Autonomic Neuroscience: Basic and Clinical 220 (2019) 102554

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Review

Restless legs syndrome, periodic limb movements during sleep and cardiovascular risk

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ARTICLE INFO

Keywords:
Restless legs syndrome
Periodic limb movements during sleep
Hypertension
Cardiovascular risk
Autonomic dysfunction

ABSTRACT

Multiple mechanisms may modulate an association between restless legs syndrome/Willis-Ekbom disease (RLS/WED) and cardiovascular disease (CVD), including chronic sleep deprivation, intermittent, periodic limb movements in sleep (PLMS)-related autonomic fluctuations and possible autonomic dysfunction intrinsically associated with RLS per se. The purpose of this paper is to review the existing RLS/WED literature focusing on the pathophysiologic evidence for possible associations between RLS/WED and PLMS with CVD and events (CVE). Specific intrinsic dysautonomic aspects of the disease, which may contribute to generating CVD, are separately discussed. The association between RLS/WED and both CV risk factors and CVD still remains elusive. Although several shared pathophysiological causes could explain these possible relationships, the emerging body of literature focusing on these disorders remains controversial. Not only longitudinal population-based studies and meta-analyses, but also more animal models and therapeutic interventions are needed in order to build a sufficiently robust body of evidence on this topic.

1. Introduction

Restless legs syndrome, also known as Willis-Ekbom disease (RLS/WED), is a bothersome neurological sensorimotor disorder that requires the following subjective clinical criteria to be diagnosed: (1) urgency to move the legs, usually with unpleasant sensations; (2) appearance of symptoms during inactivity or rest; (3) relief with movement; (4) a worsening condition in the evening or at night; (5) such features are not solely accounted for as symptoms primary to another medical or a behavioral condition (Box 1). The latest updated consensus includes the following 4 clinical features supporting the diagnosis of RLS/WED: (1) periodic limb movements (PLM) in sleep (PLMS) or resting wake (PLMW) at rates or intensity greater than expected for age or medical/medication status; (2) dopaminergic treatment response; (3) family history of RLS/WED among first-degree relatives; and (4) lack of profound daytime sleepiness (Allen et al., 2014).

RLS/WED symptoms vary considerably in frequency and severity. Symptoms may also remit for various periods of time, especially in the initial phase of the disease. The prevalence of RLS in general population ranges between 3% and 10%, with a double rate in females compared to males (Hogl et al., 2005; Ohayon and Roth, 2002; Ulfberg et al., 2001; Allen et al., 2011; Allen et al., 2003; Allen et al., 2005; Berger et al., 2004). Multiple medications may also trigger or aggravate RLS/WED such as antidepressants, lithium, neuroleptics and antihistaminics (Dauvilliers and Winkelmann, 2013).

PLMS are sleep-related stereotyped motor events, typically characterized by a dorsal extension of the foot and big toe, often in combination with partial flexion of the ankle, the knee, and sometimes the hip. First observed by Allison and first recorded by Lugaresi and colleagues (Lugaresi et al., 1972; Coleman et al., 1980; Coleman et al., 1981) PLMS are now defined by runs of at least four consecutive leg movements (CLM) with an inter-movement interval ≥ 10 and ≤ 90 s, and with a duration of each LM ranging between 0.5 and 10 s (Ferri et al., 2016). Periodic limb movements (PLMs) during sleep are present in 80–90% of patients with RLS/WED, but may occur in other sleep disorders and in the elderly (Ohayon and Roth, 2002; Montplaisir et al., 1997).

Two different phenotypes of RLS/WED may be recognized: 1) early-onset primary or idiopathic RLS/WED, the most frequent form, with a peak onset around 20–40 years of age, frequent RLS/WED familial history, slow disease evolution, and in some studies, low cerebrospinal fluid (CSF) ferritin levels; 2) late-onset RLS/WED with a peak onset

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https://doi.org/10.1016/j.autneu.2019.102554
Received 18 January 2019; Received in revised form 20 May 2019; Accepted 28 May 2019

Box 1
2012 revised IRLSSG diagnostic criteria for RLS.

Essential Diagnostic Criteria (all must be met)

1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.[1,2]
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.[3]
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.[4]
5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).[5]

Specifiers for Clinical Course of RLS[6]

A. Chronic-persistent RLS: Symptoms when not treated would occur on average at least twice weekly for the past year.
B. Intermittent RLS: symptoms when not treated would occur on average < 2/week for the past year, with at least 5 lifetime events.

Specifier for Clinical Significance of RLS

The symptoms of RLS cause significant distress or impairment in social, occupational, educational or other important areas of functioning by the impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

Footnotes:
[1]Sometimes the urge to move the legs is present without the uncomfortable sensations and sometimes the arms or other parts of the body are involved in addition to the legs.
[2]For children, the description of these symptoms should be in the child s own words.
[3]When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.
[4]When symptoms are very severe, the worsening in the evening or night may not be noticeable but must have been previously present.
[5]These conditions, often referred to as "RLS mimics", have been commonly confused with RLS particularly in surveys because they produce symptoms that meet or at least come very close to meeting criteria 1–4. The list here gives some examples of this that have been noted as particularly significant in epidemiological studies and clinical practice. RLS may also occur with any of these conditions, but the RLS symptoms will then be more in degree, conditions of expression or character than those usually occurring as part of the other condition.
[6]The clinical course criteria do not apply for pediatric cases nor for some special cases of provoked RLS such as pregnancy or drug-induced RLS where the frequency may be high but limited to duration of the provocative condition.

after 40 years of age, less frequent familial history, more rapid disease evolution, and more frequent association with other chronic diseases (neuropathy, myelinopathy, multiple sclerosis, Parkinson's disease, Crohn's and coeliac diseases, arthritis, diabetes), some associated with iron deficiency (renal failure, anemia and pregnancy).

It has recently been suggested to overcome the aforesaid dual model of RLS/WED and rather to view it as a complex interaction of genetic and environmental factors: the more genetic factors contribute to the manifestation of RLS/WED, the fewer comorbid medical conditions are needed to develop the phenotype of RLS/WED (Fig. 1). This gains importance in the context or RLS/WED and CVD, as primarily genetic manifestations of RLS/WED may not be significant contributors to incident CVD, while manifestations of RLS/WED mostly associated with comorbid conditions may be potentially important contributors to CVD, with more severe and longer duration exposures portending poorer outcomes (Trenkwalder et al., 2016; Trenkwalder et al., 2018). Indeed, secondary forms of RLS/WED may carry a greater risk for CVD through the RLS/WED-associated conditions that gave rise to the RLS/WED symptoms (Wong et al., 2015). Moreover, PLMS are often time-related with cortical arousals and autonomic activations and their long-term implications with insomnia and cardiovascular diseases (Portaluppi et al., 1997; Portaluppi et al., 2009).

Although the existing literature already boasts a few reviews regarding the topic presented in this work, our purpose is to update the readers on the latest advances regarding the pathophysiologic evidence for possible associations between RLS/WED and PLMS with cardiovascular disease (CVD) and events (CVE). Besides reviewing and integrating the data supporting RLS as a risk factor for CVD, including the role of PLMS and sleep deprivation, we put particular focus on the intrinsic dysautonomic aspects of RLS, which are specific to the disease and consist, all in all, in an increased sympathetic output from the intermedio-lateral nucleus of the spinal cord.

2. Methods

An initial PubMed search was completed from January 1st, 2000 to November 31st, 2018 using the following terms or combination of terms: restless legs syndrome, periodic leg movements, insomnia, hypertension, blood pressure, heart rate variability, sympathetic, cardiovascular, endothelium, congestive heart failure, dyslipidemia, diabetes, stroke, myocardial infarction. The search strategy was limited to studies in humans and published in the English language indexed on PubMed. Single case reports were excluded. Additional studies were identified within the bibliographies from the retrieved articles.

3. Pathophysiology of RLS/WED

The empirical evidences coming from the pharmacological treatment of RLS guided most of the research in understanding its pathophysiology. The benefit of dopamine agonists, iron supplementation and opioids in RLS suggested the investigation of the dopaminergic and the nociceptive pathways, as well as the iron regulating system as three major pathogenic hypotheses (Allen, 2015). Besides, the frequent familial segregation of RLS/WED stimulated important genetic discoveries, which may only partly be related to the three mechanisms mentioned above. So far, a total of 19 risk loci for RLS/WED have been

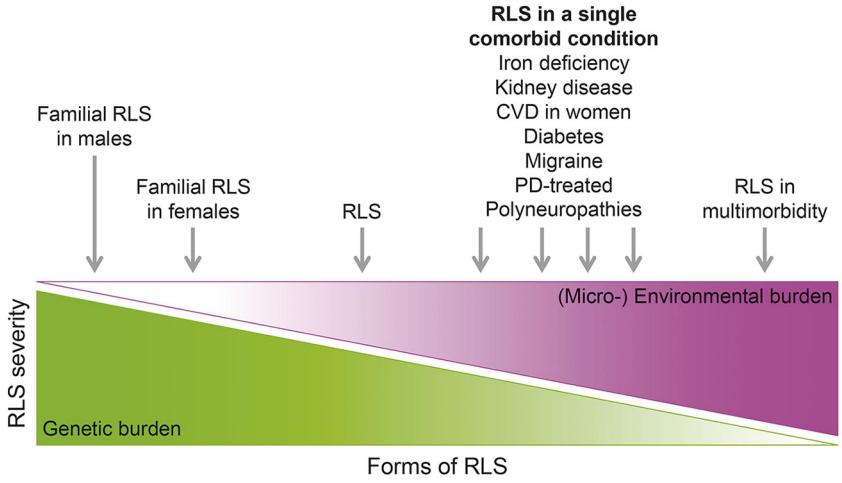

Fig. 1. Model of the hypothesis that the more genetic factors contribute to the manifestation of restless legs syndrome (RLS), the less environmental trigger is needed. CVD = cardiovascular disease, PD = Parkinson's Disease.
Reprinted with permission from Trenkwalder et al. (2016).

found through genome-wide association studies (GWAS), with the strongest signal being in *MEIS1*, a member of the three amino acid loop extension homeobox gene class involved in the development and homeostasis of numerous organs and diseases such as leukemia and neuroblastoma, and also plays a role in the development of the CNS. One of these loci, namely BTBD9, seems to hold a relationship with the PLMS motor sign of RLS/WED (Moore et al., 2014). These findings support the link to neurogenesis, changes in neuronal circuit formation, synaptogenesis, and axonal guidance, thereby strengthening the concept of RLS/WED as a possible neurodevelopmental disorder (Schormair et al., 2017).

RLS/WED has been related with iron deficiency, with a major role of the central nervous system iron status, as confirmed by cerebrospinal fluid (CSF) ferritin studies and brain iron deficiency studies (Mizuno et al., 2005; Earley et al., 2000; Earley et al., 2014; Allen et al., 2001). There seems to be a regional rather than a global brain iron deficiency, as the areas most consistently showing reduced iron deposits include the thalamus, *substantia nigra* and, to a lesser extent, the putamen and caudate (Provini and Chiaro, 2015). Overall, a failure to provide adequate iron transport across the blood-brain barrier and into critical neuronal cells because of impairment of extracellular and intracellular iron transport has also been postulated (Connor et al., 2011). Of interest, the two major expected pathophysiologic consequences of brain iron deficiency have been documented: hypoxia and myelin loss (Allen, 2015).

Over the last years, the initial deduction, based on clinical practice, that a dopamine (DA) deficiency is at the heart of RLS/WED has been substituted with the concept of a "hyper-dopaminergic" presynaptic state (increased synthesis, release and decreased uptake of DA leading to increased synaptic DA) in balance with and/or in opposition to a "hypo-dopaminergic" postsynaptic state (decreased dopamine receptors D2/3R) (Earley et al., 2014). Which components of the pre-post-synaptic interplay are primary, secondary or compensatory remains uncertain, depending on which one is considered to be the initiating problem.

Any theory regarding dopaminergic dysfunction in RLS/WED must embrace the strikingly circadian nature of RLS/WED symptom expression, a fairly unique clinical phenotype in neurology and an integral element of the disease. Indeed, there are several proofs that DA metabolism follows a circadian rhythm bot in humans as well as in animal models (Veldman et al., 2001; Garcia-Borreguero et al., 2004; Earley et al., 2006; Kim et al., 2017).

The neural substrate and circuitry contributing to RLS/WED remains speculative. Animal models of RLS/WED pointed at the descending hypothalamic inhibitory dopaminergic pathways that from the A11 region project throughout the entire spinal cord, but preferentially to the dorsal (sensory) and to the intermedio-lateral nucleus (IML, autonomic) of the spinal gray matter, with the latter representing the final common output of the spinal sympathetic system (Clemens et al., 2006; Ondo et al., 2000; Qu et al., 2006). As the sole source of spinal dopamine, reduced drive in this system can lead to spinal network changes wholly consistent with RLS/WED (Clemens et al., 2006).

Eventually, there are other less well-developed features of RLS/WED pathophysiology that could be considered, particularly cortical excitability and other neurotransmitter/neuromodulators pathways, which, as well as cellular and mitochondrial metabolism, cell adhesion molecule mechanisms, might all interact with the dopaminergic system (Allen, 2015; Ferre et al., 2018). Recent evidences suggested the glutamatergic pathway to be critically implicated in RLS. EEG studies showed a state of hyperarousal in RLS, during both wakefulness preceding sleep and sleep onset period, which might be sustained by the glutamatergic pathway (Ferri et al., 2014). An abnormal increase in thalamic glutamate/glutamine levels for RLS, indicating increased glutamatergic activity producing arousal that at night disrupts and shortens sleep, has been demonstrated (Allen et al., 2013). Moreover, perampanel, a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, had a significant therapeutic effect on both sensory and motor symptoms of RLS (Garcia-Borreguero et al., 2017). Microvascular hypotheses have also been formulated. Peripheral hypoxia, for example, has been associated with the appearance of RLS symptoms (Salminen et al., 2014). Recent animal models of RLS suggested that brain iron deficiency is associated with a hypoadenosinergic state, with downregulation of adenosine A_1 receptors (A1R) in the striatum and cortex, disrupting the adenosine-dopamine-glutamate balance, which altogether determines both PLMS and hyperarousal (Ferre et al., 2017). To this end, a non-placebo controlled clinical trial proved that an increase in extracellular adenosine induced by inhibitors of adenosine transporters, such as the non-selective ENT1/ENT2 inhibitor dipyridamole, yielded an improvement in RLS symptoms (Garcia-Borreguero et al., 2018).

4. RLS/WED and cardiovascular risk

Much of what we know about sleep-related increased risk for CVD comes from clinical investigations on patients suffering from insomnia and sleep-disordered breathing, namely obstructive sleep apnea (OSA). Research in RLS as a risk factor for CVD is less developed in comparison with the one on OSA. However, several new epidemiological evidences

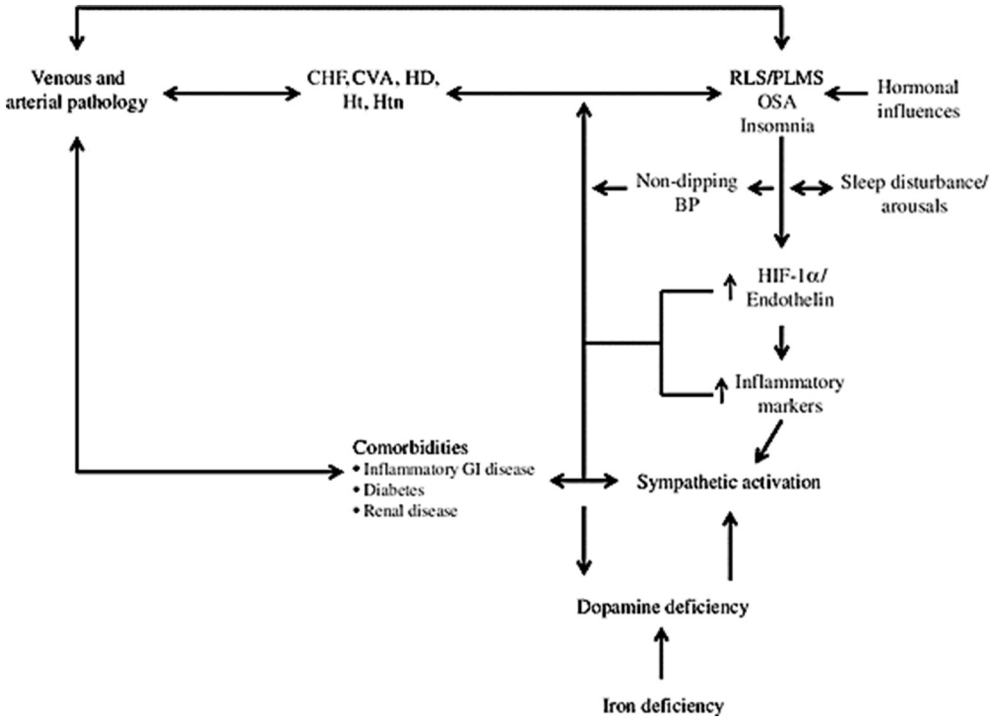

Fig. 2. Hypothetical representation of the possible pathways connecting RLS/PLMS, insomnia, and OSA to the development of hypertension and vascular diseases. CHF congestive heart failure, CVA cerebrovascular accident, GI gastrointestinal, HD heart disease, HIF hypoxia inducible factor, Ht heart transplantation, Htn hypertension, OSA obstructive sleep apnea, PLMS periodic leg movements during sleep, RLS, restless legs syndrome.
Reprinted from Ferini-Strambi et al. (2014), Open Access.

have been published during the last two decades on this interesting topic. Multiple mechanisms may modulate an association between RLS/WED and CVD, including chronic sleep deprivation, intermittent, PLMS-related autonomic fluctuations and possible autonomic dysfunction intrinsically associated with RLS per se. A hypothetical representation of the possible pathways connecting RLS/PLMS, insomnia, and OSA to the development of hypertension and vascular diseases is provided in Fig. 2.

4.1. Sleep deprivation, sleep duration, insomnia and excessive daytime sleepiness

Patients suffering from RLS/WED often complain of initial insomnia with related sleep deprivation, short sleep duration, and, only in a few cases, excessive daytime sleepiness (EDS) (Allen et al., 2005). These factors might play a significant, albeit secondary or confounding, effect on CV homeostasis.

Studies of subjects experiencing short-term sleep deprivation have demonstrated alterations in heart rate (HR) and blood pressure (BP), associated with a significant increase in sympathetic activation and a decrease in parasympathetic modulation of cardiac autonomic balance. Shortened sleep also has been associated with increased risk for CVD and coronary heart disease (CHD) in the Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands (MORGEN) study (Hoevenaar-Blom et al., 2011). Such modifications are believed to result from a reduction of NREM-sleep compared to REM-sleep (Fujikawa et al., 2009; Tochikubo et al., 1996; Lusardi et al., 1996; Lusardi et al., 1999). Moreover, meta-analytic reviews negatively associated chronic sleep deprivation with life expectancy (Laugsand et al., 2014).

Two large cohort studies, the Sleep Heart Health Study (SHHS) (Gottlieb et al., 2006) and the National Health and Nutrition Examination Survey (NHNES) (Gangwisch et al., 2006) reported an association between self-reported sleep duration of < 5 h and incident hypertension in subjects younger than 60 years, in adjusted analyses. Since these early reports, numerous population studies have assessed the relationship between sleep duration and hypertension (Knutson et al., 2006). More recent analyses of cross-sectional studies demonstrated significant association between both short and long sleep duration, whereas pooled analyses of longitudinal studies demonstrated an association only between short sleep duration and incident hypertension (Guo et al., 2013). Therefore, while sleep duration seems to be associated with prevalent and incident hypertension, any causation cannot be proven by cross-sectional studies, which are to date by far the majority compared to longitudinal studies.

Short sleep duration and insomnia are different entities. Insomnia entails dissatisfaction with the quality of sleep and daytime consequences that can be associated or not by an objective reduction in sleep duration. Individuals with short sleep duration do not necessarily suffer from insomnia since they can voluntarily restrict their sleep time. Most studies investigating a relationship between insomnia and CVD found that only chronic insomnia with “true” short sleep duration (< 6 h of sleep during polysomnography) is associated with higher nighttime systolic BP, blunted day-to-night systolic BP dipping, diabetes mellitus, obesity, and cardiovascular disorders (Tobaldini et al., 2019; Jarrin et al., 2018; Thomas and Calhoun, 2017). This has been associated with a hyperactivity of the central nervous system during sleep, which could represent one mechanism implicated in the link between insomnia and cardiovascular morbidity and mortality documented in epidemiological studies (de la Sierra et al., 2010; Vgontzas et al., 2009; Winkelman et al., 2006; Lanfranchi et al., 2009).

To our knowledge, only a few studies in elder populations found an association between EDS and CVD (Empana et al., 2009; Jaussent et al., 2013; Endeshaw et al., 2013). Whether the authors consider EDS as a result of all-cause sleep disorders or not is either unclear or investigated only through clinical interviews or questionnaires.

4.2. RLS/WED and hypertension

A large body of literature regarding the incidence of arterial hypertension in RLS/WED is available today, mostly in the form cross-sectional studies (Ulfberg et al., 2001; Winkelman et al., 2006; Winkelman et al., 2008; Catzin-Kuhlmann et al., 2015; Chen et al., 2010; Giannini et al., 2014; Wesstrom et al., 2008; Winter et al., 2013a; Winter et al., 2013b; Batool-Anwar et al., 2011; Szentkiralyi et al., 2013; Liu et al., 2018), although a few cohort studies (Van Den Eeden et al., 2015) have also been published (Table 1). The overall findings,

Table 1
RLS/WED and hypertension risk, available studies taken into consideration.
Reprinted from Hwang et al. (2018), Open Access.

Source and study publication year	Country	Population, setting, number of participants	Design	RLS diagnosis[a]	Hypertension diagnosis	Confounders adjusted for
Catzin-Kuhlmann et al., 2015	Mexico	54,925 females (9230 RLS vs no RLS 45,695)	Cross-sectional	Self-report	Self-report[a]	Age, sex (only female participants), family history of MI, hormonal contraceptive, menopausal status, BMI, physical activity, smoking, migraine, and consumption of alcohol, bread, fruits, vegetables, and total energy
Chen et al., 2010	Taiwan	CATI telephone interview 4011 subjects (RLS 64 vs no RLS 3947)	Cross-sectional	Self-report	Self-report[b]	Age, sex, BMI
Giannini et al., 2014	Italy	1709 subjects (RLS 170 vs no RLS 1539)	Cross-sectional	Face-to-face interviews	Self-report[b]	Age, sex, DM, MI, dyslipidemia, BMI
Szentkiralyi et al., 2013	Germany	Dortmund health study: 1312 (RLS at baseline 7.4%) Study of health in Pomerania: 4308 (RLS at baseline 10.1%)	Cross-sectional	Face-to-face interviews	Self-report[b]	Age, sex, education, alcohol consumption, smoking, physical activity, hemoglobin, glomerular filtration rate, cholesterol level and cardiovascular diseases except for the respective outcome
Ulfberg et al., 2001	Sweden	2608 males (RLS 181, without RLS 2427)	Cross-sectional	Self-report	Self-report[c]	Age, sex (only male participants), witnessed apneas, smoking, and alcohol consumption
Wesstrom et al., 2008	Sweden	3501 women (551 primary RLS vs 2950 no RLS)	Cross-sectional	Self-report	Self-report[c]	Age, sex (only female participants), smoking, alcohol and coffee consumption, use of sleeping pills
Winter et al., 2013a	USA	US Physicians' Health Studies I and II. 22,786 males (RLS 1710 vs. no RLS 21,076)	Cross-sectional	Self-report	Self-report[d]	Age, sex (only male participants), randomized aspirin assignment, all vascular risk factors (DM, hypercholesterolemia, parental history of MI before age 60 years, alcohol consumption, smoking, exercise, BMI)
Winter et al., 2013b	USA	US health care professionals 30,262 females (RLS 3624 vs. no RLS 26,638)	Cross-sectional	Self-report	Self-report[d]	Age, sex (only female participants), randomized aspirin assignment, postmenopausal status, postmenopausal hormone use, oral contraceptive use, all vascular risk factors (DM, hypercholesterolemia, parental history of MI before age 60 years, alcohol consumption, smoking, exercise, BMI)
Van Den Eeden et al., 2015	USA	Kaiser Permanente Northern California (KPNC) cohort Primary RLS 7621 vs. 296,574 controls	Retrospective cohort	Medical records, diagnoses and survey data[e]	Medical records[b]	Age, race, sex, smoking, BMI, DM, hyperlipidemia treatment

RLS: restless legs syndrome, BMI: body mass index, DM: diabetes mellitus, MI: myocardial infarction.
[a] Diagnosis of RLS was made based on the IRLSSG criteria,
[b] Hypertension was defined as a diagnosis established at any time by a physician or treatment with antihypertensive medication,
[c] Hypertension was defined as a diagnosis established at any time by a physician,
[d] Hypertension was defined as blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or antihypertensive treatment.
[e] Medical record diagnoses and survey for the expanded set of questions on RLS based on the IRLSSG criteria.

reviewed in more than one meta-analyses, show that individuals with RLS/WED are associated with a higher prevalence of hypertension (OR = 1.13, 95% CI = 1.04–1.23, p = 0.003). In cross-sectional studies, the prevalence of hypertension in RLS/WED patients is significantly higher (OR = 1.12, 95% CI = 1.01–1.24, p = 0.028) (Hwang et al., 2018; Shen et al., 2018; Innes et al., 2012).

However, a solid association between RLS/WED and hypertension cannot be obtained because of the small number of prospective studies included, and because the relationship between RLS/WED and hypertension tends to lose significance after adjusting for the confounders of metabolic syndrome, such as diabetes mellitus and dyslipidemia (Cholley-Roulleau et al., 2017; De Vito et al., 2014). To this end, a large systematic study measuring the 24 h BP profile in RLS/WED is still lacking.

Moreover, the direction of the association between RLS/WED and hypertension cannot be ascertained, since most studies are cross-sectional in design. Differences in follow-up may also represent a confounding factor, as it has been reported that the association between RLS/WED and CVD was stronger in patients with more frequent symptoms (at least 16 times per month) and in those with longer-course disease (Winkelman et al., 2008). Therefore, further population-based studies with larger sample sizes and longitudinal follow-up may help to determine the risk factors of RLS/WED and potential interventions for RLS/WED.

Nevertheless, RLS/WED seems to be an independent determinant for the non-dipping pattern of BP, which has been shown to be an independent predictor of cardiovascular risk, as measured through ambulatory blood pressure monitoring (ABPM) (Erden et al., 2012).

4.3. Movement, arousal and the autonomic nervous system: PLMS as the cause of intermittent recurring sympathetic activation during sleep

During sleep, PLMS usually co-occur with cortical arousals and this is quantified with the PLMS arousal index (i.e., the number of PLMS that co-occur with an arousal divided by the number of hours with sleep) (Zucconi et al., 2006). However, the notion that PLMS cause these arousals and are therefore among the major causes of sleep disturbance in patients with RLS has been fundamentally re-evaluated based on recent studies.

The 2014 updated diagnostic criteria for RLS/WED state that contrary to initial expectations, PLMS are not directly related to the primary RLS/WED morbidity of sleep disturbance, rather they may reflect some RLS/WED biology partially independent of that (Allen et al., 2014). Indeed, during sleep in patients with RLS/WED, many runs of PLMS without cortical arousals or, vice versa, EEG arousals without PLMS might be observed (El-Ad and Chervin, 2000). Even when PLMS and arousals occur together, the onset of the slow component of the arousal often precedes that of the onset of the PLM in 40% to 50%, which makes it difficult to claim that the motor events directly provoke the cortical ones (Ferri et al., 2015).

Additionally, PLMS and arousals can be dissociated with a pharmacological challenge (Manconi et al., 2012). Patients with RLS/WED receiving a single dose of pramipexole showed a strong decrease of PLMS but not of arousal, whereas a single dose of the benzodiazepine clonazepam did the opposite, although both drugs had a good effect on RLS/WED-related sensory symptoms. Nonetheless, PLMS may occur without any relation to arousals, as it has been shown in a patient with complete transverse cervical spinal lesion (Salminen et al., 2013).

A consistent finding is the observation that PLMS are accompanied by transient increases in blood pressure (Pennestri et al., 2007; Pennestri et al., 2013; Siddiqui et al., 2007) and heart rate (Allena et al., 2009; Ferri et al., 2007; Ferrillo et al., 2004; Manconi et al., 2011; Sforza et al., 1999). The magnitude of these increases is modulated by sleep stage (Lavoie et al., 2004) and is increased when PLMS are bilateral (Ferri et al., 2007) or accompanied by arousals (Pennestri et al., 2007; Sforza et al., 1999; Winkelman, 1999; Sforza et al., 2002). Indeed, a clear temporal relationship between the duration of the single PLM and the duration of the related arousals has been demonstrated (Ferri et al., 2015).

These frequent, repetitive nocturnal sympathetic system activations are the prime candidate mechanism for a possible pathophysiologic link between RLS/PLMS and cardiovascular diseases. Indeed, PLMS, rather than RLS/WED, are being discussed as a possible new sleep-related cardiovascular risk factor (Alessandria and Provini, 2013). An important finding is that the magnitude of PLMS-associated increases in heart rate and blood pressure seems to be significantly larger in patients with RLS/WED compared with healthy controls with PLMS but without RLS/WED (Manconi et al., 2012; Pennestri et al., 2013).

PLMS might simply represent a marker of sympathetic increased output or, in other words, a marker of autonomic stress signaling the vegetative state of health. If true, this might explain why other sleep disorders, such as narcolepsy, REM sleep behavior disorder, and also sleep apnea, which generate autonomic instability, are strong risk factors for PLMS (Manconi et al., 2012). The temporal relationship between EEG delta activity, cardiac activation and PLM onset suggest that these phenomena act as a preparatory condition, involving both central and autonomic nervous systems, exerting a permissive function on the activity of spinal motoneurons (Parrino et al., 2006).

In summary, PLMS might take place in the context of a complex interaction between the oscillation of the autonomic and the cortical arousal system and new models and experimental protocols should be developed for a deeper understanding of this phenomenon. The long-term effect of this oscillatory multisystem phenomenon on the cardiovascular function still needs to be demonstrated, especially in patients with PLMS without RLS/WED, as it is the case for periodic limb movements disorder (PLMD) (American Academy of Sleep Medicine, 2014).

4.4. RLS/WED, PLMS and cardio-cerebro-vascular events

Recently, a thorough meta-analysis systematically reviewed the current evidence examining RLS/WED and PLMS as prognostic factors for all-cause mortality and incident cardiovascular events (CVE) in longitudinal studies published in the adult population (Kendzerska et al., 2017). The evidence for an association between RLS/WED and CVE was mixed and was based on eight study cohorts, two of high quality (Winter et al., 2013a; Winter et al., 2013b) and six of moderate quality (Szentkiralyi et al., 2013; Van Den Eeden et al., 2015; Elwood et al., 2006; Li et al., 2013; Molnar et al., 2016).

Four study cohorts supported a positive association, while another four did not. Two of three cohort studies found an association between RLS/WED and stroke (Elwood et al., 2006; Molnar et al., 2016). A positive association with other CV outcomes was only found in chronic RLS/WED (≥ 3 years) (Li et al., 2013) or secondary RLS/WED (Van Den Eeden et al., 2015), as well as in one study based on health administrative data (Molnar et al., 2016). There is evidence that PLMS may increase incident atrial fibrillation (AF) risk in older patients (May et al., 2016).

The evidence for an association between PLMS and CVE and mortality was based on two studies, both demonstrating a significant association between PLMS, a 5–26% increased hazard for the composite CV outcome and a 5% increased risk of all-cause mortality (Kendzerska et al., 2014; Koo et al., 2011; Walters and Rye, 2009). The effect of a periodic limb movement arousal index ≥ 5 was comparable with that of a PLM index ≥ 30 (Koo et al., 2011).

All in all, the evidence supporting RLS/WED as a prognostic factor for incident CVE was mixed. Individuals with secondary (but not primary) forms of RLS/WED and longer term exposure to RLS/WED appeared to be at higher risk of incident CVE. Again, this dichotomous view of RLS/WED, which is considered somewhat obsolete (Trenkwalder et al., 2016), gains importance in this context, as primarily genetic manifestations of RLS/WED may not be significant

contributors to incident CVE, while manifestations of RLS mostly associated with comorbid conditions may be potentially important contributors to CVE. The inconsistent and limited available evidence on the association between RLS and individual CV outcomes could mean, indeed, that there are few true relationships.

The evidence supporting the role of PLMS as a prognostic factor for incident CVE was very limited. However, the collective literature to date suggests a potentially stronger association for PLMS co-occurring with arousals.

4.5. RLS/WED and diabetes

Several studies investigating possible associations between RLS/WED and type 2 diabetes mellitus have been published so far, but the comorbidity with a clinical or subclinical peripheral neuropathy often represented a pivotal confounding factor. Epidemiologically speaking, RLS/WED was found in 27% of patients with diabetes in a Brazilian study (Lopes et al., 2005). In Italy, RLS/WED was diagnosed in 18% of patients with diabetes and was independently associated with diabetes. Polyneuropathy was the main risk factor for RLS but only partially explained the increased prevalence (Merlino et al., 2007). In another study, RLS was present in 33 of 99 patients with neuropathy associated with diabetes mellitus, impaired glucose tolerance, and impaired fasting glucose. The patients with RLS were more commonly diagnosed with small fiber sensory neuropathy and more often reported symptoms of burning feet (Gemignani et al., 2007). To our knowledge, there are no prospective data inferring a causal link between RLS/WED and diabetes available to date.

4.6. RLS/WED, dyslipidemia, endothelial function and oxidative stress

To our knowledge, there are conflicting evidences regarding the association between RLS/WED and dyslipidemia. Higher levels of total serum cholesterol and triglyceride levels were significantly associated with development of RLS (OR 1.45, 95% CI: 1.18, 1.77; P-trend = 0.0004) in a large prospective study (De Vito et al., 2014). A cross-sectional study yielded similar results (0.18; 95% CI 0.034–0.90) (Schlesinger et al., 2009). In one case-control study, the presence of dyslipidemia has been associated with RLS/WED only when this was comorbid with OSA and the same association could not be detected when sleep-disordered breathing was excluded from the analysis (Cosentino et al., 2012).

On the other hand, a prospective, cross-sectional, case-controlled study measured the levels of the serum lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) in RLS/WED patients (Halac et al., 2016). This is a type II membrane protein that belongs to C-type lectin family, expressed in endothelial cells, macrophages, and in smooth muscle cells under the effect of the pro-inflammatory stimulation or in pro-atherogenic conditions (Pirillo and Catapano, 2013). Lower sLOX-1 levels were found in RLS/WED patients, suggesting a lower atherosclerotic risk among RLS patients as compared to the general population. Similar results derive from a study measuring a significantly lower mean value of the maximum intima-media thickness (IMT), a non-invasive marker of systemic atherosclerosis related to the risk of future CVD and stroke (Bots et al., 1997), in RLS/WED versus controls. This also suggests that RLS/WED may have a lower risk of progression of atherosclerosis (Park et al., 2012).

Available data regarding possible dysfunction of the endothelial system and an overall increased oxidative stress in RLS/WED are at their début phase and still controversial. Advanced oxidation protein products and total thiol levels (as markers of oxidative protein damage), nitric oxide levels (as an antioxidant and endothelial function), and malondialdehyde levels (as a marker of lipid peroxidation) have been measured in patients with RLS/WED, suggesting that that they are under oxidative stress (Baskol et al., 2012). Serum endocan levels, a molecule released by endothelial cells and whose expression might be an indicator of endothelial activation and neovascularization (Afsar et al., 2014), are lower in women with RLS/WED as compared to controls, suggesting lower degrees of endothelial dysfunction and a lower degree of predisposition to atherosclerosis (Celik et al., 2015). Similarly, total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), arylesterase (ARE), paraoxonase (PON), stimulated paraoxonase (stim-PON) acetyl cholinesterase (AChE) and butyryl cholinesterase (BuChE), which are all markers of the circulating oxidant state, were higher in RLS/WED patients than in controls (Cikrikcioglu et al., 2011). Moreover, peripheral hypoxia is associated with the appearance of RLS/WED symptoms, suggesting a close pathophysiologic link between peripheral hypoxia and the symptoms of RLS, as further supported by the simultaneous reversal of hypoxia and discomfort by dopaminergic treatment (Salminen et al., 2014).

4.7. RLS/WED and obesity

The relationship between obesity and RLS/WED was evaluated prospectively, together with other variables, in the Nurses' Health Study II and the Health Professionals Follow-up Study, yielding a positive association between both overall obesity (as assessed by BMI) and abdominal obesity (as assessed by waist circumference) were associated with a higher risk of developing RLS/WED (P-trend < 0.0001; *P*-difference for sex > 0.5), after adjusting for age, ethnicity, and potential confounders (De Vito et al., 2014).

5. Do RLS/WED and PLMS entail autonomic dysfunction per se?

The hypothesis that autonomic nervous system (ANS) impairment lies within RLS/WED arises from the aforesaid studies searching for a link between RLS/WED with and without PLMS and CVD/CVE. This hypothesis is also sustained by the idea that a dysfunction in the descending dopaminergic hypothalamo-spinal pathway might disinhibit the neurons in the intermediolateral column and in turn increase the sympathetic output (Clemens et al., 2006). Furthermore, complaints of autonomic system disorders in patients suffering from primary RLS/WED have been observed (Shneyder et al., 2013) by means of the Scales for Outcomes in Parkinson's disease - Autonomic (SCOPA-AUT) (Visser et al., 2004) Such hypothesis has been tested only partially so far.

Data from Bertisch et al. (2016) suggested attenuated baroreflex gain in RLS/WED patients off medications in comparison to normal control subjects. RLS patients also had attenuated limb blood flow and increased limb vascular resistance, conceivably suggesting the presence of increased sympathetic vasoconstrictor tone.

Spectral analysis of HR variability (HRV), calculated from the interval between two consecutive R-waves of QRS complexes in the ECG trace, is used to assess sympathetic and parasympathetic control on cardiac function, thus providing a picture of sympathovagal fluxes, in RLS patients.

Barone et al. (2017) examined basal HRV in both wake and NREM sleep across groups of subjects with RLS/WED, PLMS without RLS/WED, and the combination of RLS/WED and PLMS, as compared to controls. Patients with PLMS > 15/h but no symptoms of RLS/WED had reduced basal sympathetic activity in wakefulness, but basal sympathetic predominance during NREM sleep, when compared to all other groups. The authors argued that RLS/WED and PLMS should probably be treated as two different entities.

Izzi et al. (2014) found a significant increase in baseline systolic BP (SBP) in the rest supine condition compared to controls, satisfying the criteria of systolic pre-hypertension. The same authors documented a slightly reduced parasympathetic response at Valsalva maneuver, speculating that that the predisposition to hypertension in RLS/WED may be favored by a blunted parasympathetic response to changes in blood pressure, and a reduced amplitude of both sympathetic and parasympathetic responses at head-up tilt test (HUTT). There is evidence (Tobaldini et al., 2017), although limited, that sleep deprivation

reduces the amplitude of both sympathetic and parasympathetic responses at HUTT in healthy subjects, therefore, the authors stated that they could not rule out whether the sleep disturbances associated with RLS/WED (insomnia, poor sleep efficiency), rather than the disease itself, were responsible for lower reactivity of the autonomic system during orthostatic stress.

From the neuroendocrine viewpoint, a relation might exist between the ANS, the hypothalamic-pituitary axis (HPA), cortisol, dopamine and the circadian pattern of RLS/WED symptoms. Elevated vagal activity, lower sympathetic activity and decreased cortisol secretion in the evening might have an influence on the occurrence of RLS/WED symptoms (Cikrikcioglu et al., 2011). Indeed, cortisol and dopamine release in humans follow an inverse and parallel circadian pattern, which is opposite to the circadian pattern of RLS/WED symptoms. Patients with RLS tend to maintain a continuous level of activity and move their legs in the bed until the time of daybreak (where the cortisol levels reach a peak) in an effort to alleviate RLS symptoms. In turn, this may reduce the parasympathetic nervous system activity, and increase the sympathetic nervous system activity and cortisol release, influencing the circadian rhythm of cortisol and ANS (Allen, 2015; Celik et al., 2015). To this end, low dose corticosteroid infusion administered at night hours has been shown to reduce RLS/WED symptoms (Hornyak et al., 2008). In a recent study, RLS/WED patients have been shown to have higher overnight urinary cortisol excretion when compared with control subjects (Schilling et al., 2010). Differently, a relation of RLS to measures of RAAS activity has not been reported.

6. Conclusions

The association between RLS/WED and both CV risk factors and CVD still remains elusive. Although several shared pathophysiological causes could explain these possible relationships, the emerging body of literature focusing on these disorders remains controversial. The reasons for these inconsistent findings are mainly due to the different methodologies applied. Moreover, the cross-sectional nature of most studies cannot assess the causal relationship between them and the variables of interest (i.e., RLS/WED and/or CVDs). Also, only few studies adjusted their analyses for other cardiovascular risk factors, such as diabetes mellitus, history of myocardial infarction, Body Mass Index (BMI), dyslipidemia, and smoking status, that might act as confounders or mediators. Generally, as shown by independent studies, it can be drawn that the cross-sectional relationship between RLS and hypertension is the most solid one, especially in those patients suffering from severe or daily symptoms. Differently, the relationship between RLS, CVE and mortality seems to be somewhat weaker. Furthermore, the link between insomnia, PLMS and autonomic dysfunction needs consolidation, as they may be the causing factors for sympathetic overactivity.

Not only longitudinal population-based studies and meta-analyses, but also more animal models and therapeutic interventions are needed in order to build a sufficiently robust body of evidence on this topic. In particular, interventional studies treating RLS, PLMS or both might help clarifying if CV risk changes accordingly and disentangling the possible different roles played by RLS symptoms rather than by PLMS.

Financial support

None.

Declaration of Competing Interest

All authors report nothing to declare. All authors have seen and approved this manuscript.

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