RBD - An Emerging Clue to Neurodegenerative Disorders

Comment on Consens FB; Chervin RD; Koepp RA et al. Validation of a Polysomnographic Score for REM Sleep Behavior Disorder. SLEEP 2005;28(8):993-997

Fred W. Turek, PhD; Christine Dugovic, PhD

Center for Sleep and Circadian Biology, Northwestern University, Evanston, IL

ON THE 400TH ANNIVERSARY OF MIGUEL DE CERVANTES’ MASTERPIECE, IT IS FITTING TO NOTE THAT THE MAN OF LA MANCHA APPARENTLY SUFFERED from a parasomnia that was only formally described in this journal 19 years ago. While rapid eye movement (REM) sleep disorder (RBD) was only first identified in the scientific literature in 1986, Schenck and Mahowald noted in their 2002 review of the disorder how Don Quixote was moving about and slaying evil giants on the high plateaus of Spain’s Castile-La Mancha even in his sleep; a sure sign he was in REM sleep, but had lost the normal muscle atonia associated with REM sleep. The violent behavior of the errant knight is a hallmark of RBD, a behavior that can be acutely dangerous for the individual or his (almost 90% of people with RBD are male) bed partner. However, reports that RBD may be an early indicator for the later development of neurodegenerative disorders, raises the possibility that RBD may be of much greater medical importance than just the danger associated with acting out one’s dreams.

A paper in this issue of SLEEP by Consens et al. provides further evidence for a link between RBD and neurodegenerative disorder. This paper describes a quantitative method for assessing the severity of RBD polysomnographic (PSG) features in patients at risk for RBD secondary to neurodegenerative disorders. Conversely, there is now compelling evidence that RBD may be an initial manifestation of Parkinson disease (PD), as well as with a number of other neurological disorders, including narcolepsy, multiple symptom atrophy (MSA) and dementia. The finding that RBD represents an early warning for the later development of devastating neurological disorders makes it imperative that valid and reliable methods be obtained for assessing patients at risk for RBD.

The quantitative method for detecting RBD used by Consens et al involves 2 different PSG scores that measure tonic and phasic events associated with electromyography activity. If such a quantitative method, as originally described by Lapierre and Montplaisir, can be used to detect possible RBD in otherwise healthy individuals, it could be an important tool to be used to guide early intervention therapies to delay and/or attenuate the future development of debilitating neurological disorders.

The emerging associations between RBD and neurodegenerative disorders as well as the quest to understand the mechanisms underlying REM sleep, is turning out to be a truly exciting “bench to bedside” story; a story that should be told over and over when confronted by individuals who want to prevent research on animals. As noted by Schenck and Mahowald, “The foundation for understanding human RBD resides with the experimental animal model of RBD, which, in turn, is dependent on understanding some of the basic neurophysiology of REM sleep.” When Jouvet and Delorme discovered that pontine lesions adjacent to the locus coeruleus led to the permanent loss of REM-alonia in cats, and the subsequent “hallucinatory type behavior resembling dream enactment during REM sleep,” they were describing what would later be found to be mirrored in human RBD. Before RBD was described in humans, Jouvet and other investigators, particularly Adrian Morrison and Jerry Siegel, were using neurotoxin and electrolytic lesions to elucidate those brain areas and pathways involved in REM atonia. Morrison’s group subsequently found spontaneous cases of RBD in cats and dogs, and taking a clue from human studies, they identified clonazepam as an effective therapeutic treatment in animals. Thus, while animal models for RBD provided the foundation for understanding the physiological mechanisms underlying human RBD, the successful treatment of human RBD with clonazepam led to the successful treatment of pets: a truly remarkable “human-animal reciprocity” story.

The relationship of RBD to the subsequent development of neurological disorders has led a number of authors to question how this information can be used to perhaps delay and/or alleviate the later development of these debilitating disorders. It is of particular importance to now determine if early treatment of the symptoms of RBD will slow the progression or development of neurodegenerative disorders. While clonazepam is the treatment of choice for RBD, it is not known if an early intervention with clonazepam would have other beneficial effects. In the first report of the 11 RBD patients that subsequently developed PD, it was noted that the PD symptoms developed on average 4 years after diagnosis and 13 years after the onset of RBD. Such results challenge the sleep community to identify RBD in its early stages and to determine if early interventions to alleviate the symptoms of RBD will impact subsequent neurodegeneration. Use of validated quantitative polysomnographic methods for the detection of RBD may provide the sleep community with a tool for the early diagnosis of RBD, as well as a tool that can be used to develop new therapies for treating neurodegenerative disorders even before obvious signs of such disorders appear.

While animal models have provided the foundation for understanding the physiological and anatomical substrates underlying...
From the — Number of citations related to REM Behavioral Disorder (RBD) since its first characterization in 1986 by Schenck et al.1 Citations were searched on PubMed for three listings: RBD, REM sleep or paradoxical sleep without atonia. The numbers were grouped in five year blocks, and the year 2005* was extrapolated for the full year based on citations listed through May.

human RBD, it is not known what factors lead to the onset and/ or development of RBD, and subsequent neurological disorders. Future studies in animal models can be expected to address these issues. The recent finding that histamine H3 receptor knock-out mice show spontaneous signs of RBD-like symptoms,19 provides a possible genetic model to examine the development of RBD. There is also some suggestions that melatonin therapy can restore REM-atonia (as opposed to clonazepam which suppresses excessive phasic motor activity) and control RBD symptomatically,20-22 suggesting a role for endogeneous melatonin in RBD; a role that can now be investigated in animal models.

Professor John Dagenais, the chair of the Department of Spanish and Portuguese at UCLA, recently described the high plateaus of La Mancha as “…a vast realm for the imagination.”23 While it took almost 400 years to formally describe the condition imagined by Cervantes, we can safely predict that our understanding of RBD, and its full medical implications, will not take another four centuries as the interest in RBD in the biomedical community is emerging at a rapid pace (Figure 1). Whether or not we will also understand the meaning and vivid imaginations that are associated with dreaming during REM sleep in the next four centuries is harder to predict.

REFERENCES

23. Clark J. A quest for the Quixotic. La Mancha celebrates 400 years of Cervantes’ knight-errant. USA Today. June 17, 2005;1D, 2D.