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A Review of Normal and Abnormal Sleep Related Movement Disorder during Life Span

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ABSTRACT

The state of normal sleep is characterized by diminished responsiveness to external stimuli and a familiar feeling of delight and refreshment. This feeling is accompanied by muscle relaxation and slowing of brain activity. Nevertheless, body movements are a feature of normal sleep and when those impair sleep quality and consequent daytime function they are defined as abnormal. The introduction of polysomnography during which muscle activity is monitored by electromyography and videotaping enabled sleep researches to precisely assess the characteristics of normal and abnormal movements, to determine their appearance ~~is~~ at specific sleep stages and to define their severity in regard to sleep quality and their impact on daytime function. Indeed, abnormal movements during sleep became an essential part of the symptomatology of a number of neurodegenerative disorders. Normal and abnormal movement disorder related to sleep onset, particular sleep stages and during awakening from sleep will be described in some detail. Common and rare forms of sleep related movement disorders in children and adults will be reviewed.

Keywords: Sleep, Restless Legs, Periodic movements, REM, NREM, Myoclonus, REM behavior

Introduction:

Since ancient times the state of sleep was associated with death since in both conditions the body did not move and the brain "was uncurious". Hesiod, a Greek poet described in 800 BC the twin brothers; Thánasos (death) and Hypnos (sleep). However, motor activity during sleep was experienced and referred to as restless nights frequently associated with "pains and aches", worries, fearful dreams, disease state and aging.

The biblical description "Though I slumber, my heart is awake" (Shir HaShirim 5:1), is an ancient note that the brain is quite "awake" during sleep.

The concept of body movements during sleep as normal and abnormal sleep related phenomena was established when body movements were studied as an essential part of polysomnography. It became evident that alterations in neuronal firing controlling muscle tone at sleep onset lead to gradual decrease in muscle tone in muscles involved in postural control during Non-Rapid Eye Movement (NREM) sleep, reaching a crescendo in the form of generalized atonia spearing eye movements during Rapid Eye Movements (REM) sleep.

The average person and / or his bed partner will relate movements during sleep to either discomfort causing shifts of position, snoring and heavy breathing. Quite often will the couple decide to use different bedrooms, thus, when those normal movements became abnormal, the diagnosis and subsequent treatment may be significantly delayed. According to the International Classification of Sleep Disorders -3rd (ICSD--3) (Darien[1]), those disorders are shown in table 1.

In the present review the most common disorders will be discussed in some detail and a few rare disorders which are not included in Table 1 will be described.

Restless legs syndrome	Benign sleep myoclonus of infancy
Periodic limb movement disorder	Sleep related movement disorder due to medical disorder
Propriospinal myoclonus at sleep onset	Sleep related movement disorder due to medication or substance
Sleep related leg cramps	Sleep related movement disorder -unspecified
Sleep related bruxism	*Excessive fragmentary myoclonus
Sleep related rhythmic movement disorder	*Hypnagogic foot tremor & alternating leg muscle activation at sleep start
Excessive fragmentary myoclonus	

Table 1: Sleep Related Movement disorders according to ICSD-3 (1). *Isolated symptoms or normal variants

Normal body movements during sleep

The technical advance in sleep recordings starting at about 1970, enabled to view and record body position and movements during routine polysomnography (PSG). Early publications reported that an average of 10 posture changes and more than 200 smaller movements occur during one night sleep (Wilde-Frenz et al[2]). The rate of those movements was associated with particular sleep stages showing a gradual decrease in their rate in the following order; Wake, Sleep stage 1, and sleep stage 2, REM and sleep stage 3+4.

Stefani et al., in their seminal study of body movements during sleep (BMS) in 100 healthy adults have classified those movements into *Elementary*-small involuntary movements or stereotyped movements, and *complex*-showing complexity of action involving numerous muscle groups as well as violent movements (Stefani et al[3]). The elementary movements consist of *myoclonic* (sudden, brief, jerky), *non-myoclonic* (small non-jerky) and *stereotype* (smacking or fumbling). The complex movements involve multiple muscle groups (gesturing, reaching, grabbing) and also violent movements where the sleeper kicks or hits himself as well as talking, crying, laughing and cursing. In a quite recent study of 100 healthy adult volunteers, 6.8 large muscle movements / hour sleep, were recorded (6.2 in NREM and 8.4 in REM sleep). The number of movements was significantly higher in females while the mean duration of a movement event - about 12 seconds - was not gender related. There was a tendency to increased rate of those movements with age (Ibrahim et al.[4]).

Published data on BMS in preterm and term normal newborns are quite scares. In general, the number of BMS decrease with age (Fukumoto et al.[5]; Prechl et al[6]; Hakamada et al. [7]). However, when the rate of movements was calculated in relation to specific sleep stage, there was not decrease with age (Erkinjuntti [8]).

Disorders of body movements during sleep

When repetitive movements interfere with sleep it is considered as a "disorder". The current classification of BMS includes: periodic leg movements, alternating leg muscle activation, hypnagogic foot tremor, excessive fragmentary myoclonus, bruxism, and REM sleep without atonia (Berry et al.[9]). Additional disorders such as neck myoclonus, non-periodic leg movements, sleep-related periodic arm movements, sleep-related head jerks, and transient sleep related rhythmic movement disorder in children are also included. Of quite concern are the results of a retrospective longitudinal study by Lin et al. showing that sleep- related movement disorders increased the risk of all forms of dementia (Lin et al.[10]).

RESTLESS LEGS SYNDROME (RLS)

Willis was the first to describe in 1692 limb movements at sleep onset which impaired sleep. He also pointed out to the neurological source of those movements (Allen [11]). It was Karl-Axel Ekbom, who laid the clinical detailed basis of RLS in his seminal paper about 300 years later (Ekbom [12]). Several publications related to those movements prior to 1945 suggested that RLS is psychiatric disorder (Allen[11]). Although treatment with opioids was given already by Willis and 3 centuries later

by Henning (Hening et al.[13]), it was Akpinar who should be credited for the breakthrough in understanding the etiology of RLS and providing useful treatment (Akpinar [14]). Somewhat later this observation was confirmed by Montplaisir (Montplaisir et al. [15]), and extended also to Periodic Limb Movement Disorder (PLMD) by Lugaresi (Lugaresi, et al. [16]).

The clinical features of RLS are typical and therefore easy to diagnose with careful clinical history obtained from the patients who will report on a long lasting uncontrolled urge to move their legs as soon as they start activity from inactive or resting position. This occurs mainly in the evenings or at bedtime. The early notion that RLS is a psychiatric disorder stems from the fact that patients experience and report on feelings of creeping, crawling or tingling, which are slightly suppressed by moving their legs while in the majority of the patients there are no neurological deficits sufficient to explain the complaint. The net result of those symptoms is delayed sleep onset and shortened total sleep time with preserved daytime alertness.

It is customary to divide RLS in to "primary and secondary" types. In the primary group no apparent cause can be detected. The secondary group includes patients with multiples sclerosis, Parkinson disease, iron deficiency, pregnancy and renal disease. The prevalence of RLS is probably higher than the estimates published data due to underdiagnoses of mild cases. Nevertheless, in the adult general population of western countries the prevalence of RLS ranges between 5.5%-11.6% (Koo [17]; Didriksen et al. [18]). The prevalence of RLS in children and adolescents is about 1.9-2 % in the U.S. and U.K. Of those, 25-50 % were considered as moderate to severe (Sullivan [19]). There is a strong association between RLS and Attention Deficit Hyperactivity Disorder (ADHD). It was recently reported that 11-42.9% of children with ADHD had symptoms of RLS (Migueis et al. [20]). RLS is a common disorder during pregnancy because of hormonal issues as well as iron and folate deficiency (Mendes et al. [21]).

The neurobiology of RLS is believed to be related to low brain iron content, especially in the substantia nigra and to lesser extent in other subcortical areas (Rizzo et al. [22]). However, the issue of brain iron deficiency in RLS was recently challenged by studies suggesting that peripheral iron metabolism deregulation, rather than an absolute iron deficiency, is most probably the cause of RLS (Beliveau et al. [23]). However, the precise etiology of RLS is yet to be determined. Moderate to severe RLS affects not only sleep quality but also general health. In those cases treatment should be offered. Iron deficiency should be corrected which often will alleviate symptoms, but not in all patients. Dopamine agonist such as Gabapentin, Levodopa, Ropinirole, Pramipexole, Cabergoline and Pergolide are the drugs of choice. In many patients treated with dopamine and dopamine agonists, worsening of symptoms occur following a period of symptomatic relief. This quite common side effect known as "augmentation", may be prevented by initial treatment with gabapentin and gabapentin enacarbil instead of dopamine agonists (Garcia-Borreguero et al. [24]). It is not rare to encounter familial cases with RLS and positive family history is also very common, found in over 50% of cases. Indeed, twin and familial studies in Canada indicated that genetic factors play a role in the risk of developing RLS (Xiong et al.[25]; Xiong et al;[26]). Nevertheless, recent familial as well as genome-wide association studies were summarized as "no definitive causal variant or gene have been identified as causing RLS" (Akçimen et al. [27]).

PERIODIC LIMB MOVEMENTS DISORDER (PLMD)

This quite common disorder previously known as "nocturnal myoclonus", is associated with RLS in about 80% of the cases. The disorder is characterized by periodic, repetitive attacks of involuntary dorsiflexion of toes and ankles resembling the Babinski sign, sometimes with additional flexion of the hip and knee. Although quite simple to diagnose by careful history only, misdiagnosis and delayed diagnosis are not rare especially in patients with PLMD without RLS. Patients may be unaware of the movements but the bed partner may complain about being kicked during the night. Some of those patients are referred to the EEG laboratory to rule out epilepsy. PLMD starts during NREM sleep mainly during sleep stage 2. The exception are patients with REM sleep behavior disorder in whom PLMD starts during REM sleep. In some patients PLMD will present soon after falling asleep and will persist during the earliest sleep cycle while in others the movement events will be spread during several such cycles.

The definite diagnosis requires PSG with electromyography (EMG) recorded from the tibialis anterior muscle which is the most active muscle in producing the movements. More than 5 events per hour of sleep (PLMD index [PLMDi] $\geq$ 5/h) is generally considered as pathological, however, this cut-off point according to ICSD-3 is 15/h for adults and 5/h for children *only* when PLMD is causing sleep problems, which impacts daytime functioning in the absence of any other sleep, psychiatry, or medical illness (Stefani et al. [28]). The definite diagnosis requires the presence of sleep complains as well as daytime impaired alertness. Polysomnography with EMG and video monitoring is the golden standard diagnostic tool which in addition enables to determine the severity of PLMD and detect the presence of frequently associated conditions such as narcolepsy, obstructive sleep apnea (OSA), and REM sleep behavior disorder. Congestive heart failure, diabetes mellitus, cardiovascular, renal and hepatic disease, alcoholism, syringomyelia, as well a significant neurologic and psychiatric impairment are frequently associated with PLMD. Cognitive decline is also related to PLMD affecting specifically executive functions (Leng et al. [29]). A number of risk factors are known, among them are old age, drugs such as dopamine receptor agonists, antidepressants, Lithium carbonate and anticonvulsants (Tobback et al. [30]). The changes in sleep micro-and-macro structure in PLMD, affects negatively daytime function and modulation of sympathetic activity which negatively affects pulse rate and blood pressure (Chou et al. [31] ; Oksenberg et al.[32]) , and increases the risk of stroke (Haba-Rubio et al. [33]). It is estimated that 4-11% of adults in the general population suffer from PLMD (Drakatoset al. [34]). However, when the diagnosis of PLMD is supported by PSG enabling to score the severity of the syndrome, it was found that in subjects with PLMDi of $\geq$ 15/h, the prevalence ranged between 28-33% among

people with mean age of 56 years (Szentkirályi et al.[35]). PLMD is uncommon in children and when present it is frequently associated with co-morbidities. In a study of a large cohort of children in whom the diagnosis of PLMD and its severity were determined by PSG, 5.6% of the children were diagnosed with PLMDi of > 5/h. Out of those, 60 % suffered from OSA, while in only 1.2% of the children with PLMD, no co-morbidity was present (Kirk et al.[36]). Coexistence of PLMD and ADHD seems to be very high. Indeed, Picchietti reported that 90.6% of their cohort with moderated to severe PLMD suffered from ADHD (Picchietti et al.[37]), while Crabtree found that 44.4% of children with PLMD (PLMDi >5), had ADHD (Crabtree et al. [38]). Interestingly and challenging is the recent observation that periodic leg movements during sleep are not increased in children with ADHD (Fulda et al. [39]).

The pathogenesis of the disorder is still in debate. It was believed that cortical and subcortical regions are playing a role in causing the movement but more recent work pointed to the spinal cord as the main locus of interest. This assumption was based on the similarity of the movements of PLMD to the spinal withdrawal reflex (Bara-Jimenez et al. [40]; Aksu et al. [41]). It was suggested that the hyperexcitability of the spinal flexor network augmented during NREM sleep may trigger or exacerbate this movement disorder as well as RLS, especially in dopamine deficiency (Pockett et al.[42]). However, more recent work by Trotti suggested that the pathophysiology of PLMD could be related to reported dysfunction of calcium channels and/or dopaminergic system (Trotti [43]).

The above-mentioned theories suggest that Parkinson disease (PD) similar to RLS may be strongly related to PLMD. Surprisingly, in a quite recent observational study of 2205 patients with PD compared to only 25 patients without PD, is was concluded that PLMD was not significantly associated with PD. Moreover, the severity of PLMD did not differ between the groups studied (Hwang et al. [44]). It is quite surprising that in a recent study of sleep disorders in PD, PLMD was not included in a list of those disorders. Moreover, in this study using video-PSG, 162 patients with PD were compared to 58 controls. No significant difference in PLMDi was found between the groups (Dodet et al. [45]).

Since PLMD is considered as a continuum of RLS which is known for its association with iron deficiency (ID) and the benefit of iron supplementation, it was logical to assume that PLMD is also augmented by ID. However, the evidence of such an association is in doubt. Leung summarized their metanalysis of 93 papers related to ID and various sleep disorder by stating that the majority of the studies which were reviewed supported an association between ID and RLS and the positive effect of iron supplementation on insomnia induced by RLS. However, in regard to PLMD and several additional sleep disorders, the evidence was limited and called for additional research (Leung et al.[46]).

REM SLEEP BEHAVIOR DISORDER (RBD).

This form of sleep related movement disorder became the focus of interest for clinicians and researchers in the field of neurodegeneration. According to ICSD-3, the diagnostic criteria for RBD consist of: A. Repeated episodes of sleep- related vocalization and/or complex motor behaviors. B. These behaviors are documented by PSG to occur during REM sleep or, based on a clinical history of dream enhancement, are presumed to occur during REM sleep. C. PSG demonstrates REM sleep without atonia (REMWA). D. The disturbance is not better explained by another sleep disorder, mental disorder, medication or substance abuse (1). RBD affects about 1 percent of adults older than 60 years of age according to high quality studies in which combined video PSG and standard screening questionnaire were used (Haba-Rubio et al.[47]). The characteristic behavior of the patients during sleep is alarming for the bed partner. The patients are noticed to be awaken suddenly from a dream either laughing, gesturing, crying or singing (non- violent behavior) or screaming, kicking, punching, thrusting and leaping from the bed (violent behavior) . The patient may hit himself or his bed partner during such an episode. This behavior is the result of dream enhancement and occurs mostly in the second part of the night when REM periods become longer. Obviously, such patients will be referred promptly to medical attention. On the other hand, the diagnosis in patients with mild RBD as well as those with non-violent behavior, will be significantly delayed or reached when REMWA is detected during PSG done for other reasons, mainly OSA or PLMD. Patients with RBD are customary classified into primary or idiopathic (iRBD) and secondary or acquired RBD. The acquired form is associated with neurodegenerative disorders especially with synucleopathies such as PD, Multi-System Atrophy (MSA), and Dementia with Lewy bodies (DLB).

It is estimated that RBD is present in 30 - 50% of patients with PD, in 75% of patients with LBD and in 70%- 90% of patients with MSA (Boot et al [48]; Mahlknecht et al.[49]; Galbiati et al.[50]). Moreover, it was recently reported that 81–91% of patients with iRBD will develop either a definite neurodegenerative disorder or a mild cognitive impairment during a follow-up of at least 14 years (Schenck et al.[51]; Iranzo et al. [52]). Those findings indicate that iRBD is an early biological marker of neurodegeneration providing a chance for prevention of neurodegeneration when modifying therapies will be available. Other chronic progressive non-synucleopthies such as progressive supranuclear palsy, familial amyotrophic lateral sclerosis, frontotemporal dementia, myotonic muscular dystrophy, Wilson disease, cerebellar degeneration, and autoimmune encephalitis may be associated with, RBD, to lesser extent (Dauvilliers et al. [53]). Quite recently it was shown that the presence of variants in the gene encoding for the lysosomal enzyme glucocerebrosidase (GBA), are associated with increased risk of RBD (Krohn et al[54]). RBD can be triggered by antidepressants when taken for at least 4 years, which is usually reversible when the drug is discontinued (Boeve [55]).

The pathophysiology of RBD involves the pontine tegmentum and medial medulla, brain regions controlling muscle atonia during REM sleep. It was shown that the intermittent loss of atonia during REM sleep in BRD is caused by interruption or disinhibition of excitatory glutamatergic neurons located within the dorsal pre-coeruleus nucleus which activate spinal cord inhibitory interneurons (Boeve et al.[56]).

BENIGN SLEEP -RELATED REPETITIVE RHYTHMIC MOVEMENTS DURING SLEEP IN CHILDREN

Head-banging, head rolling and body rolling mainly at sleep- wake transition are not rare in young children and generally overlooked by experienced parents, however, only when those movements disrupt sleep, impair daytime functions or result in self- injury, they are considered as Sleep Related Rhythmic Movement Disorder (SRRMD). Indeed, those movements can cause scalp injury, skull fracture, subdural bleed and even alopecia (Lam et al.[57]). In the past, the prevalence of the disorder was studied using questionnaire information from children or parents without using questions based on ICSD -3 criteria. It was found that head or body movements in normally developing children are quite frequent during early infancy with gradual decrease in frequency with age, from about 60 % at the age of 9 months to about 6% at the age of 5 years (Klackenberg[58]). However, in a recent epidemiological study of a large population, quite lower prevalence of all forms of SRRMD was found. A prevalence of 2.7% was found among infants and toddlers using only screening questionnaires while it was 0.34% when the clinical diagnosis was confirmed by home video-PSG (Gogo et al.[59]). The most common form of SRRMD was body rocking followed by head rolling and head banging, in a descending order. It is assumed that SRRMD is caused by abnormalities of inhibitory control in the central motor pattern generator with irregular GABA release. Since impaired GABA release is also present in neurodevelopmental disorder (Chao et al. [60]), it was assumed that this fact may explain the high rate of SRRMD is those disorders.

Rare forms of Sleep Related Movement Disorders

PROPRIOSPINAL MYOCLONUS AT SLEEP ONSET AND AT SLEEP- WAKE TRANSITION

This is a rare, quite newly described form of propriospinal myoclonus (PSM) at sleep onset (Provini et al [61]). In PSM, there are rhythmic flexion /extension jerks starting in the thoracic paraspinal muscle, spreading caudally and cranially which occur typically during wakefulness just before sleep onset. PSM may be idiopathic or associated with conditions affecting the spinal cord such as trauma, tumor, MS, thoracic zoster, syringomyelia and spinal ischemia. This form of PSM occurs only during sleep-wake transition, thus it can be considered as a parasomnia (Guo et al. [62]).

PAROXYSMAL DYSKINESIA ON WAKING

This form of movement disorder belongs to a group of rare disorders classified as “Paroxysmal hypnogenic dyskinesia”. The few patients reported so far suffer from long standing episodes of involuntary movements involving face, trunk, and extremities exclusively on awakening, occurring each night and lasting few seconds during which consciousness is preserved. Neurological evaluation, EEG during and between episodes and brain MRI are normal. It was suggested that those patients belong to a more common group of patient with non-epileptic paroxysmal hypnogenic dyskinesia (Gau et al. [62]).

Conclusion:

Professor Perez Larvie, the pioneer and founder of sleep medicine in Israel, wrote in his book “The Enchanted World of Sleep “that for thousands of years sleep was viewed as a period between “Good evening and Good morning ,but no more than that…" (Lavie [63]). This could also apply to movements during sleep which were experienced for centuries either by the individual who kept turning in bed looking for a comfortable posture or by a person who was awaken when kicked by his/her sleeping bed partner. For persons with movement disorders during sleep, the “enchanted world” of sleep turns into fragmented, disrupted sleep. You may ask the intern if his last night was “enchanted “. The information given in this review is intended to increase the awareness of healthcare professionals to the presence and nature of those movements and help to provide tools for correct diagnosis and treatment. It should be obvious that recognition and treatment of those disorders are beneficial not only for sleep quality but can impact positively on general health and wellbeing.

References:

1. Darien IL American Academy of Sleep Medicine. The international Classification of Sleep Disorders –3rd mediation (ICSD -3).2014.
2. Wilde-Frenz J, Schulz H. Rate and distribution of body movements during sleep in humans. *Percept Mot Skills*. 1983; 56 (1):275-283.
3. Stefani A, Gabelia D, Mitterling T, Poewe W, Högl B, Frauscher B. A Prospective Video-Polysomnographic Analysis of Movements during Physiological Sleep in 100 Healthy Sleepers. *Sleep*. 2015;38 (9):1479-1487.
4. Ibrahim A, Ferri R, Cesari M, Frauscher B, Heidbreder A, Bergmann M, et al. Large muscle group movements during sleep in healthy people: normative values and correlation to sleep features. *Sleep*. 2023;46 (8):zsad129.
5. Fukumoto M, Mochizuki N, Takeishi M, Nomura Y, Segawa M. Studies of body movements during night sleep in infancy. *Brain Dev*. 1981; 3(1):37-43.
6. Prechl HFR, Nolte R (1984) Motor behaviour of preterm infants. In: Prechtl HFR (ed) Continuity of neural functions from prenatal to postnatal life. *Clin Dev Med* 94: 79–92. Blackwell, Oxford.
7. Hakamada S, Watanabe K, Hara K, Miyazaki S. Development of the motor behavior during sleep in newborn infants. *Brain Dev*. 1981; 3(4):345-350.
8. Erkinjuntti M. Body movements during sleep in healthy and neurologically damaged infants. *Early Hum Dev*. 1988;16(2-3):283-292.
9. Berry RB, Quan SF, Abreu AR, et al. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester: American Academy of Sleep Medicine; 2020.
10. Lin CC, Chou CH, Fan YM, Yin JH, Chung CH, Chien WC, et al. Increased Risk of Dementia Among Sleep-Related Movement Disorders: A Population-Based Longitudinal Study in Taiwan. *Medicine (Baltimore)*. 2015 Dec; 94(51):e2331.
11. Allen RP. Restless legs syndrome/Willis Ekbom disease: Evaluation and treatment. *Int Rev Psychiatr*. 2014; 26 (2):248-262.
12. Ekbom KA. Restless leg. *Acta Med Scan* 1954; 10:868-873.
13. Hening WA, Walters AS, Wagner M, Rosen R, Chen V, Kim S, et al. Circadian rhythm of motor restlessness and sensory symptoms in the idiopathic restless legs syndrome. *Sleep*. 1999 ;22 (7):901-912.
14. Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide. *Arch Neurol*. 1982; 39 (11):739 .
15. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disord*. 1997;12(1):61-65.
16. Lugaresi, E., Coccagna, G., Berti Ceroni, G., Ambrosetto, C. Restless legs syndrome and nocturnal myoclonus. In H. Gastaut, E. Lugaresi & G. Berti Ceroni (Eds), The Abnormalities of Sleep in Man (pp.285-294).*Bologna:Aulo Gaggi Editore*.1968 .
17. Koo BB. Restless leg syndrome across the globe. Sleep Med Clin. 2015;10(3):189–205.
18. Didriksen M, Rigas AS, Allen RP, Burchell BJ, Di Angelantonio E, Nielsen MH, et al. Prevalence of restless legs syndrome and associated factors in an otherwise healthy population: results from the Danish Blood Donor Study. *Sleep Med*. 2017; (36):55–61.
19. Sullivan SS. Current treatment of selected pediatric sleep disorders. *Neurotherapeutics*. 2012; 9(4):791-800.
20. Migueis DP, Lopes MC, Casella E, Soares PV, Soster L. Spruyt K. Attention deficit hyperactivity disorder and restless leg syndrome across the lifespan: A systematic review and meta-analysis. *Sleep Med Rev*. 2023; 69:1-14.
21. Mendes A, Silva V. Possible etiologies of restless legs syndrome in pregnancy: a narrative review. *Sleep Sci*. 2022; 15(4):471-479.
22. Rizzo G, Li X, Galantucci S, Filippi M, Cho YW. Brain imaging and networks in restless legs syndrome. *Sleep Med*. 2017; 31:39-48.
23. Beliveau V, Stefani A, Birkl C, Kremser C, Gizewski ER, Högl B, et al. Revisiting brain iron deficiency in restless legs syndrome using magnetic resonance imaging. *Neuroimage Clin*. 2022; 34:103024.
24. Garcia-Borreguero D, Silber MH, Winkelman JW, Högl B, Bainbridge J, Buchfuhrer M, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. *Sleep Med*. 2016; 21:1-11.
25. Xiong L, Jang K, Montplaisir J, Levchenko A, Thibodeau P, Gaspar C, et al. Canadian restless legs syndrome twin study. *Neurology*. 2007; 68(19):1631–1633.
26. Xiong L, Montplaisir J, Desautels A, Barhdadi A, Turecki G, Levchenko A, et al. Family study of restless legs syndrome in Quebec, Canada: clinical characterization of 671 familial cases. *Arch Neurol*. 2010; 67(5):617–622.
27. Akçimen F, Dion PA, Rouleau GA. Progress in the genetics of restless legs syndrome: the path ahead in the era of whole-genome sequencing. *Sleep*. 2022 11; 45(8):zsac136.
28. Stefani A, Heidbreder A, Hackner H, Högl B. Validation of a leg movements count and periodic leg movements analysis in a custom polysomnography system. *BMC Neurol*. 2017;17(1):42.
29. Leng Y, Blackwell T, Stone KL, Hoang TD, Redline S, Yaffe K. Periodic Limb Movements in Sleep are Associated with Greater Cognitive Decline in Older Men without Dementia. *Sleep*. 2016; 39(10):1807-1810.
30. Tobback E, Desmet O. Analysis of Risk Factors for Periodic Limb Movements in a Large Cohort of Insomnia and Chronic Fatigue Patients. *Pharmacopsychiatry*. 2020; 53:71-7.
31. Chou CH, Yin JH, Chen SY, Lin CC, Sung YF, Chung CH, et al. The potential impact of sleep-related movement disorders on stroke risk: a population-based longitudinal study. *QJM*. 2017; 110(10):649-655.

32. Oksenberg A, Gadoth N. Periodic limb movements and heart rate changes. *J Clin Sleep Med*. 2012 ;8(4):447-449.
33. Haba-Rubio J, Marti-Soler H, Tobback N, Andries D, Marques-Vidal P, Vollenweider P, et al. Clinical significance of periodic limb movements during sleep: the HypnoLaus study. *Sleep Med*. 2018;41:45-50.
34. Drakatos P, Olaithe M, Verma D, Ilic K, Cash D, Fatima Y, et al. Periodic limb movements during sleep: a narrative review. *J Thorac Dis*. 2021;13(11):6476-6494.
35. Szentkirályi A, Stefani A, Hackner H, Czira M, Teismann IK, Völzke H, et al. Prevalence and associated risk factors of periodic limb movement in sleep in two German population-based studies. *Sleep*. 2019; 42:zsy237.
36. Kirk VG, Bohn S. Periodic limb movements in children: prevalence in a referred population. *Sleep*. 2004; 27(2):313-315.
37. Picchietti DL, Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. *Sleep*. 1999;22(3):297-300.
38. Crabtree VM, Ivanenko A, O'Brien LM, Gozal D. Periodic limb movement disorder of sleep in children. *J Sleep Res*. 2003; 12(1):73–81.
39. Fulda S, Miano S. Time to rest a hypothesis? Accumulating evidence that periodic leg movements during sleep are not increased in children with attention-deficit hyperactivity disorder (ADHD): Results of a case–control study and a meta-analysis. *Sleep*. 2023;46(6):1-13.
40. Bara-Jimenez W, Aksu M, Graham B, Sato S, Hallett M. Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. *Neurology*. 2000 ;25;54(8):1609-1616.
41. Aksu M, Bara-Jimenez W. State dependent excitability changes of spinal flexor reflex in patients with restless legs syndrome secondary to chronic renal failure. *Sleep Med*. 2002;3(5):427-430.
42. Pockett C, Kirk V. Periodic limb movements in sleep and attention deficit hyperactivity disorder: Are they related? *Paediatr Child Health*. 2006;11(6):355-358.
43. Trotti LM. Restless Legs Syndrome and Sleep-Related Movement Disorders. *Continuum. (Minneap Minn)*. 2017;23(4, Sleep Neurology):1005-1016.
44. Hwang SR, Hwang SW, Chen JC, Hwang JH. Association of periodic limb movements during sleep and Parkinson disease: A retrospective clinical study. *Medicine (Baltimore)*. 2019 ;98(51):e18444.
45. Dodet P, Houot M, Leu-Semenescu S, Corvol JC, Lehéricy S, Mangone G, et al. Sleep disorders in Parkinson's disease, an early and multiple problem. *NPJ Parkinsons Dis*. 2024; 10 (1):46.
46. Leung W, Singh I, McWilliams S, Stockler S, Ipsiroglu OS. Iron deficiency and sleep - A scoping review. *Sleep Med Rev*. 2020; 51:101274.
47. Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, Tobback N, Andries D, et al. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. *Sleep*. 2018 1; 41(2):zsx197.
48. Boot BP, Boeve BF, Roberts RO, Ferman TJ, Geda YE, Pankratz VS, et al. Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. *Ann Neurol*. 2012; 71(1):49-56.
49. Mahlknecht P, Seppi K, Frauscher B, Kiechl S, Willeit J, Stockner H, et al. Probable RBD and association with neurodegenerative disease markers: A population-based study. *Mov Disord*. 2015;30(10):1417-1421.
50. Galbiati A, Verga L, Giora E, Zucconi M, Ferini-Strambi L. The risk of neurodegeneration in REM sleep behavior disorder: A systematic review and meta-analysis of longitudinal studies. *Sleep Med Rev*. 2019; 43:37-46.
51. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med*. 2013;14(8):744–748.
52. Iranzo A, Fernandez-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. *PLoS ONE*. 2014; 9(2):e89741.
53. Dauvilliers Y, Schenck CH, Postuma RB, Iranzo A, Luppi PH, Plazzi G, et al. REM sleep behaviour disorder. *Nat Rev Dis Primers*. 2018 30; 4(1):19.
54. Krohn L, Ruskey JA, Rudakou U, Leveille E, Asayesh F, Hu MTM, GBA variants in REM sleep behavior disorder: A multicenter study. *Neurology*. 2020 25; 95(8):e1008.
55. Boeve, BF. REM sleep behavior disorder: updated review of the core features, the RBD-Neurodegenerative Disease Association, evolving concepts, controversies, and future directions. *Ann NY Acad. Sci* 2010: 1184, 15–54.
56. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain*. 2007;130(Pt 11):2770-2788.
57. Lam N, Veeravigrom M. Sleep- related rhythmic movement disorder in children: a mini- review. *Front Neurol*. 2023; 14: 1165130).
58. Klackenberg G. Rhythmic movements in infancy and early childhood. *Acta Paediatr Scand*. 1971; 224:74.e83.
59. Gogo E, van Sluijs RM, Cheung T, Gaskell C, Jones L, Alwan NA, et al. Objectively Confirmed prevalence of sleep-related rhythmic movement disorder in pre-school children. *Sleep Med*. 2019: 53:16–21.
60. Chao HT, Chen H, Samaco RC, Xue M, Chahrour M, Yoo J, et al. Dysfunction in GABA signaling mediates autism-like stereotypies and Rett syndrome phenotypes *Nature*. 2010; 468 (7321): 263-269.
61. Provini F, Vetrugno R, Meletti S, Plazzi G, Solieri L, Lugaresi E, et al. Propriospinal myoclonus at the sleep-wake transition: a new type of parasomnia. *Sleep*. 2001; 24:835–843.
62. Guo Q, Yang Y, Lin Y, Li L, Zhan S, Liu A, et al. Paroxysmal dyskinesia on waking: two case reports. *Sleep Med*. 2016; 25:63-66.
63. Lavie P. The enchanted world of sleep. 1996, Yale University Press, New Haven and London

