

Sleep-related movement disorders

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Abstract Several movement disorders may occur during nocturnal rest disrupting sleep. A part of these complaints is characterized by relatively simple, non-purposeful and usually stereotyped movements. The last version of the International Classification of Sleep Disorders includes these clinical conditions (i.e. restless legs syndrome, periodic limb movement disorder, sleep-related leg cramps, sleep-related bruxism and sleep-related rhythmic movement disorder) under the category entitled sleep-related movement disorders. Moreover, apparently physiological movements (e.g. alternating leg muscle activation and excessive hypnic fragmentary myoclonus) can show a high frequency and severity impairing sleep quality. Clinical and, in specific cases, neurophysiological assessments are required to detect the presence of nocturnal movement complaints. Patients reporting poor sleep due to these abnormal movements should undergo non-pharmacological or pharmacological treatments.

Keywords Restless legs syndrome · Periodic limb movement disorder · Sleep-related leg cramps · Sleep-related bruxism · Sleep-related rhythmic movement disorder · Hypnagogic foot tremor

Introduction

The last version of the International Classification of Sleep Disorders (ICSD-2) includes a category entitled sleep-related movement disorders (SRMD). Restless Legs Syndrome (RLS), periodic limb movement disorder (PLMD), sleep-related leg cramps, sleep-related bruxism and sleep-related rhythmic movement disorder (RMD) are listed in the SRMD category [1].

These clinical conditions are characterized by relatively simple and usually stereotyped movements that are able to impair sleep and to cause insomnia, poor sleep quality, fatigue and excessive daytime sleepiness. Although patients with RLS perform complex and goal-directed movements, they are considered as affected by SRMD. In fact, a large part of RLS patients (up to 90%) shows simple and stereotyped movements of the lower limb, known as Periodic Limb Movements during Sleep (PLMS) (see below).

Since parasomnias, such as REM sleep behavior disorders and sleepwalking, are characterized by purposeful and goal-directed complex behaviors during the night, these complaints are not included in the SRMD category.

Physiological movements, such as hypnic jerks, may occur during sleep. However, in some patients the frequency and the intensity of these movements may be increased causing sleep disruption. The ICSD-2 includes these movements in another category named isolated symptoms, apparently normal variants and unresolved issues [1].

In the following sections of this review, the individual nosological categories of SRMD will be discussed.

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Restless legs syndrome

Diagnosis

RLS is a sleep disturbance characterized by four pathognomonic clinical features: (a) an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (b) the urge to move or unpleasant sensations begin or worsen at rest; (c) the urge to move or unpleasant sensations are partially or totally relieved by movement; (d) the urge to move or unpleasant sensations occur in the evening/night or are worse in the evening/night than during the day. These symptoms represent the four essential criteria to diagnose the presence of RLS [2]. In addition, the International Restless Legs Syndrome Study Group (IRLSSG) identified some supportive clinical features (e.g. response to dopaminergic therapy and presence of PLMS) and associated features (e.g. sleep disturbances due to RLS) useful for diagnosing RLS in uncertain clinical cases [2].

Although diagnosis of RLS is based on clinical features, some instrumental examinations can confirm the suspicion in doubtful cases, help the physician in differential diagnosis, and assess efficacy of drug treatment. In particular, Polysomnography (PSG) and Actigraphy (ACT) are commonly performed in clinical practice. Both tools may detect the presence of PLMS (see below for PLMS scoring criteria) in RLS patients. The gold standard for PLMS diagnosis is PSG with surface Electromyography (EMG) of the tibialis anterior muscles. Due to the high costs of PSG, ACT is increasingly used to detect PLMS in RLS patients. The first studies showed that ACT underestimated PLMS with respect to PSG [3, 4]. Recently, new actigraphic systems with a high sensibility and specificity in detecting PLMS, as defined by PSG with EMG, have been developed [5, 6].

Differential diagnosis

Several clinical conditions, known as RLS-mimics, are characterized by symptoms similar to those of RLS.

The most common RLS-mimics complaints are nocturnal leg cramps, peripheral neuropathy, positional discomfort, vascular or neurogenic claudication, and neuroleptic-induced akathisia.

In nocturnal leg cramps the painful sensations appear during sleep and involve specific muscles, generally the calf ones. Motor restlessness and Periodic Limb Movements (PLM) are not present. Differently from RLS patients, subjects with leg cramps present a palpable tightening of leg muscles. Leg cramps do not respond to dopaminergic agents and are alleviated by stretching and not by movement.

Patients with peripheral neuropathy frequently report painful sensations, without restlessness, in the upper and

lower extremities. As RLS, these sensations may worsen at rest, but do not improve with sustained movements and rarely worsen in the evening or at night. Peripheral neuropathy does not respond to dopaminergic therapy. Signs of polyneuropathy should be detected by means of a neurological examination.

Positional discomfort comes from prolonged sitting or lying down positions. A simple change of position relieves the sensory discomfort. A circadian pattern is absent.

Vascular or neurogenic claudication is characterized by dysesthesia and painful sensations, but no restlessness, increasing in intensity during leg movements, and relief at rest. These symptoms do not worsen in the evening or at night. Skin alterations are common.

Patients treated for a long time with neuroleptics may present akathisia, an inner restlessness involving the whole body, not associated with sensory discomfort. In order to satisfy their urge to move, these subjects perform body-rocking movements or start marching in place. Sometimes, these motor patterns are not effective in improving restlessness.

Differently from RLS, the neuroleptic-induced akathisia does not show a circadian pattern and has a significantly lower rate of PLM.

Epidemiology

Several epidemiological studies evaluated the occurrence of RLS in the general population. These surveys observed a large variability of prevalence ranging between 0.1 and 15% [7]. The discrepancies among the studies might be attributable to methodological differences, regional variations and different samples of patients included in the surveys. Self-administered questionnaires, direct observations, and telephone interviews were the methodological instruments used to assess RLS in epidemiological studies.

The use of self-administered questionnaires allows the study of large populations, but carries a risk of misdiagnosis due to erroneous understanding of the diagnostic criteria, difficulties in correctly identifying the unpleasant sensations described in the criteria or the presence of RLS-mimics conditions (see above). For example, Cirignotta et al. [8] demonstrated that using a self-administered questionnaire has a low sensitivity and specificity and does not prove reliable for screening for RLS in uremic patients. In fact, false-positive results were caused by the presence of other leg symptoms and neurological objective signs suggesting peripheral neuropathy, whereas false-negative were caused by the moderate severity of leg discomfort and its poor appraisal in these patients. Recently, the self-completed Cambridge-Hopkins questionnaire has been developed to ascertain RLS in population-based studies [9].

A face-to-face interview with a direct observation of the patient is able to overcome some limits of self-

administered questionnaires. However, the clinical interview is more expensive and may limit epidemiological studies to small samples.

The use of a telephone interview to assess RLS appears as a good compromise between a not very specific and a too expensive epidemiological instrument. Obviously, the telephone interview should be carried out by an expert on sleep disturbances to achieve a high specificity. Recently, Hening et al. [10] validated the Johns Hopkins telephone diagnostic interview for restless legs. This instrument seems to be sensitive, specific, and reliable for diagnosis of RLS by experienced interviewers.

Population-based studies report a RLS prevalence of 5–10% in western industrial countries. However, RLS rate decreased to 2.7% when a severity cut-off was used (frequency at least twice a week and distress at least moderate) [11]. Prevalence of RLS is very low in Asians compared with Caucasian and North American populations. In Singapore RLS affected only 0.1% of subjects [12]. These data were replicated in Japan and Taiwan. A population-based study of older Japanese aged >65 years reported a RLS prevalence of 0.96% [13]. Similarly, a community-based survey performed in the town of Daisen in the Tottori prefecture showed a RLS frequency of 1.8% [14]. Prevalence of RLS in Taiwanese population was found to be 1.57% in a recent study by Chen et al. [15]. These data could be explained by a variable genetic susceptibility to RLS or the different effects of unknown environmental factors able to induce the occurrence of the sleep disorder. However, cultural differences between western and eastern populations, causing a dissimilar experience of the complaint, could also be implicated in this large variability.

Classification

RLS is divided into an idiopathic and a symptomatic form.

Results of laboratory, neurological, neurophysiological, and neuroradiological examinations must be normal in patients with primary or idiopathic RLS. Almost 70–80% of all RLS patients are affected by idiopathic RLS [16]. The most common finding in patients with idiopathic RLS is the frequent occurrence of the disease among family members. Indeed, a positive family history for RLS was more commonly reported in subjects with idiopathic RLS than in those affected by a symptomatic form due to uremia (11.7 vs. 42.3%) [17].

Twin and family studies have shown a substantial genetic component to the disorder, with heritable variation estimated at 40–90% [18, 19]. Linkage studies reported several loci to be associated with RLS, namely RLS1 (12q12-q21), RLS2 (14q13-q31), RLS3 (9p24-p22), RLS4 (2q33), RLS5 (20p13), and RLS 6 (6p21). Apart from RLS1, the remaining loci have an autosomal-dominant mode of

inheritance [20]. Recent genome-wide association studies identified three different genes: BTBD9 (chromosome 6p), MEIS1 (chromosome 2p) and MAPK2/LBXCOR1 (chromosome 15q). Function of BTBD9 remains unknown. Differently, MEIS1 is a transcription factor that functions in limb development, MAP2K5 is a protein-kinase and LBXCOR1 is a repressor of LBX1, which is a homeobox gene involved in sensory pathways in the dorsal horn of the spinal cord. However, the relationship between these genes and RLS pathogenesis remains unclear [20]. Recently, an association between RLS and the genes PTPRD and NOS1 has been identified testing single-nucleotide polymorphisms only in the regions defined by prior linkage studies [21, 22].

Regarding symptomatic RLS, a clinical condition able to cause RLS can be detected in almost 25% of patients affected by the sleep disorder. Symptomatic forms of RLS improve or disappear treating the underlying disorder. Iron deficiency and end-stage renal disease represent two well-known causes of RLS.

In 1945 Ekblom reported that RLS and iron deficiency anemia were associated in almost 25% of patients [23]. Blood donors are prone to RLS. Repeated blood donation is associated with induction or perpetuation of RLS due to iron deficiency with or without coexisting anemia [24]. In 1994 O’Keeffe observed an inverse relationship between serum ferritin levels and severity of RLS symptoms (Spearman’s rho -0.53 , $p < 0.05$) [25]. These data suggest that a disturbance of peripheral iron supplies might affect central nervous system causing RLS. Indeed, reduced brain iron content was noticed in RLS patients during autopsies, magnetic resonance and transcranial ultrasound imaging studies, and cerebrospinal fluid analyses [26–29]. There is a well-established relationship between iron status and dopaminergic function [30]. Insufficiency of iron in the brain may reduce dopaminergic function by decreasing the activity of tyrosine hydroxylase, the rate-limiting step in dopamine synthesis or the expression of dopaminergic transporters or receptors. Decreased activity of tyrosine hydroxylase would result in a reduction in dopamine formation and hence in the amount of dopamine available to bind to post-synaptic receptors.

RLS occurrence is from twice to sixfold higher in uremic patients undergoing dialysis than in general population. Multicenter studies performed in Caucasian samples of dialysis patients showed that RLS prevalence is comprised between 18.4 and 21.5% [31, 32]. In this specific population the presence of RLS should be performed by a neurologist expert in sleep disorder during a direct interview; in fact, several clinical conditions, such as uremic polyneuropathy, might mimic RLS symptoms (see above). To date, pathophysiology of RLS in dialysis patients is unknown. Aksu and Bara-Jimenex reported increased spinal cord excitability in RLS/PLMS patients affected by chronic renal failure [33].

Several clinical alterations affecting dialysis patients could induce a state of spinal hyper-excitability. Previous epidemiological studies reported iron deficiency [34, 35] and calcium/phosphate imbalance [35, 36] as possible causes of RLS in end-stage renal disease. Differently, other authors suggested that uremic factors might play a role in RLS pathogenesis. In 2002 Winkelmann et al. [37] reported that RLS symptoms disappeared in 11 patients undergoing renal transplantation within 1–21 days after the surgery. The strong and positive influence of kidney transplantation on RLS symptoms was successively confirmed by a larger survey performed in Hungary. The authors observed that RLS prevalence was significantly lower in transplanted patients than those on maintenance dialysis (4.8 vs. 11.4%). In addition, RLS was strongly associated with declining renal function in transplanted patients [38]. A few studies reported an association between RLS and dialysis treatment; in particular, dialysis vintage [31, 39, 40] and frequency of HD sessions [41] were related to the sleep disorder. Recently, we investigated 58 hemodialysis patients paying attention to their dialysis treatment. Hemodialysis patients affected by RLS had a higher mean number of hemodialysis sessions per week and a longer mean duration of hemodialysis session than those without the sleep disorder. We hypothesize that hemodialysis might trigger RLS; in fact, a large part of our patients with the sleep disorder referred RLS occurrence throughout the dialysis session (personal data). Although uremic polyneuropathy affects almost 70% of dialysis patients, no studies have so far investigated the role of peripheral neuropathy as predictor of RLS in patients with end-stage renal disease. In our experience uremic polyneuropathy did not have any effect on RLS occurrence in dialysis patients (personal data). RLS symptoms impair nocturnal sleep in dialysis patients. In a multicenter study we showed that dialysis patients with RLS have a higher risk of being affected by insomnia and Excessive Daytime Sleepiness (EDS) than those without the sleep disorder [32]. Moreover, RLS is able to impair quality of life [42, 43] and to reduce life expectancy [43, 44] in this population. Uremic patients can be treated also with Continuous Ambulatory Peritoneal Dialysis (CAPD). Prevalence of sleep complaints in CAPD patients seems to be high [45], but previous studies focused their interest only on sleep apnea syndrome [45]. Data on RLS in these patients are lacking.

Pregnancy may induce RLS symptoms. Manconi et al. [46] demonstrated that 26.6% of pregnant women were affected by the sleep disorder. The disease is strongly related to the third trimester of pregnancy and tended to disappear reaching the time of delivery. In a recent paper Cesnik et al. [47] observed that the transient pregnancy RLS form represents a significant risk factor for the development of a future chronic idiopathic form of the sleep disorder and for a new transient symptomatology in a

future pregnancy. Pathophysiology of the pregnancy RLS form is unknown. Based on Lee et al.'s [48] study, iron and folate deficiency could play a primary role in RLS occurrence in pregnancy. In addition, Boetz and Lambert [49] reported that folate treatment was able to significantly reduce RLS rate in pregnant women. However, these data were not confirmed by other authors [46, 50]. Another hypothesis is that hormonal changes during pregnancy could trigger RLS symptoms [51]. The physiologic increase of estrogens, progesterone, and prolactin levels accompanies the increase of RLS severity during pregnancy and these hormones show intriguing effects on dopaminergic activity (prolactin and estrogens) and on neuronal excitability (progesterone).

Use of neuroleptics has been associated with RLS in several case-series [52]. Both first- and second-generation antipsychotics may cause the sleep disorder blocking the dopaminergic receptors. However, the difficulty in distinguishing RLS from neuroleptic-induced akathisia should be considered (see above).

Recently, several studies demonstrated a relationship between RLS and other clinical conditions, such as type 2 diabetes [53], multiple sclerosis [54], amyotrophic lateral sclerosis [55], early chronic renal disease [56], and celiac disease [57]. Further studies are needed to confirm these preliminary results.

Consequences

The unpleasant sensations due to RLS cause difficulties in falling asleep or frequent awakenings with difficulty in going back to sleep. As a consequence, a large part of RLS patients refers poor sleep quality. In a PSG study one-fifth of patients slept less than 3 h per night and the sleep efficiency was below 35% [16].

Data regarding EDS in RLS patients are not in agreement. Kallweit et al. [58] investigated 27 consecutive patients affected by idiopathic RLS in order to identify the presence of EDS. The authors observed that daytime somnolence, characterized by longer sleep on PSG recordings and reduced sleep latencies on Multiple Sleep Latency Test (MSLT), was common in RLS patients and improved after dopaminergic treatment. Differently, Gamaldo et al. [59] reported that RLS subjects had a greater sustained alertness than sleep-restricted controls.

Cognitive functions are particularly sensitive to sleep loss. However, only a few studies focused their interest on this issue in RLS patients. In 2006 Pearson et al. [60] compared the cognitive performance of RLS patients with normal non-sleep-restricted controls using a short cognitive battery designed to reflect the primary cognitive functions of the prefrontal lobe. This study demonstrated that RLS patients had significant cognitive impairment due to sleep

loss compared with their age-matched controls. These results were confirmed by another survey based on cognitive tasks [61] and by a recent neurophysiological study performing EEG and event-related potential analyses [62].

A relationship between idiopathic RLS and anxiety and depressive disorders has been documented by several studies using a face-to-face interview [63–65]. This diagnostic approach should be preferred to evaluate psychological status in RLS patients, bearing in mind that symptoms of the sleep disorder (e.g. insomnia or hypersomnia) are common among patients with anxiety and depression, causing possible problems of overdiagnosis when self-administered questionnaires are adopted. We demonstrated that RLS might cause similar consequences also in patients affected by end-stage renal disease and type 2 diabetes [31, 66].

The scientific interest moved over the burden of RLS on Quality of Life (QoL) in the past years. In the REST study, RLS patients showed a more impaired QoL than the United States general population with SF-36 scores similar to those of patients affected by type 2 diabetes, depression, and osteoarthritis with hypertension [11]. A second study re-examined the same results after controlling for the presence of comorbid conditions, and this analysis confirmed that RLS was an independent predictor of QoL [67]. These studies show that idiopathic RLS affects both physical and mental status, but in different ways. In fact, physical health domains are generally more compromised than mental ones [11, 67]. Differently, RLS shows a more severe impact on mental functions than on physical ones in dialysis patients [43, 68]. In a recent study we reported that the presence of RLS, in addition to comorbidities, insulin treatment, and HbA1C, was an independent predictor of impaired mental status in patients with type 2 diabetes. Thus, we hypothesize that RLS and its consequences on sleep may hit both physical and mental status in individuals not affected by disabling disorders, whereas patients accustomed to severe physical dysfunctions (e.g. uremia and diabetes) feel their RLS more as a mental distress [66].

RLS has been associated with increased risk for mortality in dialysis patients [43, 44, 69]. Winkelman et al. [69] showed increased odds of death associated with RLS of 1.85 when controlling for age, sex, and duration of dialysis therapy. A further study by Unruh et al. [43] confirmed that severe symptoms of RLS were significantly associated with an increased mortality hazard ratio of 1.39 (95% confidence interval, 1.08–1.79) when controlling for age, race, index of coexistent disease comorbidity score, and Karnofsky index. These results were recently replicated by La Manna et al. [44]. The authors enrolled 100 dialysis patients in an 18-month prospective observational study. Mortality was 32.3% in those with and 14.5% in patients without RLS ($P = 0.04$). Moreover, patients affected by intermittent RLS had a significantly lower mortality than

those with continuous RLS (23.8 vs. 55.6%; $P = 0.014$). Multivariate analysis confirmed the relationship between RLS and mortality. Based on these data, we think that RLS may directly increase the risk of mortality in dialysis patients. As a consequence, a suitable treatment should be started as soon as possible.

The occurrence of cardiovascular diseases in RLS patients could explain the relationship between the sleep disorder and mortality. An analysis of 2,821 individuals from the Wisconsin Sleep Cohort noted cardiovascular disease to be more prevalent in individuals with daily RLS compared with those without RLS (odds ratio = 2.58; 95% confidence interval, 1.38–4.84) [70]. A further survey of 1,559 men and 1,874 women enrolled in the Sleep Heart Health Study demonstrated that RLS patients had an adjusted odds ratio for coronary artery disease of 2.22 (95% confidence interval, 1.40–3.53) and for total cardiovascular disease, including coronary artery disease or a history of physician-diagnosed stroke or heart failure, of 2.38 (95% confidence interval, 1.55–3.65) compared with those without RLS [71]. La Manna et al. [44] reported similar results in dialysis patients. In fact, new cardiovascular events occurred more frequently in subjects with than in those without RLS (64.5 vs. 39.1%; $P = 0.019$). Sleep restriction and hyperarousability due to RLS might link the association between the sleep disorder and cardiovascular events. Sleep deprivation has been reported as a stressor inducing sympathetic overactivity [72] and increasing pro-inflammatory response [73, 74]. On the other hand, EEG arousals related to PLMS were able to cause significant raises in blood pressure in two different studies performed in RLS patients [75, 76]. These repetitive nocturnal blood pressure elevations could cause cardiovascular diseases by means of inducing daytime hypertension and/or modifying the 24-hour blood pressure profile [77].

Treatment

Patients affected by mild and intermittent RLS may undergo non-pharmacologic treatment. This approach consists of behavioral therapy, sleep hygiene, and lifestyle interventions (avoiding caffeine and alcohol intake, heavy meals, and drugs able to induce RLS). Otherwise, subjects reporting frequent and severe RLS symptoms should be treated pharmacologically.

Prior to the 1980s, RLS was largely treated using opioids and benzodiazepines. The nature of RLS treatment changed in 1982 when the efficacy of levodopa (an amino acid that is converted in the body to dopamine) in improving symptoms of the sleep disorder was demonstrated [78]. Since that time, the state-of-the-art in RLS therapy has been to use dopaminergic drugs as a first-line treatment [79].

Treatment data strongly support an involvement of dopaminergic transmission in the pathophysiology of RLS. In particular, the diencephalic A11 dopaminergic neurons appear to be engaged in RLS occurrence. These dopaminergic cells are able to modulate the nociceptive afferents by means of their projections into the dorsal horns of the spinal cord [80, 81]. Specific lesions in A11 nuclei of rats induce some features similar to those of human RLS with a long latency of sleep, a reduced sleep time, and several episodes of standing upright. As for RLS symptomatology, these abnormal behaviors decrease after pramipexole treatment [82].

Several randomized, placebo-controlled studies demonstrated that doses between 100 and 200 mg regular release levodopa are efficacious in treating the motor and sensory disturbances of RLS [83]. Some studies examined the long-term benefit of levodopa and found various rates of persistent efficacy ranging from 85% after 2 years to 31% after a mean of 31 months [79]. Since regular release levodopa has short half-life of 1–3 h, patients treated with a single bedtime dose of this compound may report recurrence of RLS symptoms and PLMS during the second half of the night. This clinical condition, known as rebound, can be treated using a combination of regular release levodopa and sustained-release levodopa [79]. In RLS patients, the most common adverse events associated with levodopa treatment are nausea, headache, fatigue, and diarrhea [79]. However, the most relevant clinical side effect of levodopa therapy is augmentation.

An internationally validated definition of augmentation for RLS was lacking until 2003, when the National Institutes of Health sponsored workshop on RLS diagnosis and epidemiology established the clinical criteria to diagnose augmentation [2]. Recently, the international criteria for augmentation were updated and the new Max Planck Institute diagnostic criteria were published [84]. The five main features of augmentation are (i) an earlier time of symptom onset in the evening or in the afternoon; (ii) a shorter latency to symptom onset when the patient is at rest; (iii) an increase in the intensity of RLS symptoms; (iv) a shortening of the period of relief following administration; and (v) an expansion of symptoms to previously unaffected body parts. The Augmentation Severity Rating Scale has been developed to assess the severity of augmentation [85]. To date, the pathophysiological mechanisms of augmentation are unknown. However, augmentation may be a reflection of chronically heightened dopamine levels in the nervous system. This hyperdopaminergic state could potentially increase the number of pro-nociceptive D1 receptors to the detriment of anti-nociceptive D2 receptors. Thus, augmentation might be the result of a relative predominance of D1 receptor stimulation [86]. Iron deficiency and sleep deprivation may

increase the risk of augmentation [87]. Augmentation appears to be specific for dopaminergic agents; in fact, apart from single cases with tramadol (an analgesic opioid) [88], no other drugs used to treat RLS induce this side effect. Prevalence rates of augmentation in open-label trials with levodopa range from 18.6 to 72% [89]. Increased severity of RLS and higher dosage of levodopa are associated with higher risk of developing augmentation: maximum dosages of 300–400 mg should not be exceeded [79]. Since augmentation appears to be more frequent with levodopa than dopamine agonists [90, 91], levodopa is recommended as an on demand treatment for intermittent RLS, while dopamine agonists represent the first line treatment for daily RLS.

Although cabergoline and pergolide are effective in improving RLS symptoms [92–96], the use of these ergot-derived dopamine agonists is discouraged because of the risk of cardiac valve regurgitation and valvular heart disease [92]. Since cabergoline and pergolide have high affinity for the 5-HT_{2B} serotonin receptors, which are expressed in heart valves and may mediate mitogenesis and, in turn, the proliferation of fibroblasts, a role of this serotonergic pathway in drug-induced valvular heart disease has been postulated [97]. In addition, a single case of pleuropulmonary fibrosis following treatment with pergolide was reported in a patient with a 30-year history of RLS, who also suffered from non-insulin-dependent diabetes, hypertension, and arteriosclerotic cerebral vascular disease [98]. Because of these known adverse events, ergot-derived dopamine agonists are not used as first-line treatment for idiopathic RLS.

Pramipexole and ropinirole are the two non-ergot dopamine agonists approved by EMEA and FDA for treatment of idiopathic RLS. Pramipexole has a selective action on the dopamine D₂ and D₃ receptors. The efficacy of pramipexole on RLS was demonstrated by six large randomized, double blind, placebo-controlled studies. All these studies showed that pramipexole was effective on RLS symptoms and PLMS at a dosage between 0.125 and 0.75 mg/daily [99–102]. Montplaisir et al. [103] investigated the long-term efficacy of pramipexole in 195 consecutive RLS patients treated with pramipexole for more than 1 year. Only 47 patients discontinued pramipexole and 12 of them because of a lack of efficacy. Patients who continued pramipexole for more than 1 year reported a mean decrease in RLS symptom severity of $80.0 \pm 20.8\%$ at follow-up compared with baseline. In an open-label trial our group demonstrated that pramipexole 0.125 mg improved sensory symptoms and motor signs of idiopathic RLS already after the first administration. The sleep macro and microstructure improved as well [104]. The acute effect of pramipexole was confirmed by Manconi et al. [105] in a single-blind study.

Several randomized placebo-controlled trials have shown that ropinirole is also effective in treating RLS [83]. In a flexible dose-titration polysomnographic trial, a mean dose of 1.8 mg ropinirole significantly reduced PLM and improved sleep parameters [106]. A long-term open-label study showed that ropinirole (mean dose 1.90 mg/daily) maintained its therapeutic efficacy in 82% of RLS patients [107]. Saletu et al. [108] demonstrated that ropinirole 0.5 mg was effective in improving RLS symptoms and sleep architecture already after the first administration.

Recently, the first direct comparison between pramipexole and ropinirole has been published. Manconi et al. [109] investigated 45 consecutive naïve patients with idiopathic restless legs syndrome in a double-blind, placebo-controlled study. Both a single oral dose of pramipexole 0.25 mg and of ropinirole 0.5 mg improved RLS symptoms and suppressed PLMS compared with placebo, without significant differences between the two compounds.

Rotigotine has a D1, D2, D3 receptors agonistic activity with about 15-fold higher affinity for the D2 receptor than for the D1 receptor. Patches are applied once daily and should be replaced every 24 h with the new patch applied to a different site. The first rotigotine dose for primary RLS is 0.5 mg/24 h, which can be increased in weekly steps of 2 mg, if necessary. The maximum dose that can be reached when treating RLS is 4 mg/24 h. Higher dosages (up to 16 mg/24 h) are utilized in patients with early or advanced Parkinson's disease. Several double-blind, placebo-controlled trials have demonstrated efficacy of this drug when used in patients affected by moderate-to-severe RLS. Indeed, RLS symptoms and QoL were improved by rotigotine in a therapeutic window between 1 and 3 mg/24 h [110–113]. Long-term efficacy (up to 2 years) of transdermal rotigotine has been recently observed [114]. Moreover, a PSG study by Oertel et al. [115] reported that PLMS decreased more with rotigotine than with placebo in RLS patients.

During RLS treatment, the most frequently reported adverse events related to dopaminergic agents are nausea, headache, fatigue, diarrhea, nasopharyngitis, and dizziness. Application site reaction may occur with rotigotine patches. These clinical symptoms are usually reported as transient and of mild or moderate severity [83]. Augmentation with pramipexole was reported in open trials in 8.5–39% of patients [79]. No signs of augmentation have been reported in the trials with ropinirole and rotigotine, but the phenomenon was not systematically assessed.

Physicians should be aware that the use of dopamine agonists might cause compulsive behaviors in RLS patients. Gambling, hypersexuality, excessive shopping, compulsive eating, and internet/computer addiction have been noted in patients with RLS [116–119]. It seems likely

that risk of compulsive behaviors and levels of dopamine agonist are associated. However, these behaviors may occur after relatively low doses of dopamine agonist [120].

Non-dopaminergic drugs could be used in selected cases of RLS. In particular, opioids are useful in patients with severe RLS nonresponsive to dopaminergics. A therapeutic approach with benzodiazepines can be tried in RLS subjects referring insomnia or parasomnias. Anticonvulsants, in particular gabapentin and pregabalin, seem to be particularly promising in patients affected by RLS and peripheral neuropathy. Gabapentin has been showed to be useful for RLS at dosages comprised between 200 and 2,000 mg/daily [83]. Sommer et al. [121] reported that pregabalin at a main daily dose of 305 mg was able to improve RLS symptoms due to peripheral neuropathy. Moreover, pregabalin, at a main dosage of 123.9 mg/day, largely reduced symptoms in patients affected by moderate-to-severe idiopathic RLS [122]. In RLS patients with iron deficiency (ferritin levels lower than 50 µg/L) iron supplementation has been shown to improve the sleep disorder. Oral treatment with ferrous sulphate 325 mg, or its equivalent, taken twice a day with vitamin C is tolerated and can be attempted. Unfortunately, iron is not absorbed very well in the gastrointestinal tract; thus, intravenous iron infusion could be more effective. Anaphylaxis may occur when intravenous iron is administered [79]. In uremic patients affected by RLS kidney transplantation improves the distressing symptoms within days or weeks [79].

Periodic limb movement disorder

Diagnosis

PLMD is characterized by periodic episodes of repetitive limb movements occurring during sleep and by clinical sleep disturbance that cannot be explained by another primary sleep disorder [1].

The ICSD-2 criteria for PLMD are as follows: (1) PSG demonstrates repetitive, highly stereotyped, limb movements that satisfy the criteria for PLMS (see below); (2) the PLMS index, i.e. the number of PLMS divided the number of hours of sleep with limb movement recording, exceeds 5 per hour in children and 15 per hour in adults; (3) presence of clinical sleep disturbance or daytime fatigue; (4) the PLMS are not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder [1].

Although the ICSD-2 reports that many individuals affected by PLMD suffer from insomnia and EDS [1], there are controversies over the clinical significance of PLMS [123, 124]. In fact, several surveys investigating this issue did not show any association between PLMS and

sleep-wake complaints [125]. In a large study including 78 patients, Hornyak et al. [126] observed that PLMS have a low impact on the subjects' perception of sleep quality. Moreover, two studies have shown a lack of correlation between the severity of PLMS and the mean sleep latency on the MSLT in patients with EDS [127, 128]. PLMS and arousals are frequently associated. An old concept assumed that PLMS induce arousals and consequently sleep fragmentation; differently, recent studies report that EEG and autonomic arousals may herald PLMS [123]. Indeed, Karadeniz et al. [129] indicated that 49% of the EEG arousals occurred before, 31% simultaneous with, and only 23% after the leg movements.

Whereas patients are often unaware concerning the presence of PLMS, bed partners frequently report sleep disruption due to leg movements. If PLMD is suspected, bed partner should be extensively investigated.

Epidemiology

Although PLMS are very common (see below), the exact prevalence of PLMD is unknown. A large epidemiological study performed in 18,980 subjects from the general population aged 15–100 years documented that 3.9% of them suffered from the simultaneous presence of PLMS and sleep complaints. Since leg movements during sleep were screened by a questionnaire, these data cannot be considered as reliable [130].

PLMS assessment

PLMS are similar to the Babinski response and are characterized by dorsiflexion of the ankle, of the toes, and partial flexion of the knee and sometimes the hip. PLMS can be detected by PSG or ACT (see above, RLS section).

Scoring criteria for PLMS were proposed for the first time by Coleman in 1982 [131]. In 1993 the American Sleep Disorders Association (ASDA) committee developed scoring rules for PLMS [132]. Based on the ASDA criteria, PLMS distinctive features are as follows: (1) 0.5–5 s in duration; (2) amplitude greater than or equal to 25% of toe dorsiflexion during calibration; (3) in a sequence of four or more movements; (4) separated by an interval of more than 5 s (from limb-movement onset to limb-movement onset) and less than 90 s (typically there is an interval of 20–40 s) [132]. The ICSD-2 largely adopted the ASDA criteria with an only change: the PLMS index cut-off to determine clinical significance in adults was modified from 5 to 15 [1]. In 2006 a task force from the IRLSSG revised the previous criteria in order to adapt detection of PLMS to the new requirements of computerized sleep recordings and to the developing understanding of the different pathologies associated with PLMS [133]. The most important

modifications made by IRLSSG concerned the definition of a significant Leg Movement (LM) event: (1) the maximum duration of a LM event is 10 s; (2) the minimum size of a LM event is an 8- μ V increase in EMG voltage above resting EMG; (3) the onset of a LM event is defined as an 8- μ V increase in EMG voltage above resting EMG; (4) the offset criteria of a LM event is defined as the start of a period of at least 0.5 s during which the EMG does not exceed 2 μ V above resting EMG; (5) an arousal by ASDA criteria and an LM are assumed to be associated with each other if they overlap or if the end of one event and the beginning of the other event are within 0.5 s or less of each other, regardless of which event is first; (6) an apnea/hypopnea and an LM are assumed to be associated with each other if they overlap or if the end of one event and the beginning of the other event are within 0.5 s or less of each other, regardless of which event is first [133].

PLMS present a high intra-individual variability [134, 135]. Recently, Trotti et al. [136] examined 20 RLS patients for 10–15 nights by means of an ACT and observed that the mean difference in PLMS index between the lowest and highest night was 25.1/h (range: 3.9–73.8). In addition, PLMS variability was unrelated to age or scores on scales of RLS severity. Consequently, if PLMS are detected in support of the clinical diagnosis or in the interpretation of studies investigating drug efficacy, a single recording night cannot be considered a reliable tool.

PLMS in different age categories, in patients with sleep disorders, and in patients with other complaints not primarily affecting sleep

Several studies have shown that PLMS may occur in healthy individuals [125, 137, 138]. In particular, PLMS seem to be an uncommon disorder in childhood, whereas PLMS prevalence increases with advanced age. Kirk et al. [137] reported that only 7 of the 591 children studied (1.2%) had evidence of PLM >5 per hour. Recently, Pennestri et al. [138] corroborated these results. In this study there was a significant increase in the PLMS index with advancing age ($r = 0.50$; $p < 0.001$) and PLMS rate was lower in younger healthy subjects compared with those 60 years or older. The largest study in the elderly was performed by Ancoli-Israel et al. [139] that enrolled 427 volunteers aged 65 years and over. The authors observed that 45% of the sample had a PLMS index >5 and that PLMS were associated with poor sleep.

Apart from RLS, insomnia, and EDS, PLMS have been associated with other sleep disorders. Obstructive Sleep Apnea Syndrome (OSAS) has been related to the presence of PLMS [140]. In OSAS patients leg movements typically occur synchronously with breathing resumption at the end of each apnea and CPAP treatment is able to decrease

PLMS [141]. Recently, Manconi et al. [142] described a case of association between Cheyne-Stokes Respiration (CSR) and PLMS. The authors reported synchronization between PLMS and hyperventilation episodes and leg movements were improved by CPAP treatment instead of dopaminergic drugs. The close link between PLMS and obstructive apneas/central breathing events, together with the responsiveness to CPAP, suggest a different pathogenesis of leg movements in OSAS and CSR compared with PLMS in other sleep disorders. PLMS with or without micro-arousals are common in narcoleptic patients with cataplexy. In particular, these patients have a high PLMS index in both REM and NREM sleep, and leg movements seem to contribute to REM sleep disruption in this clinical condition [143]. Since, Boivin et al. [144] demonstrated that levodopa and bromocriptine (a dopamine agonist) decreased the PLMS index in patients with narcolepsy, dopaminergic involvement may be suggested to explain the high rate of PLMS in this specific population. Many patients with REM Sleep Behavior Disorder (RBD) are affected by PLMS [145]. In this specific population PLMS show different features with respect to RLS patients. In fact, Manconi et al. [146] observed that PLMS occurred more frequently during REM sleep in patients with RBD and during non-REM sleep in patients with RLS. Moreover, PLMS were shorter in duration, less often bilateral, and with a higher inter-movement interval in patients with RBD compared with those with RLS.

The most common clinical conditions, not primarily affecting sleep, associated with PLMS are syringomyelia, spinal cord injury, Parkinson's disease, multiple system atrophy, cortical-basal degeneration, ischemic and hemorrhagic stroke, fibromyalgia, congestive heart failure, essential hypertension, alcoholism, and end-stage renal disease [125]. Moreover, increase of PLMS may occur in depressed patients treated with selective serotonin reuptake inhibitors or serotonin noradrenalin reuptake inhibitors [125]. Differently, bupropion that works on dopaminergic pathway may improve PLMS index [147].

Treatment

Several clinical trials performed in RLS patients show that dopaminergic drugs significantly decrease PLMS index (see above, RLS section). Unfortunately, a small number of uncontrolled studies have been performed in subjects with PLMD [125]. Based on the guidelines of the European Federation of Neurological Society, clonazepam, triazolam, and levodopa are probably effective in improving PLMS index, PLMS associated with arousals, and sleep efficiency in PLMD patients. The authors did not make any recommendation on the use of non-ergot dopaminergic drugs [89]. Conversely, pramipexole and ropinirole were recognized as

effective on PLMD by the American Academy of Sleep Medicine, although with a low level of recommendation [148]. To date, only patients affected by PLMS associated with RLS should be treated pharmacologically.

Sleep-related leg cramps

Diagnosis

Patients affected by sleep-related leg cramps report painful sensations due to sudden and intense involuntary contractions of single muscles or muscle groups. Leg cramps affect lower limbs, usually the calf or the feet. These involuntary movements, lasting for a few seconds up to several minutes, may remit spontaneously or can be relieved by strongly stretching the affected muscles or also by massages. Patients with leg cramps often report tenderness and discomfort in the affected muscles for several hours after cramping.

The ICSD-2 criteria for sleep-related leg cramps are as follows: (1) a painful sensation in the leg or foot is associated with sudden muscle hardness or tightness indicating a strong muscle contraction; (2) the painful muscle contraction in the legs or feet occur during the sleep period, although they may arise from either wakefulness or sleep; (3) the pain is relieved by forceful stretching if the affected muscles; (4) the sleep-related leg cramps are not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder [1].

Differential diagnosis

RLS, PLMS, vascular claudication, and peripheral neuropathy might mimic leg cramps. Careful clinical history and examination are needed to distinguish between these complaints. As reported earlier (see RLS section), RLS involves an urge to move not commonly seen with leg cramps; furthermore, RLS symptoms improve almost immediately by any movement of the leg, whereas relieving the pain from leg cramps requires both more time and more vigorous stretching of the muscle. PLMS are involuntary movements during sleep that differ from sleep-related leg cramps because they are not associated with painful sensations. In patients with vascular claudication the pain occurs during limb use; in contrast symptoms of leg cramps appear at rest. Although peripheral neuropathy may induce leg cramps (see below), other sensory or motor findings should be detected during the examination in these patients.

In order to diagnose sleep-related leg cramps, physicians should perform a detailed clinical and pharmacological

history (diuretics). The physical examination should be directed at looking for any signs indicative of secondary causes (see below). Blood tests, such as thyroid function, blood urea nitrogen, creatinine, and serum chemistry including sodium, potassium, calcium, and magnesium may be helpful. Furthermore, vascular studies can assess for claudication; imaging of the lumbar spine may help to diagnose nerve root entrapment, and nerve conduction and EMG may reveal peripheral neuropathy or motor neuron disease. Based on ICSD-2 criteria, PSG is not routinely recommended for identifying isolated nocturnal leg cramps.

Epidemiology

Leg cramps may occur at any age, but this disturbance is clearly more common in the elderly. A general population survey performed on 218 subjects reported an overall prevalence of leg cramps of 37% with symptoms more prevalent in older subjects and at night [149]. A study enrolling only subjects aged 65 years and above reported a prevalence of leg cramps of 50%, confirming that involuntary movements were prevalent at night [150]. Oboler et al. [151] investigated the frequency of leg cramps occurring at night. Two hundred seventy-six of 490 patients (56%) referred to be affected by nocturnal leg cramps. Peripheral vascular disease, hypokalemia, and coronary artery disease were associated with the presence of the movement disorder. Also pregnancy is linked to leg cramps, with 33–50% of pregnant women experiencing leg cramps that also tend to get worse as pregnancy progresses [152, 153]. Leg cramps rate is lower in children with a rate of 7.3% [154].

Although no apparent causes are found in many older subjects with sleep-related leg cramps, several complaints may induce these painful movements. Patients affected by neurological disturbances involving the lower motor neurons (i.e. peripheral neuropathy, radiculopathy, amyotrophic lateral sclerosis) and by metabolic disorders (i.e. uremia/hemodialysis, cirrhosis, hypothyroidism, diarrhea, vomiting, diuretic therapy) frequently report sleep-related leg cramps. In addition, leg cramps are described in some autoimmune diseases of the nervous system characterized by the presence of antibodies to voltage-gated potassium channels in neuromyotonia and Morvan's syndrome [155] and to glutamic acid decarboxylase in Stiff person syndrome [156].

Consequences

In almost one-half of patients with leg cramps symptoms are reported several times per week or daily [150] and 21% of cramp sufferers described their symptoms as very distressing [149]. In these patients nocturnal sleep may be impaired with difficulty in falling asleep and/or frequent

awakening at night. Moreover, persisting discomfort after the cramps often delays subsequent return to sleep.

Treatment

Oboler et al. [151] showed that almost all patients with daily leg cramps reported symptoms to their physicians and 55% of them received treatment. Obviously, the first step in management should include treating any underlying disorders that may be causing leg cramps. After these considerations, non-pharmacologic therapies such as walking, stretching, and massage are recommended as first-line treatment [157, 158]. Cramps can be managed acutely by stretching the muscle, but this approach appears to be not sufficient for preventing the occurrence of nocturnal cramps [159]. An evidence-based review on the symptomatic treatment of muscle cramps was carried out in 2010 by the American Academy of Neurology. Although there are Class I studies showing the efficacy of quinine derivatives for treatment of muscle cramps, the authors recommended to not use routinely these drugs because of the potential of toxicity. The most common serious side effects of quinine derivatives are hematologic alterations such as hemolytic uremic syndrome, disseminated intravascular coagulation, and bleeding diathesis. Based on Class II studies, naftidrofuryl, vitamin B complex, and diltiazem are possibly effective, whereas magnesium preparations and gabapentin are probably not effective in the treatment of muscle cramps [160].

Sleep-related bruxism

Diagnosis

Sleep-related bruxism is characterized by grinding or clenching of the teeth during sleep. Tooth destruction (e.g. tooth wear and fractured teeth), temporomandibular dysfunction [161, 162], and headaches [163, 164] are observed in patients affected by sleep-related bruxism. Poor sleep is uncommon in patients with mild or moderate bruxism, whereas bed partners' sleep disruption due to grinding sounds is commonly reported [165].

The ICSD-2 diagnostic criteria for sleep-related bruxism are (1) the patient reports or is aware of tooth-grinding sounds or tooth clenching during sleep; (2) the presence of abnormal wear of the teeth and/or jaw muscle discomfort, fatigue or pain, and jaw lock upon awakenings and/or masseter muscle hypertrophy upon voluntary forceful clenching; (3) the jaw muscle activity is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder [1].

Although diagnosis of sleep-related bruxism is clinically assessed, physicians should use caution because reports of tooth-grinding noise may not be accurate in subjects sleep alone and the presence of tooth wear may have occurred months or years ago. Moreover, several oromandibular activities during sleep (see below) might mimic nocturnal bruxism. In uncertain cases audio–video PSG performed in the sleep laboratory is needed. If EMG artifacts on EEG derivations referenced to ear electrodes occur in routine PSG, sleep bruxism can be hypothesized. To confirm a diagnosis of sleep bruxism, EMG from at least one masseter muscle with audio recording to associate muscular activity with grinding sound production should be included in PSG. Patients with sleep bruxism show three different patterns of EMG activity in masseter or temporalis muscles: tonic, isolated sustained contractions lasting more than 2 s, and phasic, Rhythmic Masticatory Muscle Activities (RMMA) lasting from 0.25 to 2 s, and mixed, both tonic and phasic types. PSG diagnosis of sleep bruxism is based on (1) more than four bruxism episodes per hour; (2) more than six bruxism bursts per episode and/or 25 bruxism bursts per hour of sleep; and (3) at least two episodes with grinding sounds. By means of the laboratory PSG criteria, bruxism can be correctly predicted in 83.3% of affected patients and asymptomatic status can be confirmed in 81.3% of controls [166]. Sleep-related bruxism shows a high night-to-night variability, so PSG criteria could not be reliable for patients affected by mild and sporadic form of the disturbance [167]. Although EMG activity in masseter or temporalis muscles and grinding sounds can be detected also in asymptomatic patients, bruxers show a significantly higher number of these events [166]. However, sleep architecture seems to be unmodified by repetitive jaw muscle contractions [166]. A large part of sleep bruxism episodes occurs in light sleep stages rather than in REM sleep [166] and these events are associated with brief cardiac and brain reactivations (microarousals) [167]. Recent pathophysiological hypothesis suggests that ongoing sleep microarousals represent the permissive windows for occurrence of bruxism during sleep in susceptible patients [168]. Ambulatory EMG recordings can be used to monitor sleep bruxism at home. Ambulatory recordings allow low-cost monitoring over several nights in the patients' natural environment. However, this diagnostic instrument is limited by the absence of audio and video recordings that are useful to assess the specificity of EMG activity over the large spectrum of orofacial activities occurring during sleep.

Differential diagnosis

Sleep-related faci mandibular myoclonus mimics bruxism [169]. However, clinical and neurophysiological data allow

distinguishing between these two disorders. Subjects with faci mandibular myoclonus show no hypertrophy of masseter or temporal muscles, mouth tenderness, temporomandibular problems, and tooth wear; in addition, neurophysiological results do not satisfy the PSG criteria for sleep bruxism [170]. Patients affected by Parkinson's disease, Maige's syndrome, choreic disorders, and tardive dyskinesia may show pathological movements involving orofacial or cervical muscles when asleep. Neurological signs and the presence of these movements also during daytime support the correct diagnosis. Rhythmic teeth grinding caused by temporal lobe seizures has been reported [171]. EEG recording does not detect epileptic activity in bruxers.

Epidemiology

Almost 20% of the adult population reports daytime clenching and the prevalence is higher in women than in men [165]. Prevalence of sleep bruxism changes over age. Epidemiological studies show that 14–20% of children are affected by sleep bruxism [165]. However, a larger rate (35.3%) is reported by a very recent paper performed in a group of Brazilian schoolchildren [172]. Prevalence of sleep bruxism decreases in adults. In a large survey, tooth grinding was reported by 13, 9, 7, and 3% of subjects 18–29, 30–44, 45–59, and >60 years of age, respectively [173]. The use of self-reported symptoms to diagnose sleep bruxism represents the most important limitation of these epidemiological studies [173].

Emotional factors (i.e. anxiety and stress) are considered in relationship with bruxism [174]. This view is in agreement with two studies in which levels of catecholamines were higher in bruxers than in subjects without bruxism [175, 176]. Differently, a survey performed in patients with sleep bruxism did not observe any association between self-reported stress and personality variables with EMG measurements of bruxism [177]. The role of occlusal interference as able to trigger sleep bruxism has been recently contested by a recent experimental study [178]. Differently, smoking, caffeine and alcohol consumption represent important risk factors for sleep bruxism occurrence [179]. Cases of bruxism after ecstasy abuse have been reported [180].

Treatment

Management of sleep bruxism is directed towards tooth protection, reduction of sensory complaints, and improvement of sleep quality, if this one is impaired. Three different approaches appear to be useful. Behavioral strategies are based on relaxation, biofeedback, and hypnosis. Although some bruxers refer a sensation of well-being, no

persistent or clear effects have been obtained with this approach [181, 182]. Obviously, standard sleep hygiene should be recommended for patients affected by sleep bruxism. Soft mouth guard and hard plastic bite splint are used to protect teeth of patients who are severe grinders. These occlusal appliances are not recommended for patients with comorbid sleep apnea [183]. Many bruxers does not utilize these devices over a long period of time due to discomfort or aesthetic reasons. Moreover, both soft and hard oral appliances may increase the oromotor activity in some patients [184, 185]. Benzodiazepines (i.e. diazepam) and muscle relaxant (i.e. methocarbamol) improve sleep bruxism [186, 187]. Recently, the interest shifted towards adrenergic drugs and botulinum toxin. The nonselective adrenergic beta-blocker propranolol has been reported to be useful for sleep bruxism [188]. On the contrary, a randomized controlled study did not show any improvement with propranolol, whereas the selective alpha2-agonist clonidine reduced sleep bruxism index by 61% [189]. As observed by a few studies, two dopaminergic agents (i.e. levodopa and pergolide) seem to decrease sleep bruxism events [190, 191]. Differently, bromocriptine has not effect on teeth clenching [192]. Consequently, further investigations are needed to understand the role of dopaminergic system in sleep bruxism. A recent randomized controlled trial performed on 12 subjects reporting nocturnal bruxism showed that botulinum toxin injections represent an effective treatment for this sleep disorder [193]. Use of small doses of amitriptyline, a tricyclic antidepressant, for sleep bruxism management is not supported by two controlled studies [194, 195]. In addition, physicians should be aware that serotonin-selective re-uptake inhibitors might worsen sleep bruxism [165].

Sleep-related rhythmic movement disorder

Diagnosis

Subjects affected by RMD show repetitive, stereotyped, and Rhythmic Movements (RMs) that involve large muscle groups and occur during quiet wakefulness or drowsiness or sleep.

RMD is typically seen in childhood (see below) and the occurrence of RMs during sleep is considered a physiological phenomenon representing a positive stimulus for motor development in the early stages of life via vestibular stimulation [196]. Differently from the previous version of the ICSD, the current one emphasizes that RMs without evidence of significant consequences should not be considered a disorder [1].

The following diagnostic criteria for sleep-related RMD are included in the ICSD-2: (1) The patient exhibits

repetitive, stereotyped, and rhythmic motor behaviors; (2) the movements involve large muscle groups; (3) the movements are predominantly sleep related, occurring near nap or bedtime, or when the individual appears drowsy or asleep; (4) the behaviors result in a significant complaint as manifest by interference with normal sleep and/or significant impairment in daytime function and/or self-inflicted bodily injury that requires medical treatment (or would result in injury if preventable measures were not used); (5) the RMs are not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder [1].

RMs during sleep can involve any part of the body. There are several subtypes of RMD. The most frequent forms of RMD are body rocking, body rolling, head banging, and head rolling, while leg rolling and leg banging are less common. Frequency of RMs can vary, but it is generally included between 0.5 and 2 per seconds, lasting less than 15 min [1]. Usually patients with RMD show only one form of RMs and rarely two forms in the same night [197, 198]. Recently, our group described the case of a patient affected by three different subtypes of RMD in the same night [199]. Successively, other two cases concerning multiple forms of RMs have been reported [200, 201]. An association between RMD and other sleep disturbances, i.e. RLS, RBD, and OSAS, has been reported in literature [202–205]. PSG recordings show that RMD can occur in sleep wake transition periods and in all stages of sleep including REM, but most often occurs in NREM stage 2 of sleep [197, 206]. RMD in REM sleep usually appears against a background of otherwise normal REM sleep with preserved muscle atonia and normal occurrence of twitches [206, 207]. However, Manni and Terzaghi described the occurrence of RMs, as part of RBD episodes, in two patients affected by idiopathic RBD [208]. PSG findings have documented that RMs, like bruxism (see above) and other motor disorders during sleep, are closely linked to arousal fluctuations. Thus, it has been suggested that RMs are modulated by these fluctuations representing permissive window for the occurrence of these abnormal movements [196].

Differential diagnosis

RMD episodes should be distinguished by nocturnal seizures. The absence of EEG epileptic abnormalities in subjects with RMD might be useful for a correct diagnosis. Other neurological symptoms, such as tics and dyskinesias, should be distinguished from RMs. Children affected by autism, pervasive development disorders, and mental retardation may exhibit RMs. In these patients an additional diagnosis of RMD should be made only if the movements are predominantly sleep related. Thumb

sucking and sleep-related bruxism might mimic the presence of RMs. Video-PSG recordings are needed in these cases.

According to the ICSD-2, RMD should be differentiated from Hypnagogic Foot Tremor (HFT). This term was used for the first time by Broughton in two patients affected by rhythmic, oscillating movements of the whole foot or of the toe, appearing during falling asleep after severe head injury [209]. In 2001, Wichniack et al. [210] reported the presence of HFT in 7.5% of 375 cases and renamed this motor pattern Rhythmic Feet Movement (RFM). Recently, we reported the case of a patient affected by several forms of RMD (i.e. body rolling, leg rolling and RFM) in the same night. Clinical and polysomnographic data confirmed that RMs impaired significantly nocturnal sleep. The association of RFM with other RMs suggests that RFM should be considered as a part of RMD [199]. Also Wichniack et al. [210] agree with this hypothesis.

Epidemiology

RMD prevalence was 66% in 9-month-old infants, decreasing to 8% in 4-year-old children [211]. Spontaneous onset of RMD in adolescence and adulthood is rare and it has been associated with neurological complaints [212, 213]. However, subjects with RMs onset in childhood may have symptoms persisting into adulthood. A recent large polysomnographic study reported that RMD persisted beyond childhood in many patients [198]. Previous observations described an association between RMD and mental retardation, autism or other psychopathologies when RMs persisting in older childhood or beyond [214]. This assumption was revised by Mayer et al. [198] showing that the majority of adult patients with RMD did not have abnormal psychopathology. Similarly, our patient affected by RMD continued through adulthood had a normal neuropsychological assessment [199]. Although no sex differences have been found in patients with RMD, Meyer et al. [198] found a clear male preponderance in adults with RMD. Familial forms of RMD have been described at a rate of up to 20% [215–217].

Treatment

Only in patients with poor sleep or self-inflicted bodily injury due to RMD a pharmacological treatment should be started. RMD resolves spontaneously in most children and it does not affect sleep quality. Rarely, head banging has been associated with carotid dissection, cataracts, and head injury in young patients [218–223]. Although some adults did not report any sleep complaint [198], RMD in adulthood might interfere with normal sleep, causing poor sleep quality or daytime dysfunction. Benzodiazepine, i.e.

clonazepam, improves RMD [201, 223–225]. In our patient clonazepam was an effective treatment for RMD already after the first night of administration and its efficacy persisted clinically up to 6 months [199]. Other treatments that have been used in RMD include antidepressants, behavioral interventions, hypnosis, and sleep restriction [224].

Isolated symptoms, apparently normal variants, and unresolved issues

The ICSD-2 includes in this chapter some types of movements occurring during a normal sleep period, but that are able to disturb sleep quality due to their frequency or intensity. In addition, other movements with uncertain clinical significance are included here [1].

Hypnagogic foot tremor

Diagnostic criteria for HFT are the following: (1) the patient reports foot movements (directly experienced or observed by others) that occur at the transition between wake and sleep or during light sleep; (2) polysomnographic or activity monitoring demonstrates recurrent EMG potentials or foot movement typically at 1–2 Hz (range 0.5–3 Hz) in one or both feet plus burst potentials longer than the myoclonic range (greater than 250 ms) and usually less than 1 s plus trains lasting 10 or more seconds; (3) the disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder [1]. As reported above, our opinion is that HFT should be considered a sleep-related RMD. In our patient the first administration of clonazepam 1 mg at bedtime was able to resolve the sleep complaint [199].

Alternating leg muscle activation

The term “alternating leg muscle activation” (ALMA) is used to describe brief activations of the anterior tibialis in one leg in alternation with similar activations in the other leg during sleep or arousal from sleep.

The following are the diagnostic criteria for ALMA: (1) PSG demonstrates a pattern of brief, repeated activation of the anterior tibialis in one leg alternating with similar activation in the other leg; (2) at least four discrete and alternating muscle activations occur with less than 2 s between activations; (3) individual activations last between 0.1 and 0.5 s and occur at a frequency of 0.5–3 Hz (usually 1–2 Hz); sequences of alternating activations last between 1 and 30 s and may recur periodically (e.g. 1–4 times per minute) [1].

In 2003, Chervin et al. [226] reported 16 cases of ALMA that were identified from almost 1,500 polysomnographic studies. Many patients with ALMA had OSAS, PLMS and took one or more antidepressants. Usually ALMA episodes were associated with arousals. A further case report of ALMA was reported by Cosentino et al. [227]. The authors confirmed that ALMA episodes were strictly related to arousals. Pathophysiology of ALMA is unknown; however, this sleep complaint appears to be generated by spinal networks under the influences of descending serotonergic and dopaminergic pathways [226, 227]. The presence of sleep instability, for example, due to OSAS or PLMS, would be able to trigger the spinal generator inducing ALMA.

Treatment with dopamine agonists is useful in patients with ALMA reporting disrupted sleep [227].

We performed a careful polysomnographic study in a patient affected by poor sleep quality and EDS. RLS symptoms were denied. The neurophysiological studies confirmed that nocturnal sleep was fragmented by several arousals associated with a quickly alternating pattern of tibialis anterior activation satisfying criteria for ALMA. An episode of ALMA associated with arousal is reported in Fig. 1. PSG excluded the presence of OSAS and PLMS. Administration of pramipexole 0.250 mg at bedtime improved sleep quality, EDS and decreased ALMA episodes.

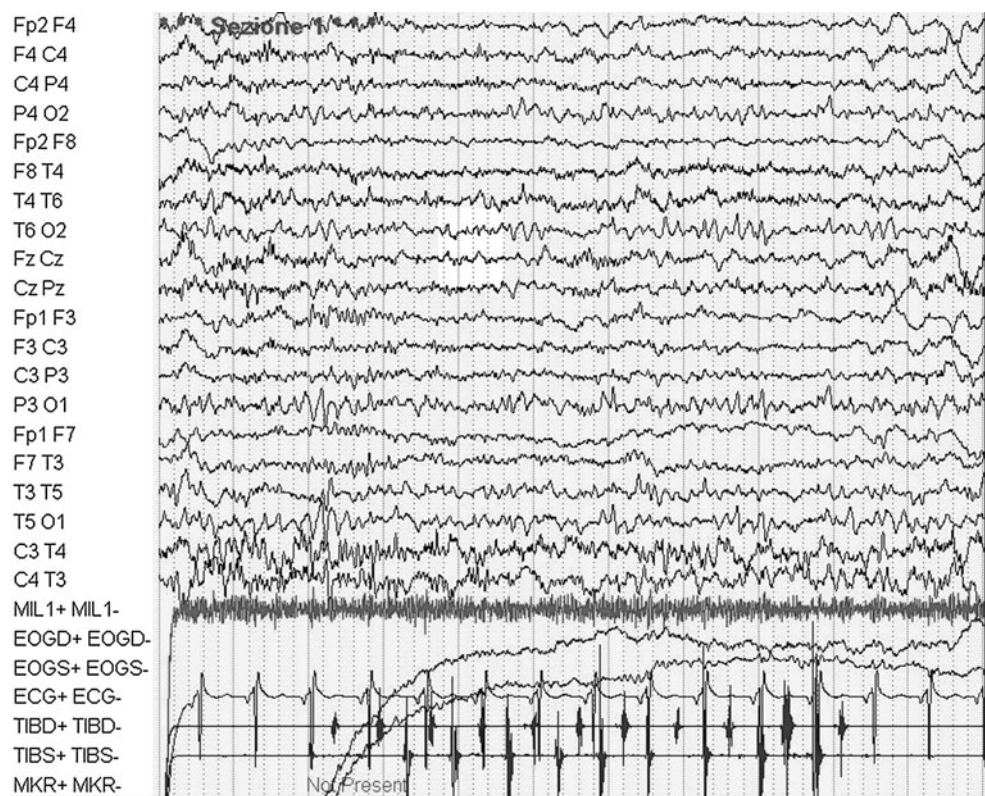
Propriospinal myoclonus

Myoclonus can originate at several levels in the central nervous system. Propriospinal Myoclonus (PSM) is characterized by brief muscular jerks generated within the spinal cord and in which the myoclonic activity spreads up and down the length of the spinal cord along propriospinal pathways intrinsic to the cord. The myoclonic activity of PSM originates in the thoraco-abdominal/paraspinal muscles; thus, affected patients have jerks in flexion or extension of the trunk or abdomen. PSM episodes occur during the transition from wakefulness to sleep causing initial insomnia. Rarely, this sleep disorder appears during intrasleep wakefulness resulting in intermediate insomnia. These jerks are usually spontaneous, even if external stimuli may evoke them.

Diagnostic criteria for PSM at sleep onset are (1) the patient complaints of sudden jerks, mainly of the abdomen, trunk, and neck; (2) the jerks arise upon relaxed wakefulness and drowsiness and disappear upon mental activation and at sleep onset; and (3) the disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder [1].

PSG demonstrates myoclonic jerks recurring nonperiodically when alpha activity is present on the EEG. PSM disappears with EEG desynchronization due to mental

Fig. 1 ALMA episode arising from arousal in NREM sleep



activity and when sleep spindle and K-complexes occur. Moreover, myoclonic jerks are absent throughout sleep, even if these movements might reappear during intrasleep wakefulness. EMG analysis reveals myoclonic jerks, lasting 100–300 ms, arise first in axial muscles (intercostalis, rectus abdominis, paraspinalis, sternocleidomastoideus), and later involve more cranial and more caudal muscles with inter-muscle latencies of 16–200 ms. The spinal propagation velocity of 2–16 m/s is suitable for a propriospinal type of propagation. Back-averaging of the EEG should not show any jerk-locked cortical activity to exclude that PSM is mimicked voluntarily [228].

Based on the presence of associated conditions PSM can be classified as idiopathic or symptomatic. Clinical conditions associated with the occurrence of PSM are infective myelitis, cervical trauma, syringomyelia, and multiple sclerosis [222]. Moreover, administration of ciprofloxacin and interferon-alpha, and cannabis use have been reported as causes of PSM [229]. A case of PSM evolving toward acute myoclonic status has been described after a vertebral fracture of T11 [222]. However, many patients with PSM have no structural abnormality of brain or spinal cord [223]. Since PSM episodes appear during the transitional period between wake and sleep, it has been suggested that

changes in vigilance levels may trigger the spinal generator of PSM [230].

Epileptic myoclonus and physiologic hypnic myoclonus should be distinguished from PSM.

Usually, PSM represents a chronic clinical condition and patients reporting sleep disruption due to PSM should be treated with clonazepam [230].

Excessive hypnic fragmentary myoclonus

During relaxed wakefulness and sleep some subjects have sudden, arrhythmic asymmetric and asynchronous brief twitches involving distal limbs and face. This EMG activity is known as Physiologic Hypnic Fragmentary Myoclonus (PHFM). In particular, PHFM is common at sleep onset and in REM sleep. Although PHFM originates in muscle endplate [231], a supraspinal modulation has been described [232].

In 1984, Broughton et al. [233] described a quite similar EMG activity with the exception that it was greater and occurred in NREM sleep. The authors defined it Excessive Hypnic Fragmentary Myoclonus (EHFM). Many patients with EHFM are not aware of the twitch-like movements and diagnosis of this SRMD is occasional when PSG is

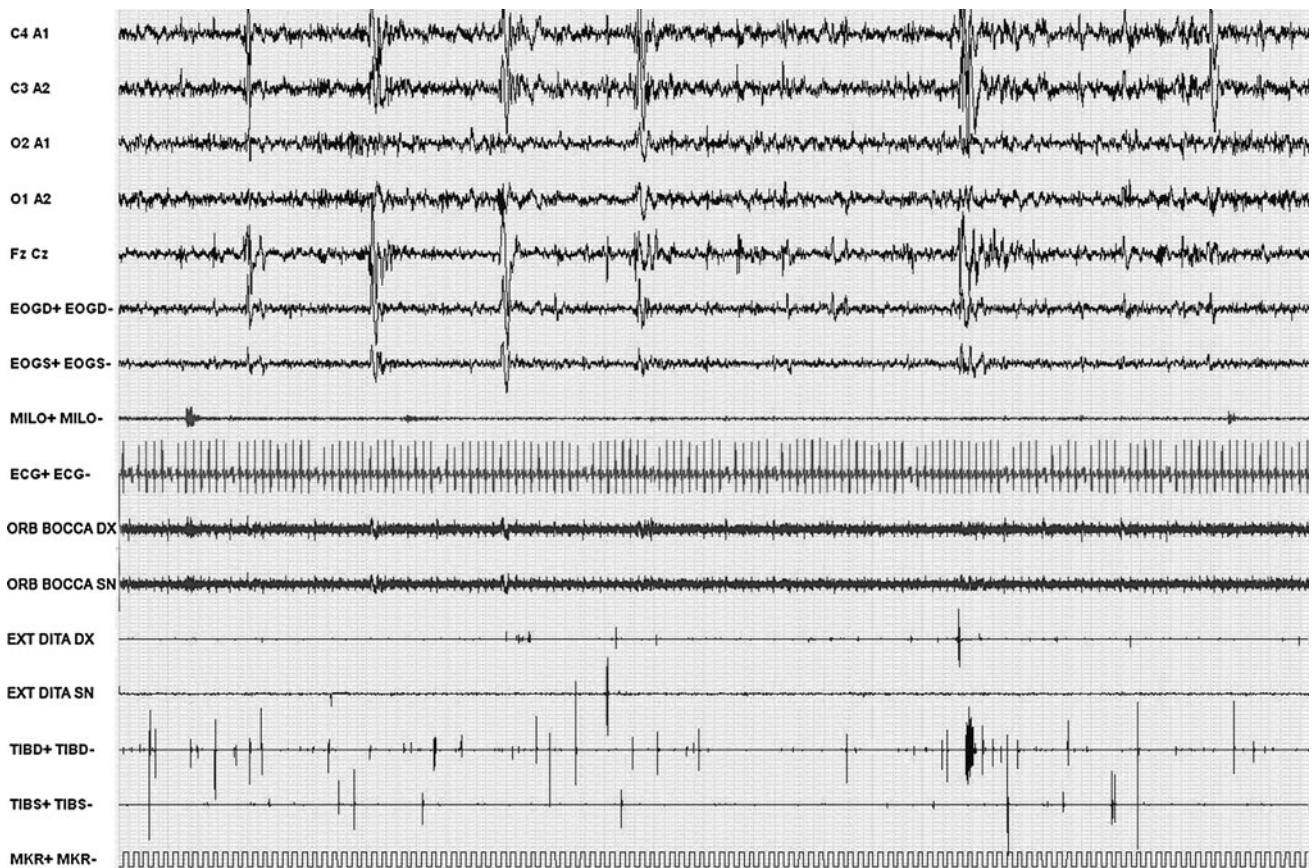


Fig. 2 EHFM episode in NREM sleep

performed to investigate other sleep disorders. In fact, EHFM has been reported to be comorbid with OSAS, narcolepsy, PLMD, RBD, and RLS [234]. A few subjects with EHFM can exhibit small movements of the fingers, toes, or corners of the mouth. Recently, a case of EHFM due to mitochondrial encephalomyopathy has been described. In this patient the magnetic resonance imaging showed brainstem lesions; thus, the authors suggested that brainstem could represent the generator of EHFM [235]. Another report of two cases agreed with this hypothesis [234].

Diagnosis of EHFM is based on the following criteria: (1) the patient exhibits small movements of the fingers, toes, or corners of the mouth or small muscle twitches, resembling either physiologic hypnic myoclonus or fasciculation. The movements may be present during wakefulness or sleep; (2) polysomnographic monitoring demonstrates recurrent and persistent very brief (75–150 ms) EMG potentials in various muscles occurring asynchronously and asymmetrically in a sustained manner without clustering; (3) More than five potentials per minute are sustained for at least 20 min of NREM stages 2, 3, or 4 sleep; (4) the disorder is not better explained by another current sleep

disorder, medical or neurological disorder, medication use, or substance use disorder [1].

The amplitude of EMG potentials in patients with EHFM varies from 50 to several hundred microvolts. EEG activity is generally unchanged by EHFM, although high-amplitude EMG potentials may be associated with EEG arousal. Back-averaged EEG does not show any twitch-related cortical potential.

To date, it is unknown whether EHFM occurs as a consequence of sleep disruption, for example in patients with OSAS or RLS, or whether it is an independent cause of poor sleep and EDS.

In our opinion, severe forms of EHFM might cause sleep fragmentation and daytime somnolence. In fact, we performed several polysomnographic recordings in a patient reporting EDS. PSG showed several arousals in NREM and REM sleep that were strictly related to EMG potentials satisfying ICSD-2 criteria for EHFM. EHFM in NREM and REM sleep are reported in Figs. 2 and 3, respectively. Our patient was unaware regarding these movements. We successfully treated him with pramipexole 0.125 mg at bedtime that was able to decrease episodes of EHFM and to improve daytime somnolence.

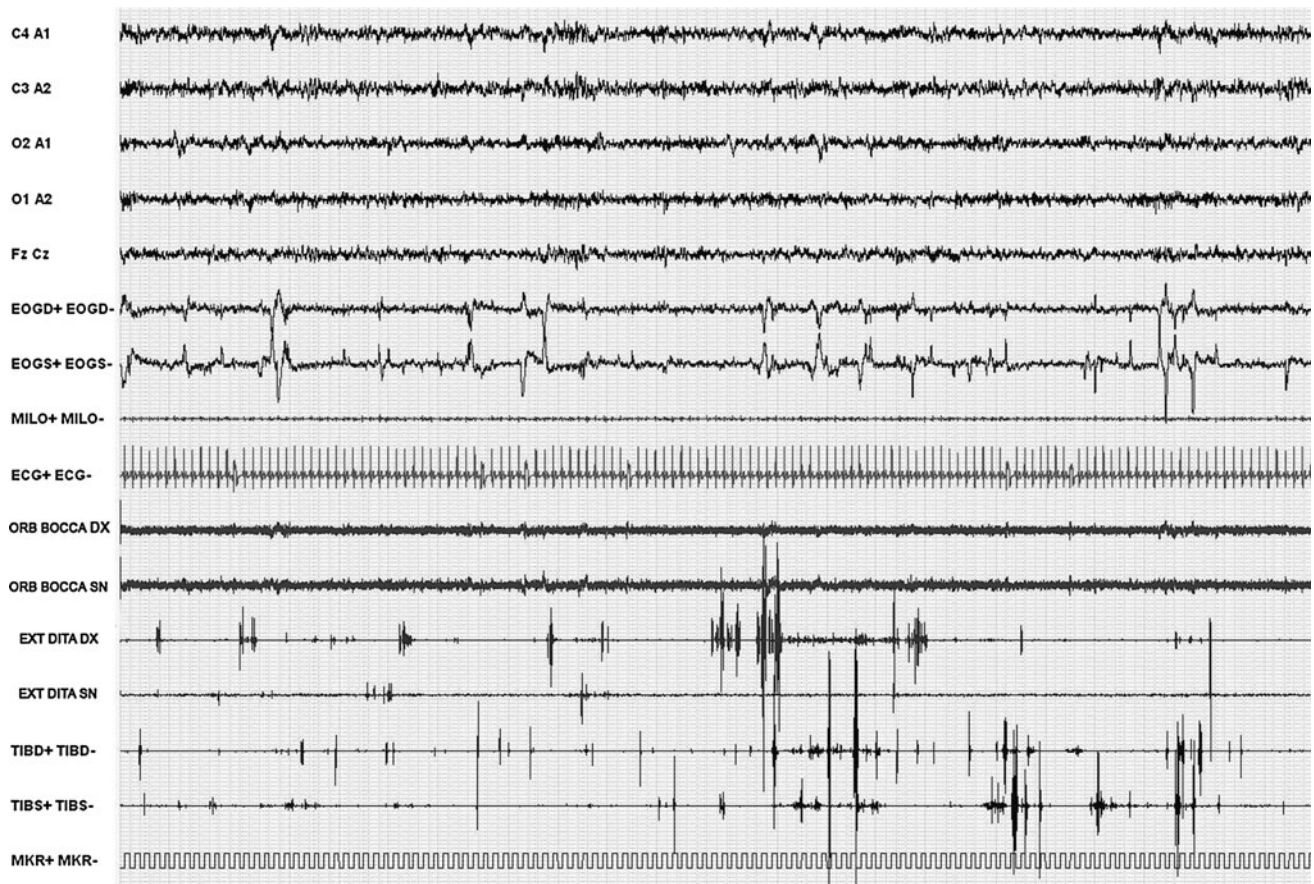


Fig. 3 EHFM episode in REM sleep

Carbamazepine 200 mg at bedtime and clonazepam 2 mg at bedtime represent alternative treatments for EHFMD [234].

Conclusions

SRMD are common and able to impair sleep. Physicians should make attention to these sleep complaints and, if necessary, perform neurophysiological examinations to diagnose them appropriately. Bearing in mind the consequences of a disrupted sleep on mental and physical health, a pharmacological treatment could be requested for severe and/or frequent forms of SRMD.

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