Study Is Shedding Light on Predementia Criteria

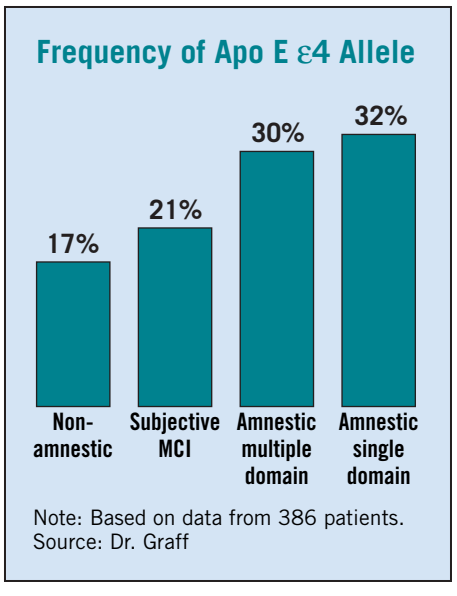
Multicenter European trial examined progression from mild cognitive impairment to Alzheimer's.

BY JEFF EVANS
Senior Writer

STOCKHOLM — Preliminary results of the ongoing European Alzheimer's Disease Consortium's DESCRIPA study are pointing the way toward clinical criteria that may help single out which types of mild cognitive impairment lead to Alzheimer's disease, speakers reported at the 12th Congress of the International Psychogeriatric Association.

Twenty-five centers conducted DESCRIPA (Development of Screening Guidelines and Diagnostic Criteria for Predementia Alzheimer's Disease), a prospective cohort study that included 850 patients with suspected mild cognitive impairment (MCI). Presentations at the congress involved data on various subsets of the 850 patients.

The study investigators had no predefined criteria for MCI but included patients who were aged 55 years or older and had received consecutive referrals for cognitive impairment. They excluded patients who had a diagnosis of dementia at baseline and obvious causes of cognitive impairment such as stroke and depression. Based on neuropsychologic testing, patients were divided into four MCI subtypes: subjective complaints (no impairments on cognitive testing), nonamnestic (impairments on 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 differences were still significant when the four subtypes were collapsed into a nonamnestic group composed of the subjective and nonamnestic MCI patients (19%, 68 years) and an amnestic group composed of the amnestic single- and multiple-domain groups (31%, 72 years).

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, she pointed out.

EEG Abnormalities in Amnestic Subtype

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.

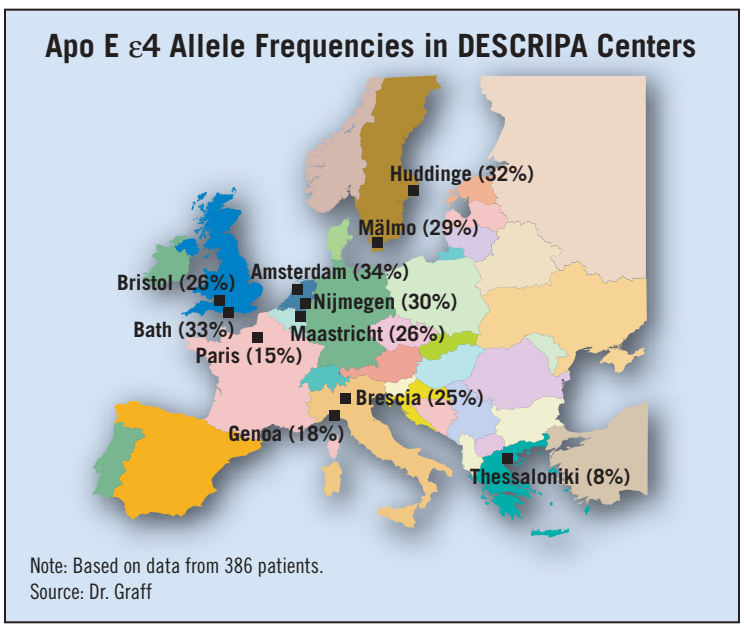
In a preliminary analysis, the temporal, occipital and parietal cortical regions of the brain in 96 patients who had digital EEG performed at five centers had significant reductions in α-1 frequency, compared with the same regions in 55 control patients matched for age, sex, and education. This result 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 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 on MRI 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. "It has been suggested that the different types of MCI may reflect differences in underlying neuropathologies and may therefore potentially progress to different sorts of dementia," 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 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, Ms. van de Pol said.

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

But vascular risk factors such as blood pressure, atherosclerosis, hypercholesterolemia, and diabetes mellitus were significantly and positively correlated with white matter hyperintensity while medial temporal lobe atrophy was not.

In a 1-year follow-up with 73 patients, medial temporal lobe atrophy was significantly correlated with a decline in delayed recall; 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

The total level of tau protein in an MCI subtype increases as the level of cognitive impairment rises 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.

To further investigate the possibility that even the 20% of subjective MCI patients with abnormal CSF protein levels could develop dementia in follow-up, Dr. Visser suggested that "other studies should not only focus on amnestic MCI but also on the other forms of MCI." ■

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