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Introduction

New connections that are being forged between sleep and movement disorders were explored during the Restless Legs Syndrome Worldwide Expert Meeting, held in March 2001 in Venice, Italy. Researchers and clinicians from Europe and North America shared study findings and insights into restless legs syndrome (RLS) and its relation to two other related movement disorders: periodic limb movements in sleep (PLMS) and Parkinson's disease (PD). The experts reviewed recent findings about RLS that may lead to promising avenues of future research. Epidemiology, basic science, clinical investigation, and therapeutic trends in this frequently misdiagnosed sensorimotor disorder were addressed to explore the scientific and medical aspects of RLS, and to determine patient needs in the clinical treatment of this disorder.

In this supplement, the first three articles focus on the genetic and epidemiologic concepts. My colleagues and I raise issues of major concern for our research efforts in RLS – the need for data on the true inheritance of the disorder, which can then be used to design the most appropriate genetic studies. The results of recent studies support a recently advanced concept for RLS: the phenotype of the disease may depend on the age at onset of the symptoms. We provide initial data indicating that a critical age between 40 and 50 divides RLS into two separate phenotypes, with the earlier-onset having a strong familial pattern not shown by the later-onset phenotype. Age at onset of RLS needs to be considered to better define the RLS phenotype in future studies.

Dr Juliane Winkelmann presents current thought on the genetic contribution to idiopathic RLS. While an autosomal dominant mode of inheritance is suspected, no specific gene has been identified. Several studies have investigated the occurrence of familial RLS in different populations of RLS patients, but only in a limited number of studies have personal interviews with relatives of the index cases been conducted to verify the diagnosis and the definite occurrence of the familial cases. Dr Winkelmann concludes that further studies should investigate the clinical picture of RLS and clearly define the exact phenotype of the disease.

Dr William Ondo surveys the epidemiology and etiology of RLS, examining racial influences on prevalence and the causes of secondary RLS. Dr Ondo notes that RLS occurs predominantly in Caucasians, is relatively uncommon in Asians, and is thought to be relatively uncommon in people of African descent, although prevalence in this population is not known. Secondary RLS may be caused by iron deficiency, uremia, neuropathy, or pregnancy, but definitive epidemiologic data are lacking. Currently, RLS is commonly undiagnosed in the general population.

The second part of this supplement includes a pair of articles covering two basic and unique clinical features of this disorder: its pronounced circadian pattern and its unusual problem of augmentation with some forms of dopaminergic treatment. Dr Diego Garcia Borreguero presents intriguing new data on circadian variation in neuroendocrine response to levodopa, an agent commonly used for the treatment of RLS. Dr Borreguero reviews the evidence showing circadian oscillation of dopaminergic function and postulates that the amplitude of circadian rhythm of dopaminergic function is increased in RLS, with hypofunction at night.

Dr Luigi Ferini-Strambi presents original data on RLS in patients being treated with the dopamine agonist pramipexole and discusses the problem of RLS augmentation; specifically, that augmentation is unrelated either to severity of RLS or to doses of pramipexole. Dr Ferini-Strambi finds that the rapid efficacy of pramipexole at a very low dosage may indicate that D_3 receptors of the mesolimbic system are more specifically involved in the pathophysiology of RLS. Further study is needed to clarify whether the elimination half-life or specific receptor activity of different dopaminergic agents is crucial for developing the augmentation phenomenon in RLS.

The third part of this supplement looks at the parallel between RLS and PLMS. While the benefits of treatment for RLS are well documented, this is less the case for those patients who have only PLMS without symptoms of RLS. Dr Lena Leissner presents data separating patients with PLMS into two types based on the pattern of their arousals with leg movements. It seems possible this may provide a basis for treatment decisions, and one of these conditions may be partially developed or expressed RLS.

The motor pattern of periodic limb movements in sleep in idiopathic RLS patients is discussed by Dr Guiseppe Plazzi, who offers new evidence consistent with two possible pathophysiologic models: a dual mechanism set into motion by sleep-related factors at a supraspinal level and another that accounts for abnormal activity arising from the supraspinal subcortical region, ultimately triggering a sort of locomotor circuitry intrinsic to the cord.

Dr Bernd Saletu relates data from a study of previously

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untreated patients with RLS and PLMS compared with unaffected controls. Electroencephalographic mapping revealed neurophysiologic correlates of depression and anxiety in RLS and PLMS, respectively, which was confirmed by self-ratings at the symptomatologic level. Excessive sleepiness, however, was not clearly documented in RLS patients; this suggests that the neurologic mechanism producing urge to move and arousal disturbing sleep may also operate in the daytime, producing an arousal that partly compensates for the significant sleep loss.

The last section of this supplement presents a complementary brace of papers both noting the relationship between RLS, probably a dopaminergic disorder, and PD, which has a well-established dopaminergic pathology.

Dr David Rye reviews his own and others' findings on the pathogenesis of PD, which support the view that excessive daytime sleepiness (EDS) in PD patients is due to a primary impairment of waking arousal and REM sleep expression, not merely to a lack of sleep. The spectrum of sleep-wake alterations seen with the loss of nigrostriatal dopamine characteristic of PD includes PLMS and EDS, yet their precise pathologic bases remain elusive. These findings are seen as applying in part to RLS.

Dr K. Ray Chaudhuri reports results of a study of the relationship between PLMS in PD patients and dopaminergic therapy. In a two-part paper, he presents new information on the clinical overlap of RLS and PD and reviews the use of sustained dopaminergic treatment as it applies to RLS. Dr Chaudhuri presents evidence for concluding that there is a considerable underdiagnosis of RLS or nocturnal restlessness in PD. RLS or RLS-type symptoms (nocturnal restlessness) do occur in PD and require specific recognition and management. Whether RLS or nocturnal restlessness is secondary to the disease process of PD or to dopaminergic therapy for PD remains to be ascertained.

The integrated approach to current knowledge on RLS and related movement disorders, exemplified by these papers from the Restless Legs Syndrome Worldwide Expert Meeting, promises new advances in diagnosis and treatment of these often neglected and undertreated conditions.

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