

Update on restless legs

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Summary

Restless Legs Syndrome (RLS) has become a well known disorder in the medical community in Switzerland within the last ten years, particularly since the official introduction of dopaminergic drugs as first line treatment. However, even today, in some patients a correct diagnosis is delayed, preventing specific therapy and prolonging discomfort or even painful symptoms over years. It is important to recognise the syndrome of restless legs, and it is essential to search systematically for treatable causes and to treat separately frequent comorbidities such as depression or polyneuropathy. It is important to understand the impact of this progressive disease on the personal and profes-

sional life of the patient. In addition, therapy resistance and severe side effects, particularly augmentation and fibrosis, can be minimised by understanding important details of treatment and by an optimal follow up of such patients. Research on the genetic basis of RLS, on purported pathogenetic mechanisms in the dopaminergic and other neurotransmitter systems, on iron metabolism in the brain and spinal cord, and the socio-economic burden of the disease, are urgently needed.

Key words: restless legs; overview; diagnosis; therapy; augmentation; fibrosis

History and nature of the disorder

The great English anatomist and physician Sir Thomas Willis already described the sensorimotor disorder Restless Legs in the 17th century. The clinical picture was fully described by the Swedish neurologist Karl Axel Ekbom in 1945 [1]. Lugaresi's research group first recorded the periodic movements in sleep in RLS [2] and Apkinar [3] was the first who prescribed a treatment with dopaminergic drugs. In the Swiss idiom dictionary (Schweizerisches Idiotikon) published in 1952 the dialect term "sterblen" is defined as "moving around with the legs in the bed", most probably also referring to restless legs syndrome.

Restless Legs Syndrome (RLS) is now considered an organic neurological disorder based on dysfunction of the dopaminergic and opioidergic neurotransmitter system with a genetic cause, modulated by the metabolism of iron. Because of its relationship with depression and anxiety it was formerly termed "anxietas tibiaram" and a psychiatric origin was then considered. A vascular cause has also been proposed but could never be convincingly proven.

Clinical diagnosis of Restless Legs Syndrome

Essential criteria

Diagnostic criteria have been established and recently revised by the international RLS study group (IRLSSG) (table 1) [4].

The essential diagnostic criteria include (1) a distressing urge to move the limbs because of paraesthesias or spontaneous jerks in the legs or less often in other body parts, (2) a worsening of these symptoms at rest, (3) a temporary relief by motor activity, and (4) worsening of the symptoms in the evening or during the night.

Diagnosis of Restless Legs Syndrome is sup-

ported by (5) a positive family history, (6) a positive effect of the dopaminergic treatment, at least at the beginning of therapy, and (7) periodic leg movements during sleep. The associated features of the syndrome include (8) a progression of the disease depending on the age of onset and/or (9) a positive family history and a normal neurological result, at least for the idiopathic form of RLS.

The main complaints are uncomfortable hard-to-describe sensations or involuntary movements of the legs, and less often, also in the arms or other body parts. Each patient describes the phenomena

Table 1

Diagnostic criteria (adapted from [4]).

Essential diagnostic criteria for RLS

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

Supportive clinical features of RLS

5. Family history: Prevalence of RLS among first-degree relatives of people with RLS is 3 to 5 times greater than in people without RLS
6. Response to dopaminergic therapy: 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
7. Periodic limb movements (during wakefulness or sleep): 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

Associated features of RLS

8. Natural clinical course: 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
9. Sleep disturbance: 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
10. Medical evaluation/physical examination: The physical examination is generally normal and does not contribute to the diagnosis except for those conditions that may be co-morbid 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

Key features of augmentation in RLS

- Augmentation is the shifting of symptoms to a period of time 2 h or earlier than was the typical period of daily onset of symptoms before pharmacologic intervention
- An increased overall intensity of the urge to move or sensation is temporally related to an increase in the daily medication dosage
 - A decreased overall intensity of the urge to move or sensations is temporally related to a decrease in the daily medication dosage
 - The latency to RLS symptoms at rest is shorter than the latency with initial therapeutic response or before treatment was instituted
 - The urge to move or sensations are extended to previously unaffected limbs or body parts
 - The duration of treatment effect is shorter than the duration with initial therapeutic response
 - Periodic limb movements while awake either occur for the first time or are worse than with initial therapeutic response or before treatment was instituted

differently and some patients hesitate to describe strange symptoms to their physician. Examples of expressions used by our own patients are the following: tension, burning inside, urge to move, nervousness, paraesthesia, aching, pain, indescribable sensations, jerking. With regard to this broad spectrum of unspecific symptom descriptions it is very helpful if the medical doctor shows appreciation for, and anticipates the oddness of these descriptions. Finally, some patients cannot articulate the symptoms other than describing a “strange sensation” located within the legs. Most commonly, the sensations are located deep in the muscle or in the bones and not in the skin (= Knochenparästhesien). Pain is reported in up to 50% of the patients [5], particularly in situations when movements are restricted, such as in a theatre or in an airplane. The legs are most often involved, but later other body parts such as the arms, hips, genitals or the face may also be affected, even predominantly. However, when the legs are spared during the entire course of the disease, a diagnosis of RLS should be questioned.

The recurrent appearance of the sensory discomfort can induce almost periodic voluntary

movements during wakefulness. A minority of patients do not report uncomfortable sensations, but instead report involuntary spasmodic jerks of the legs that follow the same rules described above for the sensory discomfort (motor variant of RLS). These jerks also called dyskinesia while awake, or periodic leg movements while awake (PLMW), can affect a single limb or the whole body and can also appear when standing but disappear while walking. These involuntary jerks most often appear in situations where voluntary movements are restricted, an observation that was used for diagnostic purposes, in the Suggested Immobilisation Test (SIT) [6]. Such an uncontrollable motor display may obviously be most disabling in social situations such as during common meals or discussions, because of the risk of losing objects out of the hands. Within the same subject the affected limb can change from one day to another, but the clinical appearance is stereotypical over hours in periodic succession with intervals between 15 to 30 seconds. The most frequent display we have observed was a spasmodic jerk starting with a strong myoclonic contraction, followed by a few additional jerks with exponentially decreasing ampli-

tude lasting 2 to 5 seconds overall. Patients can delay the jerks for a short time but are not able to suppress them completely, except by walking around or by engaging in other types of physical or mental activities.

All symptoms typical of RLS appear particularly during inactivity such as sitting or lying in bed and are relieved by activity. When patients deny an improvement with activity, it is because their symptoms start immediately after sitting or lying down again. Therefore it is important for the examining clinician to specify his question whether improvement continues as long as the activity persists. The inductive resting situation includes both physical immobility and mental disengagement, probably resulting in a state of reduced alertness. Sleepiness and fatigue worsen symptoms, but are relieved by physical activity and mental engagement such as playing cards, playing computer games or being involved in a lively discussion. Discomfort in a particular extremity can also be relieved by moving another part of the body. It is well known that rubbing the legs or taking a cold or less often a hot bath is helpful. Some of our male patients are convinced of the positive effect of masturbation.

Relief is achieved immediately after beginning an activity, although relief is not always complete, particularly later in the course of the disease. Symptoms resume with various latencies after sitting or lying down. The shorter the latency, the more severe is the RLS. Duration of latency is therefore used as a simple measure for the clinical course. In severely affected patients who deny relief with activity the diagnostic question should refer to an earlier period of the disorder.

The symptoms are worse in the evening or during the night, at least in the beginning of the disease. In two studies it was possible to separate the circadian effects from the impact of recumbency and rest on the RLS symptoms [7, 8]. In a modified constant routine protocol a peak of involuntary motor activity appeared after midnight, during the falling phase of the circadian core-temperature, and the least number of movements were observed during the rising phase of core body temperature in the early morning hours. Anecdotally a reappearance of RLS time locked with jet lag has been reported after long distance flights. When RLS has become most severe, a circadian variation may be lost and these patients suffer all day long. This circadian effect can nevertheless be found in the early phase of the patient's disease history when symptoms were less severe. Patients with a mild form of RLS, for whom discomfort is only disturbing during long sitting (eg, in long distance airplane trips), may not be aware of the fact that symptoms are worse when this prolonged inactivity occurs in the evening compared to the morning hours.

Supportive and associated features

Family history

A considerable number of RLS patients report a positive family history. In our own study a positive family history was related to an early onset of symptoms [5]. Patients with symptom onset before the age of 35 (early onset RLS) had more often a positive family history (40%) than patients with later symptom onset (late onset RLS; 25%). Several other studies also revealed that in idiopathic RLS more than 50% of the patients reported a positive family history.

Effect of dopaminergic drugs

Dopaminergic drugs have a beneficial effect on RLS symptoms, at least at the beginning of the disease, for a restricted period of time in the majority (~90%) of patients. Later, in the progressive course of the disease, this beneficial effect may be lost.

Insomnia

Up to 90% of the patients suffer from severe sleep onset insomnia and rarely from excessive daytime sleepiness (EDS) [5]. In patients with severe insomnia one should therefore always ask about distressing sensations in the legs, since RLS is the cause of insomnia in about 20% of the cases. Polysomnography in RLS patients demonstrates an extremely severe insomnia. That is, sleep may be restricted to a few hours in the early morning when the circadian nadir of RLS expression is approached. Some patients are forced to walk around the entire night and can only get sleep during the morning hours. Interestingly, a considerable percentage of our own patients have no greater difficulties falling asleep initially in the evening. The insomnia problems start after awakening one to two hours after bedtime. This is explained first by the individual circadian variation of RLS severity, and second, by the increased sleep pressure allowing them to fall asleep within a few minutes before RLS symptoms develop.

Periodic leg movements in sleep (PLMS)

When sleep finally emerges, involuntary jerks of the legs persist in periodic intervals of 15 to 40 seconds in more than 80% of all patients. The number of periodic leg movements per hour of sleep (PLMS-index) has often been used as an objective measure for severity of RLS and values above 5/hour are considered abnormal [9]. However, there are exceptions to this rule. In several of our most severe RLS patients no PLMS at all were recorded. In addition, up to 58% of elderly healthy people (>60 years), without other health complaints, and patients with sleep apnoea syndrome, narcolepsy or REM sleep behaviour disorder also show PLMS with an index above 5/hour underlining the limited diagnostic value of this finding. In patients referred to a sleep laboratory for reasons of insomnia or excessive daytime sleepiness (EDS), a PLMS index above 5/hour is sometimes the only

abnormal finding that can be found. Up to now a causal relationship between these PLMS, often associated with arousals and insomnia or EDS called "periodic leg movement disorder" (PLMD), has not been convincingly proven, and therefore any drug therapy should be regarded as experimental. Moreover, it has been reported that under dopaminergic treatment in PLMS severe RLS has evolved [10]. The continuous motor activity during the night often leads to personal problems with the partner, and the extreme discomfort over many years, combined with the ignorance of relatives and the medical community, may predispose the patient to depression and thoughts of suicide [11]. In summary, PLMS are neither sufficient nor necessary to diagnose RLS. PLMS can support a diagnosis more strongly in younger patients since PLMS does not occur frequently in this group. In elderly persons it is more the absence of PLMS that should raise some doubts about the diagnosis of RLS.

According to our own experience RLS sufferers do rarely complain of EDS despite the fact that insomnia in these patients is of the most severe type. MSLT data (unpublished) confirmed only mild or absent daytime sleepiness. Fatigue and loss of energy is often reported, impairing daytime functioning and also leading to an inability to work.

Progressive course of RLS

RLS symptoms may start at any age; in 12% of cases, symptoms appear before the age of 10 years [5]. Often symptoms are mild at the beginning, but a chronic progression is typical and remissions are rare. The latter statement may be biased by the fact that more severely affected patients are under medical care and it cannot be excluded that milder forms may remit. Diagnostic criteria for children and for cognitively impaired elderly patients have been proposed by the IRLSSG [4]. Patients with early onset of symptoms (before the

age of 35–45 years) more often have a positive family history, whereas patients with late onset more often have a secondary cause such as end stage renal disease, polyneuropathy and iron deficiency. Disease progression is more rapid in late onset RLS, whereas patients with an early onset may report a slowly progressive course and may have difficulties remembering the exact beginning of their symptoms [5, 12]. Many of these early onset patients will seek medical help only after the age of 40 [5]. In pregnancy, up to 25% of females report RLS symptoms and in most cases the discomfort disappears after delivery. It has been shown, however, that multiple pregnancies may increase the risk of chronic progressive RLS [13] and may eventually explain the greater prevalence of RLS in females.

Neurological examination is normal in the idiopathic form of RLS

Neurological evaluation will be normal in idiopathic RLS. The clinician should look for signs of polyneuropathy, such as absent ankle reflexes and impaired vibration sense at the ankles. An autonomic neuropathy should be considered when sweating at the hands and feet has changed, and when trophic abnormalities, such as dry skin or absence of hair at the dorsum of the foot, are observed. In these patients an electrophysiological investigation including autonomic tests is recommended. In case of a proven polyneuropathy additional blood tests to search for treatable causes of polyneuropathy should be performed. The neurological examination may show a complex picture in patients in who a narrow spinal canal, a spinal disease or nerve compression within the pelvic region, or a vascular claudicatio (including claudicatio spinalis) are suspected. Here it is often difficult to separate symptoms related to secondary RLS from symptoms directly induced by one or more of these causes.

Epidemiology and severity of disease

The prevalence of RLS is reported to be between 5–10% in the normal population depending on the diagnostic criteria and the age of the population under investigation. Usually a higher prevalence is found in females than in males and increasing in frequency with older age [14]. 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. Considering only those cases who report symptoms at least twice per week, and those who seek medical help, the prevalence rate is estimated still at 2 to 3% [14].

A number of questionnaires are available for assessing the severity of RLS (table 2).

Table 2

RLS Severity scales.

A.) Restless Legs Syndrome Rating Scale (IRLS) (Investigator Version 2.2)

Ask the patient to rate his/her symptoms for the following ten questions. The patient and not the examiner should make the ratings (numbers in abbreviations), however the examiner should be available to clarify any misunderstandings the patient may have about the questions. The examiner should mark the patient's answers on the form.

In the past week ...

- (1) Overall, how would you rate the RLS discomfort in your legs or arms?
 Very severe (4) Severe (3) Moderate (2) Mild (1) None (0)

- (2) Overall, how would you rate the need to move around because of your RLS symptoms?
 Very severe (4) Severe (3) Moderate (2) Mild (1) None (0)

- (3) Overall, how much relief from you RLS arm or leg discomfort did you get from moving around?
 no relieve (4) mild relieve (3) Moderate relieve (2) Either complete or almost complete relieve (1) No RLS symptoms to be relieved (0)

- (4) How severe was your sleep disturbance due to your RLS symptoms?
 Very severe (4) Severe (3) Moderate (2) Mild (1) None (0)

- (5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms?
 Very severe (4) Severe (3) Moderate (2) Mild (1) None (0)

- (6) How severe was your RLS on the whole?
 Very severe (4) Severe (3) Moderate (2) Mild (1) None (0)

- (7) How often did you get RLS symptoms?
 Very often (6-7 days per week) (4) Often (4-5 day per week) (3) Sometimes (2-3 days per week) (2)
 Occasionally (1 day per week) (1) Never (0)

- (8) When you had RLS symptoms, how severe were they on average?
 Very severe (8 hours or more per 24 hour day) (4) Severe (3-8 hours) (3) Moderate (1-3 hours) (2)
 Mild (less than 1 hour per 24-hour day) (1) None (0)

- (9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily activities, for example having a satisfactory family, home, social, school or work life?
 Very severe (4) Severe (3) Moderate (2) Mild (1) None (0)

- (10) How severe was your mood disturbance due to your RLS symptoms – for example being angry, depressed, sad, anxious or irritable?
 Very severe (4) Severe (3) Moderate (2) Mild (1) None (0)

Severity classification: 1-10 mild; 11-20 moderate; 21-30 severe; 31-40 very severe

B.) Johns Hopkins Restless Legs Severity Scale

Score	Usual time of day when RLS symptoms start
0 (never)	No symptoms
1 (mild)	At bedtime and/or during the sleep period. (Symptoms may occur within 60 minutes before the usual bedtime or simply at the time of going to bed or during the night after in bed.)
2 (moderate)	In the evening (6 PM or later). Symptoms may start anytime between 6 PM and the usual bedtime. (The definition of evening may need to be adjusted for patients who routinely have much later bedtimes, such as these who have an afternoon siesta.)
3 (severe)	Afternoon (before 6 PM). Symptoms may start in the afternoon or may be present all day long.

C.) Augmentation questionnaire

During the past week ...

- at what time of the day did your RLS symptoms usually begin?.....
- what was the severity of your RLS symptoms, on average?
- if you were sitting down during the daytime, for example in a car, plane or theatre or watching TV,
- how soon did your RLS symptoms begin?.....
- what percentage of your body was affected by RLS symptoms, on an average day?

Aetiology and differential diagnosis

There is a continuum between the causes of secondary RLS itself and the causes of the broad differential diagnosis (table 3, [15]) presenting with symptoms resembling RLS.

A primary, idiopathic form of RLS, with or without positive family history, must be separated from secondary forms caused by iron deficit, diabetes, uraemia thyroid disorder, rheumatoid arthritis, polyneuropathy, and other causes. Many of these disorders can induce symptoms resembling RLS on one hand, but can also cause typical RLS symptoms. For example, patients with poyneuropathy might also complain of burning sensations in the legs that can be somewhat re-

lieved by a cold bath or by removing the cover of the bed during the night. Patients with a narrow spinal canal may report pain or paraesthesias in the legs when lying supine in their bed with the legs outstretched, but these symptoms are ameliorated when getting up and bending forward. The treatment of similar symptoms with another pathogenesis might be different and therefore they should be separated as reliably as possible.

RLS complaints are reported by up to 15-27% of pregnant women, particularly in the last trimester. In end stage renal disease requiring haemodialysis, the prevalence of RLS is between 20 and 50%. In iron deficiency syndromes, RLS is

Table 3
Differential diagnosis
(extended after [15]).

<i>Nocturnal leg cramps</i>	Usually a single muscle is painfully contracted. The muscle bulk is prominent and the continuous contraction can be palpated and can be relieved through stretching
<i>Polyneuropathy (PNP)</i>	Sensory Symptoms commonly reported as numbness, burning, and pain superficially in the skin. Although the sensory Symptoms can increase at night, they are usually also present throughout the day, and complete and persistent relief is not obtained while walking or during sustained movement. PNP can be associated with RLS
<i>Narrow spinal canal</i>	Pain in the legs is maximal while descending and less while ascending. When lying in bed pain is more pronounced in the supine position compared to a lateral position with bended knees. Most often combined with back pain
<i>Vascular disease of lower limbs</i>	Pain is increasing while walking and relieved while sitting or lying down
<i>Arthritis in lower limbs</i>	Discomfort centred more in joints; does not usually have prominent circadian pattern as seen in RLS
<i>Volitional movements of feet (foot tapping, rocking)</i>	Occurs in individuals who fidget, especially when bored or anxious, but usually do not experience associated sensory Symptoms, discomfort, or conscious urge to move. Usually lacks a circadian pattern
<i>Positional discomfort</i>	Occurs after prolonged sitting but not lying in the same Position and is usually relieved by a simple change in position. Unlike RLS, which often returns after change of position, movement, or walking it is not continued
<i>Hypotensive akathisia</i>	Feeling of restlessness while sitting in individuals with orthostatic hypotension, which may be localised in legs. Is also relieved by movements but should not occur while lying down and does not show a circadian rhythm
<i>Neuroleptic induced Akathisia</i>	Usually whole body sensation rather than centred only in limbs with no pronounced circadian pattern and no insomnia, less associated sensations, and often no relief with movement. Should have history of specific medication exposure
<i>Burning or painful feet and moving toes or painful fasciculation syndrome (an immunoneuropathy)</i>	Feet involved more; no circadian pattern. Usually show continuous slow writhing or repetitive movements of toes

present in about 40% of the patients and it is an ongoing debate whether or not a lack of iron storage is also the cause of the former conditions. Polyneuropathy (PNP) is considered to be a cause of RLS, but epidemiological studies among patients with PNP have revealed incidences of only 5%, which is hardly greater than in the general population. It can be suggested that RLS might be the dominating symptom only at the beginning of the progressive PNP, particularly when small fibres are affected exclusively. Later, in the course of PNP, the circadian and positional dependence is lost and the observable clinical symptoms and signs are attributed to PNP itself. Charcot Marie Tooth disease type II, an axonal form of PNP, is frequently present with RLS in contrast to type I, which is a demyelisation type of PNP. Another explanation could be that type II is more often present with sensory symptoms than type I. Among the spinocerebellar ataxias, SCA-3 with frequent PNP

is present quite often with RLS. Other pain disorders with a neurological basis, such as chronic low back pain syndromes, fibromyalgia, narrow spinal canal, and myelopathy but also arthropathies, are associated with RLS symptomology.

Some of the most important differential diagnosis considerations needing specific diagnostic work-up are described in table 3.

A large percentage of children with attention deficit hyperactivity disorder (ADHD) also show a PLMS index above 5/hour. Therefore, this finding can hardly be used to differentiate ADHD from RLS and the diagnosis must therefore be based on the clinical presentation. Growing pain is another imprecisely defined condition in children. Here the complaints are usually reported over the course of several weeks and are not chronically progressive, although are sometimes reoccurring.

Diagnostic workup

The mainstay of RLS diagnosis is the history taken by a clinical expert. The official diagnostic criteria are certainly an extremely valuable tool for the clinical diagnosis, but the clinician should be aware that these criteria are by no means specific. The differential diagnosis should always be checked carefully. When other syndromes can be excluded with reasonable certainty, the next step is to establish the severity of the RLS. This can be

performed by various scales (table 2). The international RLS Rating Scale (table 2 A) is most widely used and can be ordered in a number of languages including French and German from Mapi Research Institute (<http://www.mapi-research-inst.com>; mail: canfray@mapi.fr) although no validation studies were done. The number of symptomatic nights, as well as the latency until symptoms appear after sitting down, can be used to rate

Table 4

List of diagnostic investigations in RLS.

Blood Laboratory (minimal requirements)

- Red and white blood cells
- Electrolytes including Ca and Mg
- Creatinin, urea, glucose, HbA_{1c}
- Iron, ferritin, iron saturation
- Vitamin B₁₂, folic acid
- TSH
- Ev. Pregnancy test

Neurophysiology

- Polyneuropathy screening if clinically suspected
- Ev. Leg actigraphy to prove presence of PLMS in young patients to support RLS diagnosis or to show absence of PLMS in old patients to disprove RLS
- Polysomnography when Epworth score is high (>12) or sleep apnoea syndrome is suspected
- Suggested immobilisation test (SIT) when clinical diagnosis uncertain

severity in milder forms of RLS. The subjective severity of sleep disturbance or the sleep efficiency in polysomnography or actigraphy are, in my opinion, better measures for establishing RLS severity than the PLMS index.

The clinician should be aware, that diagnosing a syndrome does usually not imply knowledge of the cause of the symptoms. Therefore, the next important step is to search for treatable causes of a possible secondary RLS (table 4). This should also be done when the family history is positive and an idiopathic form is most probable. A long list of medicaments and drugs can induce or exacerbate

RLS. Among these, the most important are dopamine-antagonists (neuroleptics, antiemetics with the exception of domperidone); calcium blockers; antihistamines; lithium; and in some patients antidepressants. Alcohol, caffeine, nicotine and chocolate can have a negative effect in some individuals.

Normal values for ferritin as indicated in most laboratories cannot be used in diagnosing RLS. It has become obvious that ferritin values in the normal lower range below 50 µg/l should be corrected in RLS.

Treatment and continuous medical care (table 5)

Causal therapy

Various disorders with chronic pain, such as low back pain, fibromyalgia, arthritis, sensory polyneuropathy, and vascular insufficiency can exaggerate RLS symptoms, although the exact causal relationship is unknown. If a cause of RLS or any inducing factor can be found, then the appropriate treatment is of course the primary goal. The above-mentioned RLS exacerbating medicaments or drugs should be avoided at least for a test period of some weeks. In end-stage renal failure it has been shown that transplantation is much more efficient for treating RLS than haemodialysis. In this condition additional iron replacement therapy and erythropoietin might be helpful. If the RLS is insufficiently treated then the symptomatic therapy can be added. Among the dopamine agonists, ropinirole is preferred in renal failure to pramipexole due to its metabolism through its hepatic metabolism. Iron insufficiency is responsive to iron replacement therapy, particularly in acute or sub-acute development of the insufficiency state such as in blood donors or other causes of relative acute iron loss. An oral iron replacement therapy (100–200 mg/day) can be tried at first when ferritin is below 50 µg/l, and if an increase of ferritin is not achieved within 3 months an intravenous application is pos-

sible. For oral substitution iron II preparations are preferred, whereas for intravenous applications iron III preparations are used. Absorption can also be improved by not taking the drug together with a meal, but together with vitamin C (fruit juice). The positive effect on RLS when ferritin is above 50 µg/l is not established and with higher iron storage the intestinal absorption is reduced. Iron treatment should not be indicated when a transferrin saturation value above 50% is observed, since this could indicate a disposition for iron overload. Parkinson's disease can occur with RLS. Here, treatment with L-DOPA may ameliorate the akinesia but produce the well known dyskinesias as well as augmentation of RLS.

Symptomatic therapy

The treatment of first choice is L-DOPA or a dopamine agonist. In direct comparison to opiates or benzodiazepines these drugs were clearly superior [16]. Dosage of L-DOPA can be increased rather quickly whereas dosage of agonists should be increased more slowly to avoid nausea and vomiting. Most often the daily dosage is taken in the evening one hour before bedtime. This is the time when most patients suffer the greatest discomfort. Some patients experience their main symptoms in

Table 5

Drug treatment in restless-legs syndrome.

Drug	generic name in CH	Initial dosage (mg)	Usual dosage (mg)	Half life (h)	Indication (I) /Side effects (SE)/remarks
<i>Dopaminergic drugs: side effects in all (SE*): nausea, hypotonia, orthostasis, dizziness, hallucinations, insomnia, leg edema, rhinitis</i>					
L-DOPA	Madopar DR® Sinemet CR®	50–62.5	100–250	1.5–2	I: indicated in mild/intermittent RLS danger of “Augmentation” in severe continuous RLS SE* mild/rare
Pramipexole	Sifrol®	0.125	0.5–1.5	8–10	SE* moderate/occasionally
Ropinirole	Adartrel®/Requip®	0.25	0.5–4.0	6–8	SE* moderate/occasionally
Pergolide	Permax®	0.025	0.5–1.0	12–16	I: Third line drug, due to risk of fibrosis. Regular 6-monthly check needed, ev. incl. Thorax Rx and echocardiography SE* frequent
Cabergoline	Cabaser®	0.25	0.5–4.0	~ 65	SE: Risk of fibrosis not yet clarified, regular 6 monthly checks recommended. SE* frequent
<i>Hypnotics: Side effects (SE*) in all: nightly falls in elderly people, overhang the following day, habituation effects</i>					
Clonazepam	Rivotril®	0.25	1.0–2.0	30–40	SE* more pronounced
Zolpidem	Stilnox®	5.0	10–20	1.6	SE*
Zaleplon	Sonnata®	5.0	10–20	1.0	SE*
<i>Antiepileptics:</i>					
Gabapentin	Neurontin®	300	1500–3000	5–7	I: Particularly in painful RLS/with Polyneuropathy rare SE: sleepy, dizziness, ataxia
Carbamazepin	Tegretol® Timonil®	50	100–400	10–25	SE: sleepy, dizziness, exanthema
Na-Valproat	Depakine® Orfiril®	300	1000–3000	5–20	Increase in body weight, tremor, fatigue, hair loss
<i>Opioids & Opioid-Agonists: Side effects (SE*) in all: Sleepiness, constipation, nausea, dry mouth, pruritus, dependence</i>					
Dextro-Propoxyphene	Distalgesic®	100–200	400–600	6–12	SE*
Tilidin	Valoron®	50	50–200	3–5	SE*; capsules -> allergy
Hydromorphon	Palladon Ret.®	4	8–24	12	SE*
Codein	Codein Knoll®	30	180	2.5–3	SE*
Dihydrocodein	Codicontin®	60	180	3–5	SE*, mild/rare!
Tramadol	Tramal®, Tramundin®	50	300	5–8	SE*
Oxycodone	Oxycontin®, Oxynorm®	5	20–30	3	SE*
Methadon	Ketalgin®	2.5	20	12–22	SE*
Morphin-Sulfat	Sevredol®, MST Continus®	10	30–45	4	SE*

the evening after dinner and must take their medication earlier. Those who can fall asleep easily but wake up one to two hours later can take the medication just before going to bed. In my personal experience a single dosage in the evening often, also improves symptoms during the following day. Considering the short half-life of most drugs this is probably a secondary effect explained by a more restful sleep and consecutively less fatigue during the day. Additional dosages during the evening or in the afternoon are needed in severe cases.

Side effects should be discussed with the patient in advance. Temporary side effects, particularly nausea and vomiting, are frequent but severe dyskinesias, as observed in Parkinson disease, were never reported in RLS patients after long time treatment. L-DOPA is indicated in mild and intermittent RLS forms and a controlled release form (Madopar DR® or Sinemet CR®) is preferred. The main side effect of L-DOPA is the so called augmentation, which was observed in up to 80%

of patients when using standard L-DOPA [17] and in 30% of the cases when using a controlled release form [18]. Despite a satisfying therapeutic effect in the hours after intake of the drug, symptoms exacerbate in the early morning (= rebound) or during the rest of the day. Augmentation is characterised by an earlier appearance of the symptoms in the evening (>2 hours earlier) that may also include involuntary jerks while awake (PLMW). Symptoms also appear in more proximal aspects of the limbs with a shorter delay after sitting or lying down (table 2 C). Most often augmentation is present within 6 months after treatment begins, but it can also occur at any time in the course of the treatment. Up to now this side effect has only been described in dopaminergic drugs but not in opioids or antiepileptics. The difference to a simple progression of disease is a reduction of the overall symptoms particularly during the day when reducing the daily dosage. The risk of augmentation is greater in more severe RLS and when using

a greater dosage of L-DOPA. With dopamine agonists this side effect appears less often, which is attributed to their longer half life [16, 19, 20]. Augmentation was described with pergolide (Permax[®]) treatment in 27% [20], with ropinirole (Requip[®]/Adartrel[®]) in 4% (Garcia Borreguerro, personal communication) with pramipexole (Sifrol[®]) in 8% [21] and with cabergoline (Cabaser[®]) in 10% [22]. Comparison of these figures is not possible due to the different diagnostic criteria and different durations of these studies. Dopamine agonists should therefore be used as the first line drug intervention in moderate to severe RLS, particularly in patients who report symptoms before 6.00 pm (John Hopkins Score = 3; table 2 B). Recently an increased prevalence of retroperitoneal, pulmonal and cardio-valvular fibrosis was described in Parkinson patients and in a smaller number of restless legs patients treated with pergolide or bromocriptin. Regular check-ups every 6 months are recommended if treatment with pergolide is continued but it is a matter of debate if a thorax radiography and an echocardiography should be performed only once or each time the patient is seen. A shift to another non-ergot agonist should also be considered. Up to now, it is not known how often this side effect might occur in other non-ergot dopamine agonists. However, this side effect was reported in rare cases with either drug [23, 24]. Personally, I recommend clinical controls every 6 months when treatment with pergolide or cabergoline is continued. Echocardiography or thorax Rx is indicated before application of these drugs and when symptoms of dyspnoea, dysuria or symptoms of cardiac insufficiency are reported.

Opioids can also be used since the risk of addiction is low [25], except in predisposed patients [26]. Benzodiazepines, or Antiepileptics (eg Clonazepam, Gabapentin, valproat, carbamazepin, pregabalin), are another alternative. Gabapentin has been recommended as first choice in painful RLS due to polyneuropathy.

Keeping in mind that any kind of rest brings about the worst discomfort, then during an externally imposed rest condition, such as is the case after an operation, the RLS patient should be treated with particular care and any efficient drugs, including opioids, should be applied when necessary. Such situations of prolonged rest conditions should always be planned ahead together with the patient.

Since RLS is in general a chronic progressive disorder, continuous medical care is important. Progression of RLS must be separated from augmentation (under dopaminergic treatment), and appearance of co-morbidities such as depression should not be overlooked. A specific questionnaire has been developed to recognise augmentation (table 3B). It is useful to instruct the patient to use weekly logs by documenting the international RLS severity score, the John Hopkins score, the latency until symptom onset after sitting or lying down, and the affected body regions. In the Swiss RLS patient association (Schweizerische Restless Legs Selbsthilfegruppe; www.restless-legs.ch) RLS patients can get valuable information and participate in discussions with other affected persons. Here, the affected can get information on social facilities eg, how to get a seat at the aisle in a long airplane flight.

Research and outlook

The pathophysiology of RLS is still unknown. Evidence concerning the pathogenesis derives from four areas of research: 1. localisation of a defect within the CNS; 2. pharmacological effects by dopamine agonists and antagonists; 3. the relationship with iron deficiency; and 4. genetic findings.

1. First, the negative effect of any neuroleptic drug, which passes the blood brain barrier, and the absence of such a negative effect by domperidone (Motilium), which does not cross the blood brain barrier, points to an abnormality in the CNS. The clinical presentation of PLMS or PLMW resembling Babinski sign or a triple flexion response and the appearance of PLMS in complete spinal cord transections or in anencephalic newborns favour a localisation of the defect in a subcortical or spinal segment of the CNS. Neurophysiological studies as well as neuroimaging including functional MRI are in accordance with this assumption. Evoked potentials and brainstem reflexes were usually normal [27]. In functional MRI (fMRI) the appearance of subjective RLS symptoms correlated with an increased blood flow in the thalamus and the cere-

bellum [28]. Motor RLS phenomena were associated with increased fMRI signal in the red nucleus and in the reticular formation. In contrast to simulated movement, no activation of the cortex was observed. The involuntary nature of these movements was also supported by the absence of a Bereitschaftspotential [29]. In most MRI investigations no abnormal findings were described [27]. There is one recent study showing very discrete morphological abnormalities in voxel based MRI, a sensitive method to detect minor changes in regional brain volumes [30]. Positron emission tomography (PET) studies and single photon emission tomography (SPECT) studies showed either normal [31] or minimally [32] abnormal results, suggesting a mild dopamine insufficiency in particular brain areas.

2. Pharmacological studies generally agree regarding a reduced activity of the dopamine, opiate- and or serotonin system in contrast to an overexcited adrenergic system [33].

3. Iron is used in the production of dopamine and also plays a role in dopamine receptor affinity.

Oral and intravenous iron application has a beneficial effect on RLS symptoms in many patients. In the cerebro-spinal fluid and in some regions of the brain of RLS subjects a reduced level of iron was measured.

4. Studies in large families with multiple affected members support the hypothesis of a wide genetic heterogeneity for RLS since various loci have been found in various families [34].

As a simplified hypothesis, it is suggested that a relative dopamine deficit in the central nervous system (CNS) develops due to a genetic predisposition. This induces symptoms in the early onset idiopathic form of RLS. In the symptomatic

group, additional factors are responsible for the clinical manifestation later in life with a more rapid progression [16].

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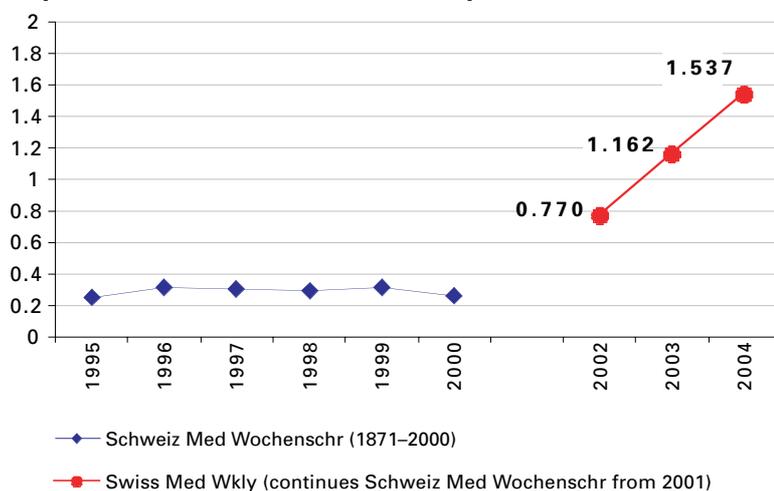
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