Movement Disorders of Sleep

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Introduction

Sleep is a complex biological process that involves cyclic changes of brain activity and is a very sensitive biomarker of brain functioning. Sleep is also important for overall physical and mental health and a sense of well-being. Several psychiatric disorders can lead to sleep disturbance and are associated with various sleep-related disorders. Conversely, sleep disorders can lead to a variety of behavioral and psychiatric symptoms. Disrupted sleep has long been linked to mental health issues. A specific subset of sleep disorders characterized by abnormal movements related to sleep can be precipitated by psychiatric disorders and medications commonly used to treat psychiatric symptoms. Mental health problems may also lead to significant sleep disruption and therefore can augment psychiatric symptoms. It is very important for mental health specialists to be familiar with the diagnosis and management of these conditions, which will be our primary focus in this chapter. We will review six different movement disorders associated with sleep, including clinical presentation, relationship to a variety of psychiatric conditions, and current treatment options.

Restless Leg Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD)

RLS is a common subjective sensorimotor condition, occurring while sedentary at night, characterized by predominantly nocturnal dysesthesias (an unpleasant sense of touch often perceived as pain) and relieved by limb movement. It was initially

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described in the mid-twentieth century [1]. In contrast, periodic limb movement disorder (PLMD) is an objective disease diagnosed with polysomnography (PSG) that can lead to frequent arousals at night. Both disorders are frequently comorbid.

Definitions and Diagnostic Criteria RLS is a sensorimotor disorder characterized by an irresistible urge to move the limbs, predominantly in the evening or at night. This is usually accompanied by a peculiar discomfort in the lower extremities often alluded to as a "creepy" or "crawly" feeling. RLS can result in sleep disturbance including insomnia and daytime fatigue. The four cardinal diagnostic features of RLS include: An uncontrollable urge to move the legs that is usually associated with paresthesias or dysesthesias; with symptoms that start or become worse with rest; at least partial relief of symptoms occurs with physical activity; and worsening of symptoms in the evening or at night [2].

PLMD is characterized by periodic episodes of repetitive limb movements during sleep, which most often occur in the lower extremities, including the toes, ankles, knees, and hips, and occasionally in the upper extremities. These movements may be associated with an arousal and, if so, the resultant sleep disruption can cause excessive daytime sleepiness (EDS). PLM-associated microarousals last between 3 and 10 seconds. Standard criterion for diagnosing PLMD has been established at ≥5 leg movements per hour during sleep; however, others have used 15 as the cutoff [2, 3]. Unlike RLS, PLMD is not usually associated with motor abnormalities or complaints during the waking state and is thus only diagnosed by PSG, with occasional complaints from bed partners.

PLMs may or may not be associated with restless legs syndrome (RLS), although most patients with RLS also have periodic limb movements (PLMs) [4]. Earlier, there was significant controversy in the medical literature about PLMD as a separate entity, particularly since initial diagnostic criteria did not include clinical symptoms as a necessary part of the definition, but only the presence of PLMs ≥5 per hour. In addition, there is no differentiation of PLMs due to sleep apnea, medication effect, or in association with some other disorder (e.g., narcolepsy or REM sleep behavior disorder) from PLMs without another specific cause, found as incidental finding in PSGs 5% to 6% in younger adults, and 25% to 58% among elderly people [5].

Prevalence The prevalence of RLS by community survey studies is estimated to vary between 1% and 29% [6–10]. RLS prevalence increases with age, in pregnancy, and among those with kidney failure. The prevalence of PLMD from small population-based studies is estimated to range from 4% to 11% in adults and up to 34% in older people [11–14]. Such repetitive leg movements are often associated with excessive sleep fragmentation, sleep disruption, and impaired daytime functioning [15].

Overlap Between RLS and PLMD Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) are distinguishable but overlapping disorders.

Both conditions are characterized by nocturnal involuntary limb movements (periodic limb movements or PLMs), but each has distinct clinical features. PLMD requires the presence of periodic limb movements in sleep (PLMS) on polysomnography as well as an associated sleep complaint whereas the diagnosis of RLS is made by meeting established clinical criteria. Approximately 80% of patients with RLS exhibit PLMs during sleep, and the presence of PLMs supports the diagnosis of RLS [16].

RLS, PLMD, and Other Sleep Disorders

RLS, PLMD, and Parasomnias A third of children with PMLD have a history of frequent parasomnias, which include sleepwalking, sleep terrors, and nightmares [17].

RLS, PLMS, and Obstructive Sleep Apnea (OSA) The association between RLS and OSA has been proposed by several authors [18–21]. Moro et al. found that 30% of patients who did not endorse any OSA symptoms, but did endorse insomnia or restless legs symptoms, were found to have OSA in PSG [18]. Passi et al., in a prospective study, found the prevalence of clinically significant restless legs syndrome (RLS) to be 8.3% in 60 sequentially polysomnographically studied patients with clinically significant OSA [19]. Patients with RLS who have comorbid OSA also are at increased risk of reporting insomnia, daytime sleepiness, nocturnal sweating, snoring, and gastroesophageal reflux. In a retrospective study of patients with OSA and RLS, the treatment of OSA significantly improved RLS symptoms in 71.4% of the patients [22]. In patients with clinically significant RLS, treatment of concomitant OSA significantly improved RLS symptoms, enabling drug therapy reduction in more than half of the patients.

RLS, PLMS, and Narcolepsy RLS and/or PLMS have also been found in association with narcolepsy, rapid eye movement behavior disorder (RBD) and insomnia [23–26]. In a study by Plazzi et al., narcolepsy patients had a significantly higher prevalence of RLS (14.7%) compared with normal controls (3.0%) [27]. The directional nature of this relationship is not clear. Modification in dopaminergic pathways has been implicated in both conditions [28, 29]. RLS must be considered in the evaluation and management of nocturnal sleep disruption in patients with narcolepsy given its high prevalence among those presenting with narcolepsy symptoms.

RLS, PLMD, and Psychiatric Disorders Difficulty falling asleep or maintaining sleep, poor sleep quality, nightmares, and EDS symptoms often seen in RLS are some of the key clinical symptoms of sleep disturbances observed in people with major depression, generalized anxiety disorder (GAD), bipolar disorder, and

posttraumatic stress disorder (PTSD) [30–34]. The symptoms of RLS are associated with reductions in patients' quality of life (QoL) and mental health. Research has established a relationship between the symptoms of RLS and mood symptoms, but causality is unclear. Sometimes symptoms of RLS precede those of depression or anxiety, and others relate the severity of mood symptoms to the severity of RLS symptoms [35].

A – Major Depression and Other Depressive Syndromes A two- to fourfold risk of depressive disorder in patients with RLS compared with healthy controls was reported in epidemiological studies [36]. Lee et al. in a large study demonstrated the interrelation between RLS, PLMD, and depression and found that compared with nondepressed people, depressed patients had a higher prevalence of RLS and PLMD [37]. Similarly, Chao et al. also found depressive symptoms to be more prevalent in the RLS group than in the non-RLS group [38]. They demonstrated that difficulty falling asleep, interrupted sleep, early morning awakening, and EDS were significantly more frequent among individuals with severe depression in the RLS group. Interestingly, red blood cell count was significantly lower in individuals with both severe depression and RLS [38]. The reason for these findings was not however clear to the authors questioning its clinical significance.

B – Anxiety Disorders Winkelmann et al., studying 130 patients with RLS, found a markedly greater prevalence of anxiety disorders among patients with RLS relative to a community comparison group RLS patients revealed an increased risk of having 12-month anxiety and depressive disorders with particularly strong associations with panic disorder (OR = 4.7; 95% CI = 2.1–10.1), generalized anxiety disorder (OR = 3.5; 95% CI = 1.7–7.1), and major depression (OR = 2.6; 95% CI = 1.5–4.4) [39]. Importantly, medications commonly used to treat anxiety disorders may play a role in precipitating RLS.

C – Schizophrenia Kang et al. studied 182 hospitalized people with schizophrenia for presence of RLS. The study was controlled with "normal" (free of psychiatric symptoms or psychiatric medications use) subjects recruited from a local community. They observed that 39 patients (21.4%) were found to have RLS and 87 patients (47.8%) met at least one of the RLS diagnostic criteria. The prevalence of RLS was significantly higher in the schizophrenia group than in the control group ($p = 0.009$), as were the RLS scores ($p < 0.001$) [40]. The presence of RLS predicted more severe psychotic symptoms. The cumulative dose of antipsychotic medication was not associated with the presence of RLS, suggesting that dosing is not the primary factor responsible for inducing RLS [40].

D – Other Psychiatric Disorders The prevalence of RLS in functional (psychogenic) movement disorders (FMD) is unknown. Serranovà et al. found FMD to be

associated with a twofold higher prevalence of RLS compared with those in the general population, consistent with prior research [41, 42]. Interestingly only 21% of patients with FMD had both RLS and clinically relevant PLM detected by actigraphy, suggesting false-positive cases either due to suggestibility or due to functional symptoms mimicking RLS [41]. Organic neurological and/or somatic comorbidities, medication use, and gender did not appear to affect RLS expression in patients with FMD, and FMD duration was not a risk factor for RLS development [41].

Psychotropic Medications and RLS Medications commonly used to treat psychiatric disorders have been found to either exacerbate or alleviate RLS symptoms. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are frequently used as first-line agents in the treatment of depression and anxiety disorders and have been associated with an increased incidence of RLS [43, 44]. Second-generation antipsychotics and antihistamines are strongly associated with RLS [39]. In contrast Bupropion, a unique dopamine-norepinephrine reuptake inhibitor with efficacy to treat major depression, does not seem to worsen RLS and may actually be beneficial [45]. Similarly, mirtazapine, which is an atypical antidepressant medication, has been shown not to exacerbate RLS.

RLS, PLMD, and Systemic Diseases

A – Kidney Disease RLS and PLMD have been found to be associated with a variety of systemic diseases. Rijsman et al. found RLS and PLMD in 58.3% and 70.8% of the patients with uremia undergoing dialysis [46]. Nearly all RLS patients had severe PLMD, and the combination was associated with poor sleep quality, insomnia complaints, depression, and emotional distress. Sleep fragmentation and sleep deprivation caused by RLS may contribute to the cardiovascular complications and infections, factors that add significant morbidity and mortality in dialysis patients [47]. Castillo-Torres et al. found a much lower incidence of RLS in Mexican dialysis patients (18%) but a strong association of RLS with iron deficiency anemia and uremic pruritus [48]. Wali et al. also found a lower prevalence of RLS in Saudi patients (19.4%) but demonstrated that most patients had moderate to severe RLS disease and a significant association with OSA and EDS [49]. Lee et al. reported greater prevalence of RLS among patients with non-dialysis-dependent chronic kidney disease (CKD), suggesting that end stage renal disease and not the dialysis procedure itself may be the culprit for RLS [50].

B – Cardiovascular Disease (CVD) Sleep is an important modulator of cardiovascular functioning that contributes to morbidity and mortality and has been linked to prevalent types of CVD, including hypertension, coronary artery disease, atherosclerosis, myocardial infarctions, coronary artery bypass surgery, congestive heart

failure, and stroke [51]. Autonomic arousals, characterized by heart rate variability, produce changes in the sympathetic and parasympathetic activity and contribute to the development of CVD [51]. A prospective study in the United Kingdom found an association between RLS and incidence of stroke, but not between RLS and ischemic heart disease [52]. Li et al. identified a significant association between long-term RLS and coronary disease showing that women with RLS lasting more than 3 years were at increased risk of coronary heart disease, independent of the main risk factors for coronary disease [53].

C – Pain Disorder RLS, pain, and sleep disorders are highly interrelated. Several studies have reported a high (31–64%) prevalence of comorbid RLS in patients with fibromyalgia [54]. The prevalence of RLS increased progressively with pain severity, and even more sharply with the degree of pain spreading with higher prevalence in multisite pain [55]. In fact, clinical management of RLS in patients with multisite pain may significantly improve sleep quality as an independent risk factor [56]. It has been suggested that the immune system plays a role in RLS development. Support for this hypothesis comes from the finding that RLS has been found in two-thirds of patient with psoriatic arthritis (PSA), which occurs when one's immune system attacks healthy cells and tissue, causing inflammation in joints and an overproduction of skin cells [57].

RLS, PLMD, and Neurological Diseases

A – Parkinson's Disease (PD) RLS and PD are conditions known for impaired dopaminergic transmission in the central nervous system and often co-occur. Silva et al. found that patients with PD and RLS have a higher prevalence of dyslipidemia than patients without RLS, suggesting a correlation between restless legs and hyperlipidemia, and leading to increased risk of cardiovascular risk in the patient population [58, 59]. According to a study by Fereshtehnejad et al., PD patients with RLS suffer from more anxiety, worse nutritional status, and worse quality of life than those without RLS [60]. Rana et al. also found an association of psychiatric problems and RLS in PD patients as they found the presence of RLS in PD patients to increase the occurrence of both anxiety and depression [61].

B – Headaches A meta-analysis of 11 case-control studies indicates a 2.65-fold higher RLS prevalence in individuals with migraine than in controls [62]. How RLS might be associated with migraine is unclear but both conditions are thought to involve the A11 dopaminergic nucleus of the dorsal-posterior hypothalamus [63, 64]. A11 nucleus is located in the periventricular, posterior region of the hypothalamus. Hypothalamic A11 nucleus receives innervation from midbrain and brainstem nuclei involved in pain modulation, particularly in the affective and emotional aspects of pain and the behavioral responses to aversive or threatening stimuli [65].

Furthermore, hypothalamic A11 nucleus is the major source of dopamine in spinal cord and is thought to have an important role in pathophysiological pathways in RLS [63]. Treatment of patients with concomitant RLS and migraine with immediate-release pramipexole has been found to improve both headache frequency and RLS symptoms [66]. The prevalence of RLS is also higher among individuals with tension headaches [67].

RLS and PLMD in Children

RLS, PMLS, Attention Deficit Hyperactivity Disorder (ADHD), and Other Psychiatric Disorders As in adults, RLS may lead to significant morbidity in children and adolescents because of the associated sleep disturbance that impacts attention, working memory and other higher-level cognitive functions, academic achievement, mood, behavior, quality of life, and family well-being [68]. Recent literature has documented the occurrence of RLS in children and adolescents, with a large population-based study finding a prevalence of 1.9% for ages 8–11 years and 2.0% for ages 12–17 years [17]. A survey of age of onset among 107 adult patients with RLS indicated that 19.6% reported an age of onset between 0 and 10 years, while 24.3% had an age of onset between 11 and 20 years [69]. Other studies have found that 38–45% of adult RLS subjects have onset of symptoms before age 20 years [69–71].

A significant association between ADHD symptoms and RLS symptoms has being reported [68, 72]. The first study on the comorbidity between ADHD and RLS, conducted with 69 children with ADHD by Picchietti et al. in 1998, showed that 11.5% of the patients with ADHD had RLS according to the pediatric version of the diagnostic criteria for RLS [71]. A study of Konofal et al. for 43 children with ADHD reported that 44% of the study subjects met RLS diagnostic criteria [73]. Kwon et al. assessed the rates of RLS in a sample of 56 Korean children with ADHD. About 42.9% of the participants presented with RLS symptoms, and 7.1% of these were diagnosed with probable or definite RLS [74].

The relationship between iron deficiency (iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis) and the hypodopaminergic theories for RLS is interesting, taking in consideration patients with ADHD. Children with ADHD are more likely to have iron deficiency and treatment with supplemental iron has been reported to improve sleep quality and subsequently decrease ADHD symptoms. Dopaminergic agents have been suggested as an option for both ADHD and RLS symptoms in children with ADHD not responsive to first line ADHD pharmacological treatment (i.e., psychostimulants) [73, 75, 76].

Genetics There has been emerging literature in support of PLMS being a marker or endophenotype for a specific common RLS genotype. In a study by Picchietti et al., a positive parental history of RLS was found in 53% of pediatric RLS cases and in 52% of pediatric PLMD cases [71]. Kotagal et al. found occurrence of RLS in 72% of biological parents of children with RLS, further supporting the familial predispo-

sition of childhood RLS noted earlier by Picchietti et al., and interpreted this finding to be consistent with an autosomal dominant pattern of transmission [77]. Interestingly, mothers were almost three times more likely to be the affected parent than fathers. A genome-wide association study by Stefansson et al. found a variant of BTBD9 on chromosome 6p to be implicated in RLS with PLMS (>5 per hour), but not RLS without PLMS [78].

RLS and Low Ferritin Levels Sun et al. found that serum ferritin levels below 50 μg/L in adults were associated with increased severity of RLS [79]. The same has been demonstrated in children [73, 77]. Adolescents may be at a greater risk of such exacerbation of RLS than adults because of the lower iron stores in this age group [77]. Oral iron therapy has resulted in subjective improvement in sleep-wake function among children with low serum ferritin levels [80].

Assessment of RLS Multiple subjective rating scales have been developed to assess RLS severity, sleep quality, and quality of life. The most commonly used are the International RLS study group (IRLSSG) rating scale (IRLS), and the Clinical Global Impression (CGI) scale [81]. Objective measurements are sleep-related parameters by polysomnography (PSG) (Periodic Limb Movements in Sleep; PLMS), PLM index (PLMI), PLMs arousal index (PLMS-AI), and sleep efficiency) or actigraphy [16].

Management of RLS and PLMD There is no specific treatment for PLMD. Treatment of PLMD is centered on pharmacological agents used in the treatment of RLS. The gold standard treatments are the dopamine receptor agonists, specifically pramipexole and ropinirole. Pharmacotherapy includes dopaminergic medications (levodopa or L-dopa, non-ergot derived dopamine agonist such as pramipexole, ropinirole), opioid medications, anticonvulsant medications (gabapentin, pregabalin, carbamazepine), and alpha-adrenergic agents (clonidine). Non-pharmacotherapies included cognitive-behavioral therapy (CBT) or exercise therapy.

Dopaminergic medications are the most used medications for RLS. Like patients with Parkinson Disease (PD), patients with RLS may develop dopamine dysregulation syndrome as well as addictive pattern of dopamine replacement therapy use and/or behavioral disturbances and impulse control disorders (pathologic gambling, compulsive shopping, compulsive eating, and hypersexuality) [16]. Pramipexole and Ropinirole are effective in the treatment of moderate-to-severe RLS. They are both well tolerated and their side effects are self-limited with cessation of therapy. The dopamine agonist pergolide is effective in the treatment of RLS but has been withdrawn in the United States because of the risk of cardiac valvulopathy. L-dopa is effective in the treatment of RLS, but often leads to augmentation phenomena. Hogl et al. reported during a 6-month multicenter, open-label trial with flexible dosing of L-dopa, augmentation occurred in 60% of the patients [82]. RLS with PLMD

is more likely to respond to dopaminergic agents than if not associated with PLMD [83].

Opioid medications are effective in the treatment of RLS, especially for patients with RLS that do not respond to other treatments. A retrospective review of 113 patients on long-term opioid therapy by Walters et al. demonstrated that opioids seem to have long-term effectiveness in the treatment of RLS and PLMD [84]. Long-term opioid therapy should be monitored clinically and/or by polysomnography monitored periodically for the development of sleep apnea.

Effective opioid doses are considerably lower in refractory RLS compared to those prescribed for chronic pain; nonetheless, our current opioid epidemic has also made opioid therapy for RLS less favorable. Other avenues of treatment should be considered before initiating treatment with opioids, including addressing low iron stores and combination therapy with nonopioid agents. In addition, before patients are started on opioids, they should be assessed for opioid use disorder and monitored closely once started.

Clonidine also has been shown to be associated with RLS symptom improvement in two small double-blind placebo-controlled studies. Side effects were frequent but mild, consisting of mostly dry mouth, impaired cognition, lightheadedness, sleepiness post dose, constipation, decreased libido, and headache [85, 86].

Gabapentin is effective in the treatment of mild-to-moderate RLS [16]. Sleep studies also showed a significantly reduced PLMS index and improved sleep architecture following use of Gabapentin [87]. Patients whose symptoms included pain benefited most from gabapentin. Potential side effects include sedation, dizziness, vision changes, and suicidal behavior and ideation. Two studies have shown the efficacy of pregabalin to treat moderate-to-severe RLS [88, 89]. Unsteady gait and daytime sedation were the most common side effects. One single large but short-term (5 weeks) double-blind study with placebo control showed carbamazepine to be significantly more effective than placebo [90]. There is insufficient evidence of efficacy of valproic acid or benzodiazepines on the treatment of RLS [91].

Iron supplementation has not been shown to be effective in the treatment of RLS, except perhaps in patients with proven iron deficiency [16]. Improvement in selected refractory cases has been reported [92, 93].

Accommodative strategies include sleep hygiene, behavioral and stimulation therapies (stimulating feet and toes with vibrations or electrical impulses), compression devices, exercise, and nutritional considerations have been tried in the treatment of RLS with insufficient data to assess its long-term efficacy [16]. A single open trial reported significant improvement with 8 weekly 90-min sessions in group therapy consisting of mindfulness-based exercises, stress-reduction strategies, diary-based analysis, and medical education [94].

Nocturnal Leg Cramps (NLC)

Nocturnal Leg Cramps (NLC) is a musculoskeletal disorder characterized by suddenly occurring, episodic, persistently painful, involuntary contractions of the calf, hamstrings, or foot muscles at night [95, 96]. It can occur in a third of

the population over age 50, with its prevalence increasing with advancing age. Some of these patients also experience cramps while resting during daytime. Living a sedentary life style as well as certain medical conditions such as chronic liver and renal failure, vascular diseases, magnesium or calcium deficiency, dehydration, and varicose veins have been identified as risk factors [96–98].

Definition and Diagnostic Criteria NLC can easily be confused with RLS and PLMD and may in fact coexist. Hallegraeff et al. identified seven criteria, derived from consensus, which can be used to differentiate NLC from RLS or PLMD [96]. These criteria include intense pain that lasts from seconds to a maximum of 10 minutes, localized to calf or foot but seldom in the thigh. It causes significant sleep disruption and distress [96].

Prevalence A large, representative study reported NLC occurring >5 per month in about 6% of the adult US population [99]. Many factors are associated with a greater risk of NLC including: older age, pregnancy, lower education, unemployment, other sleep problems (shorter sleep duration; nocturnal "leg jerks," snoring, snorting/gasping, difficulty falling asleep, difficulty maintaining sleep, nonrestorative sleep, sleepiness, use of sleep medications), higher BMI, smoking and alcohol use, hypertension, heart failure, angina, stroke, arthritis, respiratory disease, cancer, and depression [99].

NLC and Psychiatric Disorders NLC can cause significant emotional distress. It has been linked to depression, but the cause-effect relationship of these two conditions is not clear [99].

Iatrogenic NCL Certain medications are associated with increased risk for NLC including clonazepam, citalopram, celecoxib, gabapentin, diuretics, and zolpidem [100].

Management of NLC Managing the symptoms of patients with NLC can be a challenge and should include lifestyle interventions (increase fluid intake, avoid caffeine and alcohol, brief light exercise prior to bed and passive stretching/deep tissue massage), physical therapy, pain management, and treatment of underlying risk factors. Quinine, the only treatment proven to be (modestly) effective, may result in serious side effects and is no longer recommended for routine use [101]. Magnesium has a favorable side-effect profile, but appears to be no more effective than placebo [102]. Botulinum toxin (BTX) injection into the gastrocnemius muscles has shown to be effective in patients with NCL associated with lumbar spinal stenosis (LSS) [103].

Sleep-Related Rhythmic Movement Disorder (RMD)

Definitions and Diagnostic Criteria RMD consists of repetitive stereotypic movements, such as head banging or body rocking, that recur every second or so and may last from a few minutes to hours, usually prior to sleep onset [104]. RMD is common in very young children but can persist beyond childhood. RMD mostly comprises headbanging (HB), headrolling (HR), bodyrocking, and bodyrolling. It is classified as a sleep-wake transition disorder. However, it can be seen in all stages of sleep including rapid-eye-movement (REM) sleep during which muscle activity is completely absent [105].

The four cardinal diagnostic features of RMD include: (1) Patient displays repetitive, stereotyped, and rhythmic movements involving large muscle groups; (2) Movements are predominately related to sleep; (3) The repetitive movements result in a significant complaint by the patient or bed partner (this may involve at least one of the following: normal sleep interference, significant impairment of daytime functioning, actual or potential self-inflicted body injury); and (4) The movements are not explained by epilepsy or another movement disorder.

RMD is often a benign self-limited condition; however, injury, sleep disturbance, and daytime impairment are concerns of parents. Local trauma is more commonly seen as more severe injuries are rare. Cervical myelopathy, for example, has been associated with neck flexions in a child with RMD [106]. Moreover, there are social consequences of RMD as children may feel embarrassed by their behavior, leading to avoidance of social situations such as sleepovers and overnight camps [104].

Prevalence Parental reports indicate prevalence rates in children less than 3 years of age to be between 5.5% and 67% [107, 108]; however, the unusual wide prevalence is likely due to varied reporting. Gogo et al. demonstrated that the prevalence of RMD in infants and toddlers with objective home videosomnography was much lower at 2.8% [109].

Etiology and Pathogenesis The pathophysiology of RMD is poorly understood. The high reported prevalence of RMD in early childhood suggests a normal developmental variant. One plausible theory is that rhythmic movements are a learned behavior that soothes the child at sleep onset and following night awakenings [110]. This theory, however, does not explain more violent behaviors such as head-banging, nor does it explain movements during other stages of sleep.

RMD and Sleep Disorders Most isolated case reports have suggested the presence of comorbid sleep-related disorders in patients with RMD. Patients with RMD often have sleep-onset insomnia. It is unclear if sleep onset difficulties are induced by the movements or simply accompany them. The association with OSA and RMD has been reported in children and adults [111, 112].

RMD and Psychiatric Disorders An association between ADHD and RMD was suggested by Simonds et al. [113]. Whether sleep disruption from RMD leads to ADHD symptoms or whether the two problems share a common pathway is unclear [113]. Persistence of RMD beyond early childhood appears to be more common in association with neurodevelopmental disabilities. Kohyama et al. identified seven cases of coexisting psychiatric disorders or intellectual disability (ID) among 27 patients with RMD older than 10 years old [114]. ID, pervasive developmental disorder (PDD), and other psychiatric disorders must be ruled out in older children and adults with sleep-related RMD [115].

Management Etzioni et al. reported success in controlling RBD with tried sleep restriction and hypnotic medication [116]. The resolution of RMD with primarily sleep deprivation supports the hypothesis that it can be classified as a type of voluntary movement that serves as a self-soothing behavior in the process of falling asleep, rather than as an involuntary movement disorder [116]. Insomnia, if present, may need to be independently managed. Protective head gear or padding of cribs may prevent injuries from violent head movements.

There are no randomized controlled trials of pharmacological treatments for RMD and current knowledge is based on limited case studies. Benzodiazepines such as clonazepam have shown improvement in anecdotal literature [117–119]. Tricyclic antidepressants and dopamine agonist have showed some improvement in single case reports [120, 121]. More recently, a single case report showed a patient with repetitive head punching improving with dopaminergic antagonists [121].

Other concomitant sleep disorders should be excluded and properly treated. CPAP therapy, for example, has also been found to reduce the frequency of RMD in cases with comorbid sleep apnea [122]. Although usually a self-limiting disorder, RMD should be properly diagnosed and treated in order to prevent secondary social/psychological consequences, physical damage, and persistence into adulthood [116].

Bruxism

Bruxism is a condition in which you grind, gnash, or clench your teeth. If you have bruxism, you may unconsciously clench your teeth when you are awake (awake bruxism), or clench or grind them during sleep (sleep bruxism). Sleep bruxism is characterized by involuntary, unconscious movement during sleep. People with sleep bruxism may not know they're grinding their teeth, and the behavior can continue for years with significant health consequences. If untreated, sleep bruxism can break, loosen, or wear down teeth and lead to headaches, jaw pain, and temporomandibular joint (TMJ) disorder.

Prevalence A 2013 systematic review of the literature identified several large survey studies that reported a bruxism prevalence in adults of 8.0–31.4% [123].

Prevalence of sleep bruxism in children ranges from 5.9% to 49.6% [124]. Bruxism is often associated with neurodevelopmental disabilities and certain genetic conditions such as autism spectrum disorders, ADHD, Down syndrome, and Rett syndrome [125, 126].

Definition and Diagnostic Criteria Sleep bruxism is characterized by rhythmic masticatory muscle activity (RMMA) usually concomitant with microarousals that last about 3–15 seconds in duration [127, 128]. Sleep bruxism can occur during all stages of sleep, but is more common in non-REM stages 1 and 2, most frequently found within the ascending period of the sleep cycle. This period, when sleep patterns shift from NREM to REM, is associated with increased sympathetic tone and arousal activity.

Etiology and Pathogenesis Multiple etiologies have been proposed for Bruxism. The structural etiologic model argues that dental mal-occlusion is the root cause but there is lack of evidence. Adjusting dental occlusion may control the impact of sleep bruxism, but it has not been shown to lead to its resolution [127]. The functional etiologic model suggests that a combination of stress and specific personality traits such as a predisposition to anxiety plays a role. People with bruxism tend to be more introverted and anxious than people without bruxism [129]. Epidemiologic studies have demonstrated that bruxism can also be associated with emotional symptoms, peer problems, and higher total scores on a strength and difficulties questionnaire [130]. Bruxism often becomes more pronounced during stressful periods, like during school examinations, job difficulties, or marital strife [131, 132]. However, some evidence indicates negative correlations exist between psychological stress/disorders and sleep bruxism [133]. In addition, some studies have found stress to lead to awake bruxism but not sleep bruxism [134, 135].

Both awake and sleep bruxism are subclassified into either primary, not related to any other medical condition, or secondary, associated to neurological disorders or considered an adverse effect of drugs. Etiologies commonly associated to bruxism include encephalopathies, hyperthyroidism, gastrointestinal disturbances, and nutritional deficiencies [129]. Sleep bruxism has also been associated with obstructive sleep apnea, snoring, as well as daytime bruxism in children and adults [136]. Additional risk factors for bruxism include smoking or nicotine dependence [137]. Gastroesophageal reflux, movement disorders, and alcohol consumption have also been implicated [138]. Certain medications can also increase risk for bruxism, including serotonin reuptake inhibitors (SSRIs), amphetamines and L-dopa [139, 140]. These symptoms may improve once the underlying emotional stressor is treated or resolved.

Evaluation, Diagnosis, and Management As patients are usually not aware of their symptoms, making the diagnosis can be challenging. Bed partners or family members

may complain of the noise or tooth friction. Some patients present because of tooth wear or damage to previous dental work; others present due to headaches, clicking or pain in the temporomandibular joints. While bruxism has been implicated in myofascial temporomandibular disorder, a study looking at PSG of adult women with and without temporomandibular disorder did not show greater sleep bruxism in either group [141]. Extreme forms of bruxism involve forceful rhythmic grinding or clenching of the teeth with audible tooth contacts in about 20% of the patients. Excessive tooth wear and morning jaw pain seem to be the major factors in diagnosis.

Diagnosis of sleep bruxism is often based on clinical history, in addition to presence of abnormal tooth wear. Patients suspected of having bruxism should be evaluated with a PSG to rule out sleep disordered breathing. PSG with masseter muscle activity recording and audio-video recordings is important to rule out non-bruxism orofacial movements. EEG may be indicated if seizures are suspected.

Management strategies include the use of oral appliances, pharmacotherapy, and behavioral therapies. Montgomery et al. reported on the short-term use of diazepam reducing bruxism in 11 patients [142]. In two randomized, double-blind studies, administrating 1 mg single dose of clonazepam before sleep significantly reduced the bruxism index [143, 144]. Beneficial effects have also been reported with medications such as propranolol, L-dopa, pergolide, gabapentin, tiagabine, and atypical antipsychotics such as clozapine [145–147]. However, this latter medication is rarely used. A recent review concluded that bite splints are the treatment of choice, with clonidine and mandibular advancement devices demonstrating some utility [148]. In refractory patients, there is limited evidence that botulinum toxin (Botox) injections may show some benefit [140, 149].

Medication-induced bruxism improves once the implicated agent is discontinued. For patients with SSRI-induced bruxism, buspirone appears to have relieved the bruxism symptoms in a small series of cases [150]. Aripiprazole, a partial serotonin/dopamine agonist, has also been shown to effectively treat SSRI-induced awake bruxism [146].

Prevention focuses on identifying and treating risk factors associated with bruxism. Patients should be followed by a dentist to monitor dental wear and intervene if needed. For stress-related bruxism, psychological or psychiatric counseling may be helpful if underlying psychiatric disorder or emotional stress is identified.

Nocturnal Seizures/Frontal Lobe Epilepsy (FLE)

Frontal lobe seizures tend to be brief and nocturnal, with sometimes bizarre manifestations and preserved consciousness; thus, they can often be mistaken for parasomnias or psychiatric disorders.

Prevalence The frontal lobe contains 40% of the cerebral cortex, and frontal lobe seizures are the second most common type of seizures seen at presurgical centers for medical evaluation of drug resistant epilepsy [151].

Diagnostic Criteria The average age of onset is usually late childhood or early adolescence, with men and women equally affected. Frontal lobe seizures are often shorter in duration than seizures of temporal lobe origin, with a nighttime preponderance and association with the sleep-wake cycle. They can occur in nightly clusters of up to 70 seizures, and both convulsive and nonconvulsive status epilepticus are frequent [152].

Specific seizure types include focal clonic motor seizures, asymmetric tonic seizures with preserved consciousness, and hyperkinetic seizures, with the later more often occurring during sleep. Hyperkinetic seizures begin suddenly with complex behavioral automatisms. Patients may jump around, thrash, and rock to and fro. They may jump out of bed and run around in circles. Bicycling and stepping movements are often described [153, 154]. More subtle seizures can consist of awakening and moving around in bed. Motor manifestations can be accompanied by vocalization in the form of yelling, grunting, or laughing. Automatisms with sexual content are also reported in the form of pelvic thrusting and genital manipulation. Consciousness is often preserved and the patient returns to baseline quickly after the seizure. Ictal electrographic seizures may not be seen making diagnosis difficult, as they are often mistaken for psychogenic or nonepileptic events. Seizures typically occur in NREM sleep as opposed to REM behavior disorder. Seizures also tend to be very stereotypic in semiology which also helps in distinguishing epileptic events from parasomnias [154].

Etiology and Pathogenesis Frontal lobe epilepsy has multiple etiologies. Frontal lobe seizures can be due to cortical dysplasias and other malformations of cortical development, tumors, vascular malformations, or post-traumatic encephalomalacia [155]. Not infrequently, no identifiable lesion is found on brain imaging studies. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a channelopathy of the nicotinic acetylcholine receptor widely distributed in the frontal cortex. This usually manifests in childhood with clusters of brief, nocturnal seizures with bizarre hyperactive seizures or asymmetric tonic seizures without loss of consciousness [156]. Missense mutations of the gene for the neuronal nicotinic acetylcholine receptor alpha 4 subunit (CHRNA4) have been found to be the primary cause for ADNFLE [157]. More recently other gene mutations (GATOR1 complex gene, NPRL3, potassium channel KCNT1 and DEPDC5) have also been found in patients with ADNFLE [157–159].

FLE and Psychiatric Disorders FLE can often be mistaken for a psychiatric disorder, be misdiagnosed in lieu of a true psychiatric disorder, or may be comorbid with psychiatric illness. In a systematic review of patients with FLE by Gold et al., 27% of patients had a prior psychiatric history with a wide range of diagnoses, most commonly substance use and mood disorders [158]. Due to their seizure presentation, 15% of patients were misdiagnosed with psychiatric conditions such as antisocial personality disorder, dissociative disorder, ADHD, Tourette syndrome, bipolar disorder, and obsessive-compulsive disorder. Psychiatric manifestations were primarily

ictal in 74.2% of cases, postictal in 4.5%, or a combination in 21% [160]. In a psychiatric assessment of 59 children with FLE, about one-third of patients had intellectual disability and more than two-thirds had a psychiatric disorder. The most frequent psychiatric diagnosis was depressive disorder (35% of patients) followed by disruptive behaviors (23.5%), anxiety (20.6%), and bipolar or psychotic disorders (20.6%). Intellectual disability was associated with an earlier onset of psychiatric disorders and more frequent disruptive behavior disorders and aggressiveness [161].

Evaluation and Management An accurate and complete history and a neurologic exam are essential. Interictal EEG is often normal. If interictal spikes are observed, they can help to establish the diagnosis of epilepsy; however, this is often not the case. Prolonged overnight video EEG monitoring is often required for a definitive diagnosis. Not infrequently, ictal scalp EEG may not show definite epileptiform features and the diagnosis has to rely on clinical description and seizure semiology. Neuropsychological testing may show impairment of executive function, response inhibition, and social cognition [162]. Brain imaging studies are recommended to rule out structural intracerebral lesions.

Frontal lobe seizures can be challenging to treat. Several antiepileptic drugs have been used to treat frontal lobe seizures, including levetiracetam, lamotrigine, carbamazepine, oxcarbazepine, valproic acid, and zonisamide. Newer antiepileptic drugs (AEDs) such as lacosamide, perampanel, brivaracetam, and eslicarbazepine have shown to be effective in some cases [163–165]. Surgery is an option for medically refractory cases and should be considered for patients who have failed trials of two or more antiepileptic drugs. Resective surgery has better efficacy if a structural lesion is identified. In a longitudinal study of 70 frontal lobe epilepsy patients treated with resective surgery, 56% of patients were seizure-free at 1 year; however, only 45% were seizure-free at 3 years and 30% at 5 years confirming that long-term post-surgical seizure remission is not the norm [166]. The ideal surgical candidates are those who have MRI and electrophysiological evidence of epileptogenicity that is restricted to the frontal lobe, and in whom a complete resection of the epileptogenic zone is possible. Some authors have suggested the benefit of corpus callosotomy to prevent secondary generalization or of vagus nerve stimulation for medically refractory cases when other surgical procedures are not indicated [167, 168].

Conclusion

In conclusion, sleep-related movement disorders are common and can disrupt sleep. While some are benign and require reassurance with no further intervention, others may lead to significant daytime impairment, cognitive and emotional disturbances, and even more serious medical and psychiatric problems requiring further workup and pharmacological therapy. Several sleep-related movement disorders overlap with psychiatric conditions. It is therefore important for clinicians to be aware of

these disorders and to be knowledgeable about their etiology, comorbid conditions, diagnostic tools, and proper management.

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