians recommend RLS screening by a questionnaire and interview using the criteria described by the IRLSSG (11,48-50).

Obstructive sleep apnea

OSA is a common disorder defined by repeated closure upper air way during sleep that leads to a significant functional disability and end organ damage as well as mortality (51,52). Essential manifestations of OSA in adults include apneas, hypopneas, loud snoring, morning headache, daytime sleepiness, fatigue, low concentration, poor cognitive function, and restlessness (53-58). The incidence of OSA in male higher than female. Overweight is the most important risk facor, although aging, hypothyroidism, myopathy, craniofacial abnormalities and smoking are the predisposing factors (59-63).OSA is 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 AHI, a measure of the number of apnea or hypopnea events per hour during sleep (64-69). The AHI is used to diagnose and assess the severity of OSA (70). OSA patients are at risk for profound hypoventilation, respiratory failure, chronic hypoxemia and cardiovascular complications (71-73). 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 (74-77). OSA patients are prone to diabetes mellitus and resistance to insulin (78). Sleep overlap syndrome (concomitant COPD and OSA in an individual) leads to more severe nocturnal desaturations, and increases the risk for pulmonary hypertension, cardiac morbidity and mortality (79-88).

Periodic limb movements

PLMs are short involuntary movements that may occur 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 (88). The majority of RLS patients have PLM (80%-90%) (3-10). In addition, PLM is observed in OSA (50,61). Also, findings 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 based on clinical evaluation. The 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 medical history and does not need a polysomnography recording(1-4), although polysomnography confirmation would be considered when sleep disordered breathing is observed. OSA is 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 is recommended. Mild exercise, limited caffeine intake, leg message, hot baths may be beneficial .Up to 90% of patients with RLS relieve with dopaminergic agents. Benzodiazepines treat RLS symptoms, but in concomitant occurrence of RLS and OSA, benzodiazepines induce apneas and hypoventilations, and the sleep disordered breathing may also worsen (1-12). Some studies have shown that Continuous positive airway pressure treated OSA as well as RLS and PLMS. Weight reduction, using oral device, and nasal congestion relieve are the proper treatment for OSA (70-78).

Conclusion

RLS is a common neurological sensory motor disorder that interferes with sleep quality. Its prevalence is higher in COPD patients than in healthy controls; hence, the screening of RLS in patients with COPD is strongly recommended.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

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

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