Is Apo E the Key?

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fluency, trail making, or single-institution tests), amnestic single domain (impairment on a word recall test), and amnestic multiple domain (impairment on word recall and at least one other memory test).

Impact of Apo E Genotype

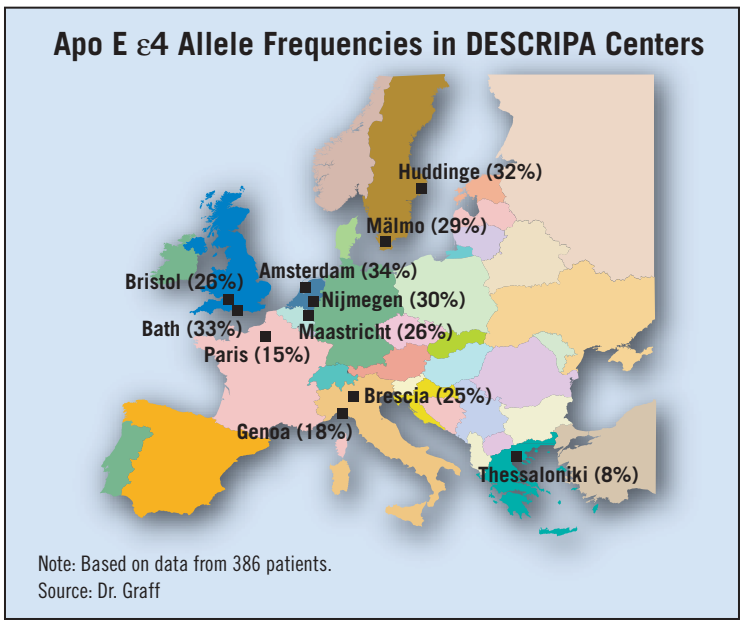
The frequency of the ε4 allele of the apolipoprotein E gene (apo E) varies significantly with specific MCI subtypes and between regions of Europe but does not have strong enough predictive value alone to distinguish among MCI subtypes, according to Caroline Graff, M.D., Ph.D., of the Karolinska University Hospital, Huddinge, Sweden.

The distribution of ε4 allele frequency and the average age of patients differed significantly among the four MCI subtypes in a group of 386 patients at 11 centers who were genotyped for apo E allele status. The frequency of the ε4 allele increased from 17% of nonamnestic patients to 21% of those with subjective MCI, 30% of amnestic multiple domain, and 32% of amnestic single domain. Age varied from 66 years in subjective MCI to 72 years in amnestic single-domain patients.

The distribution of MCI subtypes and age was significantly different among the centers. Frequency of the ε4 allele also varied according to the centers' location in Europe. The average frequency was lowest (8%) in Thessaloniki, Greece, and highest (33%) in Bath, England.

The variables of center, age, and apo E genotype were significantly associated with MCI subtype in a multivariate logistic regression analysis. The effect of center was the strongest predictor of MCI subtype, and it could not be explained by the effect of age or apo E status alone. "There is something else inherent in center," Dr. Graff said.

If one hypothesizes that the different MCI subtypes predict the type of dementia that a person will develop, this could mean that the prevalence of the different types of dementia differ among these countries, Dr. Graff pointed out.



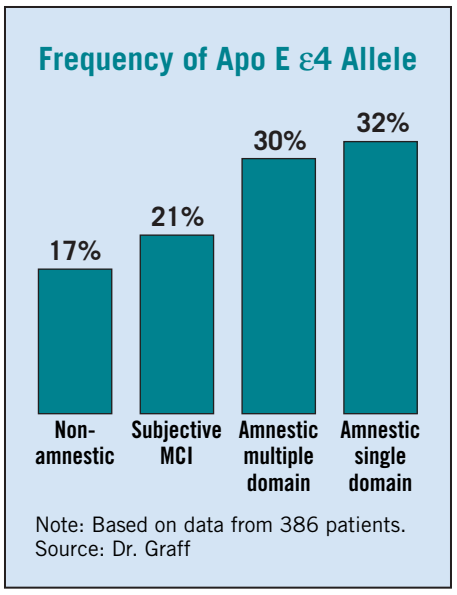
Subtype-Linked EEG Differences

Decline in the function of posterior cortical regions of the brain such as the temporal, occipital, and parietal lobes characterize the resting EEG of patients with amnestic MCI, Flavio Nobili, M.D., reported at the congress.

In a preliminary analysis, the temporal, occipital and parietal cortical regions of the brain in 96 patients who had digital EEG performed at five centers had significant reductions in α-1 frequency, compared with the same regions in 55 control patients matched for age, sex, and education. This result is "consistent with the hypothesis of a transition stage between amnestic MCI and Alzheimer's disease," said Dr. Nobili of the department of clinical neurophysiology at the University of Genoa (Italy).

Other studies of resting EEG in MCI patients have shown decreases in α frequency. It's known that deafferentation of thalamo-cortical and cortico-cortical brain connections and deficits in neurotransmission underlie the slowing down of EEG readings in Alzheimer's disease (AD) patients. Even in early stages of AD, EEG readings typically show decreases in α frequency and a shift to a lower α peak frequency.

A follow-up study will be necessary to determine the influence that the heterogeneity of the amnestic MCI population has on these results, since the distribution of EEG power in defined, early-stage AD also is very heterogeneic, he noted.



Importance of Noncognitive Symptoms

Noncognitive symptoms are common in MCI patients but do not appear to occur at significantly different rates in MCI subtypes, according to a preliminary study of 324 patients with full Neuropsychiatric Inventory (NPI) scores.

Noncognitive symptoms are common in AD patients but have been poorly studied in those with MCI. The subgroup of patients with amnestic MCI as well as the symptoms of depression have been the focus of most studies on the subject, said Inez Ramakers, a doctoral student at Maastricht University (the Netherlands).

In the study, 79% of the patients had at least one noncognitive symptom as defined by domain scores on the NPI.

Noncognitive symptoms were clinically significant in 39% of patients, consisting mainly of apathy, depression, anxiety, and irritability.

The NPI scores did not differ significantly among the MCI subtypes. But the subjective MCI group had a significantly better NPI score and significantly less apathy than did the other three MCI subtypes combined. After 1 year of follow-up in 88 patients, NPI score has not been a significant predictor of dementia.

Atrophy Related to Subtype

Medial temporal lobe atrophy is associated with MCI subtypes and measures of cognition but not vascular risk factors, Laura van de Pol reported during the DESCRIPA session. Varied neuropathologies may produce different types of MCI that progress to different dementias, said Ms. van de Pol of the Vrije University Medical Center, Amsterdam.

In 214 patients who underwent MRI scans at five centers, the severity of medial temporal lobe atrophy followed a significant trend that progressed from mild to more severe in subjective, nonamnestic, amnestic single-domain, and amnestic multiple-domain MCI patients. But the severity of white matter hyperintensity did not differ between the subtypes, she said.

Medial temporal lobe atrophy, but not white matter hyperintensity, correlated significantly and negatively with cognitive testing with the Mini-Mental State Examination (MMSE) word list learning, delayed word list recall, and fluency.

Vascular factors such as blood pressure, atherosclerosis, hypercholesterolemia, and diabetes correlated significantly and positively with white matter hyperintensity while medial temporal lobe atrophy did not.

In a 1-year follow-up with 73 patients, medial temporal lobe atrophy was significantly correlated with a decline in delayed recall while white matter hyperintensity was not correlated with any cognitive measure.

Ms. van de Pol noted that medial temporal lobe atrophy and white matter hyperintensity did not interact with each other on cognition. Their association with patients with MCI subtypes seems to reflect different etiologies in which medial temporal lobe atrophy may be a marker of AD neuropathology, and white matter hyperintensity reflects vascular disease that does not contribute to cognitive impairment in these MCI subtypes.

Total Tau Protein Signals Decline

Tau protein in an MCI subtype rises with worsening cognitive impairment and is correlated with worsening neuropsychology, according to a preliminary study of proteins in the cerebrospinal fluid (CSF) of 84 patients.

The percentage of patients with an abnormal total tau protein level produced a significant trend from 20% of MCI patients with subjective complaints up to about 80% of amnestic multiple-domain patients, said Peter Jelle Visser, M.D., also of Maastricht University. Levels of amyloid β 1-42 and phosphorylated tau did not follow a significant trend.

CSF levels of total and phosphorylated tau correlated significantly with declining performance on the MMSE and tests of delayed recall, fluency, and trail making. Follow-up at 1 year in 33 patients (27 nondemented, 6 AD) showed that the increase in levels of total and phosphorylated tau was significantly higher in patients with AD than in those without dementia. ■

Diet, Exercise May Reduce Alzheimer's Risk in Apo E ε4 Carrier

BY JEFF EVANS
Senior Writer

STOCKHOLM — Individuals who carry the apolipoprotein E ε4 allele that increases the risk of developing Alzheimer's disease may lower their risk to that of a noncarrier through regular exercise, moderate fat intake, and low alcohol consumption, reported Tiia Ngandu at the 12th Congress of the International Psychogeriatric Association.

Ms. Ngandu and her associates studied 1,449 Finnish people who participated in the longitudinal, population-based Cardiovascular Risk Factors, Aging, and Dementia study (CAIDE) in 1972, 1977, 1982, or 1987. After an average follow-up of 21 years, the participants were aged 65-79 years when they were reexamined in 1998.

Based on questions answered at midlife, active individuals (exercised at least twice per week) who carried the ε4 allele of apolipoprotein E (apo E) had a significantly lower likelihood of developing Alzheimer's disease (AD) than sedentary carriers, said Ms. Ngandu, a doctoral student at the Aging Research Center at the Karolinska Institute, Stockholm.

Intake of polyunsaturated fatty acids did not alter the odds of developing AD in carriers, but high intake of saturated fatty acids was associated with significantly greater odds of AD in carriers, compared with a low intake.

Apo E ε4 carriers who frequently consumed alcohol had a significantly higher likelihood of developing AD than carriers who drank infrequently or never.

None of the lifestyle factors reduced the risk of AD in noncarriers, she noted.

"Carriers seem more vulnerable to various environmental effects," she said.

People with a parent with late-onset Alzheimer's disease may undergo genotyping for apo E. A positive finding is not diagnostic of Alzheimer's disease, even in a symptomatic patient. The test also is done in some patients with both high cholesterol and elevated triglycerides to determine whether the patient's lipid disorder has a genetic component. ■