Autopsy Confirmed Diagnosis

Alzheimer's *from page 1*

and muscles after death. The two studies have been major undertakings, involving thousands of clinical evaluations.

To reduce costs and provide uniformity of the evaluations, the researchers in both studies avoid using informants, neuroimaging, blood work, or routine consensus conferencing. Instead, they rely on a system of guided clinical judgment developed for the studies. The system combines actuarial prediction rules with clinical judgment.

The researchers evaluate each participant yearly using complete neuropsychologic tests, involving about 20 tests—11 of which have age-adjusted cutoff scores. A neuropsychologist reviews selected data from the test results to determine the subject's level of cognition. A clinician also reviews selected data, interviews and examines the patient, and makes a determination about cognitive decline, stroke, Parkinson's disease, depression and other common conditions.

Selected data from these evaluations then are entered into a software actuarial decision tree to make a clinical diagnosis. The clinician has the opportunity to override the computer-generated decision. Clinicians and specialists are blinded to the previous years' results. When a participant dies, all the clinical data are reviewed by a neurologist, who makes a final clinical diagnosis.

Rates of the pathological confirmation of disease from the ROS and Rush MAP studies were compared with those from the Rush Alzheimer's Disease Center clinic, where over 600 Chicago-area patients, who have agreed to annual evaluations and brain donation upon death are treated.

"In the clinic, we follow commonly accepted procedures, consistent with the current practice parameters—detailed neuropsychological testing, an interview with a knowledgeable informant, structural neuroimaging, blood work, and other ancillary tests that are clinically indicated," said Dr. Bennett.

Both at the clinic and in the ROS and Rush MAP studies, Bielschowsky's method of silver staining is used at the postmortem examination to identify neuritic plaques and neurofibrillary tangles from five regions of the brain. In the case of the ROS and Rush MAP studies, these examinations are performed by staff, who are blinded to all clinical data. Diagnoses of AD were made using both the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and the National Institute on Aging (NIA)/Reagan Institute criteria. For the ROS and Rush MAP studies, the CERAD criteria were modified to be implemented without adjustment for age or knowledge of the clinical diagnosis. The CERAD diagnosis was based on semi-quantitative estimates of neocortical neuritic plaques. Braak staging of neurofibrillary spread was also performed.

To date, 339 complete postmortem neuropathologic examinations have been performed for the ROS and Rush MAP studies. Of these, 102 participants had clinically probable AD, 30 had clinically possible AD, and 9 had dementia due to another condition. At the clinic, 411 neuropathologic examinations have been completed. Of these, 293 participants had clinically probable AD, 53 had clinically possible AD, and 46 had dementia due to another condition.

Among the ROS and Rush MAP patients diagnosed with probable AD, 93% (95 patients) were confirmed by pathologic examination using the CERAD criteria, as were 93% (273) of the clinic patients with clinically probable AD. With the NIA/Reagan criteria, 91% (93) of the ROS and Rush MAP patients diagnosed with probable AD were confirmed by autopsy, as were 93% (273) of the clinic patients.

The diagnostic protocol used in ROS and Rush MAP was not as accurate in the diagnosis of possible AD patients. Among the ROS and Rush MAP patients diagnosed with possible AD, 70% (21) were confirmed by pathologic examination using the CERAD criteria, compared with 94% (50) of the clinic patients.

With the NIA/Reagan criteria, 63% (19) of the ROS and Rush MAP patients diagnosed with possible AD were confirmed by autopsy, compared with 89% (47) of the clinic patients.

The positive predictive value of the clinical diagnosis of probable AD (using CERAD) in the two study groups was 0.93, while the positive predictive value of possible AD was 0.70.

For comparison, in the clinic sample the positive predictive value of the clinical diagnosis of probable AD (using CERAD) was 0.93, and the positive predictive value of possible AD was 0.94.

Similar values were seen using high- and intermediate-likelihood of AD using the NIA/Reagan criteria. ■

TBI Test Identifies Those at Risk for Cognitive Decline After Surgery

Physicians can use the Paced Auditory Serial Addition Test (PASAT) to assess patients' cognitive decline after cardiac surgery, said Yolanda Carrascal, M.D., of the University of Valladolid (Spain) and her associates.

Postoperative cognitive deficits have been reported in up to 80% of such patients, most often after extracorporeal circulation. Typically, cognitive assessment requires a complex battery of tests that can be performed and interpreted only by experienced psychometricians. What is needed is a brief, simple test that can be administered by personnel not specifically trained in psychometrics, such as cardiac surgeons, the investigators said (Interact. Cardiovasc. Thorac. Surg. 2005;4:216-21).

They proposed that the PASAT fills that bill. The 2-minute test of simple addition has been used since the 1970s to assess neurologic deterioration after mild traumatic brain injury, and more recently has been used to track cognitive damage secondary to disorders such as multiple sclerosis.

The researchers administered the PASAT to 132 patients (mean age 67 years) before and after cardiac surgery involving extracorporeal circulation, and found that 60 (45.5%) had significant cognitive decline after the procedure. Half still had impairment 4 months later.

—Mary Ann Moon

FDA Approves Changes in Clozapine Blood Monitoring

BY ELIZABETH MECHCATIE
Senior Writer

Rockville, Md. — The Food and Drug Administration has approved two major changes to the schedule for agranulocytosis monitoring in people on clozapine, an atypical antipsychotic sometimes used off label for management of dementia: the addition of absolute neutrophil count tests to regular monitoring and a reduction in the frequency of testing after 1 year of satisfactory white blood cell counts and absolute neutrophil counts.

The revised monitoring guidelines are as follows: Before starting treatment, patients must have a baseline white blood cell (WBC) count and an absolute neutrophil count (ANC). This should be followed by a WBC and ANC test every week for the first 6 months.

An FDA analysis of the registry data found that people with moderate leukopenia appeared to be at a 'considerably higher' risk of agranulocytosis.

After 6 months, if WBC counts and ANCs have been acceptable (defined as a WBC greater than or equal to 3,500/mm^3 and an ANC greater than or equal to 2,000/mm^3) and have been maintained during the first 6 months of continuous therapy, WBC counts and ANCs can be monitored every 2 weeks for the next 6 months.

After 12 months of treatment, if WBC counts and ANCs have remained at acceptable levels during the second 6 months of continuous therapy, WBC counts and ANCs can be monitored every 4 weeks.

The previous schedule neither included ANC testing nor allowed for further reductions in the frequency of testing after 1 year, with patients continuing to be tested every 2 weeks indefinitely.

Gregory Dubitsky, M.D., of the FDA's division of neuropharmacologic drug products, Rockville, said in an interview that the reduction in the frequency of monitoring after 1 year was based on considerations of data from the Clozaril National Registry and experience in the United Kingdom and Australia.

The decision to add ANC testing was based on the United Kingdom's experience, which suggested that moderate leukopenia might be detected earlier if ANC was used as an independent measure of hematologic function, as opposed to the total WBC count alone, he added.

An FDA analysis of the registry data found that people with moderate leukopenia appeared to be at a "considerably higher" risk of agranulocytosis, Dr. Dubitsky noted. On the basis of this finding, the label says that the benefits of continuing clozapine in such patients should be carefully balanced against this risk when deciding whether to continue treatment with the drug, he said. This information was not on the label previously. On the label, agranulocytosis is defined as an ANC below 500/mm^3.

Other changes to the label include the frequency of monitoring recommended for patients who interrupt a course of clozapine treatment, and ANC criteria for various stages of leukopenia, Dr. Dubitsky said.

Further explanations of the revised monitoring schedule and other changes are included on the new label, which was posted on the FDA's MedWatch Web site last month.

Novartis, manufacturer of Clozaril, the trade formulation, is planning to send out a "Dear Health Care Provider" letter explaining the changes in the monitoring schedule as well as several other unrelated changes on the label. The letter is currently being reviewed by the FDA, according to Novartis. There are now several generic formulations of clozapine, which will also be required to make the same changes to their product labels.

The approval of clozapine in 1989 for the management of treatment-resistant schizophrenia was tied to the "no blood, no drug" requirement that the drug be made available through a special distribution system that required weekly WBC counts before the next week's supply of clozapine was provided to the patient.

All the WBC data have been entered into the Clozaril National Registry and have been used to make decisions on monitoring frequency.

At recent FDA advisory panel meetings on safety issues associated with various drugs, such as Vioxx and the other COX-2 inhibitors and the acne drug isotretinoin, the clozapine "no blood, no drug" policy was raised as an example of a risk management program that makes it possible to keep a drug on the market for patients who can benefit from it, while successfully managing the drug's potential serious risks.

The monitoring schedule has been changed once before: In 1998, the schedule was changed to allow a reduction in testing WBC counts to every 2 weeks after 6 months, in patients whose WBC counts were maintained at acceptable levels during the first 6 months of weekly testing. ■

The revised Clozaril label is available on the FDA's Web site at: www.fda.gov/medwatch/SAFETY/2005/may05.htm#Clozaril.