Restless Legs Syndrome – Secondary, Comorbid or Coincidental?

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Key Words

Restless legs syndrome · Comorbidity · Prevalence

Introduction

Restless legs syndrome (RLS) is a disease characterized by the presence of an urge to move the legs accompanied by unpleasant sensations in the legs. The symptoms appear or increase in the evening and during the night, they are provoked by rest, and are totally or partially relieved by moving the legs [1, 2]. Diagnosis of RLS is based solely on the presence of the above-mentioned symptoms without any definite objective measurement.

The etiology of RLS remains unclear, but the strongest evidence supports the 'iron theory': symptoms of RLS are a result of peripheral and central iron deficiency leading to disturbances in dopaminergic transmission [3].

RLS is a frequent disorder – primary RLS was found in 2.4% of the general population in a recent study [4]. In another study, RLS of any form (primary and secondary) and of any frequency of symptoms was found in 7.2% of the general population [5].

The above facts (subjectivity of the symptoms, unclear etiology and high frequency in the general population) should be remembered when analyzing the data on the prevalence of RLS in other diseases.

Prevalence of RLS in Various Diseases

There are three classical causes of secondary RLS: pregnancy, iron deficiency and chronic kidney disease. RLS has also been found to be a prevalent condition in many other diseases, both neurological and nonneurological. Some examples of studies on the prevalence of RLS are shown in table 1.

Discussion

The list of publications presented in table 1 is not complete. Nevertheless, the variety of conditions leading to increases in RLS prevalence suggests that there must be more than one explanation for this phenomenon.

Table 1. Prevalence of RLS in some neurological and nonneurological diseases

Disorder	RLS prevalence
Multiple sclerosis [6]	37.5
Multiple sclerosis [7]	19
Charcot-Marie-Tooth disease [8]	18.1
CIDP [9]	39.3
Primary headaches [10]	22.4
Celiac disease [11]	31
Cancer [12]	18.3
COPD [13]	36.8
HIV infection [14]	33.3
Rheumatoid arthritis [15]	27.7
Liver diseases [16]	62
Lung transplant recipients [17]	47.6
Pulmonary hypertension [18]	43.6

Values are percentages. CIDP = Chronic inflammatory demyelinating polyneuropathy; COPD = chronic obstructive pulmonary disease.

Methodological Issues

Although all of the cited publications used the same diagnostic criteria published by Allen et al. [1], the mode of implementation of the criteria was different in all of the studies with a visible impact on the results. The highest prevalence of RLS was found in studies where only a criteria-based questionnaire was used. When the questionnaire was followed by a face-to-face interview, the prevalence decreased. A model situation for that is the prevalence of RLS in multiple sclerosis. The prevalence of RLS reached 37.5% when assessed with only a diagnostic questionnaire [6], but decreased to 19% in a protocol with a face-to-face interview [7].

RLS as a Result of Peripheral Nervous System Lesion

Many of the disorders listed in table 1 damage the peripheral nervous system. It is possible that the symptoms of RLS in those patients are a specific form of pares-

thesia resulting from the lesions of the peripheral nerves or from lowering the sensory threshold in the course of neuropathy.

RLS as a Consequence of Typical RLS Risk Factors

An interesting situation was described in a study focusing on RLS in liver diseases [16]. The authors found an extremely high prevalence of RLS: 62%. The analysis of clinical data of the patients revealed that RLS was explained by the presence of classical risk factors in most of the patients and 'unexplained' RLS was present only in 16.3% of the patients. That may suggest that a chronic disease causes a condition that is a classical risk factor of RLS, which in turn leads to typical 'secondary' RLS.

RLS as a Consequence of Chronic Inflammatory Disease

RLS is more prevalent in chronic inflammatory diseases like rheumatoid ar-

thritis. It is well established that RLS is more prevalent in women – a typical trait of autoimmune diseases. It may be hypothesized that symptoms of RLS are mediated by chronic inflammatory process, systemic or limited to the nervous system.

Conclusion

The mechanism leading to secondary RLS remains unclear – and the more papers are published, the more unclear the picture becomes. Future studies should focus on modeling the relation between the basic disorder, RLS and other clinical data, using a uniformed diagnostic procedure to avoid discrepancies in interpretation of RLS diagnostic criteria. Data collected from such projects may shed light on the mechanisms of increased prevalence of RLS in other diseases.

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