Review of the Relationship of Restless Legs Syndrome and Periodic Limb Movements in Sleep to Hypertension, Heart Disease, and Stroke

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Evidence is reviewed documenting an intimate relationship among restless legs syndrome (RLS) / periodic limb movements in sleep (PLMS) and hypertension and cardiovascular and cerebrovascular disease. Sympathetic overactivity is associated with RLS/PLMS, as manifested by increased pulse rate and blood pressure coincident with PLMS. Causality is far from definitive. Mechanisms are explored as to how RLS/PLMS may lead to high blood pressure, heart disease, and stroke: (a) the sympathetic hyperactivity associated with RLS/PLMS may lead to daytime hypertension that in turn leads to heart disease and stroke; (b) in the absence of daytime hypertension, this sympathetic hyperactivity may predispose to heart disease and stroke either directly or indirectly via atherosclerotic plaque formation and rupture; and (c) comorbidities associated with RLS/PLMS, such as renal failure, diabetes, iron deficiency, and insomnia, may predispose to heart disease and stroke. One theoretical cause for sympathetic hyperactivity is insufficient A11 diencephalospinal dopaminergic neuron inhibition of sympathetic preganglionic neurons residing in the intermediolateral cell columns of the spinal cord. We cannot exclude the possibility that peripheral vascular, cardiovascular, and cerebrovascular disease may also contribute to RLS/PLMS, and mechanisms for these possibilities are also discussed.

Keywords: Restless legs syndrome, periodic limb movements in sleep, RLS, PLMS, hypertension, heart disease, stroke, cardiovascular disease, cerebrovascular disease, dopamine

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RESTLESS LEGS SYNDROME (RLS) IS CHARACTERIZED BY (A) A DESIRE TO MOVE THE LEGS OFTEN, BUT NOT NECESSARILY, ACCOMPANIED BY ABNORMAL legs sensations; (b) symptom worsening at rest, ie, sitting or lying; (c) partial or temporary relief by activity at least as long as the activity continues; and (d) worsening of the symptoms later in the day or night.[1] Periodic limb movements in sleep (PLMS) are repetitive flexions of the hips, knees, and ankles that are present in 90% of patients with RLS.[1-3] PLMS occur in patients without RLS, are found in 25% of patients undergoing routine polysomnography,[4] and are traditionally interpreted as an incidental finding, a reflection of sleep-disordered breathing,[5] or as a manifestation of pathology in supraspinal neural networks such as in narcolepsy[6] or rapid eye movement sleep behavior disorder.[7] To be characterized as PLMS, leg movements must be 0.5 to 10 seconds in duration, recur every 5 to 90 seconds, and occur in a series of at least 4 such movements in a row that are at least 8 μV in amplitude. Although RLS and PLMS can occur independently of one another, their frequent association suggests a common etiology. This has been confirmed recently by the discovery of a common gene variant (*BTBD9*) that confers susceptibility to both PLMS and RLS.[8,9]

A number of independent lines of inquiry point to an intimate relationship among hypertension, heart disease, and stroke in RLS and PLMS. This area of research has not been previously reviewed. The implications of these associations to public health are significant and warrant further attention, which is the purpose of this review.

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EARLY STUDIES OF RLS, PLMS, VASCULAR FACTORS, AND THE SYMPATHETIC NERVOUS SYSTEM

Lugaresi and Coccagna first postulated in the early 1970s that PLMS are a manifestation of sympathetic activation, noting that a number of brainstem-generated autonomic rhythms, such as heart rate and blood pressure, exhibit a 30-second periodicity remarkably reminiscent of PLMS.[10,11] In the 1940s and 1950s, Ekbom remarked that RLS symptoms commonly cooccur with complaints of cold feet, which he hypothesized shared a common pathophysiology in vasoconstriction given his experience that vasodilatory agents brought relief.[12] In the 1980s Ware et al.[13] made similar observations in patients with PLMS. A plethysmographic peripheral pulse examination of 4 in 10 patients with PLMS revealed blunted pulses (low amplitude with no dicrotic notch) and the absence of further reduction in amplitude after a deep breath. Large pulse amplitude increases followed warming and hyperemia, which indicated that the blunted pulses were the result of vasoconstriction from sympathetic overactivity rather than vascular occlusion. Two of the patients were prescribed 20 mg of phenoxybenzamine (Dibenzyline), a long-acting postsynaptic (α_1) receptor-blocking agent to produce vasodilatation, and this regimen reduced the number of PLMS. In the 1980s, Ancoli-Israel et al.[14] studied two groups of subjects older than 65 years of age, 42 of whom had moderate to severe PLMS (> 25/hr sleep) and 42 of whom had no PLMS (< 5/hr of sleep). Fifteen (36%) of those in the first group and 6 in the second (14%) complained of cold feet ($P < 0.05$). One subject was treated by thermal biofeedback with the intent of reducing sympathetic activity by way of increasing skin temperature, which reduced the total number of PLMS per night from 536 (575 and 497 on 2 nights) to 19.5 (39 and 0 on 2 nights).

In summary, the results of early studies strongly hinted at a causal relationship between sympathetic hyperactivity and RLS, and especially PLMS.

EPIDEMIOLOGY

Association of RLS with Hypertension and Heart Disease

In a study by Ulfberg et al.,[15] 4000 men aged 18 to 64 years in central Sweden were mailed questionnaires that adhered to the 4 criteria for RLS developed by the International RLS Study Group. The prevalence of RLS was 5.8% in this sample after adjusting for eligibility, incomplete questionnaires, and nonresponder rates. Statistical adjustments were also made for possible confounding factors such as age, witnessed apnea, smoking, and alcohol consumption. RLS sufferers were more likely to report hypertension (odds ratio [OR] 1.5; 95% confidence interval [CI] 0.9-2.4) and heart problems (OR 2.5; 95% CI 1.4-4.3). Some of the heart problems were presumably secondary to the hypertension, since they were correlated by a factor of 0.4 ($P < 0.01$). Correlation, however, does not imply causality, as suggested by the larger OR for heart disease, compared with hypertension. Despite the large size of this study, its limitations included the failure to examine the frequency of RLS symptoms and the potential for Type I error, given that the patients were not interviewed or examined to exclude RLS mimics.

In a study by Ohayon and Roth,[16] individuals aged 15 years and older (51.3% women) from 5 European countries (UK, Spain, Germany, Portugal, Italy) were interviewed by telephone about RLS symptoms. The 18,980 individuals represented 80.4% of the population originally selected for interview. The definition of RLS in this study was from an older edition of the *International Classification of Sleep Disorders,* which was not the most up-to-date definition for RLS from the International RLS Study Group.[1,17-19] Patients were said to meet criteria for RLS if they had: (a) a complaint of unpleasant sensations in the legs at night or difficulties in initiating sleep; (b) disagreeable sensations of "creeping" inside the calves, often associated with general aches and pains in the legs; and (c) discomfort that was relieved by movement of the limbs. The prevalence of RLS was 0.9 % for daily symptoms, 3.1% for symptoms that occurred several times per month, and 6.4% for symptoms that occurred at least 1 night per week. After statistical corrections, the OR for the association of hypertension with RLS was 1.36 (95% CI 1.14-1.61; $P < 0.001$) and for heart disease with RLS was 1.41 (95% CI 1.06-1.88; $P < 0.05$).

Phillips et al.[20] examined the data from the 2005 National Sleep Foundation *Sleep in America,* a random-dial telephone poll of 775 women and 731 men with mean age 49 years. They reported that RLS was present for at least a few nights per week in 9.7% of respondents (8% of men and 11% of women). For further analyses, statistical adjustments were made for age, sex, and an existing sleep disorder. Those with a history of hypertension were more likely to endorse RLS symptoms ($P < 0.05$), and there was a trend for those with heart disease to endorse RLS symptoms ($P < 0.10$). In this study, patients were considered as affected by RLS if they answered the following 2 questions in the affirmative and had symptoms at least a few days per week: "In the past year, according to your own experiences or what others tell you, how often did you have unpleasant feelings in your legs like creepy, crawly or tingly feelings at night with an urge to move when you lie down to sleep?" and "Would you say these feelings in your legs are worse, about the same as, or better at night or in the evening compared to other times of day?" This study did not include the "improvement by activity" criterion for RLS in the survey, and subjects did not undergo clinical interview or examinations.

Winkelman et al.[21,22] performed 2 separate analyses of data from large databases. An initial analysis of 2821 individuals from the Wisconsin Sleep Cohort noted cardiovascular disease to be more prevalent in individuals with daily RLS, compared with those without RLS (OR = 2.58, 95% CI 1.38-4.84).[21] A more recent and in-depth cross-sectional survey of 1559 men and 1874 women (mean age of 67.9 years) enrolled in the Sleep Heart Health Study identified putative RLS in 3.3% of men and 6.8% of women.[22] RLS was defined by positive responses on a self-administered questionnaire containing the 4 essential RLS criteria established by the International RLS Study Group, with at least moderately distressful symptoms occurring at least 5 times per month.[1] Coronary artery disease was determined by self-report of physician-diagnosed angina, myocardial infarction, or coronary revascularization procedure. Total cardiovascular disease included coronary artery disease or a history of physician-diagnosed stroke or heart failure. The relationship between RLS and coronary artery disease and cardiovascular was examined by logistic regression with adjustment for confounding variables. The adjusted OR for coronary artery disease was 2.22 (95% CI 1.40-3.53) and, for cardiovascular disease, was 2.38 (95% CI 1.55-3.65) for subjects with RLS, compared with those without RLS. The associations of RLS with coronary artery disease and cardiovascular disease were only apparent in those with RLS symptoms at least 16 times per month and were more robust in those with severe, as opposed to moderate, RLS. This study was conducted without a personal patient interview or examination. Unlike the positive relationship found between RLS and hypertension in the Ulberg et al., Ohayon and Roth, and Phillips et al. studies, the 2 studies by Winkelman et al. and a study by Hogl et al. found no relationship between RLS and hypertension, and, in the MEMO study by Rothdach et al., there was even an inverse relationship.[15,16,20-24]

In summary, the results of epidemiologic studies suggest a possible relationship between self-reported RLS symptoms and daytime hypertension and are more consistent in pointing to a relationship between RLS and cardiovascular disease.

Association of PLMS With Heart Disease

Congestive Heart Failure

Hanly and Zuberi-Khokhar have suggested that patients with congestive heart failure (CHF) and Cheyne Stokes respiration are more likely to have elevated PLMS rates than are control subjects.[25] In their study of 23 men with severe CHF and associated Cheyne-Stokes respiration, 52% of subjects had more than 25 PLMS per hour of sleep (one-third had a PLMS index > 50/h), as compared with only 11% of healthy control subjects. This prevalence of PLMS in control subjects is comparable to that of a large community-based sample of subjects aged 41.9 ± 12.6 years, 7.6% of whom exhibited a PLMS index of 15 per hour.[26]

Javaheri et al.[27] found that 20% of 55 men taken from a larger group of 100 men with CHF had an average PLMS index of 35 per hour and a PLMS arousal index of 3.4 per hour. Of the 100 patients, 49% had sleep apnea (37% central sleep apnea and 12% obstructive sleep apnea). No comment was made regarding the potential coincidence between PLMS and sleep disordered breathing. This study also did not have a control group, and most of the patients were in the age range in which PLMS would be expected to occur by chance in 30% of people. In this relatively large study, it is noteworthy that the fraction of patients with CHF who had a high PLMS index (20%) is similar to that of the Hanly and Zuberi-Khokhar study (52%).[25] A more recent study by Skomro et al. reports a PLMS index of more than 5 per hour in 19% of 79 subjects with stable CHF, similar to the results of Javaheri's study.[27,28] In this study, similar to that of Hanly and Zuberi-Khokar,[25] the apnea-hypopnea index was approximately the same between subjects with and without PLMS, suggesting that PLMS occurring in these subjects is unrelated to sleep disordered breathing.

Heart Transplant

The original impetus for examining the relationship between heart disease and PLMS more closely came from a single patient in whom Hanly and Zuberi-Khokhar observed near resolution of PLMS following successful heart transplantation. This 46-year-old man presented with a 3-year history of insomnia, which began following a large myocardial infarction. He subsequently developed CHF and Cheyne-Stokes respiration. Polysomnography revealed 158 PLMS per hour (one-third being associated with arousals) after careful exclusion of leg movements that occurred during the hyperpnic arousal phase of central apneas. Although the patient denied having symptoms of RLS, he clearly had periodic limb movements in wakefulness. Following heart transplantation, the insomnia, CHF, and Cheyne-Stokes respiration resolved, in concert with a reduction in PLMS to 12 per hour.[29]

In contrast with this experience, Javaheri et al., in a polysomnographic evaluation of 45 patients after cardiac transplantation, found that 15 had a PLMS index greater than 15 per hour, with an average of 55 per hour. Seven of these patients endorsed having RLS symptoms; 36% (16) of the 45 patients exhibited obstructive sleep apnea (apnea-hypopnea index > 15/h), with an average of apnea-hypopnea index of 50 per hour.[30] Although fifteen of the subjects had PLMS, and 16 had obstructive sleep apnea, in only 2 cases were the phenomena coincident.

In summary, PLMS are frequently observed in patients with CHF and also in heart transplant recipients. The data suggest that PLMS in patients with CHF and transplant recipients are independent of sleep disordered breathing. What drives an apparent increased expression of PLMS in these conditions remains unknown.

COINCIDENCE OF SYMPATHETIC DISCHARGE AND PLMS

Pulse Rate

A number of studies have demonstrated a temporal coincidence between PLMS and pulse rate elevations. A variable portion of these electrocardiographic events are accompanied by cortical arousal. In a study by Winkelman, heart rate was recorded for 10 cardiac cycles before and after PLMS in 8 patients. Leg movements during wakefulness were performed by 4 healthy control subjects as a control condition. A significant rise in heart rate above and beyond the control condition was seen with PLMS. Although heart rate was 10% to 40% higher when electroencephalographic (EEG) arousals accompanied the PLMS, these differences did not reach statistical significance. The authors concluded that pulse rate elevations that accompany PLMS occur whether or not there is an accompanying EEG arousal. Heart rate began to increase 3 cardiac cycles before the onset of PLMS and peaked at 4 cardiac cycles after the onset of PLMS. There was then a decline to below the baseline for cardiac cycles 8 through 10. The average pulse rate was 62 at baseline and 68.2 at peak; the nadir was 59.3 at cardiac cycles 8 through 10.[31]

Sforza et al. found a similar tachycardia associated with PLMS in 10 patients with RLS. PLMS were associated with visible EEG microarousals lasting longer than 3 seconds in one third of all PLMS. Accelerations in heart rate were greatest with a visibly discernible EEG microarousal. This was confirmed by spectral analysis of the EEG, which also revealed brief bursts of theta and delta activity with PLMS in which no visible microarousals were observed. From these analyses, the authors postulated that a hierarchy of arousals exists, starting with autonomic arousal and progressing to cortical arousal, as manifest in delta, then theta, then alpha activity, to full awakening.[32]

A key question is whether the sympathetic activation accompanying PLMS is specific to PLMS or is also characteristic of random nonperiodic movements in sleep. Guggisberg et al.[33] answered this question in the affirmative by demonstrating that the sympathetic activation accompanying PLMS is greater than for all movement types, as measured by heart rate variability spectra. Sympathetic activation accompanying PLMS is also evident in the setting of coincident sleep disordered breathing and exceeds that observed with apneic events unaccompanied by somatic activation.[34] This line of inquiry emphasizes that PLMS are likely a trait unique to the individual patient rather than a consequence of a coincident alternate phenomenon such as sleep disordered breathing. This view finds further support in analyses of the night-to-night variability in PLMS expressivity within and between subjects[3] and the discovery that RLS genes confer their risk by way of PLMS.[8]

Blood Pressure

The above observations on PLMS-related changes in heart rate have been extended to another manifestation of heightened sympathetic discharge, viz., blood pressure. Ali et al. demonstrated that blood pressure elevations on the order of 23% accompanied PLMS in a single patient with narcolepsy. These rises were evident in both systolic and diastolic measures, and there was a coincident acceleration in the pulse rate as well. Ali et al. pointed out that these rises were of a magnitude similar to those observed in obstructive sleep apnea.[35]

Pennestri et al. from Montplaisir's group confirmed and extended this single observation by documenting blood pressure elevations coincident with PLMS in 10 patients with RLS (systolic blood pressure average 22 mm Hg and diastolic blood

pressure average 11 mm Hg over baseline). The observed increases were greatest in patients in whom EEG microarousals accompanied the PLMS. The magnitude of the pressure elevations was greatest in elderly patients and in those with a longer duration of RLS symptoms. Increases in pulse rate also accompanied the PLMS with or without EEG arousal. Periodic limb movements while awake also showed an increase in blood pressure over baseline, but this was not as great as the increases seen in PLMS with or without EEG arousal.[36]

These results were independently confirmed by Siddiqui et al. in a study of 8 patients with RLS. To control for the possibility that movement alone could result in the accompanying changes in pulse and blood pressure seen with genuine PLMS, prior to bedtime patients performed simulated PLMS. Although none of the patients had a history suggestive of sleep apnea, in some patients some apneas were encountered for analysis. Care was taken to assess pulse rates and blood pressure that accompanied any leg movements occurring at the termination of an apnea. The magnitude and nature of diastolic and systolic blood pressure elevations and the rank order of autonomic activation were similar to those observed by Pennestri et al. For systolic blood pressure, the results were as follows: the highest blood pressure was seen with respiratory-related limb movements (mean, 18.9 mm Hg above baseline), the next highest was with PLMS with microarousals (mean, 16.7), and was similar between PLMS without microarousal (mean, 11.2 mm Hg) and periodic limb movements while awake (mean, 11.7 mm Hg), which were both higher than with the simulated PLMS (mean, 3.2 mm Hg).[37]

In summary, autonomic arousals accompany PLMS and manifest as large rises in pulse rate and blood pressure.

Systemic Hypertension and PLMS

In a study by Espinar-Sierra et al.,[38] 91 subjects with essential hypertension were studied polysomnographically for the presence of PLMS. Eighteen percent had PLMS, and the prevalence of PLMS was proportional to the severity of the hypertension. Patients with grade III hypertension had a 36.4% prevalence of PLMS, and patients with grade I and II hypertension had a 13% prevalence of PLMS. This relationship was independent of age, sex, obesity, smoking, alcohol consumption, apnea severity, and use of antihypertensive medications.

Billars et al. investigated the association between hypertension and PLMS in a much larger study of 861 patients with self-reported RLS symptoms. The likelihood of hypertension increased with PLMS severity, being present in slightly more than 60% of subjects with more than 50 PLMS per hour of sleep. The risk for having hypertension was twice as high for those with a PLMS index greater than 30 (OR = 2.26; 95% CI, 1.28-3.99) after controlling for known contributors to hypertension, such as body mass index and age.[39] These results could reflect decrements in total sleep time that one would naturally assume to accompany RLS, although, when included in the multivariate logistic regression, self-reported hours of sleep and category of antihypertensive medications did not take away from the robustness of the association between PLMS and hypertension status (personal observation). Because this study employed quantitative assessments of PLMS as the independent variable of interest, it infers that PLMS are causally related to medically diagnosed hypertension and not the reverse. It is also important to emphasize that the OR for hypertension with more than 30 PLMS per hour is of the same order of magnitude as that most often cited for hypertension and sleep disordered breathing (eg, OR = 2.89 for an apnea-hypopnea index > 15).[40]

In summary, PLMS are associated with greater daytime hypertension and the reverse is also true, ie, daytime hypertension is also associated with a greater number of PLMS.

RELATIONSHIP OF RLS AND PLMS TO STROKE

Three single case reports suggest that RLS and PLMS can be the direct immediate result of stroke. Kang et al.[41] reported on a 40-year-old man whose wife noted that he had developed involuntary kicking movements of his right leg during sleep beginning 7 days after he had had an ischemic stroke in the left corona radiata. Lee et al.[42] reported that the caregiver of 58-year-old man noted that, 2 days after the patient had experienced an ischemic stroke centered upon the left pallidum and internal capsule, he developed involuntary kicking movements of his right leg during sleep. In both of these cases, polysomnography confirmed PLMS that predominated in the leg opposite the hemisphere affected by the stroke. Anderson et al. case report included information on a woman with factor V Leiden deficiency, a positive family history of RLS, and symptoms of RLS since the age of 14. At the age of 27, she had suffered an acute ischemic stroke in the right basal ganglia that temporally coincided with exacerbation of her RLS symptoms. Involuntary kicking movements during wakefulness, presumably periodic leg movements while awake, were also noted. Dopaminergic therapy provided good symptomatic relief.[43] In each of these cases, there was evidence of weakness contralateral to the lesion, and this led all of the authors to independently postulate that these experiences supported the conventional view that that RLS and, in particular, PLMS arise from suprasegmental disinhibition of lower spinal circuitry.

It is also possible that the reverse relationship may hold, ie, that RLS and associated PLMS with accompanying autonomic arousal may be a risk factor for stroke. We determined the microvascular lesion load by brain magnetic resonance imaging in 8 patients with RLS and 11 closely matched migraineurs, all with normal findings on neurologic examination and who were without a clinical history of stroke. When data were statistically controlled for stroke risk factors, RLS by itself did not pose a risk factor for stroke, but there was a trend indicating an interaction between RLS and stroke risk factors, ie, that RLS and stroke risk factors combined posed a greater risk for silent stroke, as measured by a higher microvascular lesion load than one would expect from the stroke risk factors alone. The results were not associated with the presence or absence of obstructive sleep apnea, as determined polysomnographically.[44] Establishing whether sleep-related autonomic arousals accompanying PLMS are truly an independent risk factor for stroke will require a larger sample size employing subjects and healthy control subjects who are well controlled for known stroke risk factors. A control group without additional stroke risk factors would also be preferable.

In summary, acute clinical stroke in the basal ganglia, internal capsule, or corona radiata may lead to RLS/PLMS, although the evidence is anecdotal. The reverse may also be true. RLS

in the setting of traditional stroke risk factors may lead to an increased risk for silent stroke, as determined by microvascular lesion load, but evidence is also limited.

THEORETICAL RELATIONSHIPS BETWEEN RLS/PLMS AND HYPERTENSION, HEART DISEASE, AND STROKE

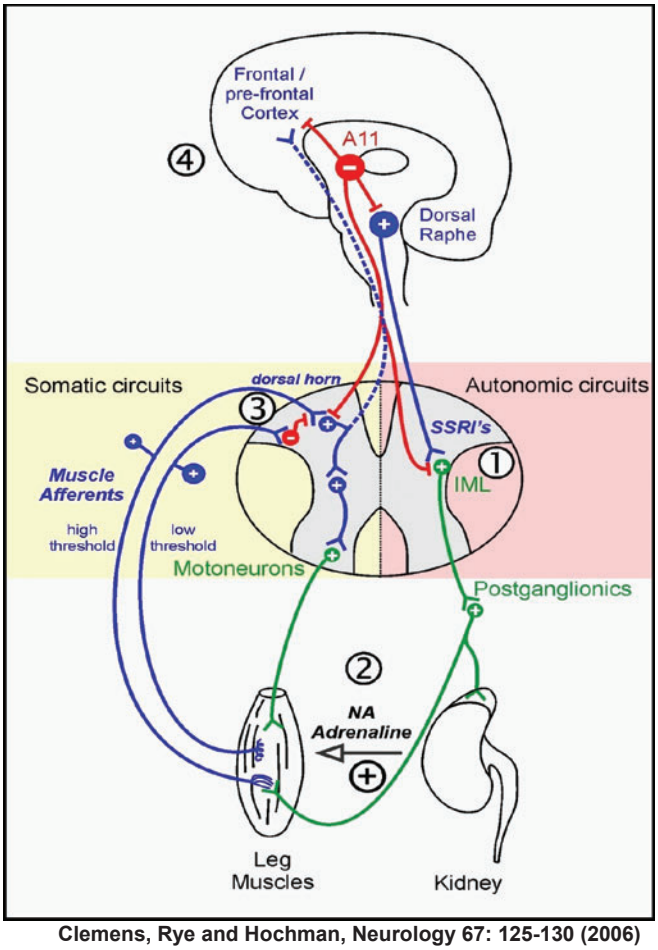
Sympathetic Overactivity in RLS and PLMS Leading to Heart Disease and Stroke Through the Mechanism of Hypertension

Although there are some inconsistencies, the literature summarized above argues that patients with RLS, PLMS, or both RLS and PLMS are at increased risk of developing hypertension, heart disease, and stroke. One of the leading hypotheses for the pathogenesis of RLS and PLMS is that there is a dopaminergic deficit in these 2 related conditions. The strongest evidence for this hypothesis is the efficacy of dopaminergic therapy for both conditions.[45,46] There are several dopaminergic pathways in the brain, including the striatonigral, mesolimbic, mesocortical, and tubero-infundibular. The A11 dopaminergic diencephalospinal pathways innervate preganglionic sympathetic neurons and the dorsal horn in the spinal cord. One hypothesis gaining substantial support suggests that hypofunction of the A11 diencephalospinal pathway leads to enhanced sympathetic outflow to the periphery, inclusive of somatic muscle fibers. As a result of this increased sympathetic activity, altered activity in afferents from the muscle fibers back to the spinal cord in turn may heighten spinal sensory signaling and thereby trigger RLS symptoms. This afferent input is also normally dampened by A_{11} innervation at the level of the dorsal horn. Thus, spinal dopaminergic hypofunctioning theoretically gives rise to a positive feedback loop whereby disinhibition manifests as both heightened sympathetic efferent drive leading to altered sensation as well as insufficient suppression of increased sensory afferent drive (ie, aberrant sensory equivalents of RLS complaints) (see Figure 1). The A_{11} diencephalospinal pathway is also the only dopaminergic pathway in which a hypofunction might be reasonably expected to lead to sympathetic hyperactivity and hypertension with a subsequent increased risk for developing heart disease and stroke.[47] Interestingly, vasodilators, one of the original therapies for RLS shown to be effective by Ekbom, also act at the dorsal horn in addition to the periphery.[48] The A_{11} hypodopaminergic theory is further strengthened by demonstration that lesioning of this pathway leads to restlessness in rats that is reversible with the dopamine agonist pramipexole.[49] It is well documented by cerebrospinal fluid analyses, magnetic resonance imaging, and autopsy studies that iron deficiency in the central nervous system plays an important role in modifying expression of RLS. Iron deficiency contributes to impairments in dopamine signaling, and it may be that the negative impact of iron deficiency upon RLS symptoms plays out at the spinal level (see Figure 2).[50]

As presented in detail above, PLMS accompanied by EEG arousals are associated with significant transient rises in pulse rates and blood pressure.[36,37] These elevations in pulse rates and blood pressure are presumably sympathetically mediated, although the possibility that reduced parasympathetic activity may play a role has not been excluded. It is attractive to postulate that these regular, repetitive blood pressure elevations at night "prime the pump" for the development of daytime hypertension and subsequent stroke and cardiovascular disease. It will be important to differentiate whether it is the PLMS themselves or the arousals associated with them that are more intimately linked to elevations in blood pressure and pulse rate. Arousals from sleep in normal individuals without PLMS are also associated with brief coincident elevations in blood pressure and pulse rate.[51] The number of spontaneous arousals during sleep in normal individuals without PLMS is also a predictor of daytime blood pressure and pulse rate. The higher the arousal rate, the higher the daytime pulse rate and blood pressure.[52] It could therefore be that the arousals associated with the PLMS, rather than PLMS themselves, are responsible for the priming of daytime hypertension. On the other hand, blood pressure elevations that are nearly as high as those seen with PLMS accompanied by arousals are present with PLMS unaccompanied by EEG arousals.[36,37] It then follows that both the PLMS and the arousals associated with them are intimately connected with the accompanying changes in pulse and blood pressure. Further work needs to be done to determine if autonomic priming of daytime hypertension truly occurs in RLS, and whether it, in turn, is causal to cardiovascular disease and stroke.

Sympathetic Overactivity Associated With RLS/PLMS Leading to Heart Disease and Stroke Without Daytime Hypertension as an Intermediary

One of the inconsistencies with the aforementioned hypothesis is that the 2 studies by Winkelman et al. demonstrate a relationship between RLS and cardiovascular disease but not between RLS and hypertension.[21,22] The study by Högl et al. found no relationships between RLS and hypertension,[23] and the study by Rothdach et al.[24] even suggests an inverse relationship. This is in contradistinction with the results of studies by Ulfberg et al.,[15] Ohayon and Roth,[16] and Phillips et al.,[20] in which positive associations were noted between RLS and hypertension. Thus, a relationship between RLS and hypertension is not firmly established. This could simply be the result of a false negative in the Winkelman et al., Hogl et al., and Rothdach et al. studies, since the entry point for the studies was a diagnosis of RLS by questionnaire and not PLMS by objective polysomnography. Periodic rises in blood pressure and daytime hypertension are intimately related to PLMS. Because only 80% to 90% of adult patients with RLS have PLMS, the relationship of the RLS/PLMS complex to hypertension could be diluted by a lack of association between hypertension and RLS without PLMS. If cardiovascular disease and stroke are not caused by hypertension in RLS, what potential alternate explanations could there be for this relationship? Winkelman et al. suggest that the transient elevations in blood pressure associated with PLMS could cause cardiovascular disease by increasing the 24-hour blood pressure profile without producing changes in daytime blood pressure. It is known that hypertension is a risk factor for atherosclerotic plaque formation and plaque rupture.[53,54] Winkelman et al. posit that rises in pulse rate and blood pressure associated with PLMS also could cause cardiovascular disease by way of an increased risk of atherosclerotic plaque formation and rupture.[22]



Hypothetical spinal cord positive feedback mechanism mediating dopamine responsive Restless Legs Syndrome

1) DA inhibits preganglionic sympathetics, thus, in its absence, basal sympathetic tone may increase.
2) Increased adrenaline via innervation of skeletal muscle, in turn, might irritate muscle spindles.
3) The resulting enhanced input from pain-encoding high threshold muscle afferents in lamina I are insufficiently suppressed in the absence of DA or D2-like receptors.

Figure 1—Decreased dopamine (DA) may lead to increased sympathetic drive in Restless Legs Syndrome/Periodic Limb Movements in Sleep (RLS/PLMS).Increased sympathetic drive in RLS/PLMS may lead to hypertension, heart disease, and stroke. Spinal somatosensory (left) and sympathetic autonomic circuits (right) are depicted separately. The consequences of a compromise of spinal dopaminergic inhibitory controls are presented as a sequential series of events numbered 1 through 4. Proposed circuitry leading to increased sympathetic drive. (1) In the spinal cord, DA actions from the A_{11} exert direct inhibitory actions on sympathetic preganglionics in the intermediolateral cell column (IML). In contrast, serotonergic dorsal raphe descending neurons have strong excitatory actions in the IML. Thus, any compromise in A_{11} inhibitory function would shift the balance of descending control of the sympathetic preganglionics toward excitation. Sympathetic hyperactivity in turn could lead to vasoconstriction and subsequently to hypertension, heart disease, and stroke.

The authors of the original publication in which this figure appeared—Clemens S, Rye D, Hochman S—propose a theoretical model of how DA deficiency could lead to the symptoms of RLS: (1) DA inhibits preganglionic sympathetics, thus, in its absence, basal sympathetic tone may increase; (2) increased adrenaline via innervation of skeletal muscle, in turn, might irritate muscle spindles;(3) the resulting enhanced input from pain-encoding high-threshold muscle afferents in lamina I are insufficiently suppressed in the absence of DA or D_2-like receptors; (4) Abnormal sensations, in turn, are perceived at the cortical level. These abnormal sensations are further enhanced by compromised A 11 dopaminergic input at the cortical level. Reproduced from Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. Neurology 2006;67:125-130. Reprinted with permission—Lippincott, Williams & Wilkins, Baltimore, MD.

Comorbidities Frequently Associated With RLS/PLMS Leading to Cardiovascular Disease and Stroke

Winkelman et al.[22] suggest that confounding factors associated with RLS/PLMS, eg, anemia and renal failure, could account for increased cardiovascular and cerebrovascular morbidity. Sleep apnea may also be 1 of these confounding factors. The literature we have quoted previously indicates that PLMS are very common in patients with CHF, and many of the patients with CHF in these studies also had sleep apnea.[25,27,29,30] It is well known that sleep apnea commonly accompanies CHF and that sleep apnea is a risk factor for cardiovascular morbidity and stroke.[27,55] In support of the possibility that RLS/PLMS may predispose to a person to having sleep apnea, we mention 2 studies that indicate that dopamine agonist treatment of RLS/PLMS leads to a coincident significant decrease in sleep disordered breathing.[56,57] Whether these effects are clinically significant is unknown because subjects with RLS and significant sleep disordered breathing (eg, respiratory disturbance index > 10/h) were excluded from both of these studies. This clinical experience, albeit limited, suggests that brain mechanisms modifying expression of PLMS interact at some level with those

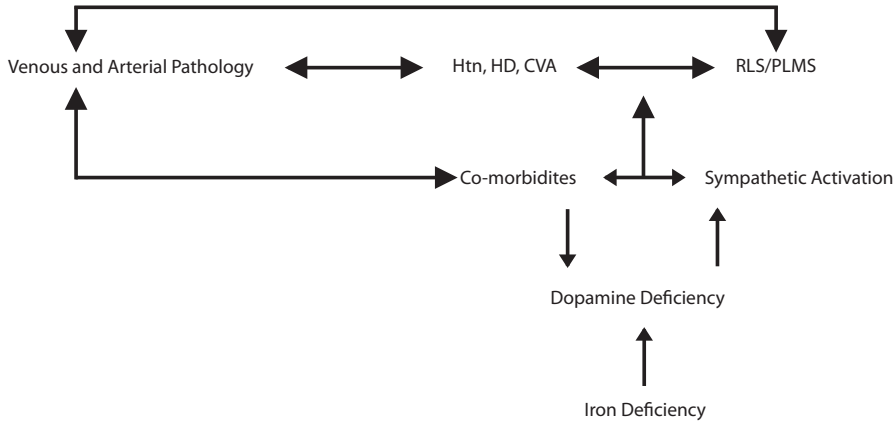


Figure 2—Hypothetical relationships among restless legs syndrome (RLS)/periodic limb movements in sleep(PLMS) and hypertension, heart disease, and stroke. One-way arrows indicate 1-way causation, and 2-way arrows indicate 2-way causation or, alternatively, cooccurrence. Possible comorbidities include insomnia, renal failure, anemia and sleep apnea. Htn refers to hypertension, HD, heart disease, CVA, cerebrovascular accident. See text for details. Not shown on diagram: The 4 recently identified susceptibility genes that could potentially interact at most, if not all, nodal points.

responsible for respiration. As 1 example of how changes in the periphery might lead to cardiovascular and cerebrovascular disease by way of RLS, we mention the study of Haxiu et al.,[58] who demonstrated that sciatic nerve stimulation can modify upper airway tone. This represents a plausible functional anatomy whereby the abnormal leg sensations of RLS might contribute to sleep disordered breathing and its downstream consequences. These putative associations are of particular relevance to RLS, since radiculopathy and peripheral neuropathy are oftcited causes of ostensibly "secondary" RLS.[59] RLS could also produce cardiovascular disease, hypertension, and stroke via decrements in sleep time, which show a modest but significant association with these outcomes in patients without RLS.[60-63]

Interactions among comorbidities associated with RLS (insomnia, obstructive sleep apnea, anemia, renal failure) and sympathetic overactivation and arterial disease[16,59] represent additional avenues through which RLS might promulgate cardiovascular disease and stroke (see Figure 2).

Heart Disease, Stroke, or Peripheral Vascular Disease Leading to RLS/PLMS

Cardiovascular disease could alternatively lead to RLS and PLMS via vascular pathologies in the central nervous system or the periphery.[22] As we have discussed, RLS, PLMS, or both can appear immediately after the onset of acute clinical stroke,[41-43] and PLMS can occur coincidentally with sleep disordered breathing encountered in the setting of CHF.[25,27,29,30] Hypoxia associated with apneic events might also lead to impaired synaptic release of spinal dopamine, as has been shown for nigrostriatal dopaminergic terminals after exposure of newborn rats to intermittent hypoxia.[64] Additional insights into pathophysiologic networks linking RLS/PLMs to cardiovascular consequences may derive from knowledge of the genes conferring susceptibility to RLS/PLMS.[8,9] Among its many functions as a homeobox gene, for example, *Meis1* is critical to vascular patterning/endothelial cell development in both mice and zebra fish.[65,66] Mice that are molecularly engineered to lack *Meis 1* exhibit vascular dysplasia that leads to lethal hemorrhagic events in the embryo.[65] Venous, as opposed to arterial, pathology may also play a role in the pathogenesis of RLS. Thirty six percent of 174 consecutive patients presenting to a phlebology practice had RLS, as opposed to only 19% of 174 matched control subjects.[67] In 2 separate studies, endovenous laser ablation or sclerotherapy improved RLS symptoms in a large percentage of patients with duplex-proven superficial venous insufficiency.[68,69] These findings will have to be validated further in blinded studies. LaBan et al.[70] offered a theoretical explanation for the association between venous pathology and RLS. The authors suggested that an increase in paraspinal venous volumes within the reduced confines of a stenotic lumbar spine could contribute to leg pain and paresthesias arousing patients from a sound sleep (viz., Vesper's curse). Symptomatic relief observed with assumption of an erect or semireclining posture in the 6 subjects examined is highly suggestive, but not diagnostic, of RLS.

Patients with RLS, PLMS, or both, also have cold feet, suggesting sympathetically mediated vasoconstriction (see previous discussion). Not only is sympathetic hyperactivity associated with RLS/PLMS, but that same sympathetic hyperactivity might in turn worsen the symptoms of RLS/PLMS. Work by Ware et al.[13] and Ancoli-Israel et al.[14] indicates that a reduction in sympathetic tone can lead to a reduction in PLMS. Rajaram et al. also explored the possibility that vasoconstriction produced by sympathetic hyperactivity was causal to RLS symptoms by employing enhanced external counterpulsation to increase long-term vascular flow to the limbs in patients with RLS. The results were initially encouraging, but the double-blind study did not show any improvement in RLS symptoms.[71,72] Medications used to treat cardiovascular disease might also play a role in the provoking RLS/PLMS although there is at present, no evidence to support this hypothesis.

FUTURE DIRECTIONS

Converging lines of evidence highlight intimate relationships among RLS /PLMS and hypertension, cardiovascular dis-

ease, and cerebrovascular disease. The theoretical mechanisms mediating these relationships, as summarized in Figure 2, are multiple and complex. Causality is far from established. The inability to impugn hypertension as directly causative to heart disease and cerebrovascular disease in RLS also speaks to the absence of a valid animal model to investigate these potential relationships. Future studies should probe for sympathetic alterations in the animal models of RLS that have been forwarded, including that of the A_{11} diencephalospinal dopamine-lesioned rat. Other, larger, and more sophisticated epidemiologic and laboratory studies in humans will also need to be conducted to extend the known associations among RLS/PLMS and vascular disease to establish causality. One of the more direct and exciting possibilities to be explored is whether the treatment of PLMS will result in resolution of the accompanying autonomic arousals with subsequent reduction in risk for developing cardiovascular and cerebrovascular disease.

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