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Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology
A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health

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Arthur S. Walters,e, Jacques Montplaisif,
the participants in the Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health in collaboration with members of the International Restless Legs Syndrome Study Group

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Abstract

Background: Restless legs syndrome is a common yet frequently undiagnosed sensorimotor disorder. In 1995, the International Restless Legs Syndrome Study Group developed standardized criteria for the diagnosis of restless legs syndrome. Since that time, additional scientific scrutiny and clinical experience have led to a better understanding of the condition. Modification of the criteria is now necessary to better reflect that increased body of knowledge, as well as to clarify slight confusion with the wording of the original criteria.

Setting: The restless legs syndrome diagnostic criteria and epidemiology workshop at the National Institutes of Health.

Participants: Members of the International Restless Legs Syndrome Study Group and authorities on epidemiology and the design of questionnaires and scales.

Objective: To modify the current criteria for the diagnosis of restless legs syndrome, to develop new criteria for the diagnosis of restless legs syndrome in the cognitively impaired elderly and in children, to create standardized criteria for the identification of augmentation, and to establish consistent questions for use in epidemiology studies.

Results: The essential diagnostic criteria for restless legs syndrome were developed and approved by workshop participants and the executive committee of the International Restless Legs Syndrome Study Group. Criteria were also developed and approved for the additional aforementioned groups.

1. Introduction

In 1945, the Swedish neurologist Ekbom described a...
condition that he named restless legs syndrome (RLS) [1]. A half-century later, the newly formed International RLS Study Group (IRLSSG) proposed and published a set of criteria to allow for a more-uniform diagnosis of this sensorimotor disorder that often profoundly disturbs sleep [2]. Since the publication of the IRLSSG criteria, research has revealed that RLS is common and treatable, yet underdiagnosed [3–6], with a wide variation in severity of symptoms. The body of literature on RLS has grown exponentially, mainly reporting clinical research. Recent animal and molecular studies have also begun to elucidate the still-uncertain nature of the basic pathophysiology of RLS [7].

Because of the great quantity of newly published information about RLS and the increased amount of clinical experience with the disorder, the RLS Foundation and the National Institute on Aging, in partnership with the National Center on Sleep Disorders Research, the National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health, the National Institute of Nursing Research, and the National Institute of Child Health and Human Development, held an RLS diagnosis and epidemiology workshop to readdress the diagnostic criteria on May 1–3, 2002, at the National Institutes of Health. Members of the IRLSSG were invited to attend and supported this meeting.

The workshop brought together RLS experts, as well as authorities on epidemiology and the design of questionnaires and scales. The diagnostic criteria were discussed thoroughly at the workshop and in subsequent exchanges. The diagnostic criteria were updated and rephrased to both incorporate new scientific knowledge about RLS and better express the criteria to reflect the actual working interpretation of them as used by clinical experts in the field. Members of the IRLSSG reviewed the revised criteria and accompanying explanatory material, and the acting executive committee of the IRLSSG also approved the final formulation of the new RLS diagnostic criteria.

In addition to readdressing the previously proposed criteria, the workshop participants also focused on developing new diagnostic criteria for two special populations—the cognitively impaired elderly and children. These groups were selected for special attention because of the difficulty encountered in eliciting from them verbal confirmation of the subjective symptoms of RLS. Because the phenomenon of augmentation in people with RLS who receive pharmacologic treatment is so common, workshop participants also developed specific criteria for the diagnosis of augmentation. Finally, given the update on the diagnostic criteria, this conference also included a working group to review the methods for epidemiologic studies and to propose standardization of these studies that would incorporate the newer diagnostic criteria. Thus, this report is divided into the following four sections: diagnostic criteria for RLS, diagnostic criteria for RLS in special populations, diagnostic criteria for RLS augmentation, and assessment of RLS in epidemiologic studies.

2. Diagnostic criteria for RLS

Restless legs syndrome is a sensorimotor disorder that often has a profound impact on sleep [2]. The severity of the symptoms varies widely, ranging from occurring only occasionally in a stressful situation to nightly and severe, with almost total disruption of sleep. An RLS severity rating scale has been developed by the IRLSSG to evaluate this wide range of symptom severity [8]. The workshop participants, in collaboration with members of the IRLSSG, determined that the following four essential criteria are all required to make the diagnosis of RLS. Three clinical features may support the diagnosis in uncertain clinical cases, and three additional features of the disorder deserve consideration when evaluating the patient with a potential diagnosis of RLS.

2.1. Essential criteria

Table 1 lists the four criteria that are essential to the diagnosis of RLS. The primary revision from the previously proposed criteria involves the substitution of criterion 3, relief with movement, for the previous criterion of motor restlessness. In the previous criterion, relief with movement was both intertwined with the concept of motor restlessness and included in the explanatory material for this criterion.

Table 1

<table>
<thead>
<tr>
<th>Essential diagnostic criteria for RLS</th>
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<tbody>
<tr>
<td>1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs)</td>
</tr>
<tr>
<td>2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting</td>
</tr>
<tr>
<td>3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues</td>
</tr>
<tr>
<td>4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present)</td>
</tr>
</tbody>
</table>
but confusion often arose about what the term actually meant. Other changes in the criteria serve to refine or clarify the concepts in the basic definitions, as discussed below.

2.1.1. Criterion 1

An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs.)

Some patients describe only an urge to move and are unaware of a sensory component, and others cannot separate out the urge to move from the sensation and cannot identify a temporal relationship. Clinical experience indicates that most patients who seek medical treatment will describe both the urge to move and the sensations. One ongoing study found that about 10 to 20% of family members of people with RLS who also have RLS themselves (albeit often mild disease) report having an urge to move without any other sensation (Wayne A. Hening, personal communication).

Because the uncomfortable and unpleasant sensations that manifest with RLS are not the same as usual sensory experiences, people often have difficulty describing the sensations. Some RLS patients simply state they cannot describe the sensations except as uncomfortable and inside the leg, while others refer to the sensations by analogy to some other feeling (Table 2) [9]. One common theme appears to be that the sensations are deep, not on the surface of the leg. A second theme appears to be the sense of movement inside the leg. At this time, however, there has been no systematic effort to more-precisely characterize the sensory dimensions of RLS symptoms.

A complaint of pain has often been thought to be an exclusion to the diagnosis of RLS, but researchers recently have come to realize that many patients with RLS express their sensations as painful [10,11]. Bassetti and his colleagues [10] reported that more than 50% of their 55 RLS patients described pain as a primary component of their RLS.

Though called restless legs syndrome, the disorder may also involve the arms or other body parts [12–14]. Winkelmann and her coworkers recently found that 34% of RLS patients in their population of 300 have symptoms in their arms as well as their legs [12]. Michaud et al. showed that almost 50% of RLS patients have symptoms in the arms, with the leg involvement probably preceding the arm involvement by several years [15]. The involvement of the arms without any involvement of the legs rarely, if ever, occurs. Increasing severity of RLS symptoms may involve the spread of the symptoms to other body parts, including the hips, trunk, and even the face [14], but the legs must be affected and are usually affected first and more severely than are other body parts.

The part of the leg involved appears to vary considerably, without any documentation that it generally starts in the more-distal part of the leg even for RLS patients with neuropathy [16], nor is there any clear pattern of progression reported, except that increasing severity involves symptoms spreading to more of the leg and other body parts. Ekbom reported that RLS symptoms almost never involve only the foot [1], but there are clinical cases of the rare patient who reports symptoms starting in a foot and progressing to the leg.

The response to an urge to move in RLS must not be confused with unconscious repetitive movements, such as foot tapping, that are more-habitual behaviors. These habitual motor behaviors are performed without the acute and distressing awareness of an urge to move.

2.1.2. Criterion 2

The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.

The vast majority of evidence in support of this criterion comes from the Montreal group, headed by Montplaisir. Over the years, they have studied the effects of immobility on RLS, using a suggested immobilization test (SIT) [13]. This test evaluates periodic leg movements (PLM) and self-reported sensory symptoms for people who are instructed to remain still for 1 h while sitting on a bed with their legs outstretched. Compared to controls, patients with RLS exhibit more PLM and an increase in sensory disturbance during the immobilization period (Table 3). It is particularly striking that in these tests the symptoms may be absent in the initial stages of the rest period, but the probability that motor and sensory symptoms will be expressed increases with the duration of rest. Moreover, the intensity of the sensory symptoms and frequency of the PLM also increases with the duration of rest.

Table 2
Descriptive terms for restless legs syndrome

<table>
<thead>
<tr>
<th>Creepy-crawly</th>
<th>Ants crawling</th>
<th>Jittery</th>
<th>Pulling</th>
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<tbody>
<tr>
<td>Worms moving</td>
<td>Soda bubbling in the veins</td>
<td>Electric current</td>
<td>Shock-like feelings</td>
</tr>
<tr>
<td>Pain</td>
<td>The gotta moves</td>
<td>Burning</td>
<td>Jimmy legs</td>
</tr>
<tr>
<td>Heebie jeebies</td>
<td>Tearing</td>
<td>Throbbing</td>
<td>Tight feeling</td>
</tr>
<tr>
<td>Grabbing sensation</td>
<td>Elvis legs</td>
<td>Iching bones</td>
<td>Crazy legs</td>
</tr>
<tr>
<td>Fidgets</td>
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</table>

The concept of rest in this criterion includes both physical immobility and central nervous system activity leading to decreased alertness. No studies have attempted to separate the relative impact of these two closely linked aspects of rest on RLS symptoms. It has been suggested that increased alertness, even while sitting or lying, may reduce the symptoms, and, indeed, patients often report using behavioral techniques such as engaging in intense conversations or playing computer games to reduce the severity of symptoms. Presumably both factors—immobility and decreased central nervous system activity supporting alertness—contribute to the onset of the condition [17].

Rest with inactivity almost always involves sitting or lying, and these particular conditions are listed in this criterion to emphasize the characteristic body position during rest. It is generally observed, however, that no specific body position causes these symptoms; rather, any rest position should engender the symptoms, provided the resting state lasts long enough. The more restful the position and the longer the duration, the more likely it becomes that the symptoms will occur. Pain or discomfort from circulatory compromise or stiffness from prolonged sitting or lying in a fixed position should not, however, be confused with RLS symptoms.

2.1.3. Criterion 3

The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.

The relief with movement is generally described as beginning immediately or very soon after the activity begins, but the rapidity of onset of any relief with movement has not been well documented. The relief with movement is not always complete; even when relief is complete, however, patients may have an abiding awareness that although the RLS symptoms are suppressed, they will resume as soon as the movement ends. Since it is movement itself that produces the symptom relief, this effect should continue as long as the activity persists. The examining clinician should ask whether relief is obtained while the patient is actually moving and should note the immediacy and persistence of the relief with physical activity. The walking, stretching, or bending that patients with RLS use to relieve their sensations are voluntary, in that patients choose which countermeasure to employ, but are involuntary, in that patients feel compelled to move.

As an alternative to movement, patients may provide a counter stimulus such as rubbing the legs or taking hot or cold baths [1]. Winkelmann et al. found that changes of temperature were an effective coping strategy in 82% of their 300 patients [12]. As their RLS becomes more severe, people may find that the amount of relief they obtain with movement lessens to the point that no amount of movement or counterstimulation relieves the urge to move and sensations. When the RLS is so severe that relief with significant movement does not occur, patients should be able to recall that, earlier in the course of their disease, they were able to obtain relief with movement. Therefore, this criterion is required to be present for all patients with RLS; for severely affected patients, however, this criterion may not reflect the current status of their RLS and may only have been true earlier in the course of their disease.

2.1.4. Criterion 4

The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present.)

In two studies, researchers have been able to separate the circadian effects from the impact of both recumbence and rest on symptoms of RLS [18,19]. Over a 72-h period, Hening et al. evaluated fairly severe RLS patients for motor restlessness [18], and Trenkwalder et al. evaluated similar patients for PLM [19]. These studies included recording after both normal sleep and a day and half of sleep deprivation. While awake, the patients remained in a semi-constant routine to the extent that was possible. During modified SIT procedures, they were told to be still but could allow PLM or motor restlessness to occur when driven by their RLS symptoms. The patients were monitored with polysomnography for electroencephalographically determined sleep and for leg movements during the entire test time. Results of these studies showed a peak in RLS restlessness between the hours immediately after midnight and a reduction in symptoms in the late-morning hours (10:00–11:00 h). The highest number of PLM occurred on the falling phase of the circadian core-temperature curve, and the least number of PLM, on the rising phase of the curve.

People with severe RLS may have symptoms 24 h a day without any apparent daily variation, but, early in the course of their disease when their symptoms were milder, these patients typically had symptoms that were worse in the evening or night. People who experience RLS only with

**Table 3**

<table>
<thead>
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<th>RLS patients (n = 19)</th>
<th>Control subjects (n = 19)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age at consultation</td>
<td>51.5 ± 11.8</td>
<td>48.3 ± 8.4</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (men/women)</td>
<td>12/7</td>
<td>10/9</td>
<td>NS</td>
</tr>
<tr>
<td>SIT MDS (mm)</td>
<td>32.6 ± 15.1</td>
<td>5.7 ± 7.9</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>SIT Dmax (mm)</td>
<td>63.4 ± 27.4</td>
<td>13.7 ± 23.0</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>SIT PLM/h</td>
<td>88.4 ± 62.6</td>
<td>10.4 ± 20.6</td>
<td>&lt;0.00002</td>
</tr>
<tr>
<td>PLMS/h</td>
<td>57.1 ± 40.1</td>
<td>3.5 ± 3.1</td>
<td>&lt;0.00002</td>
</tr>
</tbody>
</table>

RLS, restless legs syndrome; SIT, suggested immobilization test; MDS, mean discomfort score; Dmax, maximum discomfort; PLM, periodic limb movement; PLMS, periodic limb movements of sleep. P value > 0.05 denotes no statistical significance (NS). Modified from Michaud et al. [13] with permission of The Movement Disorders Society.
prolonged inactivity and rest, such as on airplane trips, may not be aware of any worsening in the evening or night, although they may report that the RLS symptoms are worse when the prolonged activity occurs in the afternoon or evening than in the morning.

2.2. Supportive clinical features

Although the features listed in Table 4 are not essential to the diagnosis of RLS, their presence can help resolve any diagnostic uncertainty.

2.2.1. Positive family history of RLS

A study conducted in the United States, mostly by telephone interviews, revealed that more than 60% of 138 RLS patients had a positive family history of the disorder, that is, at least one first-degree relative was affected with this condition [9]. A similar study performed in Canada [20] showed that 80 out of 128 patients (63%) had a positive family history of RLS. In the Canadian study, 39% of all first-degree relatives were reported to have RLS. A recent German study [12] looked at familial aggregation among 250 RLS patients – 182 had idiopathic RLS and 68 had RLS associated with uremia. Patients were divided into three categories: definite positive family history, possible positive family history (when the family history was reported by the proband but affected members could not be reached), and negative family history. A definite or possible positive family history was found in 54.9% of patients with idiopathic RLS but in only 17.5% of patients with RLS associated with uremia. In a study of a small number of patients, Ondo and coworkers [16] found a high rate of positive family history among subjects with idiopathic RLS but not among patients with RLS and peripheral neuropathy.

An alternate way to evaluate the significance of a family history is to determine the risk of RLS occurring in relatives of patients with idiopathic RLS compared to controls. In one family-history study, a clinical series of consenting RLS patients \((n = 64)\) and a small group of controls \((n = 15)\) were identified as probands [21]. The prevalence of RLS determined for all first-degree relatives was 16.5% for RLS patients and 3.5% for controls; the RLS prevalence for first-degree relatives was 23.6% for relatives of the RLS probands reporting symptom onset before age 45 (early-onset RLS), compared to 10.1% for relatives of RLS probands with symptom onset after age 45 (late-onset RLS). These figures indicate that the chance of having a first-degree relative with RLS is about 2.9 times greater for patients with late-onset RLS than for controls and about 6.7 times greater for patients with early-onset RLS than for controls. One recent study reported a possible single genetic factor contributing to RLS and further supported the significance of the family history in making the diagnosis of RLS [22].

In conclusion, these studies show that, in idiopathic RLS, more than 50% of patients report having a positive family history of RLS, and, even more significantly, a person with RLS is 3–6 times more likely to have a family history of RLS than is a person who does not have RLS. Thus, having a positive family history of RLS is supportive of the diagnosis.

2.2.2. Response to treatment

Several controlled studies [23–29] have shown that most people with RLS have a positive therapeutic response to dopaminergic drugs. These medications improve both the sensory and motor symptoms of RLS. The drugs that have been tested in double-blind placebo-controlled studies and found to be effective are the precursor of dopamine (levodopa [23,24,30]) and several dopamine-receptor agonists, including ergoline derivatives (bromocriptine [25] and pergolide [26–28]) and nonergoline derivatives (pramipexole [29] and ropinirole [31]). Based on clinical experience, more than 90% of patients report some relief of their symptoms when treated with these agents. In this respect, the condition parallels dopa-responsive dystonia, where one of the defining features is the response to dopaminergic therapy. The specificity and completeness of this response for treating all RLS symptoms at a very low dose of medication indicates that the response to the dopaminergic agents strongly supports the diagnosis of RLS. Further studies of the diagnosis of RLS should look more system-

<table>
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<th>Table 4</th>
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<tr>
<td><strong>Supportive clinical features of RLS</strong></td>
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<table>
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<tr>
<th>Family history</th>
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<tr>
<td>The prevalence of RLS among first-degree relatives of people with RLS is 3 to 5 times greater than in people without RLS.</td>
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<tr>
<th>Response to dopaminergic therapy</th>
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<tr>
<td>Nearly all people with RLS show at least an initial positive therapeutic response to either L-dopa or a dopamine-receptor agonist at doses considered to be very low in relation to the traditional doses of these medications used for the treatment of Parkinson disease. This initial response is not, however, universally maintained.</td>
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<tr>
<th>Periodic limb movements (during wakefulness or sleep)</th>
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<tr>
<td>Periodic limb movements in sleep (PLMS) occur in at least 85% of people with RLS; however, PLMS also commonly occur in other disorders and in the elderly. In children, PLMS are much less common than in adults.</td>
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2.2.3. Periodic limb movements

Periodic limb movements in sleep (PLMS) have been classically described as a rhythmic extension of the big toe and dorsiflexion of the ankle, with occasional flexion at the knee and hip. Recent studies have demonstrated that these movements vary considerably in their motor patterns, and many do not follow this physiologic flexion pattern, but they tend to occur during sleep, grouped into series with a reasonably periodic pattern of one movement usually occurring every 20–40 s. The quantification of PLMS is routinely performed in the sleep laboratory by the recording of bilateral surface electromyogram of anterior tibialis muscles. Coleman originally developed the standard method for recording and scoring PLMS [32], and a task force of the American Sleep Disorders Association later revised them [33]. According to standard criteria, PLMS are scored only if they occur in series of four consecutive movements lasting 0.5–5 s, have an amplitude of one quarter or more of the toe dorsiflexion during calibration, and are separated by intervals of 4–90 s. An index (number of PLMS per hour of sleep) greater than 5 for the entire night is considered pathologic, although data supporting this feature are very limited. Periodic limb movement disorder (PLMD) is defined as a PLMS index of five or greater that is associated with an otherwise unexplained sleep-wake complaint.

In 1965, Lugaresi and colleagues first documented the presence of PLMS in patients with RLS [34]. In a later study, Montplaisir et al. [35] evaluated 133 patients with RLS during 1 night of polysomnographic recording and found that 82.2% had a PLMS index greater than 5; in 49 patients recorded for two consecutive nights, they found that 87.8% met the criterion on at least one of the nights. This study, which also evaluated PLMS in a group of controls, showed that a PLMS index of 11 on either of two consecutive nights of recording provided the optimal sensitivity and specificity (approximately 80%) for a diagnosis of RLS. This study demonstrated the night-to-night variability in the PLMS index and, therefore, the advantage of recording PLMS on multiple nights. Future developments in activity meters to measure PLMS may facilitate the recording of PLMS over multiple nights and may thereby enhance the value of this measure for supporting the diagnosis of RLS.

Periodic limb movements of sleep also occur frequently in several other sleep disorders [36], including narcolepsy [37,38], rapid-eye-movement sleep behavior disorder [39], and obstructive sleep apnea [40]; they are also found in a variety of other medical conditions [41–46] and in patients treated with various medications [47–50]. Finally, PLMS may also be present in subjects without any complaints of sleep disturbance, especially in the elderly [51,52], but not as frequently as in patients with RLS. The percentage of all patients who have PLMS and also have RLS has not been well established, however, because many people have PLMS without symptoms of RLS, particularly the elderly, and because PLMS occurs in association with several conditions other than RLS, patients with RLS comprise a minor portion of the total population with PLMS.

Research results from the SIT have shown that people with RLS frequently have PLM while awake (PLMW); in normal control subjects, however, these limb movements are rare [53]. Using this 60-min physiologic test, the presence of PLMW in RLS patients can be considered supportive of the diagnosis.

In conclusion, although the presence of PLMS is not specific to RLS, an elevated PLMS index is supportive of the diagnosis of RLS. Eighty percent of patients with RLS have a PLMS index greater than 5; thus, it is actually the absence more than the presence of PLMS that is most significant for the diagnosis of RLS. Patients with a PLM index of less than 5 are unlikely to have RLS, and the diagnosis should be made with some caution in these patients. The PLMW, both during the sleep period and the SIT, appear to be more specific for RLS, but the data for this finding remain limited [53,54].

Table 5

Associated features of RLS

<table>
<thead>
<tr>
<th>Natural clinical course</th>
<th>Sleep disturbance</th>
<th>Medical evaluation/physical examination</th>
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<tr>
<td>The clinical course of the disorder varies considerably, but certain patterns have been identified that may be helpful to the experienced clinician. When the age of onset of RLS symptoms is less than 50 years, the onset is often more insidious; when the age of onset is greater than 50 years, the symptoms often occur more abruptly and more severely. In some patients, RLS can be intermittent and may spontaneously remit for many years.</td>
<td>Disturbed sleep is a common major morbidity for RLS and deserves special consideration in planning treatment. This morbidity is often the primary reason the patient seeks medical attention.</td>
<td>The physical examination is generally normal and does not contribute to the diagnosis except for those conditions that may be comorbid or secondary causes of RLS. Iron status, in particular, should be evaluated because decreased iron stores are a significant potential risk factor that can be treated. The presence of peripheral neuropathy and radiculopathy should also be determined because these conditions have a possible, although uncertain, association and may require different treatment.</td>
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</table>
2.3. Associated features of RLS

In addition to identifying the essential and supportive criteria for the diagnosis of RLS, workshop participants also outlined additional significant clinical features associated with the disorder (Table 5).

2.3.1. Natural clinical course of the disorder

Restless legs syndrome can occur as a primary disorder with no apparent cause other than perhaps a genetic predisposition [55] or as a secondary condition, often related to iron deficiency [56,57], pregnancy [58–60], or end-stage renal disease [61–64]. The age of onset of RLS is known to vary widely from childhood to more than 80 years of age [9,65–71]. (For a discussion of childhood RLS, see Section 3.2.) Patients with early-onset RLS symptoms are more likely to have affected family members [22], and in those patients with late-onset RLS, clinicians should look for secondary causes of the disorder.

Clinical experience, which is gained primarily from more-severe cases of RLS, has previously contributed to the conclusion that RLS is generally a chronic condition. This may be the case, but for patients with milder RLS, the pattern of expression of the disorder appears to be variable with long periods of remission and sometimes with expression only for a limited time of life. Certainly the natural course varies greatly for milder RLS, but for the patients whose symptoms start in young adult life and who eventually seek treatment, the severity and frequency of symptoms typically increases over time [9]. Because many people with RLS never seek treatment, little is known about the course of the disorder in mild or intermittent cases.

Secondary RLS appears to generally remit without evidence of recurrence when the secondary condition is resolved, for example, with renal transplantation in end-stage renal disease [72,73] and for pregnancy [59]. One particularly interesting finding in Lee et al.’s study of RLS during pregnancy is that one of the seven women who developed RLS during pregnancy continued to experience symptoms postpartum, suggesting that pregnancy may be a risk factor for developing RLS. Nonetheless, RLS that occurs during pregnancy remits for most women postpartum. It is unknown how many of these women may later develop RLS, but the frequency of RLS during pregnancy (i.e. 23%) is higher than the usually accepted frequency of RLS in older women (i.e. 14%) [74].

No long-term follow-up studies have been conducted on patients with secondary RLS who have experienced a remission to see if the RLS reoccurs later in life; neither have any evaluations sought to identify patients who experience any residual features of RLS, such as PLMS or sensitivity to iron deficiency. It appears, however, that RLS can occur for a short period of a person’s life without any indication that it will reappear.

The time course for the RLS patient whose symptoms are persistent and severe enough to warrant pharmacotherapy has been found to vary by age of symptom onset. Those with disease onset in late adult life have been found to have a generally more-rapid development of symptoms and to have no clear correlation between symptom severity and age. Patients with onset of RLS symptoms in young adult life usually show an insidious development of symptoms over many years [75] and may have great difficulty determining the age of symptom onset. Recent data have suggested that many patients with early-onset symptoms of RLS will not develop persistent daily symptoms until about age 40–60 years [76].

2.3.2. Sleep disturbance

Sleep disturbance here refers to the subjective experience of disrupted sleep, including reduced sleep time, and not to findings from objective assessments of sleep such as those from a clinical polysomnogram; the exception to this is where objective measures clearly reflect the subjective experience, such as sleep duration or sleep efficiency disrupted by awakenings. The diagnostic criteria require that RLS symptoms involve an urge to move and are quiescogenic, that is, brought on or exacerbated by rest. Since sleep onset requires a period of rest and since motor activity is alerting, the conditions needed to initiate sleep at the start of sleep time or after an awakening during the night are apt to produce RLS symptoms, and the methods to relieve the symptoms will likely interfere with sleep. Thus, RLS presents two problems for sleep: initiating sleep and maintaining sleep. When severe, the sleep disturbance clearly becomes marked and represents one of the primary morbidities of the disorder. The patient with moderate to severe RLS may sleep on average less than 5 h per night and may chronically have less sleep time than do patients with almost any other persistent disorder of sleep [77]. Moreover, the reduced sleep efficiency correlates with the reported clinical severity of RLS [77]. For patients with mild RLS, sleep disturbance may be less of a problem.

The exact timing of RLS depends on both the basic circadian pattern of expression and the conditions under which it is expressed. The onset with rest is variable, with patients with milder symptoms having an onset of symptoms only after longer periods of rest. Many patients with mild RLS, therefore, report that the symptoms only really bother them when they must be immobile and awake for a significant period of time, particularly in soporific or movement-restrained conditions such as during airplane flights or an evening at the theater. Others describe some mild symptoms at sleep onset, which easily resolve with small movements or cease when the patients fall asleep. Thus, a good sleeper or someone with chronic insufficient sleep may fall asleep rapidly enough that the period of rest before sleep is too short for any significant degree of symptom development.

The actual circadian pattern of symptoms may also vary
between patients, leaving some with symptoms mostly in the evening and not at bedtime. It is not known if this represents a real difference in the circadian phase of the RLS symptoms for these milder cases or whether it is a result of the person spending a longer time sitting in the evening than lying in bed before sleep onset. It is unclear what percentage of all RLS patients has a sleep disturbance, but clinical experience shows that virtually all patients seeking treatment have disordered sleep. Even with successful treatment of the symptoms, patients with RLS may continue to have sleep problems, perhaps due to learned responses or classical conditioning producing insomnia.

Since the sleep problems remain the primary morbidity for most patients seeking treatment, they are considered to be characteristic of the full expression of the disorder. Thus, the disturbance of sleep onset and the awakenings with difficulty returning to sleep are clinical features of moderate to severe RLS but, given the frequent occurrence of these disturbances for other disorders and the limited occurrence of these disturbances for patients with milder RLS, they are not considered as necessary for or supportive of the diagnosis of RLS.

2.3.3. Medical evaluation/physical examination

The neurologic examination is normal in patients with the primary or secondary form of RLS, but patients with late-onset RLS symptoms may show evidence of a peripheral neuropathy or radiculopathy [16]. When evaluating RLS patients, it is important for the clinician to look for factors that may exacerbate symptoms of RLS (i.e. end-stage renal disease, pregnancy, and iron deficiency), since these may alter the treatment plan or make effective treatment more difficult to establish. Aside from the established causes of secondary RLS, there are no known physical abnormalities associated with RLS. A low-normal serum ferritin level (<45–50 μg/l) has been related to increased severity of RLS and may be associated with an increased risk of the occurrence of RLS even in patients with normal hemoglobin levels [56,57]. Therefore, evaluations of serum ferritin levels and percent iron saturation are strongly recommended as part of the medical evaluation for RLS.

3. Diagnostic criteria for RLS in special populations

In addition to developing standard criteria for RLS in adults, the workshop participants also identified special populations for whom diagnostic criteria do not currently exist. These special populations include cognitively impaired older adults and children and adolescents. Because evidence to support the diagnostic criteria in these populations is less than that for the general adult population, these recommendations are based predominantly on the consensus of expert opinion. In circumstances where these criteria differ significantly from the standard criteria for the diagnosis of RLS in adults, ‘probable’ RLS is used to recognize the current limitations.

3.1. Diagnostic criteria for probable RLS in the cognitively impaired elderly

Because of language dysfunction in the cognitively impaired elderly, an ability to report sensory symptoms may be lacking; therefore, the newly revised diagnostic criteria for RLS have been modified for this population to emphasize behavioral indicators and supportive features (Tables 6 and 7). As is noted in essential criterion number 3 in Table 1, people with RLS often provide a counter-stimulus to relieve their sensations and urge to move [9]. In the cognitively impaired elderly, behaviors such as rubbing or pounding the legs and excessive motor activity can take the place of the patient’s verbal acknowledgement of the sensations and urge to move. A detailed history from caregivers and family members, as well careful exclusion of other conditions that may mimic RLS symptoms (see Table 8), are considered important in making an accurate diagnosis of probable RLS in the cognitively impaired elderly.

A literature search produced no studies of diagnostic criteria for RLS in the cognitively impaired elderly; therefore, this effort is considered a first step in developing a diagnostic tool for RLS in the cognitively impaired elderly. Validation and refinement of these criteria are suggested via research that includes: (1) comparing these parameters to expert clinical impression and (2) studying individuals who had a definite RLS diagnosis prior to developing cognitive impairment. Study of the relationship between RLS, PLMS, sleep, and pacing in the cognitively impaired elderly may be facilitated by actigraphy. With

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### Table 6

<table>
<thead>
<tr>
<th>Essential criteria for the diagnosis of probable RLS in the cognitively impaired elderly (all five are necessary for diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Signs of leg discomfort such as rubbing or kneading the legs and groaning while holding the lower extremities are present</td>
</tr>
<tr>
<td>2. Excessive motor activity in the lower extremities such as pacing, fidgeting, repetitive kicking, tossing and turning in bed, slapping the legs on the mattress, cycling movements of the lower limbs, repetitive foot tapping, rubbing the feet together, and the inability to remain seated are present</td>
</tr>
<tr>
<td>3. Signs of leg discomfort are exclusively present or worsen during periods of rest or inactivity</td>
</tr>
<tr>
<td>4. Signs of leg discomfort are diminished with activity</td>
</tr>
<tr>
<td>5. Criteria 1 and 2 occur only in the evening or at night or are worse at those times than during the day</td>
</tr>
</tbody>
</table>

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further research, a set of criteria that could be used to diagnose definite RLS in this population may be possible.

3.2. Diagnostic criteria for RLS and PLMD in children

3.2.1. Diagnostic criteria for RLS in children

Children may exhibit and report symptoms of RLS differently than do adults. Two previous groups have described the difficulties in diagnosing RLS in children [69,78,79]. Both groups had previously developed and proposed criteria for the diagnosis of RLS in children; these criteria were taken into consideration during the workshop and are reflected in this paper. Experts in the field of RLS who participated in the workshop reviewed the limited literature on RLS in children and formulated a consensus of opinion to develop these criteria for the diagnosis of RLS in children and adolescents. These criteria are a first step in creating a validated diagnostic tool for RLS in children.

Restless legs syndrome is a sensorimotor syndrome that in children may be associated with sleep disturbance and neurobehavior problems. Multiple case reports have documented the occurrence of RLS in children [68,69,71,78,80–88]. In addition, two retrospective studies in adults have found the onset of RLS symptoms before age 20 in approximately 40% of affected individuals [9,35]. No detailed prevalence data on RLS in childhood have been reported, but a recent cross-sectional study found that 17% of 866 children, aged 2–14, responded positively to a single question about restlessness of their legs at night [89]. A subset of these children may have RLS.

Two small studies have suggested a possible association between childhood RLS and iron deficiency, as determined by measurement of serum ferritin level [90,91]. Several studies have raised the association of childhood RLS and PLMD with neurobehavioral manifestations such as attention problems and oppositional behavior [69,78,83,84,86,89,92,93]. These associations are supported by sleep-deprivation studies in children [94–97] and the childhood manifestations of obstructive sleep apnea [98,99], but further study is needed to determine if there is a causal link.

The definite RLS criteria (Table 9) are intended for

Table 9

Criteria for the diagnosis of definite RLS in children

1. The child meets all four essential adult criteria for RLS and

2. The child relates a description in his or her own words that is consistent with leg discomfort (The child may use terms such as "ooories, tickle, spiders, boo-booos, want to run, and a lot of energy in my legs to describe symptoms. Age-appropriate descriptors are encouraged.)

or

1. The child meets all four essential adult criteria for RLS and

2. Two of three following supportive criteria are present (see below)

Supportive criteria for the diagnosis of definite RLS in children

(a) Sleep disturbance for age

(b) A biologic parent or sibling has definite RLS

(c) The child has a polysomnographically documented periodic limb movement index of 5 or more per hour of sleep

---

Table 7

Supportive or suggestive criteria for the diagnosis of probable RLS in the cognitively impaired elderly

(a) Dopaminergic responsiveness

(b) Patient’s past history – as reported by a family member, caregiver, or friend – is suggestive of RLS

(c) A first-degree, biologic relative (sibling, child, or parent) has RLS

(d) Observed periodic limb movements while awake or during sleep

(e) Periodic limb movements of sleep recorded by polysomnography or actigraphy

(f) Significant sleep-onset problems

(g) Better quality sleep in the day than at night

(h) The use of restraints at night (for institutionalized patients)

(i) Low serum ferritin level

(j) End-stage renal disease

(k) Diabetes

(l) Clinical, electromyographic, or nerve-conduction evidence of peripheral neuropathy or radiculopathy

---

Table 8

Differential diagnosis of RLS in the cognitively impaired elderly

- Painful neuropathy
- Arthritic conditions (involving lower limbs)
- Neuroleptic-induced akathisia
- Nonspecific pacing or sleep disturbance associated with dementia
- Pruritus
- Leg cramps
- Vascular insufficiency
- Anxiety disorder
- Agitated depression

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Table 10

Supportive or suggestive criteria for the diagnosis of probable RLS in the cognitively impaired elderly

(a) Dopaminergic responsiveness

(b) Patient’s past history – as reported by a family member, caregiver, or friend – is suggestive of RLS

(c) A first-degree, biologic relative (sibling, child, or parent) has RLS

(d) Observed periodic limb movements while awake or during sleep

(e) Periodic limb movements of sleep recorded by polysomnography or actigraphy

(f) Significant sleep-onset problems

(g) Better quality sleep in the day than at night

(h) The use of restraints at night (for institutionalized patients)

(i) Low serum ferritin level

(j) End-stage renal disease

(k) Diabetes

(l) Clinical, electromyographic, or nerve-conduction evidence of peripheral neuropathy or radiculopathy

---

Table 11

Supportive criteria for the diagnosis of definite RLS in children

(1) Sleep disturbance for age

(2) A biologic parent or sibling has definite RLS

(3) The child has a polysomnographically documented periodic limb movement index of 5 or more per hour of sleep

---

Table 12

Definite RLS criteria

1. The child meets all four essential adult criteria for RLS and

2. Two of three following supportive criteria are present (see below)
Table 10
Criteria for the diagnosis of probable RLS in children

1 The child meets all essential adult criteria for RLS, except criterion #4 (the urge to move or sensations are worse in the evening or at night than during the day) and
2 The child has a biologic parent or sibling with definite RLS or
1 The child is observed to have behavior manifestations of lower-extremity discomfort when sitting or lying, accompanied by motor movement of the affected limbs, the discomfort has characteristics of adult criteria 2, 3, and 4 (i.e. is worse during rest and inactivity, relieved by movement, and worse during the evening and at night) and
2 The child has a biologic parent or sibling with definite RLS

* This last probable category is intended for young children or cognitively impaired children, who do not have sufficient language to describe the sensory component of RLS.

children aged 2 through 12 years, with the adult criteria applicable for those aged 13 and older. The age limit of 12 for the childhood diagnostic criteria was chosen by the workshop participants to ensure that RLS in adolescents would be diagnosed as it is in adults, but it is recognized that in some cases this age limit may need modification to meet the clinical situation. Most teenagers, however, should have the language and cognitive abilities to understand the adult RLS questions, particularly those related to time (‘worse at night’) and causality (‘better with movement’). Definite RLS criteria in children younger than 2 are unlikely to be met because of these children’s inability to describe the sensory aspects that define RLS.

The probable (Table 10) and possible (Table 11) categories are intended for use in children aged 0 through 18 years. While this multilevel approach may be complicated to apply, it is more likely to capture the full spectrum of RLS in childhood. With further research, simpler criteria could possibly be devised.

The definite category for children is stricter than the adult criteria for RLS, requiring an urge to move and leg discomfort. The workshop participants wanted to avoid over diagnosing RLS in children and to take into account the higher level of motor activity that normal children often exhibit, in comparison to adults. All the categories acknowledge the frequent familial occurrence of RLS, when onset of symptoms is before age 45 (see Sections 2.2 and 2.2.1). Other childhood disorders, such as childhood migraine and myoclonic epilepsy of childhood, use familial occurrence as helpful in arriving at a diagnosis. Limited data have suggested that idiopathic RLS is inherited in an autosomal-dominant pattern [21,35,70,87,100–102]. Some school-aged children who complain of both an urge to move and leg discomfort and also have a family history of RLS, fail to show a circadian pattern of worsening symptoms at night. This finding may be related to the fact that children often endure prolonged periods of sitting during the school day, which induces the RLS symptoms, while at night they may fall asleep too quickly and sleep too soundly to experience the symptoms. (Daniel Picchietti, personal communication).

When assessing a child for RLS, the clinician should differentiate RLS from other childhood causes of lower-extremity discomfort, including that caused by arthritis, leg cramps, sore muscles from overuse, Osgood–Schlatter disease, chondromalacia patella, and familial neuropathy. Compression of nerves or vascular structures by prolonged or awkward sitting positions should be distinguished from RLS discomfort. If the child has a history of ‘growing pains,’ additional information should be obtained to define the character of these pains [80,103].

Validation of these criteria is recommended by studies that may include longitudinal follow-up of children to demonstrate which features are predictive of definite RLS by adult criteria. Many other aspects of childhood RLS require study, including population-based prevalence, associations with neurobehavior problems (attention-deficit hyperactivity disorder and oppositional-defiant disorder) and Tourette syndrome [104], as well as delineation of the natural history of RLS in childhood.

3.2.2. Diagnostic criteria for PLMD in children

In children, PLMD is characterized by episodes of repetitive and stereotyped jerks of the limbs that occur during sleep and that are associated with clinical sleep disturbance. Numerous reports have documented the occurrence of PLMD in children, including moderate to severe cases [69,71,78,81,83–86,89,91,92,105–107]. As opposed to PLMS found in adults, where nearly 40% of apparently asymptomatic individuals aged 65 or older have a PLMS index greater than 5 [108], normal children typically have low PLMS indexes [78,83,105,109]. Limited data indicate that PLMD appears to be common in children with RLS, attention-deficit hyperactivity disorder, oppositional disorders, and Williams syndrome [69,71,78,83,84,86,89,92,105,106].

The workshop participants debated the relationship of PLMD to RLS in children and decided that these two entities should best be viewed as separate but related. Therefore, a child can have both RLS and PLMD if diagnostic criteria are met for both disorders. Children with PLMD and a family history of RLS are considered to be at risk for having or developing RLS, given the common familial occurrence of RLS and the fact that almost 90% of adults with RLS also have PLMS [35].

The diagnostic criteria for childhood PLMD are listed in

Table 11
Criteria for the diagnosis of possible RLS in children

1 The child has periodic limb movement disorder (for the childhood definition, please see Table 12) and
2 The child has a biologic parent or sibling with definite RLS, but the child does not meet definite or probable childhood RLS definitions
Table 12. These criteria are intended for use in children aged 0 through 18 years. The Atlas Task Force criteria for duration, interval, periodicity, and amplitude of leg movements were chosen [33]. While the International Classification of Sleep Disorders does not require clinical sleep disturbance for a diagnosis of PLMD in adults [110], the workshop participants considered symptoms of clinical sleep disturbance in children as necessary for the diagnosis of PLMD. This helps to differentiate PLMD from the laboratory finding of PLMS. In order to make an accurate diagnosis of PLMD in children, the clinician must determine that the PLMS are not accounted for by sleep-disordered breathing (i.e. the movements are independent of any abnormal respiratory events) or medication effect (e.g. antidepressant medication) [102], or medication effect (e.g. the movements are independent of any abnormal respiratory events) [102], or medication effect (e.g. antidepressant medication) [48,49,111–113]. Determining a possible relation to abnormal respiratory events can be challenging, and the best technology for this remains to be established. Although specific data have not been published on the significance of apnea and medication-related PLMS, it is likely that the clinical relevance and management in children are different than that for either idiopathic PLMS or children with PLMD. This helps to differentiate PLMD from the laboratory finding of PLMS. In order to make an accurate diagnosis of PLMD in children, the clinician must determine that the PLMS are not accounted for by sleep-disordered breathing (i.e. the movements are independent of any abnormal respiratory events) or medication effect (e.g. antidepressant medication) [48,49,111–113]. Determining a possible relation to abnormal respiratory events can be challenging, and the best technology for this remains to be established. Although specific data have not been published on the significance of apnea and medication-related PLMS, it is likely that the clinical relevance and management in children are different than that for either idiopathic PLMS or children with PLMS and RLS.

In the presence of excessive daytime sleepiness, a diagnosis of narcolepsy should also be considered, since up to 50% of adults with narcolepsy have PLMS [114] and because excessive daytime sleepiness is uncommon in children or adults with PLMD [84,115,116]. Observation of the child for repetitive limb jerks during sleep has thus far not been shown to be sensitive or specific enough for the diagnosis of PLMD [78,83,84]. When examining the polysomnographic records of children with a presumptive diagnosis of PLMD, the clinician should carefully score the stage 1 sleep so that leg movements in lighter stages of sleep are not missed [117]. Leg movements may occur in tight clusters, requiring scoring with the minimal intermovement criterion of 5 seconds.

The workshop participants note that considerable uncertainty exists about the clinical significance of PLMD in children and, therefore, recommend that the clinical significance of PLMD be studied further, particularly with regard to behavior, cognitive, and affective parameters in children. Development of survey tools that predict PLMS in children with a high sensitivity and specificity are encouraged [106]. Collecting more-extensive, population-based normative data for PLMS in children is recommended. The development of actigraphy techniques that are comparable to polysomnography in sensitivity for PLMS in children would help promote research in this area. Further work to characterize the duration and intermovement interval of PLMS in children is recommended. Night-to-night variability of PLMS can occur in children as well as in adults [118], but no published studies have addressed the prevalence of this phenomenon in children.

4. Diagnostic criteria for augmentation of RLS

At the workshop, criteria for a common definition of augmentation in RLS were agreed upon. First described in 1996 [119], augmentation has been found to be a common complication of treatment for RLS with dopaminergic therapies [4,119–128]. A MEDLINE search performed on May 23, 2002, using the key words restless legs and augmentation produced 10 articles [4,119–127], of which five present original data, and failed to find any reports of augmentation in the treatment of RLS other than with dopaminergic agents.

Augmentation is the worsening of RLS symptoms, attributable to a specific therapeutic intervention for RLS. The primary feature of augmentation is a shift of RLS symptoms to a time period that is 2 or more hours earlier than was typical of the time of symptom onset during the initial course of beneficial stable treatment or the state before recently starting treatment. No other medical, psychiatric, behavior, or pharmacologic factors explain the exacerbation of the patient’s RLS. If a 2-h advance of RLS symptoms is not present, augmentation may also be diagnosed if therapy results in two or more of the key features outlined in Table 13.

The augmentation symptoms should be present for at least 1 week, for a minimum of 5 days per week, to meet diagnostic criteria. The common clinical view is that augmentation most typically presents within 6 months after treatment begins or the dosage of medication is increased, but it can occur at any time during the course of treatment, including within the first week. The RLS symptoms related to augmentation may be mild or severe; the presence of augmentation does not in and of itself indicate severity of symptoms.

In Allen and Earley’s analysis of 30 RLS patients taking levodopa, 82% developed augmentation with the following characteristics: symptoms earlier in the evening (100%),

Table 12. Criteria for the diagnosis of PLMD in children

| 1 | Polysomnography shows a periodic limb movement index of 5 or more per hour of sleep. The leg movements are 0.5–5 s in duration, occur at intervals of 5–90 s, occur in groups of four or more, and have an amplitude of one-quarter or more of toe dorsiflexion during calibration and |
| 2 | Clinical sleep disturbance for age must be evident as manifest by sleep-onset problems, sleep-maintenance problems, or excessive sleepiness and |
| 3 | The leg movements cannot be accounted for by sleep-disordered breathing (i.e. the movements are independent of any abnormal respiratory events) or medication effect (e.g. antidepressant medication) |

These criteria are presented to support research on the uncertain clinical significance of this disorder in children and to separate this concept from that of RLS in children.
increased symptom severity (96%), shorter latency to RLS symptoms at rest (33%), and increased body involvement (10%) [119]. An additional finding in this study was the development of RLS symptoms in 31% of patients with PLMS and not RLS who were treated with levodopa, in a pattern characteristic of augmentation. If severe, augmentation can result in the loss of essential RLS characteristics (symptoms are no longer worse with rest or inactivity, relieved by movement, or worse during the evening or at night). In these severe cases, the RLS symptoms can occur continuously, can involve the whole body, and can have a strong similarity to neuroleptic-induced akathisia.

The prevalence of augmentation with various dopaminergic treatments has been reported as follows: levodopa, 27–82% [119,128,129]; pergolide, 0–27% [26,120,121,129,130]; pramipexole, 0–39% [131–133]; cabergoline, 0% [123]; amantadine, 0% [134]; and piribedil, 0% [135]. In the three studies of pergolide in which augmentation was present, the augmentation was described as mild and easily managed or not clinically relevant. The wide variance in these figures may be influenced by several factors, including the lack of an adequate sample size (particularly for the cabergoline and amantadine studies), lack of a common graded augmentation definition, medication-dosage differences, and different entry criteria to the studies (e.g., treatment failures vs. previously untreated cases). Although randomized, controlled trials do not exist, the literature and clinical experience indicate that augmentation is more likely to occur with the use of levodopa medications than with the use of dopamine-receptor agonists.

With levodopa, augmentation has been found in two studies to correlate with the severity of RLS symptoms and higher medication dosage but not with sex or age [119,129]. In these studies, augmentation was always identified within the first 2 months of treatment but was tolerated by some patients for several months before the use of an alternative medication was instituted. Clinical experience suggests that patients with some secondary forms of RLS or RLS that is exacerbated by iron deficiency may have an increased risk of developing augmentation, but no studies have specifically addressed this issue.

When assessing a patient for the possible occurrence of augmentation, the clinician should keep in mind several factors that may present as mimics of augmentation and should be excluded. These factors include (1) a natural progression of RLS, which typically occurs slowly; (2) a temporary worsening of symptoms due to other identifiable extrinsic factors, such as sleep deprivation, alcohol use, blood loss (iron deficiency); (3) the use of medications such as dopamine-receptor blockers or antidepressants; (4) loss of efficacy to therapy or ‘tolerance’; and (5) end-of-dose rebound.

In their original description of augmentation, Allen and Earley differentiated augmentation from rebound, which had been previously reported [119,136–138]. Rebound is characterized by the development of RLS symptoms in the early morning, rather than by earlier onset of symptoms in the evening [138]. Rebound is considered to be an end-of-dose effect, related to the half-life of the therapeutic agent. With the use of levodopa, rebound has been found to be less common than is augmentation in RLS patients (rebound, 20%, vs. augmentation, 82%), and rebound is considered to be less of a problem clinically. Furthermore, the occurrence of rebound and augmentation did not correlate significantly in the Allen and Earley series [119], indicating that these are likely separate phenomena.

It is intended that specific criteria for the diagnosis of augmentation will be helpful in clinical and research settings. The workshop participants encourage research into a variety of areas regarding augmentation. Research to compare the presentation of augmentation with the use of levodopa to augmentation that occurs with other dopaminergic agents and other standard treatments for RLS is much needed.

A multicenter validation of an augmentation severity rating scale is currently being developed by Diego Garcia-Borreguero, Marco Zuconni, and the European affiliate of the IRLSSG (Appendix A). The goals of this project include the quantification of augmentation as a continuum (rather than as ‘present or absent’) and the differentiation of augmentation from rebound. The use of electrophysiologic or actigraphic measures to quantify the symptoms of augmentation will be helpful in assessing augmentation in multiple treatments. Pretreatment and posttreatment serial SIT, with or without polysomnography, could measure the time course, severity, PLMW, and sleep-related findings of augmentation. If actigraphy is validated in different levels of symptom severity, simultaneous upper-limb and lower-limb actigraphy (perhaps with position sensing) could offer cost-effective objective documentation of augmentation.
5. Assessment of RLS in epidemiology studies

Population-based epidemiologic investigations can complement knowledge gained in laboratory and clinical settings by providing precise estimates of disease prevalence and incidence. They can also generate and test etiologic hypotheses through the analysis of risk factors in cases and controls sampled from the same source population. To date, population-based studies of RLS are few in number, limited in size, and restricted in geographic scope and use inconsistent ascertainment tools. From six population-based studies with published data on the prevalence and associated characteristics of RLS [3,20,74,139–140], only two [74,140] established their ascertainment questions using the four diagnostic criteria developed by the IRLSSG in 1995. Data on the incidence are completely lacking. Despite their use of varying diagnostic criteria, most of these studies report prevalences of RLS of 10–12%, with a range of 5–20%. While the consistency of these findings is reassuring, additional population-based studies are needed because the studies that employed the standard definitions of RLS are of limited size and restricted to German and Swedish populations.

5.1. Construction of a minimum question set

The workshop participants determined that, for large-scale population studies, three or four questions about RLS could feasibly be added to the respective interview or questionnaire. More questions would obviously be desirable, but it was judged that for most large population surveys in which questions about RLS would be added to other items, the minimum adequate set of questions for RLS would include three or four distinct items. It was the consensus that this would best include three questions aimed at providing a diagnosis and a fourth optional question that examined frequency of symptoms as a convenience measure of severity, impact, or need for treatment. Some studies [3,20] have employed one or two question probes to ascertain symptoms of RLS. Such studies have typically found prevalence measures (mostly point prevalences) in a range of 5–20% of the general adult population in North America or northern Europe for persons endorsing the symptoms presented by the questions; however, none of these studies performed further validation to determine the sensitivity and specificity of these questions in elucidating diagnosable RLS. Only one study of a sample of German elderly used a three-question set based on the IRLSSG diagnostic criteria combined with a diagnostic interview by an expert physician [74]. In this study, comparing the simultaneously administered questions and the physician diagnoses resulted in a sensitivity of 87.5% and a specificity of 96%. This study found a 9.8% prevalence based on positive responses to all three questions. These questions are provided in both their original German and in an English translation (Appendix B).

In developing the recommended question set, the workshop participants adopted three guiding principles:

1. The questions would build upon the previously validated three-question set
2. The previously validated questions would be modified to incorporate the newly established diagnostic criteria
3. The framework for these questions would both provide universal verbal anchors and allow optional variable statements that could be completed with language-specific or dialect-specific descriptors

Based on these principles, workshop participants generated a set of four questions (Table 14) to be used as a minimum core for population-based epidemiologic studies (either cross-sectional or longitudinal studies, based on the specific tense of the verbs). The first three questions, or an alternate formulation that covers the same content as these questions do, are mandatory for inclusion to perform an adequate diagnostic screening; the fourth, a question that establishes frequency of symptoms, is optional but provides an important indication of the severity of the condition.

5.2. Validation of the question set for determining the epidemiology of RLS

The workshop participants recommend that validation be

Table 14
Paradigm of questions for epidemiology studies of RLS

<table>
<thead>
<tr>
<th>Question</th>
<th>Response Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have unpleasant sensations (culturally specific descriptor examples) in your legs combined with an urge or need to move your legs?</td>
<td>Yes or No</td>
</tr>
<tr>
<td>2. Do these feelings (or culturally specific wording, such as ‘symptoms’) occur mainly or only at rest and do they improve with movement?</td>
<td>Yes or No</td>
</tr>
<tr>
<td>3. Are these feelings (or culturally specific wording, such as ‘symptoms’) worse in the evening or night than in the morning?</td>
<td>Yes or No</td>
</tr>
<tr>
<td>4. How often do these feelings (or culturally specific wording, such as ‘symptoms’) occur?</td>
<td>less than one time per year, one time per month, 2–4 times per month, 2–3 times per week, 4–5 times per week, 6–7 times per week</td>
</tr>
</tbody>
</table>

A positive diagnosis requires that the respondent answer YES to the first three questions. (The words in bold in each question can be changed to establish point prevalence versus lifetime history; for example, to establish lifetime history in the first question, the words Do you have could be changed to Have you ever had.)
performed through sampling from a large, general-population study, which may be feasible by adding the question set to an established study with adequate sampling of the general population. Alternatively, validation studies should be conducted in a newly recruited sample of the general population. At first pass, validation should include face-to-face interviews with an expert blinded to the answers to the questions and, if possible, to the wording of the questions; if that is not feasible, expert diagnosticians who are similarly blinded to question responses can conduct open-ended telephone diagnostic interviews. It may also be possible to substitute structured diagnostic or telephone interviews for an open-ended expert interview, if and when suitable instruments are developed and validated. A panel of local experts (e.g. members of the IRLSSG), in collaboration with professional translators, should help ensure accurate translation and back translation (with sensitivity to local linguistic requirements and specific terms that may not translate literally).

The fourth question (on frequency) should be validated as a proxy of severity. It can be administered together with the IRLSSG rating scale [8], quality of life instruments (Allen et al., unpublished data), or other valid measures related to severity. This validation should take place with RLS-positive subjects from population-based studies as well as clinical populations.

Workshop participants also recommend that not only studies of point prevalence, but also longitudinal studies, be conducted to evaluate the natural evolution of the disorder and the incidence rate. These studies should take place at 1-year intervals, ideally with repeated annual follow-up surveys for periods extending to 5 years. A key issue would be to determine whether individuals reporting a given frequency of symptoms would show a systematic shift to higher frequencies of symptoms on subsequent follow-up cycles. This analysis would determine whether RLS is generally progressive and identify the risk factors that may lead to an accelerated increase in frequency of symptoms.

A further issue is the need to determine the basis for false-positive findings (as ascertained through epidemiology questions vs. expert opinion) by examining the nature of the false-positive groups, using available clinical measures, and possibly leading to some added objective testing. Evaluation of false-negative responses may also indicate a need for future refinement of these questionnaire items. These considerations may also indicate the need to increase the number of items in order to improve diagnostic accuracy in situations where this is possible.

5.3. Objective measures to validate epidemiology questions for RLS

The value of objective measures of RLS – such as SIT, polysomnography, and actigraphy to measure excessive motor activity, PLMS or PLMW, and sleep indexes – remains unsettled (see essential criterion 2). While subjective SIT measures and PLMW, as polysomnographically determined, demonstrate reasonable specificity and sensitivity in patients previously diagnosed with RLS [13], their use as diagnostic tools remains unclear.

The workshop participants recommend, therefore, that validation studies be used to assess the diagnostic utility of SIT, PLMW, actigraphy, or other objective measures once the recommended question set has been incorporated into larger population-based studies. This application could be used to establish whether or how these measures correlate with or help distinguish between different groups (true positives, true negatives, false positives, false negatives) – with the detailed physician interview or expert clinical judgment being recognized as the present ‘gold standard’. The goal is to determine to what extent these objective measures can help discriminate between the different groups. Given the extreme night-to-night variability in RLS and PLMS, workshop participants specifically encourage the use or further development of actigraphy (for the assessment of PLM indexes).

6. Conclusion

These revised diagnostic criteria for RLS have been developed to replace the previously proposed criteria and to extend the new criteria to the special populations of cognitively impaired elderly, children and adolescents, and patients who develop the phenomenon known as augmentation. Those individuals who have been involved in the reassessment process conclude that these revised criteria incorporate the new scientific knowledge gained about RLS and also clarify the concepts in the prior diagnostic criteria. The major changes in these revised diagnostic criteria eliminate the somewhat ambiguous concept of motor restlessness, add emphasis to the primacy of the urge to move, and separate symptom provocation by rest from symptom relief by activity. The revised diagnostic criteria are intended to foster RLS research and improve clinical practice. The new criteria for diagnosing RLS in children and the cognitively impaired elderly are put forth in an attempt to support further studies on these previously neglected populations. The more-specific definition of augmentation, which is often a significant problem for successful treatment of RLS, provides a tool for improving the assessment of future therapies. The standardized questions for epidemiology studies of RLS can serve as a suggested basic starting point for studies designed to advance the understanding of this common but under-diagnosed condition.

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We wish to thank Pharmacia Corporation for their
During the past week, what percentage of your body was affected by RLS symptoms, on an average day?

During the past week, what was the severity of your RLS symptoms, on average?

During the past week, at what time of the day did your RLS symptoms usually begin?

Table A1

During the past week, at what time of the day did your RLS symptoms usually begin?

During the past week, what was the severity of your RLS symptoms, on average?

During the past week, if you were sitting for a long period of time during the daytime, for example in a car, plane, or theater or watching TV, how soon did your RLS symptoms begin?

During the past week, what percentage of your body was affected by RLS symptoms, on an average day?

Appendix A. Augmentation severity rating scale

Augmentation can be a serious complication for people with restless legs syndrome (RLS), resulting in the need to change therapies. According to existing data, augmentation occurs most commonly in patients undergoing treatment with levodopa, where it has been reported in 27–82% of cases [119,128,129]; however, it can also be seen during treatment with the use of dopamine-receptor agonists [28,120,129,132]. To date, no cases of augmentation have been too small to adequately evaluate the occurrence of augmentation.

Table A1

Analyzing the data on the prevalence of augmentation is particularly problematic because most studies do not measure augmentation in a systematic way. Validated rating scales for augmentation are not available, making uniform measurement and comparison difficult. In addition, augmentation has typically been reported in a categorical manner, simply providing information on whether or not it exists. This aspect is particularly troublesome since augmentation can be present with various grades of severity.

Based on the need for an evaluation tool, the European Affiliate of the International RLS Study Group has recently developed a rating scale for the assessment of the severity of augmentation during the long-term treatment of RLS. The augmentation severity rating scale (ASRS) has been specifically designed to be used in clinical studies and may be particularly useful in comparative drug studies.

The ASRS consists of a self-reporting 24-h log with which patients rate the severity of their RLS symptoms every hour for 7 days. Scores for severity of symptoms range between 0 (none) and 4 (very severe) and include information on sleep time and intake of medication. After the patient has completed the log, an evaluator asks the patient a series of questions (Table A1). Responses are assigned a graded score ranging between 0 and 4. The rating scale is completed at different time points throughout the treatment period: at baseline (pretreatment) and after a defined period or periods of treatment. The sum of the scores from questions answered at baseline is subtracted (by the evaluator) from those assessed after the defined period of treatment, providing a difference (posttreatment minus baseline score). This result is the augmentation score, which ranges between 0 and 16 points.

The validation of the ASRS will be completed in two phases. The first will be an open pilot study, during which RLS experts of the European Affiliate of the International RLS Study Group will use the ASRS on any patients who begin a new therapeutic regimen for RLS, preferably those patients who are anticipated to receive long-term treatment. Based on the experience gained during this first study, appropriate changes will be made to the scale, and a modified version will be released. The second phase includes a final validation of the ASRS, which is planned to be used in the context of a comparative therapeutic trial.

For more details on the ASRS please contact: Diego Garcia-Borreguero, MD (Madrid, Spain, dgarciaborreguero-o@fjd.es); Luigi Ferini-Strambi, MD (Milan, Italy, ferinistrambi.luigi@hsr.it); or Claudia Trenkwalder (Göttingen, Germany, ctrenkw@gwdg.de).
Appendix B. Question set used in the MEMO Study [74]

B.1. Original German version

1. Haben Sie Missemempfindungen wie Kribbeln, Ameisenlaufen oder Schmerzen an den Beinen verbunden mit einem Bewegungsdrang?
2. Treten diese Symptome nur in Ruhe bzw. beim Einschlafen auf und lassen sie sich durch Bewegung bessern?
3. Sind diese Symptome Abends oder Nachts schlimmer als Morgens?

B.2. English version

1. Do you have unpleasant sensations like creepy-crawly feelings in your legs combined with an urge or need to move your legs?
2. Do these feelings occur mainly or only at rest and do they improve with movement?
3. Are these feelings worse in the evening or night than in the morning?

Appendix C

Participants and contributors

C.1. Participants in the workshop

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