Autopsy Confirmed Diagnosis

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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 guidelines and a computer program 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 year’s 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 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 neurofibrillary tangles and neurofibrillar tangles from five regions of the brain. In the case of the ROS and Rush MAP studies, these examinations are performed by a pathologist, who is 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. Brain staging of neurofibrillary spread was also performed.

To date, 339 complete postmortem neuropsychologic 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 neuropsychologic 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 99% (93 patients) 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% (30) of the clinic patients.

The diagnosis of probable AD was based on the United Kingdom’s Institute criteria. For the ROS and Rush MAP patients, the diagnosis of probable AD (using CERAD) in the two study groups was 0.93, while the positive predictive value of probable 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.


They proposed that the PASAT fills that bill. The 2-minute test of simple addition has been used since the 1970s to assess neurologi- cal 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 112 patients (mean age 67 years) before and after cardiac surgery involving extracorporeal circulation, and found that 45% had significant cognitive decline after the procedure.

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

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. One last change to the label is 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 site last month. Novartis Pharmaceuticals Corp., 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 who had been maintained at acceptable levels during the first 6 months of weekly testing. The revised clozapine label is available on the FDA’s Web site at:

www.fda.gov/medwatch/SAFETY/ 2003/may03.html#Clozaril.