Cognition Drops Sharply at Age 60

Apo ε4 *from page 1*

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 neuropsychological test battery 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 the decline of the entire cohort in one or more domains. 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."

Seven subjects developed MCI or AD during the study; five were apo ε4 homozygotes, one was an apo ε4 heterozygote, and one was a noncarrier. "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).

The lack of sufficient myelin repair "causes a progressive disconnection of widely distributed neural networks that results in cognitive decline and contributes to the age risk factor for AD," wrote Dr. Bartzokis. This pattern of demyelination may be what scans are picking up in the Arizona cohort, Dr. Caselli said.

The theory of apo ε4's pathologic effect on neurons has had an uphill battle, he added. "It was initially met with a lot of skepticism because it had nothing obvious to do with amyloid or tau, so it didn't fit the prevailing paradigm of AD pathogenesis. It's been worked on extensively to make it fit, and as of right now, we're still not completely clear about how it does." ■

Cerebral Perfusion Is Low in Hypertensive Alzheimer's

BY PATRICE WENDLING
Chicago Bureau

Chicago — Individuals with both Alzheimer's disease and hypertension had significantly lower blood flow in multiple regions of the brain on magnetic resonance imaging, compared with their counterparts without hypertension, investigators reported in a poster at the annual meeting of the Radiological Society of North America.

In the study of 88 participants with a mean age of 83 years, brain perfusion also was significantly lower in controls with normal cognitive function and hypertension, compared with their counterparts without hypertension. A trend toward lower perfusion in individuals with mild cognitive impairment and hypertension did not achieve statistical significance.

The data are consistent with recent studies showing that Alzheimer's patients with vascular disease in general had faster progression of symptoms, Dr. Oscar L. Lopez said in an interview. In addition, multiple studies in the literature have shown that hypertension—especially in midlife—is a risk factor for Alzheimer's disease.

The same researchers also recently showed that normal subjects with hypertension had diminished cerebral blood flow in cerebral areas that are usually involved in Alzheimer's disease (Stroke 2008 Jan. 3[doi:10.1161/STROKEAHA.107.495457]). This does not mean that all individuals with hypertension will develop dementia, but in those who are destined to have Alzheimer's disease, dementia symptoms may appear earlier than in those without hypertension, said Dr. Lopez, who is a professor of neurology at the University of Pittsburgh and principal investigator in the Cardiovascular Health Study (CHS) Cognition Study.

"Both studies emphasized the importance of adequate treatment for hypertension," he said. "In cognitively normal individuals, hypertension treatment may delay the onset of the dementia, and in Alzheimer's disease patients, it may ameliorate the rate of decline."

Study participants were recruited from the ongoing CHS Cognition Study, and included 48 controls with normal cognitive function (including 10 with hypertension), 20 individuals with Alzheimer's (including 10 with hypertension), and 20 individuals with mild cognitive impairment (including 10 with hypertension). Hypertension, defined as a blood pressure greater than 140/90 mm Hg, was treated in all patients.

All participants were scanned with T1-weighted and arterial spin-labeled MRI at 1.5T. This quantitative technique uses no external contrast and uses kinetics modeling equations to compute cerebral blood flow based on MR signal intensity. Cerebral blood flow values are expressed in milliliters of blood per 100 g of tissue per minute, said lead investigator Cyrus Raji, who is a student at University of Pittsburgh, where the study was conducted. The study was funded by the National Institute on Aging, and no relevant financial conflicts of interest were disclosed.

Overall, cerebral blood flow was lowest in individuals with Alzheimer's disease and hypertension (34.8 mL per 100 g/min), compared with controls with hypertension (41.4) and those with mild cognitive impairment and hypertension (47.8).

Notably, decreased flow in Alzheimer's participants with hypertension occurred in the posterior cingulate gyrus (35.9), lateral prefrontal cortex (29.5), and left thalamus (28.9). Corresponding cerebral blood flow values were 52.3, 39.4, and 38.5 for hypertensive controls and 47.8, 36.3, and 58.1 for hypertensive participants with mild cognitive impairment (MCI).

Cerebral blood flow to the left hippocampus was reduced in participants with hypertension in the Alzheimer's (33.5), control (38.7), and MCI (47.7) groups, compared with their counterparts without hypertension (41.2, 42.4, and 57.2, respectively). This finding may have implications for Alzheimer's development, because the hippocampus is an early site of Alzheimer's pathology.

Hypertension and brain vascular disease may be major risk factors for dementia, said senior author Dr. Louis Kuller, also of the University of Pittsburgh, in an interview. "Excellent control of elevated blood pressure or prevention of hypertension, especially in 'middle ages' prior to vascular brain damage, may be the most important preventable determinant for dementia." ■