

Risk Factors Suggest Preclinical Parkinson's

Look for excessive daytime sleepiness, olfactory dysfunction, constipation, and slow reaction time.

BY KERRI WACHTER
Senior Writer

WASHINGTON — The presence of constipation, poor olfaction, slow reaction time, and excessive daytime sleepiness in any combination strongly suggests the presence of preclinical Parkinson's disease, according to findings from the ongoing Honolulu-Asia Aging Study presented at the World Parkinson Congress.

Dr. G. Webster Ross of the University of Hawaii in Honolulu and his colleagues on the Honolulu-Asia Aging Study (HAAS) have been able to assess the relationship between these four factors and, not only Parkinson's disease (PD), but the presence of Lewy bodies in the brain as well.

HAAS began in 1965 as the Honolulu Heart Program, a prospective study of heart disease and stroke that followed a cohort of 8,000 Japanese-American men (all born between 1900 and 1919). The aging component of the study began in 1991 with case findings for dementia and Parkinson's disease. The researchers have continued to identify cases through examinations in 1994, 1997, 1999, 2001, and 2003. The researchers also have continued surveillance of hospital death records in order to confirm diagnoses. Preclinical determinants were assessed prior to the diagnosis of PD.

An autopsy study began in 1991. Since then, the researchers have been examining stained sections of the substantia nigra, the locus coeruleus, and the amygdala for the presence of Lewy bodies. If Lewy bodies are found in any of these three areas, the researchers then look for cortical Lewy bodies as well.

"We have been able to identify those individuals with incidental Lewy bodies—that is, those that occur in decedents without dementia or Parkinson's disease," Dr. Ross said. "We have used this incidental Lewy body stage as an ... end point in addition to Parkinson's disease, with the idea that if we find risk factors or predictors of both of these conditions that it's plausible evidence that [the risk factors] probably are truly associated with the disease or with the underlying pathophysiologic process."

The researchers recently looked at how combinations of four factors—excessive daytime sleepiness (EDS), olfactory dysfunction, constipation, and slow reaction time—might be related to the incidence of PD. For constipation and slow reaction time, they found that the incidence of PD was 1 in 1,370 for those with neither symptom, 13 in 1,402 for those with one symptom, and 4 in 82 for those with both symptoms.

They also looked at the combination of EDS and olfactory dysfunction. The incidence of Parkinson's was 1 in 370 for those with neither symptom, 5 in 452 for

those with one symptom, and 2 in 32 for those with both symptoms.

They then looked at the combination of EDS, olfactory dysfunction, and slow reaction time. The incidence of PD was 1 in 298 for those with no symptoms, 10 in 1,151 for those with one symptom, 5 in 378 for those with two symptoms, and 2 in 27 for those with all three symptoms.

Individually, all four factors have been associated with Parkinson's disease. The associations are detailed in the following paragraphs:

► **Excessive daytime sleepiness.** EDS was assessed through a questionnaire that HAAS researchers sent to cohorts in 1991. The researchers found that 23% of PD patients had EDS, compared with 8% of those who did not have PD. "The incidence of Parkinson's disease among those with excessive daytime sleepiness is about 2.5 times the incidence of individuals without excessive daytime sleepiness," Dr. Ross said.

► **Olfactory dysfunction.** Olfactory dysfunction is common among PD patients and is known to occur early in the disease process. Olfactory dysfunction also correlates with dopamine transporter density in early Parkinson's on single photon emission CT imaging. Olfaction was assessed at the 1991 and 1994 examinations of the HAAS cohort using the University of Pennsylvania Smell Identification Test, a standardized test of odor identification ability. "As odor identification improves to the highest tertile, the incidence of Parkinson's disease declines," said Dr. Ross. Likewise, as odor identification improved among patients with incidental Lewy bodies, the percentage with Lewy bodies in the substantia nigra or the locus coeruleus went down significantly.

► **Constipation.** Constipation occurs in an estimated 80% of PD patients and appears to be independent of age, medication use, or level of physical activity. There is a loss of dopaminergic neurons in the colon, and Lewy bodies in the myenteric plexus, in patients with PD. Constipation was assessed in the HAAS cohort with a question about bowel movement frequency at midlife (1971) and again in 1991. Dr. Ross and his colleagues found that the incidence of Parkinson's disease was highest in men who reported less than one bowel movement per day, and that the incidence declined as the number of bowel movements per day increased.

► **Reaction time.** PD patients have a prolonged reaction time, which reflects the akinesia and bradykinesia of the disease. Dr. Ross and his colleagues also have determined that there is prolonged reaction time with the presence of incidental Lewy bodies. Reaction time was assessed for the HAAS cohort using a computerized reaction time test (the 3RT). ■

Lowering Homocysteine Fails to Boost Cognitive Performance

BY JOHN R. BELL
Associate Editor

Elevated homocysteine levels may not be a risk factor for cognitive decline in older patients, despite previous evidence, reported Jennifer A. McMahon, Ph.D.

She and her colleagues at the University of Otago, New Zealand, conducted a 2-year randomized, double-blind, placebo-controlled trial to assess the effect of homocysteine lowering on the cognitive abilities of people aged older than 65 years through neuropsychological tests (N. Engl. J. Med. 2006;354:2764-72).

The researchers found that the reduction of plasma homocysteine in the studied elderly population was not associated with significant differences from placebo in various measures of cognitive ability.

A total of 253 participants (mean age 74 years) completed the study. To be enrolled, the patients were required to have a fasting homocysteine level of at least 13 $\mu\text{mol/L}$ and a normal plasma creatinine level; to be free of suspected dementia, current depression treatment, history of stroke/transient ischemic attack, and diabetes; and to not be taking B-vitamin supplements or medications that can affect folate metabolism.

The investigators then gave the treatment group (127 patients) a daily supple-

ment comprising 1,000 mcg folate, 500 mcg B₁₂, and 10 mg B₆. The mean homocysteine level, with this regimen, was 4.36 mol/L lower in the vitamin group than in the placebo group (126 patients), over the course of the study.

But when the cognitive tests—the Mini-Mental State Examination, the Wechsler Paragraph Recall test, and others—were administered at 1 and 2 years and adjustment for sex and education, differences between the two groups were not significant—except for those on the Reitan Trail Making Test.

On that test, participants in the vitamin group actually performed worse (took longer to complete the test) than did the placebo group ($P = .007$). The investigators remarked that this might be a chance finding, however.

Moreover, when the investigators combined the results of all the tests using a generalized estimating equation that was adjusted for baseline value, gender, and education, the resulting score for the vitamin group was lower than that of the placebo group—a finding that the investigators noted contradicts "the weight of a substantial body of observational evidence."

However, this difference barely reached significance ($P = .05$). Baseline characteristics of the patients were similar. ■

A total of 253 participants completed the 2-year randomized, double-blind, placebo-controlled trial. The mean age of the participants was 74 years.

Methylphenidate May Improve Apathy Associated With Dementia

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Methylphenidate may be effective in the treatment of apathy associated with dementia of the Alzheimer type, Dr. Prasad Padala and associates reported in a poster at the annual meeting of the American Geriatrics Society.

Results from an open-label study in 13 patients suggest that methylphenidate (Ritalin) has a substantial effect on apathy, with smaller but significant positive effects on mood, cognition, and independent activities of daily living. The findings warrant further testing with a double-blind, placebo-controlled trial, he noted.

Apathy is the most common behavior problem reported in persons with Alzheimer's disease, affecting about 70%-90% of patients. All patients in the study had dementia of the Alzheimer type, Mini-Mental State Examination (MMSE) scores greater than 18, and Apathy Evaluation Scale (AES) scores greater than 30. Their mean age was 69 years.

All patients were started on methylphenidate 5 mg twice daily; the dose was titrated to 10 mg twice daily over

a 2-week period. Follow-up visits were scheduled at 4, 8, and 12 weeks.

Significant improvement in apathy (AES 52.6 vs. 31.6) was reported from baseline over 12 weeks, reported Dr. Padala, of the department of psychiatry at the University of Nebraska, Omaha, and a psychiatrist at the Omaha division of the VA (Veterans Affairs) Nebraska Western Iowa Health Care System.

Less robust but significant improvement was noted at 12 weeks in Geriatric Depression Scale scores (93 vs. 63), MMSE scores (24.2 vs. 25.5), and Independent Activities of Daily Living criteria (13.7 vs. 16).

Subjective improvement was noted by caregivers. One caregiver reported that the patient was monitoring his medications better and started taking care of his finances again after a long hiatus.

None of the patients discontinued medication because of adverse events. In one patient, the dose of methylphenidate was reduced because of appetite loss, possibly related to treatment, Dr. Padala reported.

The study was funded by the Nancy and Ronald Reagan Alzheimer's Scholarship Fund, established at the University of Nebraska. ■