Cytokines Play Role in Sleep Disorders, Obesity

BY PATRICE WENDLING
Chicago Bureau

PITTSBURGH — Interventions to reduce or neutralize proinflammatory cytokines may be novel treatments in patients with sleep disorders and obesity, Dr. Alexandros Vgontas said at the International Congress of Neuroendocrinology.

Three inflammation-associated cytokines—tumor necrosis factor–α (TNF-α), interleukin-1 (IL-1), and IL-6—are elevated in obese and sleep-deprived patients, and may mediate excessive daytime sleepiness and fatigue. All three cytokines are part of the acute phase response and activate the hypothalamic-pituitary-adrenal axis.

"Proinflammatory cytokines may represent a pathophysiologic link to insulin resistance, obesity, and cardiovascular problems," said Dr. Vgontas, director of the Center for Sleep Disorders Medicine and professor of psychiatry at Pennsylvania State College of Medicine in Hershey.

Over the last decade, research has focused on the role of proinflammatory cytokines in sleep loss and sleep disorders such as sleep apnea, narcolepsy, and insomnia. Studies have demonstrated that IL-6 and TNF-α plasma levels are elevated in patients with sleep apnea and narcolepsy, he said.

Dr. Vgontas and his colleagues also reported a positive correlation between IL-6 and TNF-α levels and body mass index. In a study in 73 obese patients and 45 healthy controls, both without sleep-disordered breathing, obese patients were significantly more likely to have excessive daytime sleepiness.

The finding was replicated by investigators at Pennsylvania State in a large, random community sample in which the strongest risk factors for excessive daytime sleepiness were depression, body mass index, age, sleep duration, diabetes, and finally sleep apnea (J. Clin. Endocrinol. Metab. 2005;90:4510-5).

Dr. Vgontas also studied women with polycystic ovary syndrome, a condition in which the primary pathogenetic mechanism is insulin resistance. In that study, he found that daytime sleepiness is present in 80% of women who have PCOS, and that there is a 30-fold increase in sleep apnea in this population, compared with healthy controls.

'Proinflammatory cytokines may represent a pathophysiologic link to insulin resistance.'

DR. VGONTAS

Based on these findings, he postulated that sleep apnea is primarily a manifestation of metabolic syndrome rather than a local abnormality of the respiratory track. TNF-α, IL-1, and IL-6 are produced by adipose tissue, particularly visceral fat, where 30% of IL-6 is produced. CT scans have shown that sleep apnea patients have significantly more visceral fat in the abdominal area than do obese patients without sleep apnea, Dr. Vgontas said.

Several outside studies also support this systemic view of cytokines in sleep disorders and related health problems. One study showed that sleep apnea patients are more insulin resistant, older, and more obese, but also that insulin resistance is present even in nonobese apnea patients (Am. J. Respir. Crit. Care Med. 2002;165:670-6). Another study indicates that insulin resistance is present even in mild forms of sleep apnea (Am. J. Respir. Crit. Care Med. 2002;165:677-82).

Interventions in this area remain limited. The use of IL-1 or TNF-α receptor antagonists or IL-1b antibodies has been shown to reduce sleep in an animal model. A small pilot study in humans showed that the use of etanercept, a cytokine antagonist, decreased sleepiness in eight obese men with symptomatic apnea, Dr. Vgontas reported. ■

Consider Depression Severity In Comorbid RLS Treatment

BY SHARON WORCESTER
Southeast Bureau

SALT LAKE CITY — Depression severity is a key factor in determining how to treat comorbid depression and restless legs syndrome, Dr. John Winkelman said at the annual meeting of the Associated Professional Sleep Societies.

The two conditions frequently occur together, and often it is unclear which is primary. Further complicating the matter of treatment is the fact that therapies for the two can be conflicting; for example, selective serotonin reuptake inhibitors (SSRIs) frequently used to treat depression have been shown to exacerbate RLS symptoms, explained Dr. Winkelman, who is associate director of the sleep disorders program at Brigham and Women's Hospital in Boston.

'The last thing a person with depression needs is to be up walking at night [as a result of RLS symptoms] and getting more and more agitated.'

But the substantial morbidity and mortality that can be associated with severe depression take precedence when it comes to initiating treatment. In patients presenting with untreated severe depression and RLS, treat the depression first.

If possible, avoid SSRIs and try a nonserotonergic antidepressant such as bupropion instead, he advised.

The RLS symptoms should be treated shortly thereafter, because "the last thing a person with depression needs is to be up walking at night [as a result of RLS symptoms] and getting more and more agitated," said Dr. Winkelman, who is also with Harvard Medical School, Boston.

In patients who have mild depression and RLS, treat the RLS first and see if the depressive symptoms improve, he suggested.

Given that about 10% of the U.S. population is on an antidepressant, it is likely that patients with RLS will present already on an SSRI for depression; in these cases, consider switching the patient to a nonserotonergic antidepressant only if the SSRI was the first drug tried in that patient.

In a patient who was treated with multiple drugs before finding one that worked for the depression or who was hospitalized for severe depression, don't rock the boat, Dr. Winkelman said. Rather, try adding a dopaminergic to treat the RLS symptoms in these patients, he said.

Another important factor to consider in patients with comorbid depression and restless legs syndrome is the effects of sleep quality and quantity on depression and RLS.

"There is quite a bit of data documenting that insomnia is an independent risk factor for incident, new-onset depression," Dr. Winkelman noted. And there is good correlation between severity of RLS symptoms and sleep disturbance, as well.

Furthermore, in one study of more than 100 patients, there was a strong relationship between RLS-related sleep disturbance and depression, but RLS severity in itself did not predict depressive symptoms.

Similar findings have been noted in other neurologic diseases. In studies of patients with Parkinson's disease, for example, disease severity did not predict depressive symptoms, but the effects of the disease on quality of life and activities of daily living did predict depression, he explained.

This raises the question of whether sleep is a key mediator for RLS morbidity in regard to depressive symptomatology. Sleep optimization should therefore be one of the goals of treatment in these patients, Dr. Winkelman said. ■

Exercise Improves Daytime Fatigue in Sleep Apnea Patients

BY DIANA MAHONEY
New England Bureau

BOSTON — Depression, metabolic syndrome, and lack of exercise exacerbate daytime sleepiness in obese patients with sleep apnea, Dr. Alexios Sarrigiannidis said at the annual meeting of the Endocrine Society.

Dr. Sarrigiannidis and his colleagues in the Sleep Research and Treatment Center at Pennsylvania State University, Hershey, reviewed data for 708 consecutive patients, 470 men and 238 women, mean age 50 years, who had been referred for symptoms consistent with sleep apnea and had at least five episodes of apnea/hypopnea per hour. Mean body mass index was 34.9 kg/m² for men and 39.2 for women.

All of the participants completed the General Health Questionnaire to assess for depression, diabetes, cardiovascular disease, hypertension, and sleep habits; the Epworth Sleepiness Scale; and the Physical Activity Questionnaire. They were all assessed for metabolic syndrome and underwent one standard, 8-hour nocturnal polysomnographic recording.

Among men, the mean apnea/hypopnea index score (representing the total number of either apnea or hypopnea episodes/hr of sleep) was 39.9, significantly higher than the 29.2 reported in the women. Measures of sleepiness and physical activity were similar for both groups.

Of the study population, 39% of the men and 62% of the women met the diagnostic criteria for major depressive disorder, and 69% of the men and 68% of the women fulfilled the criteria for metabolic syndrome. In both groups, approximately 43% did not get regular physical exercise, the investigators said.

Using logistic regression analysis, "exercise was the strongest [statistically significant] predictor of excess daytime sleepiness in men, followed by depression," Dr. Sarrigiannidis reported in a poster presentation. "In the women, depression and metabolic syndrome, in that order, were the most important predictors."

Independent of body weight, "participating in regular exercise appears to have somewhat of a protective effect in terms of daytime sleepiness, particularly among men," Dr. Sarrigiannidis said. Exercise improves insulin resistance and reduces visceral adiposity, he said, noting that clinicians should encourage physical activity as a way to help combat daytime fatigue in individuals with sleep apnea.

Additionally, Dr. Sarrigiannidis advised physicians to evaluate sleep apnea patients routinely for depression and metabolic syndrome and to refer them for appropriate treatment when necessary.

Dr. Sarrigiannidis reported having no conflicts of interest with respect to his presentation. ■