BEST OF THE FIELD

Clifford Saper, MD: Sleep Research Wakes Up to Clinical Relevance

By Norra MacReady

Clinical utility seemed to be the operative concept in sleep research over the past year, judging from the papers chosen as the best of the field by Clifford B. Saper, MD, professor of neurobiology at Harvard University Medical School, in an interview with *Neurology Today*.

SLEEPSEX AND OTHER PARASOMNIAS

One paper that made headlines in the lay press was an intimate review of the literature on sleep and sex by Carlos Schenck, MD, assistant professor of psychiatry, and colleagues at the University of Minnesota Medical School in Minneapolis. Their objective was to classify "sleep-related disorders and abnormal sexual behaviors and experiences" (*Sleep* 2007;30(6):683-702).

The authors searched papers published between 1950 and 2006, and consulted several sleep medicine textbooks that described sexual behaviors during sleep, which they termed "sexsomnias" or "sleepsex." Those behaviors ranged from sexual vocalization and masturbation to intercourse and sometimes even rape.

The most common sleep-related disorders — 78 cases — were Kleine-Levin syndrome, characterized by periods of hypersomnia and uninhibited hypersexuality, and parasomnias with abnormal sleep-related sexual behaviors. Twice as many men had the hypersexuality of KLS. In a handful of cases, the patients' partners found the behavior pleasurable, but adverse physical and psychosocial effects, including run-ins with the law, were much more common, especially when the sexual activity was associated with parasomnia. Not surprisingly, patients are extremely reluctant to come forward, so the incidence of sexsomnias is probably underreported, Dr. Saper said. Patients with parasomnias often respond to treatment, usually with clonazepam (Klonopin). "Clinicians should know about this," he added.

Dr. Saper co-authored a review article about a parasomnia known as REM sleep behavior disorder (RBD) and its relationship to neurodegenerative disease. Reported in animals and humans,

Dr. Clifford B. Saper said that two new papers showed that there is about a 50 percent cell loss in the hypocretin neurons in the hypothalamus during Parkinson disease, adding a new dimension to the pathological sleepiness so often observed in these patients.

RBD is characterized by the loss in tone of skeletal muscle (atonia) that normally occurs during REM sleep, with consequent motor activity during dreaming. The authors, led by Bradley F. Boeve, MD, associate professor of neurology and chair of behavioral neurology at the Mayo Clinic College of Medicine in Rochester, MN, wanted "to explain the high incidence of RBD in patients with Parkinson disease (PD), often before the movement disorder becomes apparent," Dr. Saper said.

Citing evidence from drug and lesioning studies, they suggested that damage to the subcoeruleus region in humans prevents inhibition of the spinal motoneurons that normally are quiescent during REM sleep (*Brain* 2007; E-pub 2007 April 5). This model may explain why certain brainstem lesions also result in RBD. The authors postulated that loss of atonia during REM sleep may dictate dream content, explaining that the "increased locomotor drive could lead to limb movements, and the dream content could evolve secondarily around what is exhibited." They also cited evidence that patients who have a neurodegenerative disorder such as PD or Alzheimer disease plus RBD often have underlying synuclein-positive cellular inclusions; that is, they are synucleopathies.

They concluded that RBD may be analogous to mild cognitive impairment, because it is the earliest manifestation of an evolving illness: anywhere from five to 40 years may elapse between the first appearance of RBD and the onset of parkinsonism or dementia. They wrote that they hoped their review would motivate other investigators to study RBD and its related pathologies more extensively.

Hypocretin Highlights

The hypothalamic peptides known as hypocretins, or orexins, were discovered in 1998, and investigators have been unraveling their role in sleep regulation ever since. Three of the papers chosen by Dr. Saper add to that body of knowledge. One points to a relationship between low hypocretin levels and sleep disturbances in patients with traumatic brain injuries; the other two show an association between hypocretin deficiency, narcolepsy, and PD.

Christian R. Baumann, MD, a neurologist at the University Hospital of Zurich in Switzerland, and co-authors studied 65 patients who had had a traumatic brain injury (TBI) six months previously. The patients underwent clinical, laboratory, imaging, and sleep studies. Of the 65 patients, 47 (72 percent) developed a sleep disturbance after the TBI. In the days immediately following the injury, hypocretin-1 levels in CSF were reduced in 25 of 27 patients studied; at six months, CSF hypocretin-1 was low in four of 21 patients, most markedly in patients with post-traumatic excessive daytime sleepiness. Overall, in nearly 50 percent of the patients, sleep-wake disturbances (SWD) were directly related to the TBI and took a heavy toll on quality of life. The authors concluded that "an involvement of the hypocretin system in the pathophysiology of post-traumatic SWD appears possible" (*Brain* 2007;130(Pt 7): 1873-1883).

Meanwhile, researchers in the US and the Netherlands have reported an association between PD and a marked loss of hypocretin-secreting cells, which could explain why so many people with this disorder display narcolepsy-like symptoms. Thomas C. Thannickal, MD, professor of psychiatry and biobehavioral sciences at the Semel Institute for Neuroscience and Human Behavior at the University of California-Los Angeles, and co-authors Yuan-Yang Lai, PhD, and Jerome Siegel, PhD, compared postmortem tissue from the hypothalami of 11 PD patients (average age of 79 years) with that of five deceased normal controls (average age: 77 years).

"We found an increasing loss of hypocretin cells with disease progression," they reported (*Brain* 2007;130(Pt 6):1586-95). The loss of hypocretin cells ranged from 23 percent among people with [Hoehn-Yahr] stage 1 PD to 62 percent among people in stage 5, with the loss extending throughout the anterior to posterior extent of their hypothalamic distributions. They concluded that the loss of hypocretin cells may cause the narcolepsy-like symptoms, and that those symptoms "may be ameliorated by treatments aimed at reversing the Hcrt [hypocretin] deficit."

REM sleep behavioral disorder (RBD) may be analogous to mild cognitive impairment, because it is the earliest manifestation of an evolving illness: anywhere from five to 40 years may elapse between the first appearance of RBD and the onset of parkinsonism or dementia.

In another postmortem study, Rolf Fronczek, MD, and colleagues in the department of neurology at the Leiden University Medical Center in the Netherlands used immunocytochemistry and an image analysis system, Image-Pro (made by Media Cybernetics, Inc.) that displayed randomly selected fields from the samples on a computer monitor. A single observer, blinded to each patient's diagnosis, counted the positively stained neurons in each sample. The number of hypocretin cells in brains from people with PD was compared to those of age-matched control subjects. The PD patients had a median of 20,276 hypocretin neurons and controls had a median of 36,842 (p=0.016). PD patients also had significantly lower hypocretin levels in the CSF and prefrontal cortex (*Brain* 2007;130(Pt 6): 1577-1585). Taken together, "these two papers showed that there is about a 50 percent cell loss in the hypocretin neurons in the hypothalamus during PD, adding a new dimension to the pathological sleepiness so often observed in these patients," Dr. Saper said.

Dream Waves

A live patient with PD was the sole subject in a study of brain waves and rapid eye movement (REM) sleep, conducted by neurology resident Andrew S. Lim, MD, and colleagues at the University of Toronto and Sunnybrook Health Sciences Center in Canada. From animal studies, investigators have identified phasic pontine, lateral geniculate, and cortical field potentials that occur just before and during REM sleep. These ponto-geniculo-occipital (PGO) waves have been thought to figure in sleep-related neural processes, but no one had ever observed them in humans.

The most common sleep-related disorders were Kleine-Levin syndrome, characterized by periods of hypersomnia and uninhibited hypersexuality, and parasomnias with abnormal sleep-related sexual behaviors.

The patient in this study was slated for unilateral deep brain stimulation of the pedunculopontine nucleus to relieve motor symptoms of PD, so the team used the opportunity to study his sleep-related brain waves, as well. Two electrodes implanted 15 mm apart detected waves occurring before and during REM sleep "with a morphology, temporal distribution, and localization similar to those of PGO waves in other mammals," Dr. Lim and his associates wrote (*Sleep* 2007;30(7):823-7). This is the first confirmation that humans have PGO waves and gives researchers an important new tool for studying learning, memory, and neurodegenerative conditions. ■

STAGES OF PARKINSON DISEASE

The Hoehn and Yahr staging system is commonly used to describe progression of Parkinson disease. According to this scheme, the disease may be staged as follows:

- Stage Zero: No signs of disease.
- Stage One: PD symptoms on one side of the body only.
- Stage Two: PD symptoms on both sides of the body. No impairment of balance.
- Stage Three: Balance impairment. Mild to moderate disease. Physically independent.
- Stage Four: Severe disability, still able to walk or stand unassisted.
- Stage Five: Wheelchair-bound or bedridden unless assisted.

Source: NINDS

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