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 using 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 co-investigators 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,” Dr. Marek said. “One of our senior scientists at the Institute for Neurodegenerative Disorders, Dr. Marek participates in multiple research centers, including smoking and neurotoxic exposure, especially to pesticides. Recent studies have also indicated that long-term exposure to inhaled manganese is associated with neuropsychological 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 been 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 7-14; 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 diagnostically parkinsonian 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 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.”

Future work will include comparison to a nonwelding reference group, as well as blood samples indicating exposure to manganese, cadmium, lead, and arsenic.
Biomarkers Ratio Improves Parkinson’s Diagnosis

BY MICHELE G. SULLIVAN
FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER’S AND PARKINSON’S DISEASES

BARCELONA – The ratio of total tau over total alpha-synuclein gave a sensitivity of 89% and a specificity of 61% for discriminating Parkinson’s disease from other neurodegenerative diseases in a prospective study of 181 patients.

This is the first time a combination biomarker has been used to identify Parkinson’s disease patients among a group with related disorders, including Alzheimer’s disease, dementia with Lewy bodies, and frontotemporal dementia, Dr. Omar El-Agnaf said in an interview at the conference. The findings’ implications could be important in both the clinic and the lab.

“It isn’t perfect, and it’s not yet clinically usable, but it’s better than anything else we have at this point,” Dr. El-Agnaf said. The ability to discriminate Parkinson’s disease patients from those with other neurodegenerative disorders could allow earlier detection and earlier and possibly more effective treatment.

The study, which will soon appear in the journal Movement Disorders, was conducted by a group of researchers involved in the Parkinson’s Progression Markers Initiative (PPMI), a 5-year project seeking to identify and validate biochemical and imaging markers for the disease.

Healthy neurons normally release the alpha-synuclein protein into intracellular fluid; it’s thought to be important in presynaptic signaling. Decreasing levels may be related to neuronal damage, and in previous studies they have been associated with Parkinson’s disease and dementia with Lewy bodies, said Dr. El-Agnaf, a biochemist and professor at the United Arab Emirates University, Al Ain. But these prior studies found conflicting evidence that alpha-synuclein alone adequately identifies Parkinson’s disease.

This is partially a result of the wide reference range for normal alpha-synuclein levels (5-40 ng/mL) and to its natural, age-related decline. Other factors might be different methods of sample collection, different antibodies used in the immunoassay, and even the age of the samples. In samples stored more than 120 months, the level of alpha-synuclein goes down significantly, he said.

Those earlier studies confirmed that Parkinson’s patients tended to have the lowest level of alpha-synuclein, but there were huge overlaps with other disorders, and even with normal controls, which Dr. El-Agnaf said negated any significant association with Parkinson’s. “If this was going to become a clinically useful tool, we needed a better way to measure” the potential biomarker.

Dr. El-Agnaf and his colleagues have been pursuing alpha-synuclein as a Parkinson’s biomarker since 2002. In 2010, the group found that Parkinson’s patients expressed increased levels of the protein’s oligomeric form. Oligomers usually form before more complex molecules, and their increased presence suggested that these species might be particularly useful in detecting Parkinson’s in its earliest stages, he said.

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The next step will be to look at how these biomarkers might change in the patient over time. This is where the Parkinson’s Progression Markers Initiative (PPMI) comes in, with its goal of identifying biomarkers of Parkinson’s progression. The research of Dr. El-Agnaf and his colleagues, and other teams, is helping us build a cupboard of potential biomarkers that we have at our disposal. Research scientists can go to the PPMI and use the samples and data there to verify their hypotheses and initial findings in a different and very diverse – population from both the United States and Europe.

We recently announced the launch of the PPMI Data and Biospecimen Request process, which makes the data from recently diagnosed Parkinson’s patients and healthy controls available to researchers.

If scientists use the PPMI data, they will be asked to provide annual updates on their analyses. These will then be publicly displayed on the PPMI Web site and integrated back into the database with the goal of rapidly identifying and validating the biomarkers we need.

MARK FRASER, PH.D., is the director of research programs for the Michael J. Fox Foundation for Parkinson’s Research, which organizes and funds the PPMI project.

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aluminum, copper and other metals. These analyses will be part of a multivariate regression that will control for age, she added.

The pallidal index, an imaging outcome, was one of the primary end points of a separate study of welding and Parkinson’s disease (Neurology 2011;76:1296-301). The index is a ratio of T1-weighted imaging signal in the global pallidus compared with a reference region of white matter.

Primary investigator Dr. SuSan Criswell, also of Washington University, Seattle, conducted an imaging study of 20 asymptomatic welders, also primarily recruited from shipyards. These were compared with 20 subjects with idiopath-

Biospecimen Request process, sought to identify any clinically useful relationship between alpha-synuclein and the biomarkers used in Alzheimer’s research (amyloid beta 42, total tau, and phosphorylated tau). The study cohort comprised subjects with Parkinson’s (38), Alzheimer’s (48), dementia with Lewy bodies (32), frontotemporal dementia (31), and other neurologic disorders (32).

All of these patients donated cerebral spinal fluid, which underwent the same immunoassay.

All patients with a disorder had significantly lower alpha-synuclein than did control subjects, again showing its inability to adequately discriminate Parkinson’s disease from other conditions. The story was different with the other individual biomarkers tested; the group overlap was still too great for clinical usefulness.

“We then tried ratios again: amyloid beta 42, total tau, and phosphorylated tau over alpha-synuclein,” Dr. El-Agnaf said. “Both forms of tau over alpha-synuclein distinguished the Parkinson’s patients, who had significantly lower ratios than the other groups.” Total tau over alpha-synuclein gave the best results, with a sensitivity of 89% and a specificity of 61%.

Major Finding: The ratio of total tau over alpha-synuclein discriminated Parkinson’s patients from those with other neurodegenerative disorders, with a sensitivity of 89% and a specificity of 61%.

Data Source: A prospective cohort study of 181 patients, 32 of whom had Parkinson’s disease.

Disclosures: The study was funded by the Michael J. Fox Foundation for Parkinson’s Research. Dr. El-Agnaf had no financial disclosures.

A First Step to Improving Diagnosis

One of the biggest challenges with Parkinson’s disease is the ability to accurately diagnose it vs. other movement disorders.

This paper represents a first step toward solving the problem of differential diagnosis.

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