Sleep-Related Movement Disorders

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B. A. Stuck et al., *Practice of Sleep Medicine*, https://doi.org/10.1007/978-3-030-17412-5_8

Several sleep-related movement disorders may cause insomnia complaints and daytime sleepiness; however, patients are not always aware of these disorders. They are characterized by simple, often stereotyped movements that can interfere with the restorative function of sleep by inducing vegetative and/or EEG arousals. The restless legs syndrome (RLS) is also grouped into the sleep-related movement disorders; not because of its clinical symptoms but due to its high association with periodic limb movements in sleep. Even if RLS is one of the most important neurological diseases and reduces the quality of life of patients considerably (even early retirement has been reported) it is often not recognized and/or correctly diagnosed.

The regulation of motor function during sleep is controlled by a complex neurochemical and neurophysiological mechanism that matures with childhood development. Thus, it is plausible that many sleep-associated motor disorders occur during childhood, and again with increasing age or in the context of neurological diseases (increasing chances of dysfunctioning) (▶ Chap. 11).

In this chapter, the most relevant sleep-related movement disorders occurring in adult patients are described. Nighttime epileptic seizures that are also associated with motor disorders during sleep are not included, but they are discussed in the context of possible differential diagnoses. The characteristics of sleep-related movement disorders in childhood are summarized in ▶ Sect. 11.1.

According to the ICSD-3, the following sleep-related movement disorders are differentiated:

- Restless legs syndrome
- Periodic limb movement disorder
- Sleep-related leg cramps
- Sleep-related bruxism
- Sleep-related rhythmic movement disorders
- Sleep-related myoclonus of infancy
- Propriospinal myoclonus at sleep onset
- Sleep-related movement disorder resulting from a medical disorder
- Sleep-related movement disorder caused by a medication or substance
- Sleep-related movement disorder, unspecified

8.1 Restless Legs Syndrome

8.1.1 Definition

The restless legs syndrome (RLS) is also called Ekbom syndrome, discomfort in the legs, or focal akathisia of the legs. Currently, American patient groups would welcome the use of Willis-Ekbom disease as the official term because they perceive "restless leg syndrome" as disparaging.

RLS is characterized by mostly circadian paresthesia (discomfort) in the lower, more rarely upper, extremities, associated with the urge to move, and sleep disorders. During sleep, periodic limb movements occur in about 80% of patients (▶ Sect. 8.2).

8.1.2 Etiology and Pathophysiology

The pathophysiology of RLS is still not fully understood. Dopamine, iron, and genetic predisposition seem to play a major role.

Recently, genome-wide association studies discovered *RLS genes*. Carriers of high-risk variations in these genes have an increased risk of developing RLS. Based on the function of the identified genes, RLS might be partly explained by an early development disorder of the central nervous system.

Iron deficiency also seems to be a crucial factor, at least in all secondary forms, because an increase of the iron reservoirs in the body reduces RLS complaints in patients with low iron values even if clinically no other symptoms of iron deficiency are observed. Investigations of the cerebrospinal fluid indicate a possible iron deficiency in the central nervous system. Postmortem studies in patients with early onset of RLS showed alterations in the substantia nigra. Reduced ferritin and reduced iron transportation in these areas are very likely.

The dysfunctional iron metabolism could subsequently interfere with the *dopamine system*. This hypothesis is supported by pharmacological studies as dopamine agonists reduce RLS symptoms whereas dopamine antagonists may enhance them. The positive effect of opiates on

RLS symptoms indicate that opioid systems in the central nervous system are also involved.

In secondary RLS, *hormone inbalances* or *renal failure* seems to be involved in addition to iron deficiency. Patients undergoing dialysis show a high risk of RLS. The co-occurrence with peripheral polyneuropathy indicates that a modified peripheral neural perception possibly induces the motor and sensor symptoms of RLS.

Drug-induced RLS as a side-effect can occur in dopamine antagonists, metoclopramide, atypical neuroleptics, antidepressants, and lithium. In particular, tricyclic antidepressants may induce RLS quite often but, for example, mirtazapine, a noradrenergic and specifically serotonergic antidepressant (NaSSA), can also trigger significant RLS complaints.

8.1.3 Epidemiology

Prevalence rates of RLS depend on methodological aspects of the studies and the severity criteria. The prevalence ranges between 1% and 15% in the general population. RLS seems more prevalent in European than in Asian populations. In Europe, and in particular in Germany, about 1.7% to 3% of the population report RLS that requires treatment. RLS symptomes typically start in the middle and older ages. About 10% of individuals between 65 and 83 years of age suffer from RLS and require therapy. Children might be affected by RLS, and there might be a differential diagnosis of attention-deficit/hyperactivity syndrome (ADHS) (▶ Chap. 11). Up to 15% of the general population show symptoms and complaints of RLS on and off; however, if the severity is mild to moderate, treatment is typically not indicated. Whereas several studies did not show gender differences, others indicate a 1.5- to 2-fold higher prevalence of RLS in women. In addition, the risk of developing RLS seems to increase with the number of pregnancies.

The percentage of *idiopathic* RLS ranges between 45% and 57%, depending on the study. In cases of idiopathic or primary RLS, an early onset is typically observed. In about 40% of patients with primary RLS, the first symptoms emerge before the age of 20. In cases of idiopathic RLS, more than 50% of patients have a positive family history. Prevalence among first-degree relatives of RLS patients increases three- to fivefold.

Secondary RLS, is often associated with the following factors:

- RLS symptoms occur in 15% to 40% of dialysis patients.
- Among pregnant women, 12% to 20% show temporary RLS, with remission after delivery.
- Of patients with rheumatoid arthritis, 30% report RLS.
- Among patients with iron deficiency, 25% report RLS. Thus, it must be taken into consideration that the low to normal values of these patients may also benefit from iron substitution.
- RLS is found in 20% to 25% of the patients with polyneuropathy even though the differentiation between these two entities is not easy.
- Twenty percent of patients with uremia suffer from RLS symptoms.
- RLS can also occur in rheumatoid and neurodegenerative diseases such as ataxia, multisystem atrophies, Parkinson's disease, diseases of the spinal cord (multiple sclerosis, syringomyelia, paraplegia, etc.), after stroke, folic acid deficiency/vitamin B_{12} deficiency, chronic obstructive pulmonary disease, and cancer.

8.1.4 Clinical Presentation

Patients complain about distressing *discomfort* (tingling, crawling, itching) in the lower legs, and more rarely the thighs or arms. In some cases, discomfort is also experienced over the entire body. Frequently, additional pain in the extremities is reported. Consequently, sleep onset or going back to sleep during the night may be disturbed. The symptoms occur in the evening, at rest, in a lying position, and sometimes during longer resting periods during daytime (e.g., in front of the TV, sitting in a car as passenger, in airplanes). Relief is often achieved by moving the legs, sometimes also by physical stimulation (rubbing, cold water). In bed, patients often stretch their legs out from under the blankets or get up at night to put cold water on their legs.

Case Report

"In the late afternoon, it is difficult for me to sit quietly because my legs are tingling. Meetings at work can become a torture. Watching a movie in the

evening (TV) has not been possible for a long time. I always have to get up and walk around. Meeting friends or going to the cinema is also impossible. Later in bed, I am really tired, I want to sleep but my restless legs urge me to get up. At nighttime I walk around for hours, only walking provides relief for the uncomfortable pains and cramps in the lower legs."

In this or similar ways, RLS patients report their complaints emerging in resting phases during nighttime or sometimes during daytime. For many affected people, the disturbed sleep rhythm with the associated consequences during the daytime, e.g., tiredness is distressful both for professional and family life.

8.1.5 Diagnostic Procedures

RLS is a clinical diagnosis that can generally be made based solely on the patient's history.

Diagnostic Criteria According to the International Restless Legs Study Group (IRLSSG)

- An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
- The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
- The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
- The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
- Nonessential criteria:
  - Positive family history: more than 50% of the patients with primary RLS have at least one first-degree relative suffering from RLS.
  - Response to L-DOPA test: 90% of the patients show an improvement application of small doses of L-DOPA (100 mg). A negative test, however, does not exclude RLS.
  - Periodic movements during sleep (PLMS) occur in about 80% of the patients, often associated with arousals.
  - Disorders initiating and maintaining sleep, daytime sleepiness, and impaired performance.
  - Neurological examinations often yield negative results in idiopathic RLS.

The clinical diagnosis may be complemented by using *questionnaires* measuring RLS symptoms (see ▶ Chap. 2). Questionnaires are also used to assess RLS severity in a standardized fashion.

Practical Tip

Sleep disorders such as insomnia due to RLS have to be actively elicited.

Drug and substance history is necessary to exclude substance-induced RLS. Special attention has to be paid to dopamine antagonistic compounds, e.g., classic and atypical neuroleptics, metoclopramide, tri- and tetracyclic antidepressants, and serotonin reuptake inhibitors. Among antidepressants, mirtazapine is considered to be a drug with RLS as a quite common side effect. Based on Stiasny-Kolster [7], paroxetine, sertraline, escitalopram, venlafaxine, duloxetine, fluoxetine, and citalopram may also cause RLS symptoms.

General *physical examination including laboratory parameters* (◘ Table 8.1) and bilateral nerve conduction studies (ENG) of the anterior tibialis nerve, if necessary also of the sural nerve and the median nerve, should be included in the basic diagnostic procedures (▶ Chap. 2).

The physical examination in primary RLS is often without specific findings. However, it is useful for identifying secondary RLS, to assess possible underlying diseases.

Table 8.1 Laboratory parameters for exclusion of secondary restless legs syndrome (RLS)

Group	Single parameter
Blood analysis	Full blood count (erythrocytes indices)
Iron metabolism	Serum iron, ferritin, transferrin
Vitamins	B_{12}, folic acid
Kidney values	Creatinine, urea
Glucose metabolism	Serum glucose, HbA1c if needed
Thyroid parameters	fT3, fT4, TSH
Parathyroid parameter	Parathormone (facultative)

The response to L-*DOPA* (L-DOPA test) is sometimes applied for diagnostic confirmation of RLS, in particular when a dopaminergic therapy had not yet been performed or the initial therapeutic effect of the dopaminergic therapy cannot be clearly evaluated. A single dose of 100 mg L-DOPA should be applied after the onset of RLS complaints; the response is then measured via severity scales; an improvement of 50% in the severity index is defined as responder. This test can confirm the diagnosis of RLS in about 90% of untreated patients. Not responding to the L-Dopa test (i.e., improvement of less than 50% with L-DOPA), however, does not exclude a possible RLS.

8.1.6 Sleep Diagnostics

Sleep diagnostic procedures should include a *sleep history* to rule out other disorders that may be associated with insomnia complaints. Sleep-related history taking also helps to assess impaired performance during daytime and the risk of daytime sleepiness in dangerous situations like driving a car or supervising heavy machinery.

A *sleep diary* may provide data about RLS severity and frequency. For assessing severity as well as for therapy evaluation, ambulatory measurement of periodic leg and arm movements during sleep in the home situation may be beneficial, for example, using *actigraphy*. In diagnostically unclear cases, an *immobilization test* (systematic assessment of the complaints during immobilization of the legs) and *polysomnography* (*PSG*) may provide further evidence regarding the presence of PLMS (periodic leg movements in sleep) (see ▶ Chap. 2).

Especially in the following cases of RLS, PSG is indicated (▶ Sect. 2.6.4):

- Cases with unclear diagnosis
- Children and adolescents with RLS
- Therapy-refractory RLS
- Persisting daytime sleepiness or sleep disorders under dopaminergic therapy (or other therapeutic options)
- Complex RLS needing pharmaceutical strategies including opiates, anticonvulsants, or other treatment approaches

PSG provides data about the severity of the sleep complaints and can exclude other sleep disorders that might be responsible for hypersomnia or insomnia symptoms. Typically, a fragmentary sleep profile with slow wave and REM sleep suppression and increased light sleep stages (N1) is a consequence of arousals associated with periodic arm and/or leg movements during sleep. Sleep latency is generally increased because of the urge to move the extremities while trying to fall asleep (▶ Sect. 2.13).

Periodic arm and/or leg movements are not essential criteria of RLS; about 20% of the RLS patients do not show these symptoms. The assessing of period limb movements associated with arousals is only possible via polysomnography. A maintenance of wakefulness test (MWT) or other procedures to assess the propensity to fall asleep in monotonous situations and impaired performance during daytime might be required (▶ Chap. 2).

Practical Tip

In the context of high-risk patients, medical reports, or severe RLS, neuropsychological tests are necessary to assess sleepiness- and fatigue-related impairments of the patient's daytime performance.

The IRLSSG (▶ Sect. 8.1.5) and the AASM formulated diagnostic criteria for RLS. The IRLSSG criteria are highly significant for the diagnostic process;

the AASM criteria represent the international consensus.

Diagnostic Criteria of RLS (Subjects Older Than 12 Years) Based on ICSD-3

- The patient reports an urge to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs.
- This urge begins or worsens during periods of rest or inactivity, such as lying down or sitting.
- The urge to move is partially or completely relieved by movement such as walking or stretching, at least so long as the activity continues.
- The urge to move occurs or worsens exclusively or predominantly in the evening or at night.
- The condition cannot be explained by other sleep disorders, medical condition (leg cramps, myalgia, venous stasis, arthritis, etc.), or a behavioral disorder (e.g., agitated depression), drug intake, or substance abuse.
- The symptoms of RLS cause concern, distress, sleep disturbance, or impairment in the mental, physical, social, occupational, educational, and behavioral aspects of life or in important areas of functioning.

8.1.7 Differential Diagnoses

One of the most important differential diagnoses of RLS is *peripheral polyneuropathy*, with symptoms like painful legs and moving toes, and *venous malperfusion*. Also *irritable nerve roots* and *spinal syndromes* often are accompanied by complaints that are similar to RLS symptoms. On occasion, RLS is misdiagnosed as a *psychosomatic disorder with restlessness* or an *agitated depression*.

In chronic pain syndromes affecting the legs, careful differential diagnostics have to be carried out. Small-fiber neuropathy, (sleep-related) muscle cramps, peripheral vascular disease, akathisia due to neuroleptics, and myelopathy are possible differential diagnoses. On the other hand, RLS might be the underlying cause of insomnia complaints.

Practical Tip

All differential diagnoses did not show the circadian rhythm of symptom severity that is typical for RLS.

8.1.8 Therapy

Pharmaceutical therapy is symptomatic. The treatment of RLS is focused on the individual patient and is often characterized by complications if long-term application is necessary. Lack of effectiveness, tolerance, and side effects can be a challenge for the sleep specialist. In severe cases, combination therapies with different compounds might be necessary, thus, requiring knowledge about their pharmacology and interactions with each other. Finally, the circadian rhythm of the symptoms and the associated sleep disorders also require from therapists to suggest a drug schedule based on the individual rhythms of the patients.

8.1.8.1 General Therapeutic Principles

The individual treatment stategy is adapted to the complaints of the patient. The burden of RLS is due to reduced quality of life and massive daytime sleepiness and fatigue as well as the disrupted sleep. The primary therapeutic target is the improvement of sleep. For the majority of affected subjects with severe symptoms a permanent drug treatment has to be carried out.

In secondary RLS, the underlying disease has to be treated - if possible. Measuring ferritin levels to assess the iron status is one of the diagnostic procedures that should be part of the routine. Iron substitution is recommended in cases with regular but low ferritin values. According to clinical experience, at least 50 µg/l should be reached.

The treatment of RLS during *pregnancy*, however, may be difficult and should be limited to conservative measures without resorting to pharmaceuticals.

In cases where monotherapy is not sufficient even after long-term application, the physician may prescribe combination therapies (e.g., dopamine agonist plus L-DOPA).

The following compounds are recommended for the treatment of RLS. L-DOPA and dopamine agonists are considered as first-line drugs.

8.1.8.2 L-DOPA

In Germany, L-DOPA is approved in combination with benserazide for treatment of RLS, and clinical trials have demonstrated its effectiveness in doses up to 300 mg per day.

For the treatment of sleep disorders caused by RLS, a combination with immediate release (effect duration, 3–5 h) and retarded (maximum plasma level after 3 h) levodopa may be beneficial. Tolerance developments requiring dosage increase and an "end-of-dose" rebound are quite common (Table 8.2).

Table 8.2 Therapy of RLS with L-DOPA and dopamine agonists

Substance	Half-life in hours	Dosage in mg
Levodopa with benserazide	3–5	50–300
Levodopa with benserazide (retard)	Maximum plasma level after 3 h	50–400
Pramipexole	8–12	0.088–0.54
Ropinirole	5–7	0.25–2
Rotigotine	2–3	1–3 per 24 h

8

Practical Tip

It is recommended to adapt the time of intake to the occurrence of the complaints in the individual patient and to establish an exact intake scheme together with the patient (based on a sleep protocol). L-DOPA is effective in mild or episodic RLS. In contrast to dopamine agonists, the dosage has not to be slowly increased, so that it can be applied in situations with severe complaints, such as traveling by bus or airplane with lack of movement opportunities. It can also be used in combination with dopamine agonists as an add-on in cases of severe complaints.

Augmentation under L-DOPA medication is a frequently observed phenomenon (it can also occur in dopamine agonists) and, according to clinical studies, can occur in up to 70% of the patients.

Augmentation is defined as:

- An earlier onset of the symptoms within the 24-h cycle, e.g., midday or morning
- A more rapid onset of the complaints when the patients are at rest
- Complaints in other body parts that have not been affected prior to therapy

A dose-dependent risk for augmentation has been described for levodopa/benserazide. Dosages above 200 g per 24 h may lead to augmentation. In severe cases, switching to another drug is recomomended. If augmentation under L-DOPA occurs, the treatment should be switched to dopamine agonists, if possible with low doses.

Practical Tip

Augmentation is considered as the most significant complication of dopaminergic therapy. It has been described most frequently for L-DOPA but also for dopamine agonists.

Increase of the symptom severity is another sign of augmentation. In addition, decreasing effectiveness of the current drug dosage (tolerance) is also a problem.

Diagnostic Criteria of Augmentation According to IRLSSG 2007

(a) Basic features (all of which need to be met)
- The increase in symptom severity was experienced on five out of seven days during the previous week
- The increase in symptom severity is not accounted for by other factors such as a change in medical status, lifestyle, or the natural progression of the disorder
- It is assumed that there has been a prior positive response to treatment

(b) Persisting (although not immediate) paradoxical response to treatment: RLS symptom severity increases sometime after a dose increase, and improves sometime after a dose decrease
(c) Earlier onset of the symptoms by at least 4 h or by 2 to 4 h, whereby in the latter (2 to 4 h) the following criteria also have to be met:
- Shorter occurrence latency while at rest
- Extension of the symptoms to other parts of the body
- Higher intensity of the symptoms
- Duration of the relief is reduced because of the therapy

Augmentation is confirmed when the following criteria combinations are met: a + b, a + c, or a + b + c.

8.1.8.3 Dopamine Agonists

Dopamine agonists are classified into ergoline and nonergoline dopamine agonists (Table 8.2). Clinical trials have demonstrated the effectiveness of ropinirole, pramipexole (non-ergoline dopamine agonists), and rotigotine in large patient populations. Generally, daily doses for RLS treatment are smaller than for the treatment of Parkinson's disease. Thus, it is always recommended to test the effectiveness of the smallest dose.

The recommended initial dose of *pramipexole* (half-life, 8–12 h) is 1/2 tablet of 0.18 mg once per day. If the effect is not sufficient, the dose can be increased to 1 tablet of 0.18 mg and every 4th day additional increases of 0.09 mg up to a maximum dose of 0.54 mg per day (Table 8.2). If needed, combination with L-DOPA is possible.

The recommended initial dose of *ropinirole* (half-life, 5–7 h) is 0.25 mg. According to the recommendations from clinical studies, the dose is increased to 0.5 mg on day 3, as of the 2nd week to 1 mg, as of the 3rd week to 1.5 mg, and after the 4th week to 2 mg. To achieve an optimal effect, further dose increase might be necessary (e.g., week 5, 2.5 mg; week 6, 3 mg; week 7, 4 mg). Dosages beyond 4 mg have not been evaluated in the clinical studies for RLS (Table 8.2). If needed, combination therapy with L-DOPA is possible.

The positive effect of *rotigotine* for RLS has been demonstrated by several studies. The half-life of rotigotine is 2 to 3 h. The transdermal application seems to have certain advantages. From the continuous transdermal release, rotigotine patches with doses of 1, 2, or 3 mg for 24 h maintain a stable level that is usually achieved after 2 days. The constant level may reduce the augmentation rate. Because of skin irritations, the patch has to be placed each day on another body location for a cycle of 2 weeks. The recommended initial dose is 1 mg; the dose may be increased by 1 mg every week. If needed, combined therapy with L-DOPA is possible.

The ergoline dopamine agonists such as *cabergoline* and *pergolide* that are also used in treating Parkinson's disease are highly effective for RLS; however, the substances have significant side effects. Among others, there are reports on fibrous cardiac valve pathologies and imperative sleep attacks after higher doses. Hence, they are no longer recommended for the treatment of RLS.

Practical Tip

Because of the side effect of nausea observed at therapy onset with dopamine agonists, the additional intake of a noncentrally effective dopamine antagonist is recommended, if needed, such as domperidone.

8.1.8.4 Opioids

Being the most potent medication, opioids such as *tilidine*, *oxycodone*, or *codeine* are available to treat severe and very severe, especially painful, RLS cases or nonresponders to dopaminergic treatment.

Controlled observational studies and case reports have been published for oxycodone. The approval of oxycodone/naloxone was achieved in Europe as second-line therapy for patients with severe to very severe idiopathic RLS after not responding to dopaminergic therapy. The initial dose amounts is 5/2.5 mg oxycodone hydrochloride/naloxone every 12 h. If the effect is not sufficient, a weekly dose increase may be recommended. The limit is 60/30 mg oxycodone hydrochloride/naloxone per day. Additional therapy with L-DOPA or dopamine agonists can be applied.

The dopaminergic component of opiates influences the extrapyramidal motor mechanisms via an activation of central μ-receptors. Increasing tolerance and a ceiling effect (no further increase in the therapeutical effect after reaching a certain dose) represent a problem so that the application of these substances should be delayed as long as possible. Therapy with apomorphine or methadone might be required in individual cases to achieve the therapeutic objective of maintaining substantial quality of life in the patients with very severe RLS.

Practical Tip

Because RLS may also occur as a withdrawal effect of opiate addiction, opiates have to be reduced very slowly.

8.1.8.5 Other Substances and Treatment Modalities of RLS

Among the anticonvulsant drugs, pregabalin and gabapentinenacarbil (a precursor of gabapentin in retarded form) are the drugs that were best investigated in controlled trials. In April 2011, gabapentin enacarbil was FDA approved in the US with the brand name Horizant and is discussed as the first-line therapy of RLS if the classic side effects such as daytime sleepiness, nasopharyngitis, suicidal thoughts, and weight gain are minimal. This substance is not available in Germany. The sedating and anxiolytic effect of pregabalin may have an additional therapeutic advantage if comorbid insomnia disorders are present. Neither pregabalin nor gabapentin is FDA or EMEA approved for the treatment of RLS. Other medications like, clonazepam, carbamazepine, clonidine, and valproic acid are off-label.

An oral iron substitution may be indicated for patients whose ferritin level is below 75 μg/l. Several studies in patients with severe RLS have shown that intravenous application of iron improved RLS complaints in 40% to 60% of cases, sometimes complete remission lasting for several months occurred.

Two studies confirmed a positive effect of high-dose magnesium (12.5 mmol before going to sleep) in mild RLS.

Practical Tip

In cases of mild or intermittent RLS, treatment with high-dose magnesium may be beneficial.

Nonpharmaceutical strategies such as sleep hygiene, sports (gymnastics, stretching, yoga), massages, or showers with cold or hot water may alleviate RLS symptoms in patients.

Contraindicated or ineffective are treatment attempts with hypnotics, antidepressants, neuroleptics, and beta blockers, as well as psychotherapeutic measures. Passive relaxation techniques such as autogenic training, progressive muscle relaxation, or meditation can enhance the symptoms and, thus, have negative effects.

8.2 Periodic Leg Movement Disorders During Sleep

8.2.1 Definition

The periodic limb movement disorders (PLMD) during sleep are also known by these terms:

- Periodic movement disorder of sleep (PMDS)
- Periodic limb movements in sleep (PLM)
- Leg convulsions
- Nocturnal myoclonus syndrome
- Sleep myoclonus syndrome

In particular, the term myoclonus should be avoided because in epileptology it is used for completely different symptoms.

PLMD is characterized by periodic and repeated stereotyped movements of the limbs during sleep. PLMD may cause insomnia symptoms and/or result in nonrestorative sleep and subsequently daytime sleepiness.

8.2.2 Etiology and Pathophysiology

The exact etiology of PLMD is unknown. In addition to genetic factors, a dysfunctional dopaminergic or opioidergic system with suppression of the supraspinal inhibitory pathways or rhythmic fluctuation of reticular activity might be

responsible. Furthermore, a disturbed iron metabolism is considered as a potential factor in PLMD because low ferritin values seem to favor the development of PLMD or enhance frequency of PLM. The centrally induced repetitive limb movements can be accompanied by arousals and sleep fragmentation.

These etiological considerations are supported as disorders with dysfunctional dopaminergic systems such as RLS, narcolepsy, and REM behavioral disorder often also show PLMD. The increasing prevalence of PLMD in the elderly might be explained by reduced dopamine levels or the physiological decrease of dopamine receptors.

Periodic movement disorders in sleep are understood as separate entity. As PLMD are frequently associated with RLS, REM behavior disorder, obstructive sleep apnea, and narcolepsy, the additional diagnosis of PLMD is not necessary. PLMDs can also occur in patients with the following diseases:

- Kidney failure
- Congestive heart failure
- Arterial hypertension
- Polyneuropathy
- Multiple sclerosis
- Multisystem atrophy
- Spinal lesions
- Psychiatric disorders such as posttraumatic stress disorder, depression, and sleep-related eating disorder
- Chronic insomnia
- Attention deficit/hyperactivity syndrome
- Parkinson's disease
- Withdrawal of benzodiazepine
- Therapy with anticholinergic substances, for example, tricyclic antidepressants and serotonin reuptake inhibitors

8.2.3 Epidemiology

Periodic limb movements in sleep are quite prevalent and are a nonspecific symptoms related to many sleep disorders and diseases. However, often the PLMs are not directly affect sleep continuity. Sometimes the bed partner experiences sleep problems due to the periodic limb movements of the patient. Movement disorders can occur in children as well as in adults. The prevalence of PLMD with an index higher than 15 movements per hour is about 8% in 18- to 65-year-old individuals and more than 45% in persons older than 65 years. Gender differences in prevalence rates have not been studied.

Regarding the epidemiology of PLMD, the following aspects have to be taken into consideration:

- In about 80% of RLS cases, periodic limb movements during sleep co-occur.
- In 1% to 15% of patients with insomnia, PLMD occurred, varying between studies.
- In REM behavior disorder, PLMD occurs in 70% of the patients and in 45% to 60% of patients with narcolepsy-.

A high incidence of PLMD is described in patients with mental disorders (mood disorders, anxiety disorders, etc.) and neurological diseases (multisystem atrophy, spinal cord lesions) (see ▶ Chap. 2).

The present data regarding the epidemiology of PLMD, however, are limited because the diagnostic criteria vary from study to study and researchers did not always define strict inclusion and exclusion criteria.

8.2.4 Clinical Presentation

In PLMD, the patients complain about nonrestorative sleep (often associated with hypersomnia symptoms) but also quite often PLMD is accompanied by insomnia symptoms. Reduced feelings of being refreshed by sleep, daytime sleepiness, and monotony intolerance as well as depressive symptoms, memory problems and reduced concentration spans may be a consequence of the fragmented sleep.

Sleep continuity is negatively affected by the periodic movements of the legs, sometimes arms are moving too mostly after flexion of the large joints and stretching the big toes. Subsequently, associated arousals impair sleep continuity. The tonic contractions can also occur in wakefulness in many patients, but often they are go unnoticed.

Periodic limb movements are clinically relevant and should be treated if they cause clinically significant insomnia or hypersomnia

symptomatology that cannot be explained by other sleep disorders or somatic diseases.

Practical Tip

Generally, patients are not consciously aware of the periodic movements of the extremities. More often, the bed partners observe the restless sleep in the patient with jerky movements of the extremities.

The limb movements are frequently accompanied by fast frequencies in the EEG due to a central nervous activation that triggers PLM, among other events, and not as a consequence of the PLM. The movements may also be associated with autonomous arousals like brief increases in heart rate and blood pressure.

8.2.5 Examination Procedures

The examination includes individual *history taking* as well as *interviewing with the bedpartner* because the patient is often only aware of the daytime symptoms.

Eliciting medication and substance consumption is crucial to rule out medication-induced types of PLMD. The following procedures should be part of diagnostic standards:

- Vitamin B12 levels
- Iron, ferritin levels
- Folic acid level
- Diagnostics of polyneuropathy
- Diabetes mellitus diagnostics

Other (neurological) diseases possibly underlying symptomatic forms of PLMD, but also can cause insomnia disorders, have to carefully evaluated.

Practical Tip

Insomnia complaints are often misattributed to periodic limb movements. In psychopathology of insomnia, periodic limb movements might be considered associated and not does not require treatment.

8.2.6 Sleep Diagnostics

Sleep diagnostics include *sleep anamnesis*, *sleepiness-related anamnesis*, and a *sleep diary*. *Actigraphy* performed in the home setting may be helpful to complete assessment of the severity (► Chap. 2).

PLM are determined according to the current criteria of the AASM (► Chap. 2).

Severe forms of PLMD show as many as 1500 periodic limb movements per sleep period. Depending on the number of PLMs with arousals (index of periodic limb movements in sleep = number of limb movements per hour of sleep; see ► Chap. 2), sleep fragmentation, reduced slow wave sleep and REM sleep can occur.

Practical Tip

To avoid false-negative diagnoses, it has to be kept in mind that PLM indices vary significantly from night to night. Even in severe PLMD, nights with low PLM indices might occur.

In high-risk patients or severe cases, neuropsychological tests are required to assess the sleepiness-related impairments of performance such as MWT, multiple sleep latency test (MSLT), or pupillography measuring the propensity to fall asleep during the day (► Chap. 2).

Diagnostic Criteria of PLMD based on ICSD-3

1. Polysomnography shows PLM as it was defined according to the current version of the AASM manual on the assessment of sleep and associated phenomena (► Chap. 2).
2. The PLM index exceeds 5 per hour in children and 15 per hour in adults. Note: The movement index is interpreted in the context of the patient's sleep-related complaints and not in a normative way. In adults, normative values might be even higher in studies that did not exclude PLMs related to respiratory events or other causes.

3. The PLMs cause clinically significant sleep disturbance and/or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning. Note: An increased PLM index without clinical symptoms can be documented as polysomnographic finding; however, it does not meet the criteria for diagnosing PLMD.
4. PLMs cannot be explained by other sleep disorders, medical or neurological diseases, mental disorders, or medication or substance abuse. It is recommended not to diagnose PLMD in patients with untreated sleep-related breathing disorders, RLS, narcolepsy, and REM sleep behavior disorder.

8.2.7 Differential Diagnoses

In *sleep-related breathing disorders*, PLM may occur in association with apnea-related arousals. Diagnostic assessment of PLM should be carried out after successful treatment of the sleep-related breathing disorder.

PLM may be observed in the context of nocturnal *cerebral seizures* and of *myoclonic epilepsy*. In these cases, additional epilepsy diagnostics and PSG with more EEG electrodes may be necessary.

If PLM is suspected in the context of neurodegenerative diseases such as Alzheimer's disease, nerve root irritations, or spinal syndromes, further neurological examination is indicated. Benign phenomena like hypnagogic foot tapping and the alternating leg muscle activation (ALMA) can be differentiated by polysomnography.

8.2.8 Therapy

Treatment is only required if PLM *indices* are elevated and associated with clinically relevant to *insomnia* or *hypersomnia* symptomatology.

Other etiological factors explaining the clinical symptoms have to be excluded; if needed, a therapy attempt with L-DOPA may help to identify PLMD. There are no randomized trials on the effectiveness of medication for treating PLMD that does not occur within RLS syndromes. If treatment is required, the therapeutic approach is similar to treating patients with RLS (► Sect. 8.1).

In patients with RLS, L-DOPA, dopamine agonists, and second-line medications have a positive effect on RLS symptoms but also on the frequency of periodic limb movements in sleep. If PLMD is symptomatic, causal therapies, e.g., iron substitution, have to be performed first. Adherence to the principles of sleep hygiene may be useful; however, pharmacological strategies are the major focus. The treatment effects can only be evaluated by polysomnography assessing PLM indices.

8.3 Sleep-Related Leg Cramps

8.3.1 Definition

These terms are used synonymously:
- Leg cramps
- Nocturnal leg cramps
- "Charley horse"

The etiology of the idiopathic form has not yet been clarified. In contrast to dystonia, these cramps are not characterized by simultaneous contractions of agonists and antagonists.

8.3.2 Etiology

Most sleep-related muscle cramps seem to be idiopathic. As a transitory phenomenon, nocturnal leg cramps can occur in healthy individuals after intense physical activity whereby microtraumas of the muscles and electrolyte disbalances may be involved. Symptomatic muscle cramps can also occur in magnesium or calcium deficiency, in pregnancy, and in neuromuscular and metabolic diseases. Genetic factors have not been identified yet.

8.3.3 Epidemiology

About 10% to 16% of the population suffers from clinically relevant nocturnal leg cramps, with increased prevalences in the elderly. Thirty-three percent of persons older than 60 years and 50% of persons older than 80 years report nocturnal leg cramps at least once every 2 months. In 6% of individuals older than 60 years, these leg cramps occur at night. The lifetime prevalence for leg cramps is probably near 100%.

8.3.4 Clinical Presentation

The cramps occur spontaneously, mostly during sleep, but sometimes during wakefulness, without any precursor or after short mild pain and are associated with painful hardening of the muscles. In most cases, the calf and foot muscles, rarely the thigh muscles or other muscle groups, are affected. Those cramps may last for a few seconds up to several minutes. They subside spontaneously or after stretching, massaging, movements, or application of heat. Sporadic events may occur, but also series of cramps have been reported. The disorder is more common in older adults. If cramps recur, the frequency might fluctuate over many years. The disstress can be high, but objectifiable lesions do not occur. As a consequence of these mostly painful events, problems of initiating and maintaining sleep can occur.

8.3.5 Diagnostics

During *PSG*, the events usually emerge spontaneously during sleep or awake phases. *Electromyography (EMG)* of the affected muscles, shows a sudden, persisting activity.

Diagnostic Criteria of Nocturnal Muscle Cramps According to ICSD-3

- A painful sensation in the leg or foot with sudden, involuntary muscle hardness or tightness, indicating strong muscle contraction
- Emerging in bed, in either sleep or wakefulness
- Pain relief is achieved by forcefully stretching the affected muscles

8.3.6 Therapy

Intensive and regular stretching, massage, and application of heat may relieve the acute symptoms.

For longer-term prophylaxis or therapy, causal measures (e.g., balancing of electrolytes) should be initiated if possible.

Symptomatically, magnesium, quinine sulfate, verapamil, and theophylline may be applied in off-label use. Contraindications of the medications have to be carefully evaluated, rare occurring but severe side effects have to be evaluated against the expected benefit.

8.4 Bruxism

8.4.1 Definition

Synonymous terms:

- Nocturnal bruxism
- Nocturnal tooth grinding
- Tooth clenching
- Sleep-related bruxism

Bruxism is an involuntary grinding or clenching of the teeth, mostly during sleep but can occur also in wakefulness. This activity causes abrasion of the teeth, and even lesions of the maxillary joints are possible.

8.4.2 Etiology

The etiology of the disorder may include these factors:

- Psychological factors (increased levels of tension, anxiety disorders)
- Central nervous factors (congenital or acquired brain lesions)
- Anatomical factors (malocclusion, malformation)

These factors may be associated with bruxism although pathophysiological mechanisms have not been identified.

Personality traits associated with high achievement need and tension might be associated with bruxism. Bruxism runs in families but genetic associations have not yet been identified.

8.4.3 Epidemiology

Typically, the disorder starts in childhood and prevalence decreases with age. Rhythmic masticatory activity is seen also in almost every healthy sleeper. About 15% to 20% of children show transitory bruxism, the lifetime prevalence is about 50%. In adults, women report bruxism more often than men. The prevalence of clinically relevant bruxism is less than 5%.

8.4.4 Clinical Presentation

Activation of the masticatory muscles during sleep can be accompanied by disturbing grinding sounds that are unpleasant for others and also leads to an intensive abrasion of the teeth's enamels, associated with pain around the teeth and within the masticatory muscles. In severe cases, sleep may be fragmented due to arousals and insomnia complaints are reported. Most often, however, a dentist or a neurologist (because of headaches) is consulted. The contractions of the chewing muscles may be tonic or phasic, the so-called rhythmic masticatory muscle activity (RMMA). The typical event is of a stereotyped nature, starting with autonomous and EEG arousals that are followed by the contraction of the masticatory muscles. Sometimes swallowing can occur at the end of an episode.

8.4.5 Diagnostics

Sleep anamnesis combined with *dental examination* is essential and sufficient in most cases. *PSG* is only required to rule out other disorders. An increased *EMG activity* of the masticatory muscles associated with arousals that occur most often in light sleep are indicative. Masticatory muscle activity is sometimes associated with REM sleep in older people and this might be a symptom of a beginning REM sleep behavior disorder. Movements of the body or the extremities can occur in 25% of arousal reactions associated with bruxism. The EMG activity of the maxillary muscles (masseter and temporal muscles) may be increased phasically in intervals between 0.25 and 2.0 s, tonically of more than 2.0 s, or with a mixed rhythm.

Diagnostic Criteria of Bruxism According to ICSD-3

- Regularly occurring sounds of tooth grinding or tooth clenching during sleep
- At least one of the following clinical symptoms occurs:
  - Abnormal tooth wear associated with tooth grinding during sleep
  - Transitory morning jaw muscle pain or fatigue, and/or temporal headaches; and/or jaw locking upon awakening, consistent with reports of nocturnal tooth grinding.

8.4.6 Therapy

In pediatric patients, it is possible to "wait and see". After maxillary deformities have been diagnostically ruled out spontaneous remissions are frequent. In cases of (threatening) dental damage, occlusal splints should be applied. If the patient is very tense, relaxation techniques, hypnotherapy, biofeedback, and psychotherapy may be helpful. For acute pain relief, physiotherapy and massages are recommended.

Medications such as muscle relaxants are only indicated in very severe cases (short-term benzodiazepines, antidepressants). Before initiating pharmaceutical therapy strategies, a thorough risk to benefit evaluation should be done.

8.5 Sleep-Related Rhythmic Movement Disorder

8.5.1 Definition

Synonymous terms:

- Jactatio capitis nocturna
- Jactatio corporis nocturna
- Rhythmie du sommeil
- Head banging
- Body rocking
- Head rolling
- Body rolling

Sleep-related rhythmic movements are defined as repetitive, stereotyped, and rhythmic motor movements of large muscle groups, occurring mainly

during sleep onset and or during sleep. The diagnosis requires that the behavior have clinically significant consequences.

8.5.2 Epidemiology

In infants, stereotyped movements can occur as normal transient phenomenon related to self-stimulation. About 50% to 70% of infants show temporarily such a behavior. In persisting symptomatology or later beginning, sleep-related movement disorders are likely to be associated with psychiatric/neuropsychiatric disorders. The gender ratio of boys to girls varies from 2:1 to 4:1.

8.5.3 Clinical Presentation

The clinical picture is characterized by stereotyped rhythmic head or body movements during sleep onset or light sleep, with these possible variations:

- Head banging from back to forth (anterior–posterior)
- Head rolling in lateral direction
- Body rocking in elbow-knee position
- Body rolling in prone position

Occasionally, the head banging is accompanied by monotonous singing or humming. In some cases, injuries have been reported - caused by hitting the head against a hard surface (hematoma, intracerebral, and retinal bleedings). Very often the rhythmic movements are associated with sleep onset or light sleep. The movements usually begin in infancy; in healthy children, the symptoms disappear spontaneously. In older children, this simple form of self-stimulation, however, has to be considered as a symptom of a more severe mental disorder.

8.5.4 Diagnostics

The diagnostics consist of *history taking* by interviewing parents or bed partners (in adult patients) and assessing developmental aspects. A *pediatric-neurological examination* including EEG to exclude cerebral seizures is recommended. If cerebral lesions are suspected, *developmental diagnostics* including *MRI* or cranial computer tomography CCT are required.

Sleep diagnostics comprise *sleep history* and keeping a *sleep diary* in order to assess the frequency and the severity of the episodes. *PSG with video monitoring* should be performed. Because the symptoms occur before falling sleep, the sleep profile is tpyically in the normal range compared to age-matched healthy sleepers. The rhythmic movements occur when falling asleep, less frequently in light sleep, and very rarely in N3 or REM sleep. Regarding differential diagnosis, cerebral seizures have to be ruled out by carefully analyzing the EEG of PSG.

Diagnostic Criteria of Sleep-Related Rhythmic Movement Disorders Based on ICSD-3

- The patient shows repetitive, stereotyped, and rhythmic motor behaviors involving large muscle groups.
- The movements are predominantly sleep related. They occur near naps or near bedtime, or when the individual appears drowsy or asleep.
- The behavior leads to significant complaints as manifest by at least one of the following aspects:
  - Interference with normal sleep
  - Significant impairment in daytime function
  - Self-inflicted bodily injury or likelihood of injury if preventive measures are not applied
- The rhythmic movement disorder cannot be better explained by another movement disorder or epilepsy.

Note: The diagnosis is only made when the behavior has clinically significant consequences.

8.5.5 Therapy

If infants are affected, it is important to reassure the parents to wait for spontaneous remission. In cases of symptomatic types, causal therapy, in exceptional cases with adjuvant neuroleptics or benzodiazepines, is indicated after elaborate diagnostics. In older children, psychotherapy and relaxation procedures are a promising option.

8.6 Questions

1. Please describe pharmaceutical options of RLS therapy.
2. What are the indications for RLS treatment?
3. Which diseases are likely to be associated with periodic limb movements during sleep?
4. When are periodic limb movement disorders treated?
5. Which approaches are beneficial for treating bruxism?

Further Reading

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