Restless Legs Syndrome A Risk Factor for LVH

BY ALICE GOODMAN

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – Frequent periodic leg movements during sleep were associated with left ventricular hypertrophy in patients with restless legs syndrome, according to a retrospective study.

Moreover, patients who had sleep disturbance due to frequent periodic leg movements and severe LVH were at increased risk for heart failure, recurrent hospitalizations, and death.

"We have known for a long time that LVH is a poor prognostic factor that increases the risk of cardiac events. What is new about this study is that it appears that restless legs syndrome is another risk factor that may predispose patients to, and lead to more complications of, LVH," Dr. Arshad Jahangir said at a press conference during the meeting.

Dr. Jahangir, principal investigator in the study and professor of medicine at the Mayo Clinic in Scottsdale, Ariz., said that the findings need to be confirmed in larger studies. Also, it will be important to evaluate whether effective treatments for restless legs syndrome can prevent adverse outcomes associated with LVH.

Approximately 12 million Americans have restless legs syndrome. The condition is increasingly common with age and is implicated in about one-third of all cases of insomnia. Up to 90% of patients also have periodic limb movement disorder, which is characterized by involuntary jerking movements during sleep. The mechanisms that drive the disorder are not fully understood, Dr. Jahangir said, but the sympathetic nervous system is involved and patients typically have increased heart rate and blood pressure.

The study enrolled 584 restless legs syndrome patients who underwent overnight polysomnography studies. Patients were stratified according to frequency of leg movements during sleep: 45% had frequent leg movements, defined as a Periodic Movement Index [PMI] of more than 35 per hour, and 55% had infrequent leg movements, defined as a PMI of 35 or fewer movements per hour. Despite having a left ventricular ejection fraction of around 60% at baseline, the group with frequent periodic limb movements had a significantly higher left ventricular mass ($P = .01$), mass index ($P = .002$), and posterior wall thickness ($P = .01$), indicating the presence of LVH.

At baseline, the groups with frequent versus infrequent periodic limb movements had similar clinical and echocardiographic parameters, and were comparable for the presence of cardiovascular risk factors, including hypertension, diabetes, heart failure, high cholesterol level, or renal dysfunction. Patients with frequent periodic limb movements were older (median age 67 vs. 61 years), more often male, had more atrial fibrillation (30% vs. 17%), and more underlying coronary heart disease than those with infrequent periodic limb movements.

The presence of severe LVH [defined as left ventricular mass index greater than 116g/m^2] and atrial fibrillation led to a significantly greater likelihood of heart failure, recurrent hospitalizations, and death over a mean follow-up of 3 years. Dr. Jahangir said that even in participants with frequent periodic limb movements and no atrial fibrillation, patients with severe LVH had a greater number of cardiac events.

Severe LVH was found in 37% of those with atrial fibrillation and 20% of those without it, suggesting that underlying electrical dysfunction and restless legs syndrome may act together to lead to adverse cardiovascular outcomes.

"This is a retrospective study that points out an interesting association between RLS and LVH. This could be an important observation, but the findings need to be validated in a prospective study," commented Dr. William Zoghbi, who chaired the press conference and is the chair of cardiovascular imaging at the Methodist DeBakey Heart and Vascular Center in Houston. ■

To see a video interview with Dr. Jahangir, scan the QR code with a smartphone.

VITALS

Major Finding: Despite having a left ventricular ejection fraction of around 60% at baseline, restless legs syndrome patients with over 35 periodic limb movements per hour during sleep had a significantly higher left ventricular mass ($P = .01$), mass index ($P = .002$), and posterior wall thickness ($P = .01$), indicating the presence of left ventricular hypertrophy.

Data Source: Retrospective study of 584 restless leg syndrome patients who underwent overnight polysomnography studies.

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Prodromal Symptoms Trace Parkinson's Progression

BY MICHELE G. SULLIVAN

EXPERT ANALYSIS FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S AND PARKINSON'S DISEASES

BARCELONA – Early neuronal death may spark symptoms that can precede the classic motor dysfunction of Parkinson's disease by up to 20 years.

Rather than beginning in the substantia nigra and moving into the cerebellar regions, nerve damage may begin in the dorsal motor nucleus of the vagal nerve and progress upward into the midbrain, killing neurons all along its path. Constipation, cardiac denervation, and rapid eye movement sleep disorder are some of the conditions that may appear as the march of cell death continues, Dr. Yoshikuni Mizuno said at the conference.

"Parkinson's probably starts in the peripheral portions of the vagal nerve," said Dr. Mizuno, director of the Research Institute for Diseases of Old Age at Juntendo University, Tokyo. "When the neurons die, their content is expelled into the extraneural space in the medulla oblongata." Other nerve terminals pick up this intracellular debris and die as well, expelling their own contents as damage progresses. "Eventually, this reaches the substantia nigra and the higher cerebellar neurons. This, I believe, is the model for the spread of Parkinson's."

Constipation can be one of the first symptoms, occurring when Lewy body lesions first appear on the vagal nerve's dorsal motor nucleus. This is generally 15-20 years before the onset of motor symptoms, Dr. Mizuno said.

The Honolulu Heart Program study clearly showed the association between Parkinson's disease and constipation. The study followed almost 7,000 men. Over an average of 12 years, 96 developed Parkinson's disease. In a multivariate analysis, men who had fewer than one bowel movement per day were four times more likely to develop the disease than were men with two or more bowel movements per day (Neurology 2001;57:456-62).

"I think most of these patients already had Parkinson's before the onset of motor symptoms," he said.

As cell death proceeds along the nerve, it can affect cardiac innervation. Cardiac scintigraphy with the imaging agent iodine-123 metaiodobenzylguanidine (MIBG) highlights norepinephrine transport cells in the normal heart. "In patients with Parkinson's and dementia with Lewy bodies, you don't see this, because of the loss of postganglionic parasympathetic nerve fibers," Dr. Mizuno said. "In Alzheimer's, as well as in progressive supranuclear palsy and multisystem atrophy, you do have nice visualization of these fibers, and this is a very useful test for differentiating Lewy body disorders from these other diseases."

His own studies suggest that MIBG cardiac uptake may parallel the progression of Parkinson's disease. About half of patients with stage 1 disease show reduced uptake, but "there is much more markedly diminished cardiac MIBG uptake in those with stage 2 disease or higher," Dr. Mizuno said.

Disordered sleep can occur when cell damage advances to the pons – about 10 years before motor symptoms are apparent. "Half of the patients with idiopathic REM sleep disorder will go on to develop Parkinson's disease," he said.

As nerve damage progresses further, the olfactory bulb may be affected. Hyposmia affects most (80%) Parkinson's patients, but about 40% report a decline in olfactory function before the onset of motor symptoms. "The interval between hyposmia and motor symptom onset is about 5 years," Dr. Mizuno said.

The characteristic motor symptoms appear only when most of the dopaminergic neurons in the substantia nigra have died. If the damage progresses further, the cortex may be affected, leading to dementia.

"If you compare clinical and lab findings in Parkinson's disease dementia and dementia with Lewy bodies, you will notice a lot of similarities: constipation, loss of smell, executive dysfunction, fluctuating cognition, and visuospatial dysfunction," Dr. Mizuno said. "The only difference between the two is the presentation of initial symptoms. If motor symptoms appear first, we call it Parkinson's disease, while if dementia is the initial symptom, we call it dementia with Lewy bodies."

Dr. Mizuno declared no potential financial conflicts of interest. ■