For Gene Carriers, Age 60 Is Key

BY MICHELE G. SULLIVAN
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Age 60 seems to be the defining year for many homozygous carriers of the apolipoprotein ε4 gene—the time when age-related changes in cognition focus more on memory and begin a steeper decline into mild cognitive impairment and, eventually Alzheimer's disease, according to new unpublished observations from a longitudinal study of apo ε4 carriers and normal controls.

"We saw normal age-related patterns of memory loss that occurred before age 60, but during this period, we didn't see any significant cognitive differences between the apo ε4 homozygotes, heterozygotes, and noncarriers," said Dr. Richard Caselli, a lead investigator for the Arizona Apoε4 Cohort Longitudinal Study of Cognitively Normal Individuals. "But our latest information shows that at around age 60, a separation begins and continues for as long as we have been able to follow our subjects. There is a particular pattern of decline in apo ε4 homozygotes that tends to precede any diagnosis of mild cognitive impairment [MCI] or anything that can be seen with routine clinical brain imaging," he said in an interview.

This pattern suggests that pathologic changes could be occurring earlier in homozygous ε4 carriers, although the exact nature of these changes, and their triggers, remain speculative, said Dr. Caselli, chairman of the department of neurology at the Mayo Clinic, Scottsdale, Ariz., and a member of the Arizona Alzheimer's Disease Consortium.

The Arizona cohort was initiated in 1994, and now includes more than 600 people, enrolled at ages 20-90 years, who have at least one first-degree relative with Alzheimer's disease. The subjects are all genotyped for the apo ε4 allele, and undergo extensive neuropsychological testing every 2 years.

Dr. Caselli's recent substudy focuses on 214 of these subjects aged 50-69 years. Almost half are apo ε4 carriers—43 homozygous and 59 heterozygous.

The study set out to characterize the effect of apo ε4 status on the development of presymptomatic cognitive changes. It's well known that the gene has a dose-response effect on the age at AD diagnosis: 80%-90% of homozygotes will develop the disease, at a mean age of 68 years. About 30% of heterozygotes will develop AD and will do so at a mean age of 73, while 9% of noncarriers will develop the disease and are usually diagnosed around age 80.

As in the larger cohort, subjects in the substudy took the battery of neuropsychological tests every 2 years. The battery consists of four tests in each of five domains: executive, memory, language, spatial, and behavioral. Significant decline was defined as a drop of two standard deviations beyond that of the entire cohort in one or more domain test scores. Subjects were judged to have cognitive domain decline if their scores were lower on at least two tests in any single domain.

"We found that there was really no difference between the genetic subgroups in patterns of decline in the younger group of patients, aged 50-59 years," Dr. Caselli said. "Some had no decline, some showed improvement, and some had domain decline, but there were no statistically significant differences."

Significant differences did emerge in the group of 60- to 69-year-olds, however. Homozygotes had the highest proportion of cognitive decline, with 40% showing domain decline, compared with 8% of heterozygotes and noncarriers. None of the older noncarriers or heterozygotes experienced a decline in two or more domains, while this occurred in 20% of the homozygous subjects.

Dr. Caselli has additional data on 97 subjects who have been tested again in the years following their initial decline. "We saw that it was those who initially declined on memory who tended to continue to decline significantly in other areas, and if that subsequent decline was in the memory domain, it was even more pronounced."

Among homozygous carriers of the gene aged 60-69, 40% showed domain decline, compared with 8% of heterozygotes and noncarriers.

Seven subjects developed MCI or AD during the study; five of these were apo ε4 homozygotes, one was an apo ε4 heterozygote, and one was a noncarrier. "Typically, it took about 2 years following the epoch of domain decline for the diagnosis to occur."

By looking at the larger cohort and including subjects aged 30-90 years, Dr. Caselli also found a striking age-related separation of memory domain performance between apo ε4 carriers and noncarriers. From age 30 to 60, memory performance on the Auditory Verbal Learning Test, which requires subjects to recall 15 words from a list, declined slowly and consistently, from a mean of 11 words at age 30 to about 9.5 words at age 60. Immediately thereafter, however, the groups separated. Noncarriers continued a slow, almost linear decline, and by age 90, their predicted mean word recall was about 8.5 of 15. But carriers entered a phase of sharper decline; by the time they reached 90 years, their predicted mean word recall was about 5.5.

The slope of decline exhibited by the noncarriers represents normal, age-related memory loss, Dr. Caselli said. The sharper post–60-year decline in apo ε4 carriers probably reflects a direct or indirect effect of the ε4 gene.

But although these cognitive changes appeared mainly after age 60, imaging studies on some of the younger carriers suggest that some brain areas may be vulnerable much earlier in life. PET scanning of presymptomatic 50- to 59-year-old homozygotes showed areas of decreased glucose metabolism in brain regions associated with Alzheimer's disease pathology: the posterior cingulate gyrus, parietal and temporal lobes, and prefrontal cortex. PET scans of 20- to 39-year-olds with one copy of the allele showed similar, although smaller, areas of decreased metabolism.

"So what does that mean?" asked Dr. Caselli. "If you look at all the work out there—the Nun Study, brain imaging, and pathology studies of apo ε4 carriers—you get the idea that little pieces of AD pathology happen throughout young adult life, but we don't see young people developing progressive dementia unless there's an autosomal dominant mutation. The fact is, we don't know whether these early changes reflect a sort of nonprogressive pathology or some basic biologic vulnerability that marks the territory of later decline."

There are plenty of theories about the possible connection between apo ε4 status and Alzheimer's pathology, Dr. Caselli said. Most focus on the pathologic function of the apo ε4 isoform. Research from the 1990s suggests that it enhances amyloid deposition, reduces neurite outgrowth and protection against oxidative stress, and cuts the efficiency of neuronal and synaptic repair. Most recently, researchers at the University of California, San Francisco, have suggested that the apo ε4 isoform can generate a cytotoxic carboxyl fragment. This truncated form of the protein is thought to induce neuronal inclusions that are similar to neurofibrillatory tangles, containing phosphorylated tau and high-molecular-weight neurofilaments (Proc. Natl. Acad. Sci. USA 2001;98:8838-43).

"The science on this is pretty well established, but whether it's key to AD pathogenesis is still undergoing further study," Dr. Caselli said. Another recently proposed connection is the relationship between apo ε4 status and the demyelination in the frontal lobe and corpus callosum, Dr. Caselli noted. These brain regions, which continue to lay down myelin until middle age, also appear most susceptible to myelin breakdown, wrote Dr. George Bartzokis, director of the UCLA Memory Disorders and Alzheimer's Disease Clinic in Los Angeles.

Dr. Bartzokis's study of 104 healthy subjects aged 75 years and younger found that those with the apo ε4 genotype had the highest level of demyelination in frontal lobe white matter and the genu of the corpus callosum. The apo ε2 genotype appeared protective of demyelination, while those who were apo ε3 positive had an intermediate level of demyelination.

The connection may be the dearth of apo ε molecules in the ε4 genotypes. Apo ε helps maintain neuronal health by degrading damaged myelin and recycling the lipids for rapid repair. Those who are apo ε2 positive have the highest number of apo ε molecules available for this constant repair process; those who are apo ε4 positive have the lowest number, while apo ε3–positive subjects have an intermediate number (Arch. Gen. Psychiatry 2006;63:63-72; Proc. Natl. Acad. Sci. USA 2006;103:5641-3). ■

Longevity After Dementia Onset Is Estimated

BY JONATHAN GARDNER
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Dementia patients live a median of 4.5 years following the estimated onset of the condition, with male, older, and disabled patients having a significantly shorter survival time, according to a population study published online in BMJ.

The large multicenter study of English and Welsh patients found that those who were aged 65-69 years at dementia onset survived a median of 10.7 years, nearly three times the 3.8 years seen in patients with disease onset at age 90 or later (BMJ 2008 Jan. 11 [Epub doi:10.1136/bmj.39433.616678.25]).

Researchers said their study provides the first estimate of survival times for dementia patients in England and Wales.

"Some of these results may seem self-evident but they answer questions asked by those caring for and advising people with dementia," wrote the researchers, led by Jing Xie, research associate with the Cambridge (England) University Institute of Public Health.

The analysis involved 13,004 patients taking part in the Medical Research Council's longitudinal cognitive function and aging study in England and Wales in 1991-2003. Participants were assessed for dementia at regular intervals. A total of 438 patients developed dementia by 2003 and were followed until Dec. 31, 2005. Of these 438 patients, 70% were women. They had a median age of 84 at dementia onset. A total of 356 dementia patients had died by the end of 2005; their median age at death was 89.

The investigators found a greater adjusted risk of death for men, compared with women (hazard ratio 1.4). In addition, disability with dementia was associated with a 3-year reduction in survival between the most and least functionally impaired. (Those who scored in the bottom third of the Blessed dementia scale had a hazard ratio for death of 2.1, compared with those in the top third.)

Hazard ratios for death were 2.7 in those aged 80-89 years at dementia onset and 3.1 in those aged 90 and older, compared with those aged 65-69.

The researchers found no difference in survival based on marital status, accommodation type (living in the community or residential home), self-reported health, score on Mini-Mental State Examination, educational status, or socioeconomic class.

In an accompanying editorial Murna Downs, Ph.D., of the University of Bradford (England) Dementia Group and Barbara Bowers, Ph.D., of the University of Wisconsin, Madison, nursing school wrote, "The study provides clear evidence that people with dementia need coordinated care and support from a range of professionals and practitioners from diagnosis to death to ensure maximum quality of life and prevent unnecessary disability and suffering" (BMJ 2008 Jan. 11 [Epub doi:10.1136/bmj.39433.616678.25]). ■