Cytokines Play Role in Sleep Disorders, Obesity

BY PATRICE WENDLING
Chicago Bureau

PITTSBURGH — Interventions to reduce or neutralize proinflammatory cytokines may improve treatment in patients with sleep disorders and obesity, Dr. Alexandros Vgontzas 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 acti-vate the hypotha-lamic-pituitary-adrenal axis.

‘Proinflammatory cytokines may represent a pathophysiologic link for resistance.’

Dr. Vgontzas

‘Proinflammatory cytokines may represent a pathophysiologic link for resistance,’ said Dr. Vgontzas, director of the Center for Sleep Disorders Medicine and professor of psychiatry at Pennsylvania State College of Medicine in Hershey.

One area of 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. Vgontzas 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 disorders, 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. Vgontzas 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.

‘Exercise improves daytime fatigue in sleep apnea patients.’

Dr. Winkelman

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. Vgontzas said.

Several outside studies also support this notion of a link between cytokines and 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-1β 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. Vgontzas reported.

‘The last thing a person with depression needs is to be up walking at night.’

Dr. Winkelman

By Patrice Wendling

SALT LAKE CITY — Depression severity is a key factor in determining how to treat comorbid depression and restless legs syndrome (RLS), 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.

But the substantial morbidity and mortality that can be associated with severe depression take precedence when treating depression and RLS. 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, 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,” Dr. Winkelman said.

In a study in 73 obese patients and 45 normal community sample in which the women fulfilled the criteria for major depressive disorder, 60% of the women and 69% of the men and 68% of the women, depression and metabolic syndrome, in order, were the most important predictors of severity in regard to 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.

Consider Depression Severity In Comorbid RLS Treatment

BY SHARON WORCESTER
Southeast Bureau

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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 Penn-sylvania University Hospital, Her-shey, reviewed data for 707 consecu-tive patients, 470 men and 238 women, mean age 50 years, who had been referred for symp-toms 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 Ques-tionnaire 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 polycystic ovary syndrome, and underwent one standard, 8-hour nocturnal polysomnographic recording.

Among men, the mean apnea/hypopnea index score (repre-senting the total number of either apnea or hypopnea episodes/hr of sleep) was 39.9, significantly higher than the 28.2 reported in the women. Mea-sures 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 35% of the men and 48% 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 analy-sis, “exercise was the strongest [statistically significant] predictor of excessive 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 pre-dictors.”

Independent of body weight, “participating in regular exercise appears to have somewhat of a protective effect in terms of day-time sleepiness, particularly among men,” Dr. Sarrigiannidis said. A second sign of insulin resistance and reduces visceral adiposity, he said, noting that clinicians should encourage phys-ical activity as a way to help com-petent daytime fatigue in individuals with sleep apnea.

Additionally, Dr. Sarrigianni-dis advised physicians to evaluate sleep apnea patients rou-tinely for depression and metabolic syndrome and to refer them for appropriate treatment when necessary.

Dr. Sarrigiannidis reported hav-ing no conflicts of interest with respect to his presentation.