EDITORIALS

Periodic Limb Movements in Sleep — Endophenotype for Restless Legs Syndrome?

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Today, 350 years after its first description, the restless legs syndrome (RLS) is strangely controversial. Experts and patients alike describe RLS both as a miserably impairing disorder and as "the most common disorder you have never heard of." Critics do not regard RLS as a disorder at all but, rather, as the fabrication of an omnivorous pharmaceutical industry. RLS is a waking sensorimotor disturbance with features of both neurologic and sleep disorders. Those afflicted describe an intensely uncomfortable, overwhelming urge to move the legs (often accompanied by dysesthesias), predominantly in the evening or at night, that is present at rest and relieved only temporarily by movement. These leg sensations dramatically disturb sleep, and impairment in quality of life is common.[1]

Once asleep, the majority of (but not all) patients with RLS have periodic limb movements in sleep, which was originally called "nocturnal myoclonus." These movements consist of recurrent (every 20 to 30 seconds), involuntary dorsiflexion of the foot and lower leg, with each movement lasting about 2 to 5 seconds. Such movements can be recorded in the home with simple surface monitors on the leg. Roughly one quarter of such limb movements are associated with arousal from sleep, as seen on electroencephalography, and all are followed by large elevations in systolic (20 to 25 mm Hg) and diastolic (10 to 15 mm Hg) blood pressure.[2] However, the vast majority of persons with periodic limb movements in sleep do not have waking symptoms of RLS. Such movements are common without RLS, with increased age, in patients who are taking antidepressant medications and in those with certain neurologic and sleep disorders (e.g., narcolepsy and rapid-eye-movement sleep behavior disorder). Outside of RLS, the clinical significance of periodic limb movements in sleep remains uncertain, though concern exists regarding the effects of the movements on sleep quality and cardiovascular functioning.[3]

Some of the earliest descriptions of RLS recognized its strongly familial nature. Recent linkage studies have shown a number of susceptibility loci for familial RLS.[4] However, until now, no gene has been identified. For this reason, the report by Stefansson et al.[5] in this issue of the *Journal* showing an association between a sequence variant in chromosome 6p and periodic limb movements in sleep in distinct Icelandic and American cohorts of subjects with RLS and their families, as well as controls, is exciting and important. The simultaneously published report by Winkelmann et al.[6] showing an association between RLS and the same sequence variant, as well as two additional single-nucleotide polymorphisms (SNPs), in German and Canadian cohorts with RLS makes this finding even more secure.

Inspection of the data provided by Stefansson et al., however, shows that this sequence variant does not appear to be a gene for RLS but, rather, for periodic limb movements in sleep. The investigators observed the highest odds ratio in subjects with periodic limb movements in sleep without RLS. As this group became increasingly diluted with subjects with RLS, the association with the SNP became less and less apparent. Although a significant association with the SNP was still present in the entire group with RLS (with and without periodic limb movements), it disap-

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peared completely in subjects with RLS without periodic limb movements in sleep. Since Winkelmann et al.[6] did not report on periodic limb movements in sleep in their study, it is unclear whether the other sequence variants they found are truly for RLS, for periodic limb movements in sleep, or for some other RLS marker.

What is the advantage of knowing the genetic basis for periodic limb movements in sleep? These movements may serve as a heritable biologic marker, or endophenotype, for RLS. Disorders with a complex phenotype and heritability, such as RLS, are increasingly being dissected into their component parts with the use of endophenotypes. Endophenotypes are relatively simple, stable biologic phenomena that can be measured objectively and are genetically determined. To function as an endophenotype, a marker must be present both in affected patients with the disorder and in unaffected family members. In theory, although the disorder itself will usually result from a mixture of multiple genetic and nongenetic abnormalities, the endophenotype, as a simpler biologic phenomenon, will have a more straightforward genetic and pathophysiological basis. This method has been constructively applied to a number of disorders, such as hemochromatosis (with serum iron as the endophenotype), the long-QT syndrome (QT prolongation), and familial adenomatous polyposis coli (intestinal polyps).[7]

The use of periodic limb movements in sleep as an endophenotype for RLS may present a number of valuable opportunities and insights. From a genetic perspective, it might assist with linkage to other relevant susceptibility genes so that polygenic interactions can be discerned. From a diagnostic perspective, the use of periodic limb movements in sleep may improve diagnostic accuracy and provide a more homogeneous RLS phenotype for epidemiology, physiology, genotyping, and treatment studies. RLS has a number of clinical mimics (e.g., peripheral neuropathy and nocturnal leg cramps), and its diagnosis with the use of questionnaires is fraught with difficulty. The study by Stefansson et al. provides some insight into this problem since their questionnaire had a false positive rate of 25% and a similar false negative rate, as compared with an expert clinical interview.

In addition, RLS may have a number of subtypes, some with and some without periodic limb movements in sleep. For instance, many, but not all, patients with RLS have an excellent response to dopaminergic therapy, which also nearly eliminates periodic limb movements in sleep.[8] The subtyping of patients with RLS may predict treatment responses to these agents. Finally, patients with end-stage renal failure who have periodic limb movements in sleep are at increased risk of death,[9] and such movements may also contribute to the observed elevated risk of cardiovascular disease in patients with RLS.[10] Use of the endophenotype for periodic limb movements, or even of the sequence variant itself, may allow stratification of these risks in patients with RLS or other conditions marked by such movements.

The association between the SNP and reduced serum ferritin indexes is an important feature of the study by Stefansson et al. Multiple studies that used magnetic resonance imaging scans, analysis of cerebrospinal fluid, transcranial ultrasonography, and analysis of autopsy specimens[11] showed that patients with RLS had a reduction in iron in the central nervous system. Iron levels in the brain may thus reflect an independent endophenotype for RLS or may be a causative factor for RLS or periodic limb movements in sleep.

The demonstration of a strong association between a sequence variant and periodic limb movements in sleep and, to a lesser extent, RLS does not validate RLS as a "genuine" disorder. Many physiological features that vary in the otherwise normal population (e.g., baldness, height, and eye color) have genetic bases. The legitimacy of RLS as a bona fide disorder is provided by the clinically apparent and well-documented sleep disturbance and distress of the roughly 3% of the adult population with frequent and bothersome RLS symptoms. The genetic finding reported by Stefansson et al. offers hope to patients with periodic limb movements in sleep and RLS that the syndrome's pathophysiology will be understood and that such knowledge will lead to additional effective and durable treatments.

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Ultrasound — Now Also for Microbiologists?

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The ultrasound system used by bats, dolphins, and whales has developed into a technology that has found numerous applications in diverse fields, including the biomedical domain, where it has been used particularly as an imaging device. Now low-frequency ultrasound of low acoustic intensity could also become a useful tool for the clinical microbiologist in the diagnosis of biofilm-associated infections, such as prosthetic-hip infections, and others as well.

The development of robust and safe prosthetic material for orthopedic surgery is one of the remarkable cooperative achievements between the fields of materials research and modern medicine: implantation of orthopedic prostheses is now common practice everywhere. Although the outcome is usually favorable, two major complications are always feared: infection and aseptic failure of the prosthesis. The infection rate of hip and knee arthroplasty has been considerably reduced in recent years by systemic preventive measures, including perioperative antibiotics, and has stabilized at 5.9 infections per 1000 joint-years at 2 years of follow-up.[1] Nevertheless, prosthetic-joint infections still plague a high number of patients because of the large number of operations performed, the protracted course of the disease, and the delay in diagnosis. Finally, the isolation of the offending organism is difficult and, therefore, treatment strategy often is speculative.[2,3] Improved diagnostic tools clearly are warranted.

Recently, unequivocal evidence has accumulated that orthopedic-implant infections have all the microbiologic characteristics of device-associated infections, including sessile growth, adherence to foreign material, encasement in a hydrated extracellular matrix (biofilm), altered phenotype, and resistance to the bactericidal effects of most antibiotics.[4] Other diseases obeying the same biologic rules include infections associated with intravascular catheters, prosthetic valves, pacemakers, and intraocular lenses, to name but a few.[5]

Starting from these observations and from their own preliminary work, Trampuz et al.[6] describe in this issue of the *Journal* a well-designed, carefully conducted prospective clinical study in which they improve the microbiologic diagnosis by liberating the sessile bacteria encased in the biofilm that coats infected prostheses. The technique used is a short, low-energy ultrasound treatment (to avoid affecting bacterial viability). This procedure is not new. It has been used extensively in vitro and has already found clinical application in the diagnosis of catheter-related infections and in selected cases of orthopedic-implant infections.

What are the key results? Trampuz et al. show that their method can indeed help in differentiating septic from aseptic failure: it improves significantly the sensitivity of sonicate-fluid culture, as compared with periprosthetic-tissue culture or with culture of a joint aspirate, without decreasing its specificity. The positive results of soni-

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