Assay Was One Part of Diagnosis

Urine Test *from page 1*

in conjunction with, and not in lieu of, current standard diagnostic procedures, to aid the physician in the diagnosis of definite non-AD versus probable AD, possible AD or MCI [mild cognitive impairment]." Nymox CEO Paul Averback, M.D., emphasized that the test should not be considered a stand-alone diagnostic, but, rather, "a measurement that adds useful information" and "moves the diagnosis along." He said the test was particularly useful for primary care physicians, although it is intended for use by specialists as well. The FDA usually follows the recommendations of its advisory panels, which are not binding. A statement issued by Nymox after the panel's vote said that the company will continue to pursue approval of the test kit and would work with the FDA to meet possible requirements for more data resulting from the panel's suggestions.

The panel's vote was based on the results of a prospective study of 200 patients presenting to one of nine cognitive/memory disorder centers for an evaluation by experts in AD and related cognitive disorders. The aim of the study was to show that the NTP test had a high degree of correlation with the results of a comprehensive specialist exam using National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for diagnosing probable AD.

Patients had the urine NTP measurement and, based on a comprehensive evaluation that included a neurocognitive assessment, a Mini Mental State Examination, and structural imaging with CT, MRI, or other scans, were classified as having probable AD, possible AD MCI, or definite non-AD.

Patients categorized as "definite non-AD" were determined to have conditions that included age-related memory decline, pseudodementia due to depression, and metabolic disorders. An elevated NTP was set at above 22 mcg/mL, with a normal level at 22 mcg/mL or less; the test was performed on a first morning urine sample.

Nearly 80% (156 patients) had probable AD, possible AD, or MCI and were lumped together in the category of "not definite non-AD" in the study. Of the 57 patients with probable AD, 51 had an elevated NTP level and 6 had a normal level. Of the 56 with possible AD, 21 had an elevated NTP level and 35 had a normal level. The 43 patients with MCI were split, with 22 having an elevated level and 21 having a normal level. Only 4 of the 44 patients with definite non-AD had an elevated NTP level.

The sensitivity of the test—the proportion of patients in the "not definite non-AD" category who had an elevated NTP measurement—was 60% (94 of 156 patients), according to the company's analysis of the results.

The specificity of the test—the proportion of those with definite non-AD with a normal NTP measurement—was 91% (40 of 44 patients).

The test may have had little value distinguishing patients with probable AD and definite non-AD from those with possible AD or MCI.

The positive predictive value—the percentage of patients with elevated NTP in the "not definite non-AD" category—was nearly 96% (94 of 98 patients). The negative predictive value—the percentage of subjects with normal NTP who were in the definite non-AD category—was nearly 40% (40 of 102), according to Nymox.

Brain biopsy results confirming the diagnosis in a subject with clinically probable AD and an elevated NTP test were available in only one patient, a 39-year-old man with a family history of early-onset AD who died 2 years after diagnosis. This case was one of the clinical examples cited by the company to illustrate the usefulness of the test, particularly for primary care physicians.

Company documents included the case of a 73-year-old woman, with a 4- to 6-month history of forgetfulness, problems performing activities of daily living, and an elevated NTP of 33 mcg/mL. She was diagnosed with probable AD and over the next 2 years, declined significantly and was institutionalized, despite treatment. In another case, a 72-year-old man whose cognitive function had declined for 1-2 years and who had diffuse atrophy, prominent ventricles, and white matter lesions on MRI, but a normal neurologic exam and a normal NTP level of 19.4, was determined as falling in the definite non-AD category, and was normal over 2 years of follow-up.

But Ranjit Mani, M.D., a neurologist and medical reviewer in the FDA's division of neuropharmacologic drug products, Rockville, Md., pointed out that while the results demonstrated that the NTP level can help discriminate between probable AD and a patient with definite non-AD, a significant number of patients in the possible AD and MCI categories had NTP levels on both sides of the cutoff. This indicates that the test may have little value in distinguishing these two groups from the other two groups, raising the concern over the value of the test in clinical practice.

Panelist Joseph Parisi, M.D., professor of pathology at the Mayo Clinic, Rochester, Minn., raised the issue of whether NTP served as a reliable biomarker of the disease.

"Ideally, a biomarker should have some kind of relationship to disease pathogenesis, and I don't think we have data to support that point." He also found the data on the test's sensitivity and specificity conflicting.

Other concerns raised by Dr. Mani and panel members included the intrasubject biologic variability seen in a small number of subjects who had more than one test and the high proportion of NTP measurements in the four diagnostic categories that clustered around the cutoff point. Some uncertainty remained as to whether urine NTP levels could be elevated in patients with other neurodegenerative diseases.

Neurologist Avindra Nath, M.D., Ph.D., of Johns Hopkins University, Baltimore, a panelist, said he was not entirely convinced that the study was adequate to justify its intended use, citing the small sample and the lack of longitudinal data on the patients.

A longitudinal study could answer some outstanding questions, such as the outcome of patients with "possible" AD, he added. He and other panelists observed that primary care physicians would likely refer any patient with memory problems to a specialist, regardless of the NTP result.

One of the two panelists who voted against the motion of nonapprovable for the test, Oscar L. Lopez, M.D., associate professor of neurology at the University of Pittsburgh, remarked that the test probably would be useful for primary care physicians in rural areas who have no close access to specialists, although he added that the test results would not provide much information for the specialist who can make the diagnosis without the test. ■

Hypertension May Impair Memory

Impaired cerebral blood flow may contribute to the mild deficits in memory and other cognitive functions in people with hypertension, compared with their normotensive peers, according to J.R. Jennings, Ph.D., of the University of Pittsburgh, and associates.

The researchers assessed regional cerebral blood flow using MRI and PET brain scans in 37 hypertensive and 59 normotensive subjects (median age 60 years) who performed a battery of memory and sensorimotor tasks. The blood flow response to performance demands was significantly blunted in certain areas of the brain in hypertensive subjects, who also showed mild deficits in performance, compared with the normotensive subjects (Neurology 2005;64:1358-65).

"Our results are far from conclusive but suggest that vascular factors may play a role" in mild memory and cognitive deficits seen in hypertensive people, the researchers said. Moreover, the findings show that common systemic diseases such as hypertension can have unanticipated effects on brain function, they added.

—Mary Ann Moon