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Improving RLS diagnosis and severity assessment: Polysomnography, actigraphy and RLS-sleep log

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Abstract

Restless legs syndrome (RLS) has proven to often have both a difficult differential diagnosis and also problems with assessing severity. These problems contribute to some of the confusion about medication effects on RLS and also to the large placebo effect seen in clinical trials. We need to find better diagnostic and evaluative methods. The following three promising methods for better diagnosis and evaluation have been somewhat overlooked. (1) The polysomnogram with a preceding suggested immobilization test offers objective measures of the motor sign of RLS, the periodic leg movements in sleep (PLMS) under standard conditions of sleep and during quiet resting, both of which provoke RLS symptoms. The diagnostic sensitivity and specificity for these measures is about the same as that for MSLT diagnosis of narcolepsy and the use of these tests deserves to be reconsidered. (2) Leg activity measures provide an attractive less costly and more accessible alternative to the polysomnogram and can be used on repeated nights, reducing measurement problems occurring because of the well-recognized variability in symptom expression across days. (3) RLS-logs provide a more concurrent assessment of RLS symptom occurrence that provide a more direct measure of severity than questionnaires completed at clinic visits. Similar logs have been found useful in evaluating other sensory disorders such as headache.

These methods need to be developed and evaluated in both our research and clinical trials of RLS because they may enhance accuracy of diagnosis and reduce the placebo response to treatments.

Keywords: Placebo response; Restless legs syndrome; Leg activity measures; Actigraphy; Periodic leg movements; PLMS; PLMW

1. Introduction

The diagnosis of restless legs syndrome (RLS) while often relatively easy can be complicated by the differential diagnosis for several other conditions including positional discomfort, pain syndromes, neuropathy, anxiety, psycho-physiological insomnia, and milder leg cramps. Evaluating the benefit of RLS treatment can similarly be difficult in situations with other concomitant disorders and in clinical trials evaluation can be complicated by a placebo response. In the clinical setting confusion caused by symptoms from other conditions, particularly those that cause pain or disrupt sleep, complicates and often misleads the clinical assessment.

Even more of a problem occurs in clinical trials where the procedures and evaluations used in these trials leads to a large placebo effect. Two large trials showed placebo rates of at least 40% on global scales and improvement on the primary severity scale for placebo that was about 80% of the treatment benefit [1,2]. Squarely facing these results requires giving serious consideration to doing something different.

The three measures described here provide possible alternatives. These approaches to both diagnosis and severity evaluation may reduce the error and placebo response in our current assessments. They rely upon more direct, and to some degree, objective assessment and they are advanced here for consideration, recognizing a pressing need to further develop these or other measures to obtain a better evaluation of RLS. They should be considered for inclusion in clinical trials both

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to support the development of the measures and to enhance the accuracy of the trial.

2. Polysomnography with preceding suggested immobilization test (SIT)

The full polysomnogram (PSG) preceded by a suggested immobilization test (SIT) provide several objective measures important for diagnosis and evaluation of RLS. The PSG provides a direct measure of the periodic limb movements (PLM) in sleep (PLMS) and while awake (PLMW) during the night's sleep. PLMS were initially referred to as nocturnal myoclonus [3] but further investigation showed these events to generally be smooth and sometimes brief but not myoclonic movements. They have since been defined as a series of at least four leg movements each lasting 0.5–10 s with 5–90 s from onset to onset of consecutive movements [4]. They characteristically occur in sleep of RLS patients [5] and in one large series occurred at a high rate (>5/h) in 80% of RLS patients. These leg movements are sufficiently distinct and common among RLS patients to be considered a motor sign of RLS [6]. Most, but not all of these complex movements, involve major components of the physiological flexor at the ankle and sometimes knee or even hip [7] and thus the standard physiological measurement is that of the anterior tibialis electromyogram (EMG) [4]. Unfortunately this motor sign is not specific to RLS but appears to occur in many disorders, particularly those involving dopaminergic dysfunction such as narcolepsy and REM behavior disorder [8]. PLMS also occur more in the elderly but this age-related increase may occur most clearly in families of RLS patients, even among those family members who do not have RLS [9]. While the PLMS are not specific for RLS, they provide a sensitive objective test to confirm a clinical diagnosis of RLS and are considered one of the key features supporting the diagnosis [10].

There are four major problems with using the PLMS from the PSG to support the RLS diagnosis. First, there is large night-to-night variability [11] so that group measurements require reasonably large samples to reduce this effect. Adequate characterization of the PLMS for an individual requires several nights of recording [12]. Second, the test is expensive and access is limited by availability of recording resources and the inconvenience to the patient. Third, the physiological recordings for PLM use an uncalibrated EMG from electrodes placed on the surface of the skin. These suffice for establishing criteria to detect occurrence and duration of events but they fail to provide a reliable measure of the amplitude of the event or the force in the leg movement. Duration can be used as a surrogate measure for amplitude but clearly is not an entirely satisfactory substitute. Fourth, sleep-disordered breathing events may produce artifactual leg movements whose characteristics overlap those of PLMS. Activity monitoring and sleep-disordered breathing screening as described below can largely overcome these four problems.

Sleep is a primary morbidity for RLS and a primary complaint for most patients seeking treatment [13,14]. The PSG evaluation informs about the critical sleep characteristics contributing to this complaint including the quality and quantity of sleep. The PLMS have also been found to relate to autonomic arousal events with altered EEG and transient increases in heart rate [15–17] and possibly also in blood pressure [18]. This interesting concept may explain in part the possible relation of RLS to cardiac problems and hypertension noted in one epidemiological study [19]. Thus, documenting sleep status and particularly the PLMS may provide a very useful assessment of RLS morbidity.

PLMS in RLS patients have been found to continue as PLM after a patient wakes up during the sleep period. These PLMW at night are also characteristic of RLS patients and tend not to occur with other conditions. Thus, the PLMW may be more specific for RLS but sensitivity appears uncertain. Generally, there is relatively little time that an RLS patient lies in bed awake thereby reducing the opportunity to detect these events and decreasing the number of events.

The suggested immobilization test (SIT) performed in the evening before the nocturnal PSG uses rest duration to provoke the symptoms of RLS. During the SIT the patient sits up in bed reclining at a 45-degree angle with his/her feet outstretched. Any stimuli, pictures or sounds that are changing in the next hour are minimized in the patient's room. The patient is to stay relaxed and to keep the legs relaxed and as still as possible. Muscling up to avoid moving is not allowed, nor is sleep allowed. The test lasts 60 min. Rest duration acts like a stimulus provoking the RLS symptoms with greater symptoms for longer rest both for the PLMW and the subjective report of sensations [20,21]. This test produces more symptoms when conducted at night than when conducted in the morning or afternoon [22], thus the best time for the SIT test to reveal RLS symptoms is this period preceding the normal PSG.

One study examined the diagnostic utility of the PLMS, PLMW from the nights sleep and the PLMW and sensory symptoms on preceding SIT. The single best measure for diagnosis was the PLMW during the night's sleep which had an optimum sensitivity of 87% and specificity of 80%. The PLMS had, as expected, a poor specificity of 76% but also a poor sensitivity of 78%. The PLMW on the SIT had an optimum cut-off that gave high specificity (84%) but very low sensitivity (62%). Thus, while most normal controls could sit still with few leg movements for 60 min, there were also almost 40% of the RLS patients who could also do that. In contrast, the sensory stimuli during the SIT test gave a cut-off value that was both reasonably sensitive (82%)