New diagnostic and follow-up tools in RLS/ WED

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Revised diagnostic criteria for RLS/WED

**Essential criteria**
- An urge to move the legs usually accompanied by dysesthesias.
- Worsen during periods of rest.
- Partially or totally relieved by movement.
- Worse in the evening or night.
- Not solely accounted for as symptoms primary to another medical or a behavioral condition.

**Supportive criteria**
- PLMs
- Positive response to dopaminergic drugs
- Family history
- Lack of expected daytime sleepiness

Differential diagnosis for RLS/WED

- **Nocturnal disorders**
  - Nocturnal leg cramps
  - PLMS
  - Confusional arousal
  - Hypnic jerks
  - RBD

- **General conditions**
  - Peripheral neuropathy
  - Positional discomfort
  - Venous or vascular problems

- **Movement disorders**
  - Akathisia
  - Myoclonus of different origin
  - PLMA
  - Painful leg + moving toes
specifier for clinical significance of rls/wed

- the symptoms of rls/wed cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

Specifiers for Clinical Course of RLS/WED

- **Chronic-persistent RLS/WED:**
  
  Symptoms when not treated would occur on average at least twice weekly for the past year.

- **Intermittent RLS/WED:**
  
  Symptoms when not treated would occur on average $< 2/week$ for the past year, with at least 5 lifetime events.

A retrospective view on the long-term course

- **Continuous**: 78.9%
- **Intermitent**: 15.8%
- **Continuous progressive**: 5.3%

Tzonova et al., SLEEP MED 2012
“When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?”

- Positive predictive value: 89.6%
- Created for use in epidemiological studies.
- However, not validated in that setting.
# RLS diagnostic index

## Restless Legs Syndrome Diagnostic Index (RLS-DI)

Please interview the patient about the occurrence of complaints typical of RLS or complaints frequently associated with RLS. The period of assessment refers to the past 7 days. **Please make sure to complete all 5 questions.**

### Essential criteria

1. Do you feel an urge to move your legs (arms)?
   - Occurs regularly (on ≥ 5 of 7 days)
   - Occurs occasionally (on 1 to 4 of 7 days)
   - Not applicable / not present
   - Score: 2
2. When feeling an urge to move, do you experience unpleasant sensations in legs (arms) such as itching, stabbing, pulling, pain?
   - Occurs regularly (on ≥ 5 of 7 days)
   - Occurs occasionally (on 1 to 4 of 7 days)
   - Not applicable / not present
   - Score: 2
3. Do your urge to move / unpleasant sensations begin or worsen when you are at rest (lying, sitting) or when you are inactive?
   - Occurs regularly (on ≥ 5 of 7 days)
   - Occurs occasionally (on 1 to 4 of 7 days)
   - Not applicable / not present
   - Score: 2
4. Is there relief of urge to move / unpleasant sensations, partial or complete, by movement (eg, walking or stretching)?
   - Occurs regularly (on ≥ 5 of 7 days)
   - Occurs occasionally (on 1 to 4 of 7 days)
   - Not applicable / not present
   - Score: 2
5. Are urge to move / unpleasant sensations worse in the evening or at night than during the day? (That means, complaints are worse at night than during the day or occur only in the evening or at night). In severe RLS, this criterion must have been previously present.
   - Occurs regularly (on ≥ 5 of 7 days)
   - Occurs occasionally (on 1 to 4 of 7 days)
   - Not applicable / not present
   - Score: 2

### Calculations

Total "A": Item 1 to 5

\[
\begin{align*}
\sum (1+2+3) &= \sum 1 + \sum 2 + \sum 3 \\
\end{align*}
\]

The following items are to be assessed by the physician interviewing the patient as well as in consideration of medical records and clinical findings. **Please make sure to complete all questions.** In the event the data were not (yet) collected, please tick the column "Not assesseable / not done".
RLS diagnostic index

- Ten questions
- Structured interview
- Checks for the presence and attributes a diagnostic weight to essential criteria
- RLS diagnosis if Index > 11
- Requires PSG or actimetry
- Ideal for clinical trials
- Not validated in primary care populations
Hening Telephone Diagnostic Interview

- **Structured phone interview**
- 45 min
- Excludes mimics such as leg cramps and positional dyscomfort
- Has not been used outside specialized clinics.
Cambridge- Hopkins
Diagnostic Questionnaire for RLS

- Self-completed
- 13 questions
- Does not require a trained interviewer
- Excludes leg cramps and positional dyscomfort
- Positive predictive value: 86%
- Validated in a general population of blood donors
Do we need objective testing?

- Clinical diagnosis may yield 16% false positives (Hening, 2009)

- Even when structured interviews are used, the positive predictive value does not exceed 86% (Allen, 2009)

- Most importantly, clinical diagnosis can cause 15-20% false negatives (Hornyak, 2003)
Main limitations of rating scales as endpoints for RLS/ WED

- Based exclusively on subjective assessment
- Based on memory recall (7 days)
- No assessment of motor dysfunction
- No control for activity
- Unlike PLMS, rating scales are highly vulnerable to placebo effects
Objective testing

- Polisomnography
- Actimetry
- Suggested Immobilization Test
- Multiple SIT (m-SIT)
PSG: Rating scales (IRLS) vs PLMS

![Graph showing the relationship between IRLS and PLMS, with a correlation coefficient r = 0.46 and p < 0.01.](image)

Main limitations of PSG

- Low specificity (45%) (Hornyak et al., 2007)
- Will merely describe the presence of PLMS
- PLMW are a good diagnostic marker, but are unspecific
- PSG will mainly report quality and quantity of sleep
- No account on dysesthesias
- Cost
Actimetry
Main advantages and limitations of actigraphy

**Advantages**
- Simple
- Home-based
- Evaluates several days
- Accounts for day-to-day variability
- Cost

**Limitations**
- Not sufficiently validated for diagnosis
- Not formally validated for therapeutic response
- No measurement of subjective component
# Leg Dyscomfort Scale

What was the severity of your symptoms over the past 10 minutes?

<table>
<thead>
<tr>
<th>Time</th>
<th>Real time (24h clock)</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No symptoms</td>
<td>Mild symptoms</td>
</tr>
<tr>
<td></td>
<td>(HH : MM)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>50</td>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>
Limitations of the SIT

- Not formally validated to evaluate treatment response
- High day-to-day variability (Haba-Rubio, 2006)
- It is a “single shot” approach, not sufficiently sensitive
- Might depend too much on:
  - time of day
  - previous level of activity
- RLS severity does not increase lineally during the PM.
Is the SIT sufficiently sensitive?

Threshold of clinical significance
Instructions for the mSIT

- Four tests, to be performed every two hours, between 4P and midnight.
- Each 60 min long
- Position:
  - Legs are stretched out, with a pillow under the knees
  - No blankets over the feet
  - Trunk elevated at 45%
  - Awake
- Measurement of PLMW and subjective symptoms
  (m-SIT discomfort scale)
Validation of the Multiple Suggested Immobilization Test: A Test for the Assessment of Severity of Restless Legs Syndrome (Willis-Ekbom Disease)

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mSIT Study-Design

Treated | Not treated | Treated

RLS 24-hr diary

m-SIT

V1 (Scr.) V2 V3 V4

19 RLS (treated IRLS<15)

10 Controls

Sleep July 2013, 36(7):1101-1109
Sensory and motor symptoms during the mSIT

m-SIT-DI

- treated vs untreated: p<0.0001
- V2 vs V3: n.s.
- untreated vs cont: p<0.0001

PLMW/hr

- treated vs untreated: p<0.001
- V2 vs V3: n.s.
- untreated vs cont: p<0.001

Controls
RLS treated V1
RLS treated V2
RLS untreated
What is the added value of the multiple SIT (vs a single SIT)?

- Single SIT at 8PM (1 hr)
- Four consecutive SITs (1 hr) at 4, 6, 8 and 10PM
Alleviating role of physical activity as disease progresses

severity of symptoms

Early RLS/WED

Advanced RLS/WED
Conclusion

- Diagnosis or RLS-ED should always contemplate exclusion of RLS mimics.

- In most patients, the diagnosis can be done on a clinical basis. However, objective testing is necessary for difficult cases.

- RLS symptoms during the day appear to be more common in advanced RLS than in early RLS.

- Several contributing factors might exist, but disease progression and type of treatment might be among them.

- As disease progresses, patients are vulnerable to RLS symptoms for at least 2/3 of the day.