

## Neuroscience of Sleep and the Recent Advances in Diagnosis, Genetics and Treatment of Restless Legs Syndrome

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**Abstract:** Restless leg syndrome as a condition characterized by uncomfortable and unpleasant sensation in the legs, with an urge to move impairs the sleep and may so negatively affect quality of life and individual functioning of the sufferers. During the night and while asleep, restless legs syndrome which is now turned into periodic limb movements (PLM) can be more frequently seen. This condition is frequently under-diagnosed. They movements may range from a barely visible small extension of the foot or big toe, to classical periodic limb movement with knee and hip bending, to periodic limb movement involving the arms and/or the trunk and so the whole body. In the face-down position, a pelvic component of muscle contractions is sometimes notable in periodic limb movement. PLM can also be smoother or jerkier. A different and very specific situation is the augmentation of restless leg syndrome. Here, the urge to move sometimes becomes overwhelming and very intense or almost violent movements can be observed, often involving the whole trunk with rocking movements. In addition, PLM during the day and night time are present. When observing with a trained eye, there are many opportunities to observe PLM in the public spaces, e.g. in waiting lounges at airports and concert halls. There is a clear division between voluntary and involuntary movements in RLS which can be reported by patients and further evaluated by expert physicians. Today we have a remarkable amount of data coming from the evidence-based medical practice and research with regard to diagnosis, genetics and treatment of RLS. This will be the focus for the present short review.

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### 1. Introduction

Restless legs syndrome (RLS) is a frequently underdiagnosed condition, characterized by uncomfortable and unpleasant sensation in the legs, with an urge to move [1]. Over the past decades, RLS has emerged not only as a common, but also as a sometimes severe disorder. The symptoms begin or worsen during the periods of rest and inactivity. Patients describe exacerbation of symptoms in situations such as watching television, driving or flying long distance or attending business meetings [2]. The urge to move and unpleasant leg sensations are relieved by activity, and this relief generally persists as long as the activity continues.

Another central characteristic of RLS is the worsening of symptoms in the evening or during the night [1]. Some studies that investigated the circadian pattern in the occurrence of RLS symptoms showed that the severity of leg discomfort followed a circadian rhythm with the maximum occurring after midnight and a minimum occurring at 10:00 in the morning [3]. Some authors found that changes in melatonin secretion precede the increase in sensory or motor symptoms of RLS [4]. Interestingly, there is an inverse relationship between the circadian curve of melatonin secretion and that of dopamine activity [5].

RLS can occur in all ethnic backgrounds. However, epidemiological studies showed that Caucasians are most affected. Most Caucasians surveys show an approximate 10% prevalence, while surveys from South-eastern Europe and from Asian populations report much less prevalences. A rate of 3.2% has been reported in Turkey[6], 3.9% in central Greece [7] and 0.6 in Singapore [8]. In an epidemiological survey conducted in the United States and 5 European countries [9], RLS symptoms of any frequency was reported by 7.2% of the general population. Symptoms occurred at least 2 times per week and were reported as moderately or severely distressing by 2.7%, and these subjects were defined RLS sufferers and probably represented the ones that should be adequately treated.

A recent study [10] evaluated a sample of 61792 subjects from a retrospective US panel that completed an online “global opinions” survey for identifying respondents reporting all four essential diagnostic features of RLS. 4484 subjects met all criteria and 1400 were randomly selected to complete a questionnaire to exclude those with diagnosis indicating possible secondary RLS.

Prevalence was estimated for the following groups: (1) RLS symptomatic, (2) primary RLS, and (3) primary RLS sufferers (symptoms  $\geq$  2 per week

with moderate to severe distress). The validated diagnostic tool and exclusion of medical conditions likely to cause RLS provide a very conservative estimate of US census-weighted prevalence of 2.4% for primary RLS and 1.5% for primary RLS sufferers. Primary RLS sufferers had a mean productivity loss of 1 day per week. All RLS rated costs increased with RLS symptoms severity, with increasingly significant decrements in health status, sleep disturbance, and work productivity.

## 2. RLS diagnosis

The diagnosis of RLS is largely based on the patients' report of clinical symptoms.

The majority of RLS patients complain of poor sleep [11]. Most patients report difficulty falling asleep since both immobility and circadian factors facilitate the occurrence of RLS symptoms at bedtime. However, some patients fall asleep rapidly but wake up shortly after with unpleasant legs sensations that force them to get up and walk around in order to alleviate symptoms. In a general population study more than 75.55 of RLS sufferers report at least one sleep-related problem [12]. Complaints about sleep problems or leg problems as a potential indicator for RLS were investigated by Crochard et al.[13]. In this study a diagnosis of RLS was given to 42.6% of patients with leg complaints, 35.5% of those with sleep complaints, 54.9% of those with both complaints, and 12.9% of those with no complaints.

Periodic limb movements during sleep (PLMS) occur in 80% to 90% of RLS patients, but in most of the cases patients are not aware of the limb movements. The polysomnographic report usually includes the absolute number of PLM, and the PLM index (number of PLM per hour of sleep), both of parameters may be considered separately for wakefulness and sleep time and with arousal per hour of sleep. A PLM index greater than 15 is usually considered pathologic in adults. Concerning the time distribution of PLMS, the majority of RLS patients show a progressively decreasing course during the night in contrast to other clinical conditions with PLMS, such as narcolepsy and REM sleep behavior disorder [14,15]. Objective investigations are not really required for the diagnosis of RLS, however instrumental evaluations may be useful in some situations such as doubtful RLS cases, differential diagnosis, distinction between primary and secondary RLS forms, sleep impact estimation, diagnosis and quantification of PLMS, and evaluation of treatment efficacy on sleep and PLMS.

The gold standard in documenting the above mentioned RLS features is considered the full night polysomnography study (PSG), which would always include the monitoring of both tibialis anterior

muscles for the PLM detection. The actigraphy, the suggestion and the forced immobilization tests, have been proposed as possible cost effective substitute of PSG.

## 3. Genetics underpinnings for RLS

RLS may be classified in primary or secondary forms. In the primary forms, there are substantial evidences for genetic contribution to RLS [3]. Familial aggregation has been well documented with about 50% of idiopathic cases reporting a positive family history of RLS. In most pedigrees it segregates in an autosomal dominant fashion, with a high penetrance rate (90-100%).

Linkage studies in RLS families have revealed eight loci but no causally related sequence variant has been identified using this approach [16]. A genome wide association study of RLS identified common variants in three genome regions: MEIS1, BTBD9, and MAP2K on chromosome 2p, 6p and 15q, respectively. Each genetic variant was associated with more than 50% increase in risk for RLS [17]. MEIS1 has been implicated in limb development, raising the possibility that RLS has components of a developmental disorder. A genome-wide significant association with a common variant in an intron of BTBD9 on chromosome 6p was found independently in the Icelandic population [18]. An association between this variant and PLMS without RLS ( and the absence of such an association for RLS without PLMS) suggests that it is a genetic determinant of PLMS.

## 4. RLS etiology and treatment perspective

Amongst the most common causes of secondary RLS is the iron deficiency, end staged renal disease and pregnancy [1-3]. Peripheral neuropathies of different origin, diabetes mellitus and multiple sclerosis have been seen at higher than expected frequency in RLS patients. In a recent study population [19], it has been reported that the prevalence of RLS in chronic inflammatory demyelinating polyneuropathy is significantly higher than in controls, approaching 40%.

It is well known that pregnancy is a risk factor for transient RLS, which usually recovers during the post delivery period. A recent survey [20] investigated whether RLS during pregnancy represents a risk factor for later development of RLS. After a mean interval of 6.5 years, 207 parous women were contacted to compare the incidence of RLS among subjects who never experienced the symptoms with those who reported RLS during the previously investigated pregnancy. The incidence of RLS was 56% person/year in women who experienced the transient pregnancy RLS form, and 12.6% person/year in

subjects who did not, with a significant 4-fold increased risk of developing chronic RLS in women who presented RLS in the previous pregnancy.

RLS as side effect is ascribed to several drugs. The majority of published papers have focused on this issue as case reports. An epidemiological study [21] on the prevalence of RLS showed that the intake of selective serotonin reuptake inhibitors (SSRIs) is associated with an increased risk of RLS (odd ratio=3). A prospective study addressed this problem for the class of second generation antidepressants (ADs) [22]. Patients treated for the first time with an AD were prospectively evaluated with regard to the question of whether RLS occurred or pre-existing RLS worsened as a result of the AD. In 9% of patients, RLS was observed as a side effect related to AD treatment. This finding was most pronounced with mirtazapine provoking or deteriorating RLS in 28% of patients. Of patients who had no RLS, before the start of treatment, 8% develop RLS during AD treatment and the side effect occurred after a median of 2.5 days.

Concerning pharmacological treatment of idiopathic RLS, the high prevalence of RLS does not necessarily mean that all patients should be treated with pharmacological therapy. A pharmacological treatment should be limited to those patients who suffer from clinically relevant RLS symptoms including intermittent RLS with impaired sleep quality or quality of life [16].

According to evidence-based medicine criteria, dopaminergic medications should be the first line therapy in RLS [23]. It is fundamental to remember that RLS treatment so far is symptomatic, not preventive. Treatment improves the quality of life of the patients and it is therefore important for the physician to work closely with the patients in tailoring treatment to their individual needs and paying close attention to any symptom fluctuations. In addition, RLS treatment does not have a constant effect over the 24 hour period, as many RLS treatment options have a short half life and should only be administered a few hours before symptoms begin in the evening [24]. The main exception to this need is rotigotine, a 24-hour acting drug that is usually administered as a patch in the morning and does not need to be adjusted to the individual time of onset of symptoms[25].

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