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 interstitial 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.

VITALS

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.

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 cluster in 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.

The 2010 paper found that a ratio of alpha-synuclein oligomers to total alpha-synuclein had 89% sensitivity and 91% specificity for Parkinson's patients, compared with those with progressive supranuclear palsy (Neurology 2010;75:1766-72). "The ratio measurement was a much better indicator, but there was still a large overlap" with Alzheimer's disease patients and normal controls.

His current study, still in press, 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 no 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%. ■

VIEW ON THE NEWS

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.

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.

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Continued from previous page

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 idiopathic Parkinson's disease and 20 normal controls. Positron emission tomography with 6-[^{18}F]fluoro-L-dopa (FDOPA) measured dopaminergic presynaptic nerve terminal dysfunction in different brain regions in all of the participants.

The mean ages of the groups ranged from 45 to 55 years, but the difference was not statistically significant. The welders had a mean exposure of 30,968 hours. The average level of manganese in their blood was 20 mcg/L – twice the upper limit of normal.

At baseline, those with Parkinson's disease had a significantly higher mean UPDRS3 score (19.7) than did either welders (8) or normal controls (1). The welders' mean UPDRS3 score was significantly higher than was the normal controls' score. But Dr. Criswell noted that welders were not significantly different from controls in terms of clinical parkinsonian symptoms.

The prevalence of parkinsonism rose with the total number of hours in which individuals had welded in their lifetime.

MS. LUNDIN

Imaging revealed significantly higher pallidal index scores among welders than those of both control subjects and those with Parkinson's disease. This difference was significantly related to increased exposure hours, but not to blood manganese levels.

After the researchers controlled for age, dopaminergic function also differed significantly between the groups. Welders had nearly 12% lower dopaminergic uptake in the anterior putamen than did the other two groups. The uptake pattern also varied significantly from those with Parkinson's disease, measuring lowest in the caudate, followed by the anterior putamen and then the posterior putamen.

"This pattern was reversed from the idiopathic Parkinson's disease subject pattern," in which dopaminergic uptake was lowest in the posterior putamen, followed by the anterior putamen and finally, the caudate, Dr. Criswell said.

There were no significant interactions between dopaminergic uptake and pallidal index, manganese levels, and UPDRS3 scores.

However, Dr. Criswell noted, the decrease in dopaminergic uptake among welders suggests presynaptic nigrostriatal dysfunction.

The findings suggest that manganese preferentially affects dopaminergic neurons in the caudate, rather than the putamen, Dr. W.R. Wayne Martin wrote in an accompanying editorial (Neurology 2011;76:1286-7). "In Parkinson's disease, decreased caudate [dopaminergic uptake] correlates with impaired executive function," wrote Dr. Martin of the movement disorders clinic at Glenrose Rehabilitation Hospital in Edmonton, Alta. ■