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COMMENTARY

Restless Legs Syndrome: What Have We Learned from Prevalence Studies and How Will Incidence Studies Further Clinical Knowledge?

Commentary on Budhiraja et al. Incidence of restless legs syndrome and its correlates. J Clin Sleep Med 2012;8:119-124.

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"...it must be remembered that the intensity of the symptomatology presents notable spontaneous oscillations."
Coccagna and Lugaresi, *Int J Neurol*, 1981

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is now generally appreciated in the medical literature as common and complex. Over 50 prevalence studies, most published since 2005, have been crucial in defining many important clinical aspects. In this issue of *JCSM* is one of the first general population-based incidence studies of RLS.[1] How are incidence studies different, and how might they further clinical knowledge?

First, let us review the "Top Five" agreed upon findings from prevalence studies of RLS.[2] Number 5: Prevalence in females is about twice as high as in males, beginning in the late teens or 20s. Number 4: Association with other conditions. Individuals with RLS are at least twice as likely to have scores indicating a depressive or anxiety disorder. This has major clinical implications in that common treatments for these disorders can worsen RLS,[3] and because ongoing sleep disturbance is a known risk factor for the onset and persistence of depressive disorders, as well as for suicidality. Interestingly, emerging evidence indicates at least twice the risk of cardiovascular disease in RLS. Less agreement has been found regarding increased comorbidity with numerous other disorders, including hypertension, diabetes, and obesity. Number 3: Quality of life (QOL) impairments are significant in moderate-to-severe RLS, comparable to diabetes and congestive heart failure.[4] These include lower physical and mental health scores, with disturbed sleep very common by both subjective and objective measures. Number 2: There is a wide spectrum of frequency/severity. Of those meeting the four essential IRLSSG criteria, application of frequency at least 1x/week represents 60% of the RLS population; at least 2x/week is about 50%; and daily is about 20%. Clinically significant RLS—RLS associated with higher morbidity and where treatment should be considered—can be defined by frequency/severity measures. Occurrence at least 1-2x/week, typically with moderate to severe distress, is the most common definition in the epidemiologic studies that show impairment. Number 1: Consideration of differential diagnosis is very important. Exclusion of "mimics" of RLS, such as leg cramps, positional discomfort, arthritis, and leg edema, leads to specificity of diagnosis,[5] and prevalence rates of 1.9% to 4.6% for moderate-to-severe RLS in European and North American studies.[2] Without differential diagnosis prevalence estimates are about 1.25 to 2 times higher. Importantly, the 2012 revision of the International RLS Study Group (IRLSSG) diagnostic criteria will include differential diagnosis as a 5th essential criterion, as is also planned for the *International Classification of Sleep Disorders* (ICSD-3) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) in 2013.

Incidence rate is an estimate of the number of *new* cases in a population over a given time period, as compared to prevalence, which estimates the total number of cases in a population at a given time. Incidence presents a temporal dimension to the disorder, rather than a single "snapshot" of it. While both typically assess disease associations and neither can prove etiology, incidence studies are usually more useful in identifying potential etiologic factors because incidence studies can identify factors associated with the new onset of a disorder, such as weight gain in obstructive sleep apnea.

The paper by Budhiraja et al. in this issue of *JCSM* is a significant contribution, showing that new cases of RLS are common, a yearly incidence of 1.7% for moderate-to-severe RLS (defined as RLS occurring at least 5 days/month and associated with at least moderate distress).[1] Extrapolated to the adult population in Tucson, Arizona, this represents six to seven thousand new cases a year; to the US, four million a year. With the severity definition as above and exclusion of some mimics, this study found prevalence rates of 4.1% at baseline and 7.7% at follow up, which are within typical prevalence rates for the US. These findings are comparable to the only other general-population incidence studies of RLS, both published in the last six months. In two different German population-based cohorts, Szentkiralyi

et al. reported incidence rates of 9 and 22 per 1000 person-years (= annual incidence of 0.9% and 2.2%).[6] In Japan, Kagimura et al. found an annual incidence rate of 0.8%.[7] This is remarkable due to a lower RLS prevalence of 2% in this Japanese cohort. Incidence was significantly higher for women in only one of the four cohorts.

Perhaps the most striking finding from these incidence studies thus far is the remission rate—that is, the percent of cases where RLS criteria were not met at the follow-up survey. This was about half of the cases when all four cohorts are considered. An explanation was not evident, although data analysis did not focus on this aspect. In contrast, a large clinical case series that included affected family members reported RLS symptoms over time as follows: progressive in 36%, stable in 41%, diminished in 15%, and remitted in 8%.[8] Persistence of RLS in one of the incidence studies correlated with frequency (≥ 2x/month), but not with severity (by the IRLS rating scale) or consistently by age or gender.[7] Clearly, factors related to persistence and remission need further study.

Multiple correlates of new onset RLS were examined in the Budhiraja et al. paper, with self-reported obstructive lung disease (asthma, chronic bronchitis, COPD, or emphysema) and estrogen use found to be independent risk factors. They cite six studies that support an increased prevalence of RLS for individuals with lung disease. Indeed, a 3-4 times higher risk of RLS has been found in COPD.[9-11] Conversely, a large population-based study of COPD found significantly more COPD in individuals with RLS, as defined by spirometry.[12] Clinically, it is important to note that peripheral neuropathy is common in COPD and can mimic RLS, but it probably does not fully account for the increased prevalence.[9,10] Budhiraja et al. suggest hypoxemia as the pathophysiological mechanism by which RLS is exacerbated in obstructive lung disease, via influence on brain dopamine pathways. Of note, there is *not* good evidence that serum ferritin levels or systemic inflammation (which limits iron availability) explain the increase.[10,12] Importantly, RLS represents a potentially treatable cause of sleep disturbance and decreased QOL in COPD.[10,12]

Estrogen's role in the exacerbation and pathophysiology of RLS is less clear. RLS is more common in women than men and is very common during pregnancy. While estradiol levels were found to be higher in pregnant women with RLS compared to those without RLS in one study,[13] this was not confirmed in another study.[14] Similarly, hormone replacement therapy use was found to be significantly more frequent in women with RLS in one study[15] but not in two others.[16,17] In a randomized study of hormonal therapy for postmenopausal women, RLS complaints were significantly *less* for those on estrogen + progesterone compared to baseline, but not different for those on estrogen or progesterone alone.[18] Perhaps there is a genetically predisposed subset of women for whom estrogen is an exacerbating factor, but this relationship may be diminished when all women are considered.

Future incidence studies of RLS are likely to reveal additional clinical findings and etiologic clues. Because incidence studies provide a temporal dimension, these studies could provide new insight into the observation by Coccagna and Lugaresi more than 30 years ago of "notable spontaneous oscillations"—by helping answer why.

CITATION

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REFERENCES

1. Budhiraja P, Budhiraja R, Goodwin JL, et al. Incidence of restless legs syndrome and its correlates. *J Clin Sleep Med* 2012;8:119-24.
2. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: A synthesis of the literature. *Sleep Med Rev* 2011 Jul 25. [Epub ahead of print].
3. Hornyak M. Depressive disorders in restless legs syndrome: epidemiology, pathophysiology and management. *CNS Drugs* 2010;24:89-98.
4. Earley CJ, Silber MH. Restless legs syndrome: Understanding its consequences and the need for better treatment. *Sleep Med* 2010;11:807-15.
5. Hening WA, Allen RP, Washburn M, Lesage SR, Earley CJ. The four diagnostic criteria for Restless Legs Syndrome are unable to exclude confounding conditions ("mimics"). *Sleep Med* 2009;10:976-81.
6. Szentkiralyi A, Fendrich K, Hoffmann W, Happe S, Berger K. Incidence of restless legs syndrome in two population-based cohort studies in Germany. *Sleep Med* 2011;12:815-20.
7. Kagimura T, Nomura T, Kusumi M, Nakashima K, Inoue Y. Prospective survey on the natural course of restless legs syndrome over two years in a closed cohort. *Sleep Med* 2011;12:821-6.
8. Xiong L, Montplaisir J, Desautels A, et al. Family study of restless legs syndrome in Quebec, Canada: clinical characterization of 671 familial cases. *Arch Neurol* 2010;67:617-22.
9. Kaplan Y, Inonu H, Yilmaz A, Ocal S. Restless legs syndrome in patients with chronic obstructive pulmonary disease. *Can J Neurol Sci* 2008;35:352-7.
10. Lo Coco D, Mattaliano A, Lo Coco A, Randisi B. Increased frequency of restless legs syndrome in chronic obstructive pulmonary disease patients. *Sleep Med* 2009;10:572-6.
11. Aras G, Kadakal F, Purisa S, Kanmaz D, Aynaci A, Isik E. Are we aware of restless legs syndrome in COPD patients who are in an exacerbation period? Frequency and probable factors related to underlying mechanism. *COPD* 2011;8:437-43.
12. Benediktsdottir B, Janson C, Lindberg E, et al. Prevalence of restless legs syndrome among adults in Iceland and Sweden: Lung function, comorbidity, ferritin, biomarkers and quality of life. *Sleep Med* 2010;11:1043-8.
13. Dzaja A, Wehrle R, Lancel M, Pollmacher T. Elevated estradiol plasma levels in women with restless legs during pregnancy. *Sleep* 2009;32:169-74.
14. Tunc T, Karadag YS, Dogulu F, Inan LE. Predisposing factors of restless legs syndrome in pregnancy. *Mov Disord* 2007;22:627-31.
15. Brown LK, Dedrick DL, Doggett JW, Guido PS. Antidepressant medication use and restless legs syndrome in patients presenting with insomnia. *Sleep Med* 2005;6:443-50.
16. Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. *Neurology* 2000;54:1064-8.
17. Wesstrom J, Nilsson S, Sundstrom-Poromaa I, Ulfberg J. Restless legs syndrome among women: prevalence, co-morbidity and possible relationship to menopause. *Climacteric* 2008;11:422-8.
18. Hachul H, Bittencourt LR, Andersen ML, Haidar MA, Baracat EC, Tufik S. Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women. *Int J Gynaecol Obstet* 2008;103:207-12.

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.