The significance of periodic limb movements in sleep (PLMS) in the absence of Restless Legs Syndrome (RLS) or Periodic Limb Movement Disorder (PLMD), has been a controversial issue in recent years. Nevertheless, based on evidence gathered in recent years on the associations and consequences of PLMS, the issue needs to be reconsidered. Here it shall be demonstrated, that PLMS are associated with disturbed sleep far beyond the affected individual noticing it, and that they have significant and potentially severe consequences on health, which also extend far beyond subjective sleep impairment.

Periodic Limb Movements are Associated Sleep Fragmentation

It is well established that PLMS are associated with microarousals, sleep onset latency and other changes in autonomic activity and therefore associated with an alteration in sleep structure. Whereas older concepts assumed that PLMS caused those arousals, more recent studies revealed, that PLMS and arousals are associated in another, more complex and non-unidirectional manner:

Arousal equivalents, e.g. delta waves, heart rate increases or other changes in cerebral and autonomic activity can herald PLMS. In the most recent scoring criteria for periodic leg movements (PLM), this has been taken into account and a PLM with an arousal can be scored even if the arousal precedes the onset of a PLM.

PLMS are a Marker of Sleep Fragmentation

PLM and arousals are not only associated, but might even better be viewed as a common complex, the PLM arousal complex. Terzano and Parrino have described the cyclic alternating pattern (CAP) as a sequence of biphasic cycles reflecting unstable sleep (phase A: activation – phase B: deactivation).\(^1\) CAP A reflects arousal and arousal equivalents. They have demonstrated that in patients with RLS, 92% of all PLM occurred during CAP, and 96% of them during CAP phase A. They conclude that CAP is not the generator of PLM, but acts as a gate control mechanism, phase A representing a permissive window for the occurrence of PLM.\(^3\)

Even if PLM co-occur with CAP phase A, not all CAP phase A are associated with PLM.\(^4\) It has been observed that in a sequence of PLM, sometimes leg movements appear to be “missing”, whereas the series of underlying CAP phase A – phase B oscillations continues.\(^5\) This observation indicates that the underlying CAP arousal oscillation is de facto superior to PLM, or that PLM are just a downstream manifestation of the underlying CAP phase A – CAP phase B oscillating mechanism. The latter is generally considered as a measure of unstable sleep.\(^6,7\) Therefore, one might argue that PLMS are not only associated with sleep disturbance, but that they are a marker of sleep instability per se.

PLMS: A Potential Cardiovascular Risk Factor

Even when a PLM associated arousal is not evident on the polysomnogram, one cannot conclude that it is not there: Arousals not visible to the human eye have been clearly recognized by fast fourier transform.\(^8\) Sforza and co-workers analyzed the electroencephalogram (EEG) correlates of PLMS by visual scoring and spectral analysis. They found that PLMS were associated with a significant increase in theta/delta activity, and a significant shortening of the RR interval. EEG activation and tachycardia were present with PLM irrespective if a microarousal was detectable or not.\(^8\) Based on their results, they proposed a hierarchy in the arousal response from autonomic activation through bursts of delta activity and alpha activity, to a full awakening.\(^8,9\)

Winkelman warned as early as in 1999 that it was premature to conclude that PLMS not associated with visible EEG arousals were clinically insignificant.\(^10\) They reported that PLMS are associated with cardiac acceleration, even in the absence of arousal. This heart rate increase was significantly larger than that seen after waking leg movements.\(^10\) Gosselin and co-workers investigated the RR intervals in relation to PLM onset in patients with RLS. They found that PLMS were associated with tachycardia followed by bradycardia which were somewhat age and gender dependent. They further suggested that this might help to explain increased cardiac risk observed in elderly.\(^11\)

In addition, there is increasing evidence that even more extended vegetative changes are associated with PLMS. Ali and co-workers first reported on the relationship between PLMS and recurrent elevations in systemic blood pressure in a patient with narcolepsy. The mean increase in systolic blood pressure following leg movements was 23%, and was unchanged even after treatment which temazepam, which significantly attenuated the cortical arousals.\(^12\) In a recent study, an increase in blood pressure was...
observed associated with PLM, which was even higher in PLM associated with microarousals compared to those without. The most striking data stem from a recent study in Iceland. Rye and co-workers reported that the likelihood of hypertension increased with PLMS severity and was particularly high in subjects with a PLMS index greater than 50/hour. PLMS were associated with hypertensive status, independent of age and BMI. In this context, it is interesting to note that PLMS are common in people with essential hypertension. Furthermore, RLS patients with daily symptoms had an increased prevalence of cardiovascular disease compared to those with no RLS symptoms.

The Impact of PLMD

Even if it is widely accepted that the overall influence of PLMS on the perception of sleep quality is very low, and that subjects with PLMD have a similar Pittsburgh sleep quality index as controls, PLMS may profoundly impact a subject’s sleep as has been shown above.

The concept of periodic limb movement disorder PLMD (in the absence of RLS) has been much criticized, because according to the previous International Classification of Sleep Disorders (ICSD) criteria it was possible to make this diagnosis based on bed partners’ report of leg movements during sleep alone, even in an otherwise asymptomatic individual. This probably inflated the frequency of PLMD due to the fact that PLMS also occur in healthy people without sleep complaints. In the recent ICSD 2, this has been corrected and diagnosis of PLMD can only be made in the presence of a clinical sleep disturbance or daytime fatigue, which are not otherwise explained. If PLMS are present without clinical sleep disturbance, they can be described as a polysomnographic finding, but criteria are not met for a diagnosis of PLMD. A PLMD diagnosis requires that very much care is taken to exclude a false positive PLM caused by respiratory events, not to miss any infrequent or atypical RLS in patients with insomnia and PLM, and not to miss a diagnosis of narcolepsy in patients with PLM during sleep and daytime fatigue or sleepiness. Nevertheless, it has also been demonstrated, that patients with PLMD only (without RLS) have significant sleep disturbances, e.g. increased stage 1 sleep, decreased stage 2 sleep, increased stage shifts, and awakenings, than controls or patients with RLS alone. From an outcome-driven point of view, it is irrelevant if PLM occur as sole PLMS or in a context of PLMD; what counts are their vegetative and other consequences.

CONCLUSIONS

The studies reported here should prompt us to abandon our conventional concept that PLMS have no meaning in patients without RLS, or that they are just an insignificant collateral finding. Regardless, if PLM occur in a context of RLS, PLMD or just as a polysomnographic finding of PLM, we can no longer ignore the cumulative evidence that PLM in sleep are associated with a significant sleep state or arousal instability, and we have discussed recent and strong evidence, that they might constitute a cardiovascular risk factor with a potential long term negative outcome.

We also have to recognize that our capacity to appreciate whether or not PLMS are associated with sleep disturbance, depends very much on the detail we dedicate to looking at this issue, and that consequences of PLM are present, even if the sleep disturbance is not visible at a first glance. We can no longer conclude from the absence of subjective sleep impairment in patients with PLMS alone that treatment is not indicated. Arterial hypertension and diabetes must be treated in the absence of subjective impairment. Maybe we will soon have to think of PLMS in a similar way.

REFERENCES


