# Fitness May Limit Brain Atrophy in Alzheimer's

## *The level of fitness was strongly related to volume in the parietal area and also in the hippocampus.*

ARTICLES BY
MICHELE G. SULLIVAN
*Mid-Atlantic Bureau*

CHICAGO — Keeping fit may help reduce brain atrophy in patients with early Alzheimer's, researchers said at the International Conference on Alzheimer's Disease.

An exercise-tolerance study confirmed that the hippocampus, one of the first brain regions to be affected in Alzheimer's, was significantly larger among patients who had higher fitness levels, Dr. Jeffrey Burns said at the meeting, which was sponsored by the Alzheimer's Association.

The association was also found with whole-brain volume during a previous study in the same cohort, Dr. Burns said in an interview. "Our data suggest that those in the lower half of fitness level have four times more brain atrophy than those in the higher-fitness group, compared to normal aging," said Dr. Burns, director of the Hoglund Brain Imaging Center at the University of Kansas, Kansas City.

"Although we're a long way from proving that exercise decreases brain atrophy in Alzheimer's, this study certainly suggests that maintaining fitness has some kind of disease-specific effect."

Dr. Burns and his colleague, Robyn Honea, Ph.D., evaluated cardiorespiratory fitness in 119 subjects older than 60 years; 56 had no dementia, while 63 had early-stage Alzheimer's.

All of the subjects undertook a treadmill test, which measured peak oxygen consumption during the most strenuous part of the test. All subjects also underwent magnetic resonance imaging to determine brain volume, Dr. Burns said in an interview.

All of the Alzheimer's patients showed disease-related atrophy in the hippocampus, temporal cortex, and parietal cortices. But those patients who had higher fitness levels had significantly greater white matter volume in the hippocampus, inferior temporal gyrus, and precentral gyrus.

"We found that the level of fitness was strongly related to volume in the parietal area, and also in the hippocampus," Dr. Burns said. "That was most interesting because this is an area that's affected early in Alzheimer's, and the brain undergoes a lot of atrophy in that region as the disease progresses."

Because the measurement tool—voxel-based morphometry—only provides a linear correlation, it was not possible to characterize the percentage of volume preserved in subjects who were more fit. "But on the whole, people who were more fit had larger brains, suggesting that maintaining fitness may slow the brain atrophy process in Alzheimer's," Dr. Burns said.

Some animal studies suggest that exercise directly influences the disease process through a variety of pathways. "It may do something to the amyloid, but we also see lots of other changes in the body related to exercise. There are hormonal changes, changes in growth factors within the brain, and increased cerebral blood flow during exercise, which may increase brain vascularization."

As understanding of the relationship grows, exercise prescriptions could become part of an Alzheimer's treatment program, Dr. Burns suggested.

"We want to be able to prescribe exercise and tell people how much is effective, but we're not there yet. The best advice we can give right now is what's good for the heart is good for the brain."

The study presented at the meeting was the second study on this cohort, he added. In July, Dr. Burns and Dr. Honea published results showing that fitness positively influenced whole-brain volume in these same patients with early Alzheimer's (Neurology 2008;71:210-6).

Neither of the researchers disclosed any potential conflicts of interest. ■

# *Antihistamine May Slow Pace of Cognitive Decline in Alzheimer's*

CHICAGO — An off-the-market antihistamine previously shown to slow cognitive decline over 1 year in Alzheimer's patients continued to preserve cognition and memory during a 6-month open-label extension trial.

The drug, dimebon, also stabilized cognition in patients who started on it after taking placebo during the original trial, Dr. Jeffrey Cummings said at the International Conference on Alzheimer's Disease.

"People initially treated with placebo and then crossed over to dimebon did not show the same level of benefit as those people who took dimebon for 18 months after starting the [initial] study," said Dr. Cummings, the Augustus S. Rose Professor of Neurology at the University of California, Los Angeles. "This emphasizes the benefit of earlier treatment, and suggests the possibility that dimebon may slow the progression of Alzheimer's."

**'Open-label extensions are not the same as placebo-controlled trials, and extrapolation of the treatment results should be done with caution.'**

He pointed out, however, that the open-label extension trial can't provide definitive conclusions about any disease-modifying effects the drug might exert. "Open-label extensions are not the same as placebo-controlled trials, and extrapolation of the treatment results should be done with caution."

The original trial enrolled 183 patients with mild to moderate Alzheimer's disease at 11 sites in Russia. Patients were randomized to placebo or dimebon 20 mg three times a day.

By the end of the study, those who took dimebon actually gained about 2 points on the Alzheimer's Disease Assessment Scale-Cognition (ADAS-cog), while those taking placebo had declined almost 6 points from baseline.

Behavioral and psychiatric symptoms also were significantly improved in the active group, compared with the placebo group (Lancet 2008;372:207-15).

All 120 patients who completed the 12-month trial were offered the chance to continue for 6 more months in the open-label extension. Most (54 dimebon, 50 placebo) elected to enroll; of these 104, 92 (88%) completed the study.

Patients who completed a full 18 months of dimebon continued to show benefit on ADAS-cog and measures of behavioral and psychiatric symptoms. While there was a decline from the mean 12-month cognitive status, by 18 months cognition and memory were not significantly worse than they were at baseline. A similar pattern emerged in behavior and psychiatric symptoms.

Former placebo patients who crossed over to dimebon showed a cessation of their placebo-related decline, with a mean ADAS-cog score that stabilized at the 12-month crossover level.

The drug was well tolerated in both studies. Adverse events that were significantly more common among dimebon patients included dry mouth and depressed mood.

The drug's method of action is not fully understood, Dr. Cummings said. Dimebon had been used in Russia as a general antihistamine, but was withdrawn from the market when selective agents became available. Researchers discovered some potentially neuroprotective effects in the late 1990s; the drug may also have benefit in Huntington's disease.

Studies suggest that dimebon improves impaired mitochondrial function, which may prevent neuronal death and increase synaptic number and signalling, Dr. Cummings said at the meeting, which was sponsored by the Alzheimer's Association.

Dr. Cummings disclosed that he is a consultant for Medivation Inc., the San Francisco–based company that provided the dimebon for the study. ■

# Marital Status at Midlife Linked to Alzheimer's Risk Later

CHICAGO — People who are married from mid- to late life are significantly less likely to develop Alzheimer's disease, while those who remain single face up to an eightfold increased risk, Krister Hakansson said at the International Conference on Alzheimer's Disease.

The protective benefit is probably related to the mental stimulation of living as a couple, said Mr. Hakansson, who is a researcher at the Karolinska Institute in Stockholm.

"Living in a couple relationship is normally one of the most intense forms of social and intellectual stimulation. If social and cognitive challenges can protect against dementia, so should living as a couple," he said.

The population-based study used data collected in the Finnish Cardiovascular Risk Factors, Aging, and Dementia study. Baseline data were captured from 1972 to 1987. In 1998, follow-up interviews were conducted with 1,500 (72%) of the participants. The average follow-up period was 21 years.

Mr. Hakansson examined data on 1,432 of the follow-up subjects to assess the association of marital status to dementias. In 1998, 832 subjects were married or had live-in partners, 100 were lifelong singles, 111 were single after a separation or divorce, and 389 were single after having been widowed. At follow-up, mild cognitive impairment (MCI) was present in 82 subjects, and Alzheimer's in 48.

Those who were single during midlife were twice as likely to develop cognitive impairment or Alzheimer's as were those who had been married during midlife—a significant difference.

Those who remained single throughout follow-up were even more likely to develop the disorders. Their risk for both MCI and Alzheimer's was three times greater than the risk for those who had a partner from midlife to late life.

The highest risk occurred in those who were widowed in midlife and never remarried. The subjects were three times more likely to develop MCI and almost eight times more likely to develop Alzheimer's.

The results were even more striking when Mr. Hakansson broke down the study group by Apo E4 status. Noncarriers who were divorced or widowed from mid- to late life had a tripling of Alzheimer's risk compared with married noncarriers. But carriers who were divorced or widowed in midlife and never remarried were 25 times more likely to develop Alzheimer's than were carriers with partners.

"A 'socio-genetic' disease model may explain the dramatic Alzheimer's risk increase for the widowed and the Apo E4 interaction effect," Mr. Hakansson said. The conference was presented by the Alzheimer's Association. ■