Inclusion of REM Sleep Behavior Disorder Improves Diagnostic Classification of DLB

Dementia with Lewy bodies (DLB) is the second most common type of progressive dementia. It causes a progressive decline in mental abilities. Similar to Parkinson disease, DLB can result in rigid muscles, slowed movement, and imbalance. It may also cause visual hallucinations and fluctuations in alertness and attention.

In 2005, the Consortium on Dementia With Lewy Bodies modified the diagnostic criteria to include dementia plus the core features of fluctuations, parkinsonism, and visual hallucinations—and 3 new suggestive features:

- Severe neuroleptic sensitivity
- Reduced basal ganglia dopamine uptake on functional imaging
- Rapid eye movement (REM) sleep behavior disorder (RBD), a REM sleep parasomnia that involves dream enactment behavior during sleep

With this revision, clinically probable DLB is now represented by dementia plus 2 or more core features or 1 core feature and 1 suggestive feature.

Validation of RBD in the DLB Criteria
Tanis J. Ferman, PhD, and a research team at Mayo Clinic in Florida and in Rochester, Minnesota, wondered whether the addition of RBD to DLB criteria would improve the classification accuracy of autopsy-confirmed DLB. “The modification gave RBD a legitimate place in the diagnostic criteria, but, as with any criteria, it needs to be validated,” says Dr Ferman.

The results of their study, “Inclusion of RBD Improves the Diagnostic Classification of Dementia With Lewy Bodies,” were published in the August 30, 2011, issue of Neurology (77[9]:875–82).

The team’s research confirms that inclusion of RBD improves the diagnostic accuracy of autopsy-confirmed DLB, and can be considered a core clinical feature.

The team evaluated 234 study participants with dementia, observed annually as part of the Mayo Clinic Alzheimer’s Disease Research Center, who came to autopsy. Participants received annual neurocognitive and neurologic evaluations and informant questionnaires. A subset underwent overnight polysomnography to confirm the presence of REM sleep without atonia, the electrophysiologic substrate of RBD.

All patients underwent a standardized neuropathologic assessment and were assigned a pathologic diagnosis. As a result, the participant group was divided into 2 subsets: those with high and intermediate likelihood of DLB (DLB autopsy group) and those with low or no likelihood of DLB (non-DLB autopsy group).

The team made comparisons between the DLB and non-DLB autopsy groups, calculating sensitivity, specificity, and odds ratios to assess the diagnostic utility of differing combinations of clinical features in predicting pathologically confirmed DLB.

“The Mayo questionnaires were created to operationalize and standardize how we identify..."
Study Confirms Fibrillar Amyloid Correlates of Decline Among Cognitively Normal Pre-MCI Individuals

The gene most commonly associated with late-onset Alzheimer disease (AD) is apolipoprotein E (APOE). It has 3 common forms: APOE e2, which appears to reduce the risk of AD; APOE e3, which does not seem to affect the risk of AD either way; and APOE e4, which appears to increase the risk of AD.

Studies have shown that the APOE e4 genotype influences the age of onset of abnormally declining memory scores on longitudinal neuropsychological tests in cognitively normal individuals. Cognitively normal APOE e4 carriers also have a greater amyloid beta (Aβ) burden than APOE e4 noncarriers.

Cynthia M. Stonnington, MD, and a research team at Mayo Clinic in Arizona tested the hypothesis that an increased rate of presymptomatic cognitive decline is associated with fibrillar amyloid deposition that can be identified with brain imaging even when controlling for APOE e4 status. Their results were presented at the American Academy of Neurology annual meeting in April 2012.

Specific Definition for Pre-MCI

From a database of participants in a prospective observational study of cognitively normal APOE e4 homozygotes, heterozygotes, and noncarriers, the team selected all persons who continued to be cognitively normal yet showed decline at least...
2 standard deviations beyond the decline of the entire group (decliners) in 2 different memory or 2 different executive function test scores across 2 time points. The team then matched those persons by APOE e4 status, age, sex, and education to persons with no such decline (nondecliners).

All matched persons who consented to undergo Pittsburgh Compound B positron emission tomography (PiB PET) scanning were included. Dynamic PiB PET scans, the Logan method, statistical parametric mapping, and automatically labeled regions of interest were used to characterize and compare cerebral-to-cerebellar PiB distribution volume ratios, reflecting fibrillar Aβ burden.

In PiB PET scans conducted for 14 decliners and 14 matched nondecliners, decliners showed increased amyloid uptake compared with nondecliners at the paracentral lobule, precentral and postcentral gyrus, supplemental motor area, and occipital, insula, prefrontal, and temporal regions. Nondecliners had increased PiB PET uptake in no areas compared with decliners.

Pre-MCI as a Precursor to Future Disease

“This study indicates that subtle longitudinal decline of certain test scores is associated with fibrillar amyloid deposition, even when controlling for APOE e4 genotype,” says Dr Stonnington. “If confirmed with larger samples and outcome data, these findings support the concept of pre–mild cognitive impairment (pre-MCI) as a precursor to future disease.”

The study did identify 3 people with 2 copies of the APOE e4 allele who did not show evidence of decline or a relative increase in Aβ deposition. “High-risk people aren’t absolutely destined to develop MCI or dementia,” says Dr Stonnington. “What we really need to do is study those people who have risk factors but are doing well. How and why are they defying the odds? We should apply the lessons learned from these exceptions to help everyone decrease their odds of developing dementia.”

Neuropsychological Assessment Crucial to Evaluation of Patients With Dementing Illness

Advanced neuroimaging techniques may, according to new criteria, permit the diagnosis of neurodegenerative conditions years in advance of currently measurable cognitive changes. The Alzheimer’s Disease Neuroimaging Initiative has proposed new diagnostic criteria based on the idea that changes in the brains of patients with Alzheimer disease and other dementias occur decades before the first manifestations of cognitive decline can be detected.

Is neuropsychological assessment still necessary? The answer is a definitive yes, says Julie A. Fields, PhD, LP, primary author of a review that describes the current role of such measurement in patients with dementing illness.

The review, “Neuropsychological Assessment of Patients With Dementing Illness,” affirms that in the evaluation and care of patients with all forms of preclinical and clinical dementia, neuropsychological measurement plays 5 important roles:

- Identifying changes that serve as biomarkers of disease
- Predicting the trajectory of dementia
- Monitoring the trajectory of dementia
- Estimating functional status
- Aiding the design of intervention strategies

Dr Fields and her colleagues elucidated the clinical utility of neuropsychological testing by clarifying psychometric test properties, such as construct validity, test stability, and use of appropriate norms in terms of how they influence the application of neuropsychological testing and the interpretation of test results.

The study was published in the December 2011 issue of *Nature Reviews Neurology* (7[12]:677-87).

Collaborative Evaluation

At Mayo Clinic, neuropsychological testing and...
neuroimaging studies are used together to establish a baseline from which to monitor patients over time.

“Molecular, structural, and functional neuroimaging studies have advanced our understanding of the pathophysiology underlying neurodegenerative disease,” says Dr Fields. “The overlap in clinicopathological features of different dementia-associated diseases, however, limits drawing definitive conclusions from information obtained from advanced imaging techniques or blood and cerebrospinal fluid assays alone. In this regard, neuropsychological assessment continues to have a complementary and distinct role in the detection and monitoring of cognitive and functional changes associated with dementing illness.”

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  - San Diego, California

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  - September 14, 2012
  - Minneapolis, Minnesota

- **Acute Care Psychiatry Clinical Review**
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- **Biological Frontiers of Addiction**
  - Fall 2012
  - Rochester, Minnesota

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  - Rochester, Minnesota

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**Adult Mood Psychiatrist.** Mayo Clinic in Rochester, Minnesota, seeks an exceptional junior or midcareer clinician and researcher at the level of assistant professor or higher to join the psychiatric clinical practice. To learn more, visit www.mayoclinic.org/physician-jobs/ and reference job posting number 7596BR.