Is restless legs syndrome a sleep disorder?

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A compelling urge to move the legs, often accompanied by uncomfortable dysesthesias, is the fundamental element of restless legs syndrome (RLS). To make a diagnosis of RLS, this core sensory-motor symptom must be present at rest, at least temporarily relieved by movement, and most pronounced at night.[1] Sleep disturbance is usually present in RLS and is traditionally considered as a consequence of either the sensory-motor symptom interfering with sleep or of periodic limb movements of sleep (PLMS), present in roughly 80% of RLS patients. However, dysesthesias, sleep disturbance, or PLMS are not required for an RLS diagnosis, though they are supportive. In this way, difficulties with understanding, recognition, and treatment of RLS may be related to its definition: is it a sleep disorder, a movement disorder, or a chronic pain disorder?

In this issue of *Neurology*®, Allen et al.[2] investigate the role of the excitatory neurotransmitter glutamate in RLS with the use of magnetic resonance spectroscopy (MRS). They document elevations in daytime thalamic glutamate levels in RLS (measured in the evoked spectrum as a peak with glutamine, the combination denoted Glx, as a ratio to creatinine, Glx/Cr). They also find that glutamate levels are correlated with objectively and subjectively recorded sleep disturbance, but not with the primary RLS symptoms or PLMS. They conclude that it is the combination of glutamatergic (sleep disturbance) and dopaminergic (sensory symptoms, PLMS) abnormalities that produce the full RLS symptomatology.

There are a number of novel features to this study and its conclusions. The authors identified abnormalities in a nondopaminergic neural system; they suggest that the core features and sleep disturbance of RLS have a separate pathophysiology from that of RLS-related PLMS; and they introduce the concept of hyperarousal in RLS.

Much of the previous work on RLS neurochemistry has focused on the dopaminergic system, fueled by the therapeutic success of levodopa and the dopamine agonists. However, no consistent dopamine system abnormalities have emerged from over 20 years of neuroimaging, neuroanatomy, and neuroendocrine research.[3] CNS iron abnormalities are the most consistent findings in RLS, with a possible tie to the dopaminergic system.[4] For this reason, the introduction of glutamate as a system of interest will stimulate new research.

The proposed dichotomy of dopaminergic and glutamatergic mechanisms in RLS is based on the observation that dopaminergic agents are far more effective in improving core RLS symptoms and reducing PLMS than they are in improving objectively recorded sleep architecture.[5] However, dopaminergic agents have been clinically successful because they produce dramatic benefits for subjectively recorded sleep.[6,7] Thus, as in other contexts in sleep research, objectively and subjectively recorded sleep quality measures often do not agree.

The authors describe the elevated glutamate levels as a reflection of "hyperarousal" of RLS, which they contend leads to sleep disturbance at night and counterbalances the potential daytime sleepiness that might result from poor sleep. This concept of hyperarousal in RLS is very similar to the same construct used to understand insomnia. In the latter disorder, multiple lines of investigation, including relative spectral power present in the sleep EEG, neuroendocrine data, reduced cortical GABA, and cognitive studies, all suggest an activated mind, brain, and body.[8] As with insomnia, the hyperarousal of RLS is present during both daytime and nighttime (as indicated by the elevated daytime glutamate levels in the present study), suggesting that the nocturnally predominant core symptoms of RLS are only one piece of the overall symptomatic and biological picture. From this perspective, RLS (like insomnia) is not predominantly a sleep disorder, or even a nocturnal disorder, but rather a 24-hour disorder in which sleep is just one manifestation. Although interesting, the hyperarousal concept of RLS will require much more evidence before it can be accepted, as the glutamatergic excess could be nothing more than a reflection of sleep disturbance as a result of the primary RLS symptoms.

The lack of correlation of MRS-derived glutamate levels with the RLS sensory-motor symptoms (as opposed to the sleep disturbance and PLMS) in

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Allen et al. has also been an observed failing in studies of dopaminergic and opioidergic systems and in studies of established genetic markers. However, as dramatic improvements are observed in these same core symptoms with dopaminergic, opioid, and Ca channel α2δ agents (e.g., gabapentin, pregabalin),[9] any explanation of the biology of RLS must first account for the therapeutic benefits of these drugs and the discrepancies between objective neurobiological data (neurotransmitter/receptor/transporter levels) and subjective distress and improvement. One possibility is that our tools for measuring the experience and consequences of RLS may be inadequate. Another explanation is that RLS may be a heterogeneous disorder, with multiple etiologies or expressions. From this latter perspective, Allen et al. have performed an important first step, proposing a neurobiological hypothesis that divides RLS into individual features: primary sensory-motor symptoms, PLMS, and sleep disturbance. This approach has been fruitful in RLS genetics: the BTBD9 SNP is associated with PLMS but not the core RLS symptoms,[10] indicating that the gene may be an RLS endophenotype[11] (genetic heritable marker). Similarly, subtyping RLS (and individual patients) into more meaningful biologically based phenotypes (e.g., with or without sleep disturbance, PLMS, or painful RLS) may not only advance biologically based investigation and promote the development of animal models but may, as Allen et al. point out, optimize patient care. Thus, in answer to the original question of whether RLS is a sleep disorder, a movement disorder, or a chronic pain disorder, the most accurate answer may be that it depends on the patient.

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