

# Hiding in plain sight

## Risk factors for REM sleep behavior disorder

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REM sleep behavior disorder (RBD) is a parasomnia characterized by loss of normal REM sleep muscle atonia that is usually accompanied by dream enactment.<sup>1</sup> The prevalence of this disorder is unknown, but has been estimated at 0.4%–0.5% among adults. RBD is notable both for its potential for disruption of the sleep milieu by complex and aggressive behaviors with resulting injury, and for its identity as a “preclinical” sign of synuclein-mediated neurodegenerative disease such as Parkinson disease (PD) and dementia with Lewy bodies (DLB). The association with neurodegenerative disease is complex, and some investigators argue that RBD marks a subtype of PD. Until now, the genesis of RBD is most often considered “idiopathic,” with little known of potential risk factors for development other than male sex and age greater than 50 years.

In this issue of *Neurology*®, Postuma et al.<sup>2</sup> present data on risk factors for idiopathic RBD using questionnaire data from a multicenter, cross-sectional study of 347 RBD cases treated at sleep centers and 347 age- and sex-matched controls. The authors found that smoking, head injury, occupational pesticide exposure, low education, and farming are potential risk factors for RBD. Interestingly, pesticide exposure is a well-established risk factor for PD,<sup>3</sup> while smoking is a protective factor in studies of PD.<sup>4</sup>

One of the major advantages of this study is the relatively large number of RBD subjects enrolled, which was made possible by the collaborative efforts of 13 institutions (in 10 different countries), involving members of the International REM Sleep Behavior Disorder Study Group. The number of RBD subjects in this study is greater than 2 other reported and oft-cited series, with 93 and 96 subjects, respectively.<sup>5,6</sup> This type of collaborative effort, involving the development and characterization of pools of patients with a relatively uncommon or underreported disorder, is desperately needed and promises unprecedented discoveries.

While this is the first case-control study of RBD of this magnitude to be systematically performed, this ambitious effort is somewhat limited by selection methodologies for cases and controls. As the authors point out, those with RBD in the general population may differ from those who find their way to sleep clinics, where recruitment took place. Understanding the specific characteristics of RBD among the cases in the study group would be a good start to understanding differences between the sleep clinic RBD population and population-based RBD. Presumably, population-based studies would pick up milder RBD cases, and possibly more female cases, highlighting the usefulness of a reference point from this study—and future studies—on level of RBD severity and presenting complaints. Controls, too, can be vexatious. The controls in this study had other sleep disorders (n = 218), including obstructive sleep apnea; further, normal volunteers (n = 129) were recruited in an unspecified manner, from an unknown number of sites. Ideally, as this area of research moves forward, drawing from the general population using well-defined criteria will help eliminate unintended biases in the control group.

The questionnaire used for this study can be viewed in the supplemental data, and includes information of known importance in PD. It also assesses a diverse set of lifestyle, occupational, and health/exposure risk factors. Assessing health/exposure risk factors for RBD beyond sex and age is new and needed, and while the authors did not specifically report on the methodologies involved in constructing this questionnaire, its design and validation are of great interest and worth understanding. Furthermore, as the authors note, the questionnaire was designed in English and then translated into multiple languages, although test-retest reliability was not conducted in any language. While one of the major advantages of this study is that it assessed individuals with RBD in 10 countries, a corresponding limitation is the difficulty of such international collabora-

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tive efforts in the translation and testing of assessment tools. As this questionnaire is tested, used, and refined, adding additional questions, for example on history of alcohol and drug abuse, withdrawal, and dependence, may prove to be particularly relevant for further assessing risk factors for RBD.

One of the most intriguing aspects of this work is the picture of similarities and differences among risk factors for RBD and PD. While pesticide exposure appears to be a risk factor for both disorders, smoking, for example, which is protective for PD, is a risk factor for RBD. In the absence of a PD-without-RBD comparison group, or a PD-with-RBD comparison group, it remains uncertain whether RBD—particularly in a cross-sectional study utilizing a male-predominant, older age group—has an independent risk profile, since current research indicates that most patients in this study group will eventually convert to parkinsonism/dementia. It is certainly possible that RBD preceding PD/dementia has some separate risk factors from RBD emerging with PD/dementia. This would be an important insight into the pathogenesis of these disorders.

This is a novel, timely study that opens up a new branch of RBD research, and points the way to additional, larger studies; the authors are to be congratulated for “getting the ball rolling.” Without such

sweeping collaborations among multiple sites, risk factors for relatively uncommon and underreported sleep disorders such as RBD may remain hidden in plain sight.

## DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to [Neurology.org](http://Neurology.org) for full disclosures.**

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