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Original article

Correlation between rating scales and sleep laboratory measurements in restless legs syndrome

Diego Garcia-Borreguero[a,*], Oscar Larrosa[a], Yolanda de la Llave[a], Juan José Granizo[b], Richard Allen[c]

[a]*Department of Neurology, Fundación Jiménez Díaz, Sleep Disorders Unit, Universidad Autónoma de Madrid, Avda. Reyes Católicos 2, Madrid 28040, Spain*
[b]*Department of Epidemiology and Biometrics, Fundación Jiménez Díaz, Madrid, Spain*
[c]*Johns Hopkins University, Neurology and Sleep Medicine, Baltimore, MD, USA*

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Abstract

Objectives: The aim of this study was to test the external validity of the International Restless Legs Scale (IRLS) by assessment of the correlation between IRLS scores and objective measures of severity such as polysomnography (PSG) and Suggested Immobilization Test (SIT).

Designs: Correlation analysis between rating scales for RLS (IRLS and Johns Hopkins RLS Scale –JHRLSS-) and sleep laboratory measurements in untreated RLS patients.

Methods: The study included 30 untreated patients diagnosed with RLS according to the criteria of the International RLS Study Group. Diagnostic procedures included physical exam, laboratory analysis, PSG and a nocturnal SIT. Statistical analysis was performed by means of Spearman's correlations and Kruskal-Wallis test.

Results: IRLS correlated significantly with Periodic Leg Movement of Sleep-index (PLMS), and PLMS-arousal index during PSG as well as with Periodic Leg Movement of Wakefulness (PLMW) during SIT (SIT-PLMW) (all $r=0.4$; $p<0.01$). There was no correlation between IRLS and the number of PLMW in PSG (PSG-PLMW) or any other sleep variable during PSG. Nor was any correlation found between IRLS scores and ferritin, age, duration of illness or any other clinical variables.

Conclusions: This study represents the first demonstration of a correlation between IRLS and objective parameters of motor dysfunction such as PLMS-index or SIT. This finding is particularly relevant for the design of future clinical trials. Furthermore, the association between PLMS and SIT-PLMW supports the view that both PLMS and PLMW might share a common mechanism.

Keywords: Restless legs syndrome; Rating scales; Periodic leg movements; Suggested immobilization test; Polysomnography

1. Introduction

Restless legs syndrome (RLS) is a common central nervous system disorder with a significant impact on resting and sleep. This disorder presents a wide range of severity both in relation to the intensity, as well as to the frequency of symptoms [1]. Over the past few years, several rating scales and objective tests have been used to evaluate the severity of RLS and its response to treatment.

Two main rating scales have been used thus far. The first one, the International Restless Legs Severity Scale (IRLS) [2], covers 10 RLS features on symptom severity and frequency. The scale is completed by the patient during an interview with a clinician, and it consists of 10 items that are rated on a five-point scale from 0 to 4 (maximal RLS severity). Recently, a large, international, multi-centered validation study found adequate inter-rater and test–retest reliabilities, as well as good external validity against a clinical global rating (CGI). However, external validation against objective measures of severity have not been performed thus far [2].

* Corresponding author. Tel.: +34 91 550 4927; fax: +34 91 543 9316.
E-mail address: dgarciaborreguero@fjd.es (D. Garcia-Borreguero).

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The other rating scale is the Johns Hopkins Restless Legs Syndrome Severity Scale (JHRLSS) [3]. Its main advantage is its simplicity, although it only focuses on one feature of RLS: the usual time of day at which RLS symptoms start. Thus, it establishes four categories of RLS severity (0, no symptoms; 1, symptoms only at bedtime; 2, symptoms starting at or after 18:00; 3, symptoms present before 18:00). In one study, the JHRLSS correlated well with both periodic leg movements of sleep (PLMS) index and with sleep efficiency [3]. However, the JHRLSS is used infrequently, probably because it is based on the assessment of one single feature of RLS.

Alternatively, physiologic recordings of periodic leg movements during either polysomnography (PSG) [1,4] or during the Suggested Immobilization Test [5–7] have also been used to measure RLS severity. Thus, periodic leg movements (PLMS or PLMW) recorded during PSG or SIT, are considered to be markers of severity. The main objective of this study was to determine the degree of correlation between the IRLS scale and the other methods of determination of RLS severity, such as the JHRLSS or sleep laboratory instrumental methods (PSG and SIT).

2. Methods

2.1. Subjects

Thirty patients who met the criteria for idiopathic RLS as established by the International Restless Legs Syndrome Study Group [8] were included in the study. The diagnostic process consisted of medical history (which included a comprehensive interview for sleep disorders) in addition to physical and neurological exams, which were performed by two physicians experienced in sleep medicine and in RLS (DGB, OL). Subjective severity of symptoms was measured by means of the IRLS total score, while frequency of symptoms was assessed by means of the information provided by item 7 of the IRLS [13].

All patients underwent PSG and SIT. PLMS and PLMW were scored according to published criteria [5,9]. The SIT was a 60-min test, performed between 22:00 and 24:00 in this study. During the SIT, patients reclined in bed at a 45° angle with their eyes open and legs stretched out and were instructed not to move or to fall asleep. Leg activity was recorded using standard bilateral m.anterior tibialis surface electromyography. In addition, patients were asked every 5 min for the entire hour to fill in a visual analogue scale for sensorial discomfort in their legs. After the SIT was completed, an 8-h PSG was performed.

Furthermore, blood count and blood chemistry that included serum levels of creatinine, iron, ferritin, and transferrin were performed along with a determination of urinary creatinine clearance.

Statistical correlation between the quantitative variables was determined by using Spearman's non-parametric correlation coefficient. However, differences between the four severity groups on the JHRLSS were determined by using the Kruskal–Wallis test, with a significance level of 0.05.

The study was approved by the local Institutional Ethics Committee and a written informed consent was obtained from all patients.

3. Results

3.1. 1 Demographics

The sample consisted of 30 patients [9 men and 21 women; mean age (SD): 50.8 years (10.5)] diagnosed as having RLS. The mean (SD) IRLS score was 25.5 (±5.4). Twenty-six of the 30 patients reported daily RLS symptoms, and the remaining four had symptoms at least 2–3 days a week. Thirteen patients were classified as having early onset form, while 17 had late onset phenotype [10]. The mean (SD) duration of illness was 9.13 (±2.12) years. Twenty-eight out of 30 patients were classified as having idiopathic RLS, while two were considered to have secondary RLS due to iron deficiency. None of the subjects had been previously treated with dopaminergic medication. Mean values for demographic, clinical and polysomnographic features are shown in Table 1.

Table 1
Main demographic, clinical and sleep laboratory parameters in RLS patients

Age (yr)	50.8±10.49
Gender (F/M)	21F/9M
Age of onset (yr)	41.67
Duration of illness (yr)	9.13±2.12
Family history (+/−)	7+/23−
Ferritin (mcg/ml)	76.07±81.84
Epworth Score	7.27±4.38
IRLS score	25.53±5.43
SIT	
SIT-PLMW	11.78±60.45
PSG	
PLMS-index	25.02±40.84
PSG-PLMW	39.49±37.48
PLM-arousal index	13.09±21.09
Arousal-index	37.96±23.71
Apnea-hypopnea index	4.18±4.06
TST (min)	284.8±80.78
SL (min)	27.17±37.16
RL (min)	108.92±45.41
SE (%)	73.33±21.92
Stage 1 (%)	12.6±8.95
Stage 2 (%)	47.03±9.37
SWS (%)	25.10±11.18
REM (%)	14.21±7.27

Values are shown as mean±SD. TST, total sleep time; SL, sleep latency; RL, REM latency; SE, sleep efficiency; SWS, slow wave sleep.

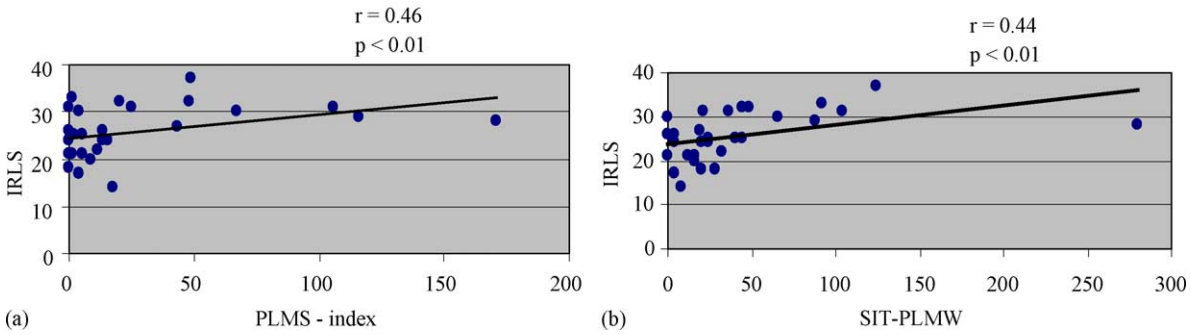

Fig. 1. Correlation between IRLS score and (a) PLMS-index, and (b) SIT-PLMW.

3.2. Correlation between IRLS, objective test and clinical variables

IRLS had a positive correlation with PLMS ($r=0.46$; $P<0.01$) and also with PLMS-arousal indices ($r=0.44$; $P<0.01$) (Fig. 1a). Furthermore, a significant association was found between IRLS and SIT-PLMW ($r=0.44$; $P<0.01$) (Fig. 1b). No correlation was found between IRLS and any other polysomnographic (sleep efficiency, sleep latency, total sleep time, percentage of sleep stages, etc.) or clinical (including age, duration of illness, or ferritin) variables.

The different groups of severity on JHRLSS showed statistical differences for SIT-PLMW ($P<0.05$), PSG-PLMS ($P<0.05$), PSG- PLMW ($P<0.05$), sleep efficiency ($P<0.05$), and total sleep time ($P<0.01$). No statistical association was found between IRLS and JHRLSS.

A correlation was observed between frequency of symptoms (item 7) and IRLS total score, but not with any of the other demographic, clinical or sleep laboratory variables.

3.3. Correlation among PSG and SIT parameters

The analysis of the correlation between the main sleep laboratory parameters is shown in Table 2. The PLMS index showed a positive correlation with the PLM-arousal index ($r=0.86$; $P<0.001$), as well as a marginal association with SIT-PLMW ($r=0.35$; $P=0.06$) and sleep efficiency ($r=0.32$; $P=0.08$) (Figs. 2 and 3). Furthermore, a trend towards a negative association was found between the PLMS index and the total wake time ($r=-0.33$; $P=0.07$).

As shown in Table 2, PSG-PLMW correlated positively with serum ferritin concentration ($r=0.50$; $P<0.01$), PLM-arousal-index ($r=0.38$; $P<0.05$), and with SIT-PLMW ($r=0.43$; $P<0.05$). Additionally, SIT-PLMW was associated with the PLM-arousal index ($r=0.50$; $P<0.01$), and was marginally associated with sleep latency ($r=0.32$; $P=0.08$). None of the above-mentioned parameters correlated with age or duration of disease.

Table 2
Spearman's correlations between the main clinical and laboratory parameters of RLS

		Ferritin	PLMS	PSG-PLMW	SIT-PLMW	PLMS-AI	AI	TST	SL	SE (%)	Age
Ferritin	*r*		−0.05	**0.5**	−0.03	0.10	0.16	−0.09	0.09	−0.20	0.15
	P		n.s	**	n.s	n.s	n.s	n.s	n.s	n.s	n.s
PLMS	*r*	−0.05		0.19	**0.35**	**0.86**	0.15	0.28	−0.28	**0.32**	0.14
	P	n.s		n.s	(*)	**	n.s	n.s	n.s	(*)	n.s
PSG-PLMW	*r*	**0.5**	0.19		**0.43**	**0.38**	0.13	0.19	−0.02	0.09	−0.19
	P	**	n.s		*	*	n.s	n.s	n.s	n.s	n.s
SIT-PLMW	*r*	−0.03	**0.35**	**0.43**		**0.50**	0.27	0.30	**−0.32**	0.29	0.05
	P	n.s	(*)	*		**	n.s	n.s	(*)	n.s	n.s
PLMS-AI	*r*	0.10	**0.86**	**0.38**	**0.50**		0.19	0.28	−0.20	0.28	0.09
	P	n.s	**	*	**		n.s	n.s	n.s	n.s	n.s
AI	*r*	0.16	0.15	0.13	0.27	0.19		**−0.47**	**0.38**	**−0.54**	**0.41**
	P	n.s	n.s	n.s	n.s	n.s		**	*	**	*
TST	*r*	−0.09	0.28	0.19	0.30	0.28	**−0.47**		**−0.56**	**0.82**	−0.26
	P	n.s	n.s	n.s	n.s	n.s	**		**	**	n.s
SL	*r*	0.09	−0.28	−0.02	**−0.32**	−0.2	**0.38**	**−0.56**		**−0.71**	−0.02
	P	n.s	n.s	n.s	(*)	n.s	*	**		**	n.s
SE (%)	*r*	−0.20	**0.32**	0.09	0.29	0.28	**−0.54**	**0.82**	**−0.71**		−0.17
	P	n.s	(*)	n.s	n.s	n.s	**	**	**		n.s
Age	*r*	0.15	0.14	−0.19	0.05	0.09	**0.41**	−0.26	−0.02	−0.17	
	P	n.s	n.s	n.s	n.s	n.s	*	n.s	n.s	n.s	

Significant correlations are shown in bold numbers. $^{**}P<0.01$, $^{*}P<0.05$, $(*)P<0.1$.

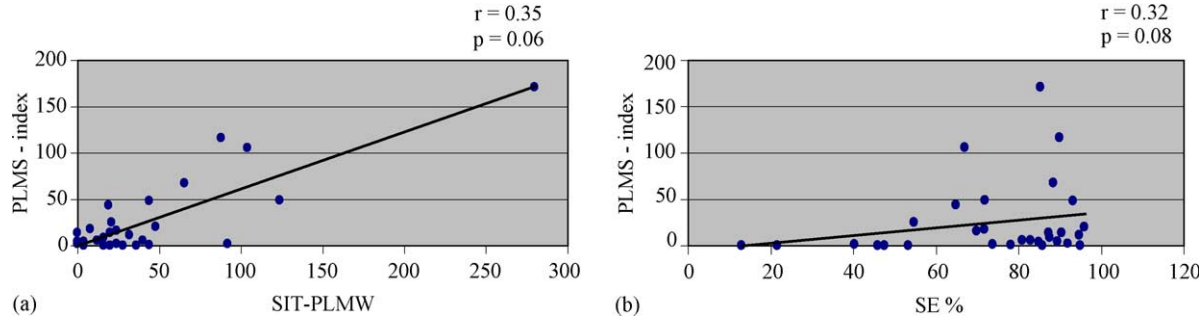

Fig. 2. Correlation between PLMS-index on PSG and (a) SIT-PLMW, and (b) sleep efficiency.

4. Discussion

The main finding of this study was the presence of a positive correlation between IRLS and three objective markers of RLS severity, namely PLMS, PLMS-arousal, and SIT-PLMW. This study is, to our knowledge, the first report to show that the IRLS and objective sleep laboratory tests correlate with each other. The two measures of PLM (PLMW and PLMS) represent a motor sign of RLS present in almost all patients. The correlation of the clinical rating of severity and the expression of the motor sign mutually supports the validity of these measures. The IRLS is currently the most widely used rating scale that evaluates symptom severity in RLS. It has been recently validated in a large, multi-centered study that showed adequate reliability, internal consistency and criterion validity [2]. However, in that study, criterion validity was tested against a clinical global impression rating rather than against the objective motor sign of the disorder.

Both PSG and SIT are helpful when used to support a clinical diagnosis of RLS, although they lack the sensitivity and specificity to procure a firm diagnosis. However, despite their diagnostic limitations, both parameters have been suggested to be useful in measuring the symptom severity in RLS [1,3,7]. As our study shows, subjective and objective parameters of symptom severity are closely related to one another.

In agreement with previous findings [3], our study shows a statistical association between JHRLSS and PSG or SIT. However, no significant correlation was found between the severity values on the IRLS and JHRLSS. Nor could any association be found between IRLS and sleep efficiency, a sleep parameter that had been found to correlate with JHRLSS [3]. While the IRLSS evaluates severity based on 10 questions, the JHRLSS uses a single criterion which differs from those used for the IRLS scale, namely the time of onset of symptoms. Thus, it is conceivable that the time of the day at which RLS symptoms begin is more specifically related to the degree of sleep disruption than to any of the 10 questions included in the IRLS. Given the fact that sleep complaints are common and likely determinants of quality of life, future versions of the IRLS should consider including further questions on sleep-related symptoms [11–13]. Certainly, this question will remain a matter of investigation for the future.

This study also showed that the markers of motor dysfunction during sleep and wake were related to one another. Thus, a marginal association between PLMS on PSG and SIT-PLMW, suggests that both manifestations of motor disturbances might share a common mechanism. In other words, the main markers of motor dysfunction during sleep studies suggested that the immobilization test and PSG were strongly correlated, as previously reported by Michaud et al. [7]. Should this finding be replicated in the future by a larger sample of patients, it could lead to the gradual replacement of PSG by SIT as the main confirmatory test for RLS diagnosis or for the assessment of RLS severity. In general, as shown in Table 2, indices of motor disturbance were strongly correlated, regardless of whether they were performed during sleep or during wakefulness.

However, only marginal associations were found between indices of motor dysfunction (regardless of PSG or SIT) and sleep disruption indices. Given the fact that pharmacotherapy frequently normalizes the PLMS index while sleep disruption still persists [14,15], or at least sleep disruption does not improve until a higher dosage of the drug is administered [16], it is conceivable that the mechanism underlying sleep disruption in RLS is only partially related to PLMS. Interestingly enough, PSG-PLMW was associated with serum ferritin level, further reinforcing the notion that iron deficiency is linked to motor restlessness [17–19] in the pathophysiology of RLS [20]. Age, duration of illness, and phenotype (early vs. late onset) were not related to parameters of motor dysfunction.

In our view, the study contains two main limitations: First, the number of patients is relatively small. Second, the sample

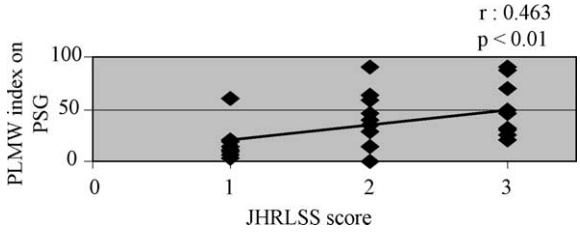

Fig. 3. Correlation between JHRLSS and PLMW-index on PSG.

contained a significant number of mild to moderate RLS patients, for which night-to-night variation in PLMS index might have affected the findings considerably. Specifically, four of the 30 patients reported less than daily RLS symptoms and had thus a higher probability of having less disturbance on the night of the PSG evaluation. We conducted a separate analysis of the data set excluding these four cases, but found the same major results as those reported above for all of the patients.

In summary, our study demonstrates an objective external validation of IRLS against the PLMS index and SIT-PLMW. In addition, it also shows a strong correlation between different measures of motor dysfunction during sleep/wakefulness in PSG and SIT. Our findings are preliminary and are based on a small and specific population of idiopathic RLS patients. Therefore, a larger sample population is needed in order to confirm our findings and also to see how the subjective and objective markers of severity are influenced by treatment.

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