

Symptom Triad May Identify Parkinson's Risk

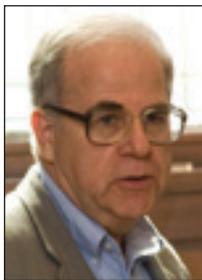
BY MICHELE G. SULLIVAN

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

BARCELONA – Severe hyposmia may be associated with a deficiency of striatal dopamine transporter protein and slight cognitive decline – characteristics that could identify people with an increased risk of developing Parkinson's disease, according to preliminary findings from the Parkinson's Associated Risk Study.

"This is an interesting observation: [Cognitive] decline may be occurring well in advance of motor symptoms," Dr. Kenneth Marek said at the conference. "This might be something we could use to predict who will develop dopamine transporter deficiency and, eventually, symptomatic Parkinson's."

The prospective PARS (Parkinson's Associated Risk Study) aims to test the effectiveness of two biomarkers – sense of smell and dopamine transporter imaging – in identifying subjects who are at risk of developing the disease. First-degree relatives of Parkinson's disease patients and control subjects will be followed for 2 years to determine whether a deficiency in striatal dopamine transporter (DAT) increases their disease risk.



Dr. Marek and his coinvestigators recruited subjects by a mass mailing of the UPSIT (University of Pennsylvania Smell Identification Test); those scoring in the 15th percentile and lower are invited to participate. So far, 9,400 tests have been mailed out, half to relatives of patients and half to subjects recruited by community notices. About 5,000 have sent the test back.

"We have identified 650 people who were hyposmic below this 15th percentile," said Dr. Marek, president and senior scientist at the Institute for Neurodegenerative Disorders in New Haven, Conn. "This is considered rather severe hyposmia and, interestingly, only about a third of these folks noticed that they even had this symptom."

He presented data on 303 participants (203 hyposmic, 100 normosmic) who had undergone the baseline evaluation. Tests included a neuropsychological test battery, early Parkinson's symptom score, and SPECT (single-photon emission CT) brain imaging of striatal DAT binding with the imaging compound iodine-123-beta-CIT. The study is grouping participants according to their striatal DAT levels: Greater than 80% is considered normal, 65%-80% is considered indeterminate, and less than 65% is considered a deficiency consistent with Parkinson's disease.

Of the 203 hyposmic subjects, 11% had a DAT level less than 65%, compared with 1% of the normosmic group, a significant

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Major Finding: Significantly more individuals with hyposmia had DAT levels of 65% or lower, compared with normosmic individuals (11% vs. 1%).

Data Source: Preliminary findings among 303 participants in PARS.

Disclosures: The study is sponsored by the U.S. Department of Defense, the Michael J. Fox Foundation for Parkinson's Research, and the National Parkinson Foundation. As an employee of the Institute for Neurodegenerative Disorders, Dr. Marek participates in multiple clinical studies, some of which are funded by drug companies.

difference. "That one person in the normosmic group also has a REM sleep behavior disorder," Dr. Marek noted.

Indeterminate DAT levels were seen in 17% of the hyposmic and in 7% of the normosmic groups, and normal levels were seen in 71% of the hyposmic and 92% of the normosmic groups. (Percentages in the

Hyposmia, loss of dopamine transporters, and cognitive decline might predict risk for symptomatic Parkinson's.

DR. MAREK

hyposmic group do not equal 100% because of rounding.)

Bowel habits also varied significantly between the groups. Nearly half (48%) of those with the lowest DAT density reported

fewer than one bowel movement per day, compared with 21% of the normal-level group. Conversely, 13% of the lowest-level group reported one or more bowel movements per day, compared with 51% of the normal-level group.

"Similarly, [the lowest DAT-level group was] much more likely to endorse questions related to REM sleep behavior disorder," Dr. Marek said. "And when we used another tool – a nine-item symptom rating scale that assesses early Parkinson's – those individuals in the lowest DAT group were more likely to endorse the symptoms."

Taking these data into account, he said it seems as if "these individuals express a number of features that we might call 'premotor Parkinsonism.'"

The researchers have completed cognitive testing on 131 participants (17 with decreased DAT levels and 114 with normal levels). Mean age was the same (68 years) in both groups and their educational levels were not significantly different.

"Even in this group, [in which all the] subjects were entirely cognitively normal, it was possible to distinguish individuals based on their cognitive function related to whether they had this early DAT deficit or not," Dr. Marek said. "I would not call them cognitively impaired, because they were not, but they were different and easily distinguished, based on their scores and imaging outcomes." ■

Manganese Exposure May Boost Risk for Parkinsonism

BY MICHELE G. SULLIVAN

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

BARCELONA – Long-term welding work may be a risk factor for developing parkinsonism – perhaps because manganese can travel directly into the midbrain via the olfactory nerve.

Two recent studies suggest a dose-response association, with increased risk as years of exposure accumulate.

"Manganese, in particular, has been shown to be a neurotoxin," said Jessica Lundin, a PhD candidate at the University of Washington, Seattle, who presented early findings from a cross-sectional study during a poster session at the meeting. "There is some evidence that it enters via an olfactory route."

The metal is a large component of fumes created by the welding process. According to the Centers for Disease Control and Prevention, "Prolonged exposure to high manganese concentrations (greater than 1 mg/m³) in air may lead to a Parkinsonian syndrome known as manganism. Chronic exposure to the manganese-containing pesticides is also reported to cause Parkinson-like symptoms."

Recent studies have also indicated that long-term exposure to inhaled manganese is associated with neurologic and neurobehavioral deficits, according to the agency. "These effects include changes in mood and short-term memory, altered reaction time, and reduced hand-eye coordination. Affected workers frequently show abnormal accumulations of manganese in a region of the brain known as the globus pallidus."

Ms. Lundin and her colleagues recruited 581 welders from three U.S. shipbuilding sites for a 3-year follow-up study. All welders underwent a baseline neurologic assessment by a movement disorders specialist. Assessments in the National Institute of Environmental Health Sciences-sponsored study included the Unified Parkinson's Disease Rating Scale (motor subsection 3), timed motor tasks, and a questionnaire about occupational history (including prior welding jobs), lifestyle, and medical history, including smoking and neurotoxic exposure, especially to pesticides.

At baseline, individuals in the cohort had a mean age of 45 years and had welded for a mean of 23,000 hours. Individuals in the study were considered to be normal if their UPDRS3 scores were 6 or less; to be mildly affected by parkinsonian symptoms with scores of

6-14; and to have parkinsonism with scores of 15 or higher. At baseline, 199 were considered normal, with a score of 3 or lower; 306 had mild parkinsonian symptoms, with a mean UPDRS3 score of 10; and 76 qualified as having diagnosable parkinsonism with a mean UPDRS3 of 19.

Ms. Lundin compared UPDRS3 scores with total hours of welding exposure at baseline. She found a linear association, with risk increasing along

VITALS

Major Finding: Welders with long-term manganese exposure may be at an increased risk of developing parkinsonism.

Data Source: A prospective cohort study of 581 welders, and an imaging study of 20 welders, 20 Parkinson's disease patients, and 20 normal controls.

Disclosures: Ms. Lundin reported no financial disclosures. Dr. Criswell reported receiving research support from numerous pharmacologic companies; her study was funded by the Michael J. Fox Foundation for Parkinson's Research, the National Institutes of Health, the American Parkinson Disease Association, the Advanced Research Center at Washington University, the Greater St. Louis Chapter of the APDA, the McDonnell Center for Higher Brain Function, and the Barnes-Jewish Hospital Foundation. Dr. Martin has received speakers' honoraria from Allergan.

with total exposure.

Subjects considered normal had a mean age of 41 years and a total exposure of 18,300 hours. Those with mild parkinsonian symptoms were a mean of 46 years old and had a mean total exposure of 25,100 hours. Those with parkinsonism had a mean age of 48 years, with a mean total exposure of 26,800 hours.

The prevalence ratio also rose with increasing exposure. Those with a total of less than 2,900 hours were considered the reference group, with no increase over expected background rates. The prevalence of parkinsonism increased by 20% for those with a total exposure of 2,900-9,600 hours, by 40% with 9,600-26,400 hours of exposure, and by 60% with more than 26,400 hours.

None of these baseline differences in UPDRS3 scores and prevalence of parkinsonism were statistically significant, but they provided a trend strong enough to justify the 3-year follow-up, Ms. Lundin said in an interview. "We will follow this group to determine incident cases of Parkinson's symptoms and symptom progression. We also have some industrial hygienists working with us to collect samples of manganese [on surfaces] in the shipyard and in the air."

Further work will include comparison to a nonwelding reference group, as well as blood samples indicating exposure to manganese, cadmium, lead,

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