**COMMENTARY**

Periodic Limb Movements in Sleep: Irrelevant Epiphenomenon, Marker for a Potential Problem, or a Disorder?

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“Things are not always what they seem and the first appearance deceives many...”—Phaedrus by Plato, written 360 BC.

As a young sleep physician in a new field 20 years ago, it was hard not to get caught up in the excitement of periodic limb movements in sleep (PLMS) as an important indicator of poor sleep and the assumption that treatment was warranted to “normalize sleep.” After all, it was known that disruption of sleep by loud tones produced negative daytime consequences. In addition, it was found that both PLMS and insomnia increased with age—so why not assume clinical relevance? Unfortunately, first appearances were deceiving. Research found that PLMS severity did not correlate well with daytime sleepiness or with insomnia complaints. Incredibly high PLMS indexes in rapid eye movement sleep behavior disorder (RBD) and in spinal cord injury appeared to be of no clinical relevance, and small case series of PLMS treatment in narcolepsy and poorly defined periodic limb movement disorder (PLMD) cases showed no clinical benefit. Thus, PLMS were declared “not clinically significant” by some, and PLMD was to be stricken from the latest version of the International Classification of Sleep Disorders, ICSD-2. But wait—could “second appearances” be deceiving?

PLMS are a common and readily identified finding on polysomnography. Over time, it has become clear they are seen in heterogeneous conditions: obstructive sleep apnea (OSAS) (limb jerks at the termination of respiratory events), restless legs syndrome (RLS) (80%-90% of patients with RLS have 5 or more PLMS per hour), narcolepsy, RBD, and spinal cord injury. PLMS are a strong predictor of mortality in end-stage renal disease. In addition, most antidepressants have been found to induce or exacerbate PLMS. Clearly, significance and treatment considerations are much different in these different groups. For example, dopaminergic therapy is appropriate for RLS but not for OSAS. Thus, when PLMS are found, it is appropriate for the clinician to ask, “Are these a marker for 1 of the above problems?” If so, the focus should be on that diagnosis. Sixteen years ago, we reported on a man referred for OSA, who had severe PLMS on polysomnography, but not significant OSAS, and subsequently did meet RLS diagnostic criteria. He had notable benefit from dopaminergic therapy. We have continued to find RLS cases this way—not because of a lack of adequate history taking, but because of the difficulty some patients have in characterizing RLS symptoms. Likewise, we have “backed into” RBD cases. But what if none of these conditions are evident—are PLMS clinically relevant?

The paper by Claman et al is a significant contribution to the growing body of literature on the extremely high prevalence of PLMS in the elderly—more than 15 PLMS per hour in more than half of elderly women studied—and on the potential significance of PLMS. They obtained an amazing amount of polysomnographic data and analyzed it to see if PLMS, PLMS with arousals (PLMA), or both PLMS and PLMA correlated with known polysomnographic measures of disturbed sleep. Indeed, both were associated with poor polysomnographic sleep—PLMA more so than PLMS. However, they did not find an association with daytime sleepiness (by the Epworth Sleepiness Scale), cognitive impairment (by Mini-Mental State Examination), or a mood disorder (by Geriatric Depression Scale). So, is this for or against the clinical relevance of PLMS?

For the researcher, it turns out that PLMS are much more complicated to study than it first seems. Three vexing problems have plagued investigation: (1) OSAS caused PLMS, including those caused by upper airway resistance; (2) antidepressant-induced PLMS; and (3) known night-to-night variability of PLMS. Claman et al acknowledged and addressed the first 2. Emphasized in other publications by them, but again demonstrated in this work, is the incredibly high prevalence of OSAS in the elderly—an apnea-hypopnea index of 5 or higher in 76.5% and an apnea-hypopnea index of 15 or higher in 37.8% of their participants. They developed a scoring algorithm to include periodic limb movements at the end of respiratory events only if periodic limb movements were in the cluster independent of scorable respiratory events. While they used standard apnea and hypopnea definitions, they...
unfortunately did not score for subtle respiratory events, even though pressure transducer airflow sensors were used. It would have been interesting to see, if, taking into consideration subtle sleep disordered breathing would have affected their results. Recognizing the second problem, they did collect data on antidepressant use, found higher use in those with 15 or more PLMS per hour and adjusted for this as a confounder. The night-to-night variability of PLMS was not addressed but could be addressed in future studies by methods such as a combination of 1-night polysomnography (to assess for sleep-disordered breathing or not) and 5 nights of actigraphy for PLMS. With a larger number of nights sampled, the night-to-night variability could be averaged, leading to potentially stronger correlations with cognitive and affective outcome measures. Also, based on recent work in RLS, in which impaired cognitive function, mood, and quality of life have been found to correlate with the severity of the RLS, fairly sensitive outcome measures are needed to pick up the real deficits in these areas, typically using total scores rather than cutoff scores. To assess the significance of PLMS, it is likely that a relatively “pure PLMS” study population, without sleep-disordered breathing or antidepressant use, would be a good group to study. A “pure PLMS” population, without 1 of the known disorders associated with PLMS but with clinical sleep disturbance, is what was retained as PLMD in the current International Classification of Sleep Disorders.

For the clinician, where does that leave us? Ideally, treatment decisions should be based on demonstrated adverse consequences of a disorder and outcomes data showing treatment effectiveness. Unfortunately, it is rare for such data to exist for all age groups. A recent review of the PLMS literature nicely summarizes the current evidence.2 When PLMS are found, they should not be immediately dismissed as irrelevant. The clinician should ask, “Are these a marker for 1 of the known problems in which PLMS are found?” If so, that specific disorder should be addressed. If not, a course of action is less clear. There are some studies that have found PLMS to correlate with daytime symptoms3 and for treatment in a blinded, placebo-controlled manner to produce positive results.4,5 However, other studies have not shown correlation or positive treatment effect. Of note is the emerging evidence at the other end of the age spectrum that PLMD in children may be a very useful construct to characterize the sleep disturbance in a subgroup of children with attention-deficit/hyperactivity disorder, as well as be a predictor for the later development of RLS. Claman et al1 have again pointed out how very common PLMS are in the elderly—much work remains to be done on the issue of clinical significance.

REFERENCES