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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 RDB 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.

Tanis J. Ferman, PhD

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

Points to Remember

- Clinically probable DLB is represented by dementia plus 2 or more core features or 1 core feature and 1 suggestive feature.
- Inclusion of rapid eye movement sleep behavior disorder as a core clinical feature significantly improves the diagnostic accuracy of autopsy-confirmed DLB.

the presence of fluctuations, hallucinations, and dream enactment behavior during sleep, so that we can be objective in our assessments of these phenomena," says Dr Ferman. "The Mayo sleep questionnaire has been validated with overnight polysomnography. We ask the informant, 'Have you ever seen the patient appear to act out his or her dreams while sleeping?' As the neurodegenerative disease progresses, the frequency of the sleep behavior often lessens, so it is important to determine if there is a history of RBD and not just a current problem with it."

DLB Impacts Outcomes

"Our research shows that patients with RBD were 6 times more likely to have autopsy-confirmed DLB than other neurodegenerative dementia conditions," says Dr Ferman. "Patients with RBD and dementia and no other clinical features were also more likely to have DLB." RBD improved sensitivity to 88% and specificity to 73% and when RBD plus dementia alone was considered as probable DLB, sensitivity increased to 90%.

Dr Ferman notes, "We also found that males tend to present with RBD more than females. This sex difference parallels what's seen in Parkinson disease, a similar clinical condition that also has Lewy body deposition."

In the DLB autopsy group, 76% (74/98) of patients had RBD. In the non-DLB group, 4% (5/136) had RBD. Of the 5 latter patients, 2 had limbic-only Lewy body pathology but also had a high degree of co-occuring Alzheimer disease pathology, which gave them a pathologic diagnosis of low-likelihood DLB.

Patients who met clinical criteria for DLB but did not have it (false-positive findings) included 27% (37/136) of the non-DLB cohort. This group included individuals with Alzheimer disease, Creutzfeldt-Jakob disease, cerebrovascular disease, and other parkinsonian conditions. In this group, 7 patients had low-likelihood DLB with limbic-only Lewy body pathology and a high degree of Alzheimer disease pathology.

Individuals with autopsy-confirmed DLB who did not meet DLB clinical criteria (false-negative findings) included 12 patients, 9 of whom had at least 1 DLB clinical feature. Of these 9 patients, 2 had RBD and died in the early stage of dementia. If they had lived longer, other DLB core features may have developed.

Early Detection Is Important for Treatment

The ultimate goal, notes Dr Ferman, is to properly diagnose DLB as early as possible to better manage the symptoms and avoid medications known to aggravate it. Since RBD may precede the development of the dementia or parkinsonism by years, early diagnosis provides a unique window in which to implement new preventive therapies.

Study Confirms Fibrillar Amyloid Correlates of Decline Among Cognitively Normal Pre-MCI Individuals

Cynthia M. Stonnington, MD

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."

Points to Remember

- *APOE* e4 genotype influences the age of onset of abnormally declining memory scores in cognitively normal individuals, who also have a greater amyloid beta (Aβ) burden than *APOE* e4 noncarriers.
- 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.
- Study findings support the concept of pre–mild cognitive impairment (MCI) as a precursor to future disease.

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).

Julie A. Fields, PhD, LP

Collaborative Evaluation

At Mayo Clinic, neuropsychological testing and

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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."

Upcoming Courses

For more information or to register for courses, visit www.mayo.edu/cme/psychiatry-and-psychology, call 800-323-2688 (toll free), or e-mail cme@mayo.edu.

Psychiatric Genomics: Applications for Clinical Practice
August 9-11, 2012
Rochester, Minnesota

Mini-Fellowship in Primary Pediatric Psychopharmacology
August 16-18, 2012
San Diego, California

Clinical Management of Borderline Personality Disorder
September 14, 2012
Minneapolis, Minnesota

Acute Care Psychiatry Clinical Review
October 18-20, 2012
Chicago, Illinois

Biological Frontiers of Addiction
Fall 2012
Rochester, Minnesota

National Network of Depression Centers Conference
Fall 2012
Rochester, Minnesota

Movers and Shakers in Neurology: Epilepsy and Movement Disorders
November 3, 2012
Jacksonville, Florida

Positions Available

Addiction Psychologist. Mayo Clinic in Rochester, Minnesota, seeks an exceptional junior or mid-career clinician and researcher at the level of assistant professor or higher. To learn more, visit www.mayoclinic.org/physician-jobs/ and reference job posting number 9955BR.

Child Clinical Psychologist. Mayo Clinic in Rochester, Minnesota, seeks an outstanding child clinical psychologist with expertise in the assessment and treatment of children with autism spectrum disorders. To learn more, visit www.mayoclinic.org/physician-jobs/ and access job posting number 192BR.

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.

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