Cognition, Mood Disorders Rise With Age in Epilepsy

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — By the age of 65, patients with epilepsy were found to have reduced cognitive function, a higher prevalence of depression and anxiety, and poorer sleep hygiene compared with their seizure-free peers, data from a small cross-sectional study showed.

The finding "underscores the need for looking at age-specific effects in epilepsy rather than assuming that everyone in the adult population is the same," Dr. Sheryl R. Haut said in an interview during a poster session at the annual meetings of the American Epilepsy Society and the Canadian League Against Epilepsy. "When you're evaluating patients with epilepsy who are over the age of 65, you should be specifically inquiring not only about seizure frequency, but you must inquire and perhaps screen for depression, anxiety, and sleep [problems], because these are having an impact on their quality of life."

Dr. Haut, of the department of neurology at Montefiore Medical Center and Albert Einstein College of Medicine, New York, and her associates recruited 32 patients aged 65 years and older who had a diagnosis of epilepsy confirmed by an epileptologist and 32 age-matched controls who had no history of seizures. The researchers administered a battery of tests to all study participants, including the Blessed Information Memory and Concentration Test (BIMC), the Prime-MD Depression and Anxiety Scale, and the Medical Outcomes Study (MOS) Sleep Scale.

The mean BIMC scores were significantly higher for epilepsy patients, showing a higher level of cognitive disturbance versus controls (6.3 vs. 1.2, respectively); while the mean Prime-MD Depression scores were significantly worse for epilepsy patients versus controls (4.2 vs. 0.8, respectively). Six cases (18%) met criteria for depression.

Similarly, the mean Prime-MD Anxiety scores were significantly worse for patients with epilepsy compared with controls (3.7 vs. 0.0, respectively).

Dr. Haut also reported that epilepsy patients scored significantly worse than controls on the MOS Sleep Scale measures of somnolence and shortness of breath/headache (13.1 vs. 3.3, respectively).

Mean depression scores were significantly worse for epilepsy patients compared with controls (4.2 vs. 0.8).

DR. HAUT

"Even though you sometimes assume that the elderly overall have worse sleep and may be more prone to depression and anxiety, in fact it's specific to epilepsy in our study," she said. "What was surprising was that the depression and anxiety prevalence was so much higher in the cases than in the controls. In fact, none of the controls scored significantly in the anxiety scales whereas many of the cases did."

She noted that she has started to include the battery of tests used in the study in her routine care of elderly epilepsy patients. "You can give them to the patient to take home and bring back to you. These are useful screening tests that don't take a long time to fill out."

The study was supported in part by the National Institutes of Health and by an unrestricted grant from Pfizer Inc. ■

Don't Exclude Mentally Impaired From Exercise

BY DOUG BRUNK
San Diego Bureau

CARMEL, CALIF. — Cognitively impaired older adults who take part in exercise rehabilitation programs have similar strength and endurance outcomes as cognitively intact peers, results from a large meta-analysis showed.

The finding suggests that cognitively impaired older adults should not be excluded from rehabilitation programs, Kyle E. Johnson reported at the Western regional meeting of the American Federation for Medical Research.

"It's a fallacy that cognitively impaired older adults are unable to follow instructions and that they will not benefit from physical therapy," said Mr. Johnson, who is a second-year medical student at the University of Colorado, Denver.

He and his associate, Patricia C. Heyn, Ph.D., of the university's division of geriatric medicine, searched electronic and printed databases for randomized, controlled trials that included physical rehabilitation outcomes of cognitively impaired older adults (defined as those with a Mini-Mental State Examination score of less than 24) and cognitively intact older adults (defined as those with an MMSE score of 24 or higher).

Of the more than 500 articles reviewed, 41 met inclusion criteria. Of these, 21 trials involved 1,411 older adults with cognitive impairment and 20 trials involved 1,565 older adults who were cognitively intact. The mean age of the patients was 81 years.

The mean MMSE score among the cognitively impaired older adults was 16, compared with a mean score of 28 among those who were cognitively intact.

When the researchers combined the strength and endurance outcomes from the two groups, they observed an effect size of 0.51 for the cognitively impaired elderly and an effect size of 0.49 for the cognitively intact elderly. No statistically significant differences were seen in the strength and endurance outcomes between the two groups.

"Every study showed a positive result" from physical exercise, Mr. Johnson said. "We need more research to directly compare these two groups and to consider the need for different exercise guidelines for varying degrees of cognitive impairment."

He added that exercise rehabilitation for older adults "should be aimed to positively affect participants' quality of life. By doing so, there should be significant functional improvements in activities of daily living in cognitively impaired individuals." ■

Genetic Variant Tied to Amyloid-β Generation in Alzheimer's

BY JEFF EVANS
Senior Writer

Genetic variants of a protein involved in determining the fate of amyloid precursor protein are associated with an increased risk of developing Alzheimer's disease, reported Dr. Ekaterina Rogaeva of the University of Toronto and her associates.

The increased risk for the disease appears to be caused by certain haplotypes of the SORL1 gene that decrease the expression of the gene. As a result, more amyloid precursor protein follows a pathway in which excess amyloid-β peptide is produced in the brain—one of the central events in the pathogenesis of Alzheimer's disease (AD), according to the investigators.

Dr. Samuel E. Gandy, director of the Farber Institute for Neurosciences at Thomas Jefferson University, Philadelphia, said the study's results "fit well into the amyloid model for Alzheimer's, and that's certainly the one that's getting the most attention and most assessment clinically."

Dr. Rogaeva and her colleagues found that several overlapping haplotypes in two different regions of the SORL1 gene increased the likelihood of developing late-onset familial Alzheimer's disease (FAD), based on results obtained from two cohorts of families with late-onset FAD and later replicated in a cohort of cases and controls in other studies.

"Taken together, our results suggest that genetic and possibly environmentally specified changes in SORL1 [protein] expression or function are causally linked to the pathogenesis [of Alzheimer's disease] and have a modest effect on risk for this disease," the researchers said (Nat. Genet. 2007 Jan. 14 [Epub doi:10.1038/ng1943]).

The initial "discovery cohort" comprised 124 northern European FAD families and 228 Caribbean Hispanic FAD families. The "replication cohort" consisted of northern European individuals from a case-control study (178 cases with sporadic AD and 242 controls with self-identified white European ancestry), 276 white sibships from the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study, 238 African American sibships from the MIRAGE study, and Israeli Arab individuals (111 with AD and 114 normal controls from the Wadi Ara population study).

The researchers confirmed the association between AD and the SORL1 gene by genotyping the single-nucleotide polymorphisms that were contained in the haplotypes and then analyzing them at an independent facility in three series of cases and controls of European ancestry from different Mayo Clinic centers (totaling 1,405 late-onset AD cases and 2,124 controls).

In genetic studies, particularly those involving Alzheimer's disease, there has "been an issue of one group making a report and then a number of other groups being unable to replicate [the results] across different ethnic groups," Dr. Gandy said in an interview. "The good thing about this paper is that they've already tested several totally independent ethnic groups, so you can feel a bit more confident that this is true."

SORL1 protein directly binds amyloid precursor protein and differentially regulates whether it sorts into a recycling pathway or into a pathway that generates amyloid-β. Experiments that suppressed SORL1 protein expression—mimicking what is speculated to be the effects of AD-associated variants in the SORL1 gene—led to an overproduction of amyloid-β.

The actual disease-causing variants of the SORL1 gene are unlikely to be the single-nucleotide polymorphisms and haplotypes that were identified in the SORL1 gene's exons, the researchers noted. Instead, the pathogenic variants are likely located in sequences in the introns of the SORL1 gene and may "modulate the cell type–specific transcription or translation of the SORL1 gene in carriers of the Alzheimer's disease–associated haplotypes," the investigators said.

One of the disease-associated haplotypes of the SORL1 gene was expressed in AD haplotype carriers at less than half the levels of carriers of nondisease haplotypes. But univariate regression analyses showed that the disease variants of the SORL1 gene accounted for about only 14% of the variance in the SORL1 protein expression that was seen in those individuals.

"This latter result implies that other genetic and nongenetic factors can also modulate SORL1 [protein] expression and, perhaps, therefore, risk for Alzheimer's disease," the researchers said.

Although variants of the SORL1 gene may not raise the risk of AD as much as the apo E ε4 allele, Dr. Gandy noted that the results point out a new target for drug therapy that can raise SORL1 protein levels.

"We never know when we're going to encounter side effects, so it's good to have multiple possible targets," he said. ■