Insulin Tied to Decreased Brain Plaques in AD

ARTICLES BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

CHICAGO — A postmortem analysis of subjects with both Alzheimer's disease and diabetes found up to 80% fewer amyloid beta plaques in the brains of those who took both insulin and oral diabetic medication while alive.

The finding might shed some light on a discrepancy that has puzzled Alzheimer's researchers: Epidemiologic studies confirm a significantly increased risk of Alzheimer's and other dementias among subjects with diabetes, but their brains generally appear less physically ravaged by the disease, Michal Schnaider Beeri, Ph.D., said at the International Conference on Alzheimer's Disease.

"It appears that medication might be one explanation for this apparent discrepancy between epidemiologic and neuropathology studies," said Dr. Beeri of the Mount Sinai School of Medicine, New York. "It also suggests that diabetes medications may beneficially influence neurologic pathways involving Aβ [amyloid beta] processing and Aβ-related brain lesions."

The study involved 148 brains from the Mount Sinai School of Medicine Brain Bank. All were from subjects with Alzheimer's disease, half of whom also had diabetes. The subjects were matched for age (mean age 81 years), sex (57% female), and dementia severity (mean clinical dementia rating score 2.4).

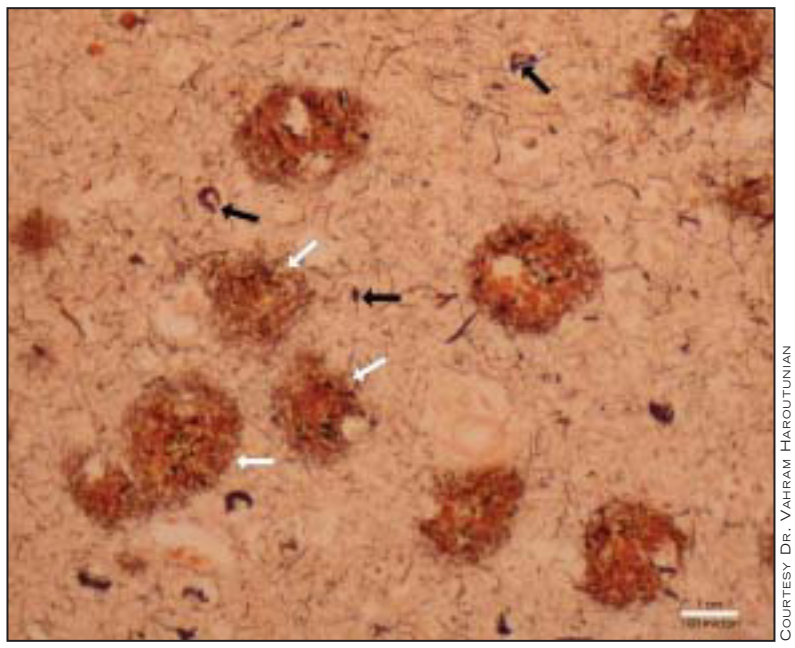
Dr. Beeri and her colleagues divided the subjects into categories according to the use of diabetic medications. Of the 124 subjects with diabetes, 49 were taking insulin only, 28 were taking oral diabetes medications only, 18 were taking a combination of agents, and 29 were on no medications. All of these groups were compared against one another, and against the subjects without diabetes.

No significant associations were seen between medication and the presence of tau neurofibrillary tangles. But they found a very strong interaction between medication and $A\beta_{42}$ plaques in the entorhinal cortex, hippocampus, and amygdala.

Plaque presence was rated from 0 (none) to 2 (severe). Subjects without diabetes had a rating of about 1.5, as did those with diabetes who were taking only oral medications. Subjects with diabetes who took no diabetes medications had a rating of about 1.25. Subjects taking insulin had a lower, but not significantly lower, plaque rating (1, considered sparse), compared with those without diabetes, those with diabetes who were not taking medications, and those who took only oral agents, Dr. Beeri said.

The largest differences were found between subjects on combination therapy (insulin and oral medications) and those who took only oral agents and subjects without diabetes. Combination therapy subjects had a plaque rating of about 0.25, or 80% lower than in the subjects in the other two groups. Those who had taken combination therapy also had far fewer plaques than did those who took no medications, as well as those who took only insulin, she said.

"The results of this study suggest that combination of insulin with other diabetes medication is associated with a substantial reduction in brain neuritic plaque density consistent with the effects of both on the neurobiology of insulin," Dr. Beeri said at the meeting, presented by the Alzheimer's Association. "Insulin and insulin sensitizers (oral hypoglycemics) are designed to target organs at the periphery, but they also seem to have also an effect on the brain. This suggests the possibility of therapeutic targeting of insulin signaling pathways of the brain for the reduction of Aβ-associated neuropathology of Alzheimer's." ■



COURTESY DR. VAHRAM HAROUTUNIAN

Brains exposed to both insulin and oral hypoglycemic drugs showed fewer amyloid plaques (white arrows) than those of without diabetes, but no fewer neurofibrillary tangles (black arrows).

Experimental Drug That Targets Tau May Aid Memory in Dementia

CHICAGO — An experimental drug designed to attack neurofibrillary tau tangles significantly improved some measures of memory among patients with mild cognitive impairment, although it failed to meet its primary cognitive end point.

Because of its significant effects on visual and verbal memory, AL-108 will continue on to a phase II trial in its target population, patients with mild to moderate Alzheimer's disease, Dr. Donald E. Schmechel said at a press conference during the International Conference on Alzheimer's Disease.

"Twelve weeks of AL-108 resulted in statistically significant, dose-dependent, and durable improvement on measures of short-term memory, including visual, verbal, and auditory working memory, which is a type of memory function that deteriorates throughout the progression of Alzheimer's," according to Dr. Schmechel. "This makes AL-108 the first drug to validate in humans the importance of the tangle, or tau, pathway in the disease."

Along with toxic plaques made up of amyloid beta, neurofibrillary tau tangles are a diagnostic hallmark of Alzheimer's disease. The tangles are composed of hyperphosphorylated tau, a protein that normally occurs in neurons. In its hyperphosphorylated state, tau forms tangled fibrils that interfere with neuronal function. AL-108, developed by Allon Therapeutics Inc. of Vancouver, is the first drug in development to exert action on those tangles.

Many more Alzheimer's drugs under investigation target the amyloid pathway of neurodegeneration. Dr. Schmechel, whose research was funded by Allon, said AL-108's success shows that tangles also can be a useful therapeutic target. "These new data suggest that 'tangles' may be as important—or perhaps more important—than 'plaques,' " he said.

The phase IIa study comprised 144 patients (mean age 69 years) with amnestic mild cognitive impairment. All patients had a Mini-Mental State Examination of at least 24.

The patients were divided into three groups: placebo, 5 mg AL-108 daily, and 15 mg AL-108 twice daily. The drug was administered for 12 weeks; cognition was tested at baseline and at weeks 4, 8, 12, and 16.

The drug was safe and well tolerated, Dr. Schmechel said at the meeting presented by the Alzheimer's Association. The dropout rate was 13% and not different between the active and placebo groups. Compliance was high (98%).

The study's primary end point was a composite of memory component scores from four standard cognitive tests. By 16 weeks, neither of the active groups scored significantly better than the placebo group on this measure.

However, those taking the higher dose showed a trend toward better performance than either the low-dose or placebo groups, noted Dr. Schmechel, professor of neurology at Duke University, Durham, N.C.

Significant differences emerged on some of the individual measures of memory. On the digit span forward test—a measure of verbal recall and short-term memory—the high-dose group performed significantly better than either the low-dose or placebo groups, with a 12% increase over baseline. ■

Investigational Antibody May Dissolve Plaques

CHICAGO — An investigational monoclonal antibody may dissolve amyloid brain plaques in patients with Alzheimer's disease, although patients receiving the vaccine did not show any signs of improved cognition during a 12-week randomized, placebo-controlled trial.

Dr. Eric Siemers, who presented the data from the trial, which was sponsored by Eli Lilly & Co., at the International Conference on Alzheimer's Disease, said the lack of cognitive improvements didn't trouble him. The phase II study was primarily intended as a safety, tolerability, and dosing trial, with cognition a secondary end point; the 12-week period was probably too short to show any cognitive changes that the antibody might induce, said Dr. Siemers, medical director of Lilly' s Alzheimer's Disease Research Team.

Importantly, the vaccine (LY2062430) was safe for the Alzheimer's patients and healthy volunteers who received it. There were no infusion reactions or drug-related adverse events, including meningoencephalitis, microhemorrhage, or edema.

The study comprised 52 patients with mild-moderate Alzheimer's (mean Mini-Mental State Exam score 20), and 16 healthy volunteers. Patients were randomized to placebo or to one of four antibody infusion dosages: 100 mg every 4 weeks, 100 mg every week, 400 mg every 4 weeks, or 400 mg every week. Volunteers got just a single 100-mg dose.

All study participants underwent magnetic resonance imaging and blood and cerebrospinal fluid (CSF) sampling to determine the level of soluble amyloid β. A subgroup of 24 patients and 13 volunteers also underwent single-photon emission computed tomography (SPECT) to determine cortical amyloid plaque load. Cognitive status was assessed by the Alzheimer's Disease Assessment Scale–Cognition (ADAS-cog).

CSF and blood samples showed that the antibody affected levels of both $A\beta_{40}$ (a less-neurotoxic protein) and $A\beta_{42}$ (the toxic form found in Alzheimer's brain plaques) in a dose-dependent manner. Patients taking the 400-mg/week dose had a significant decrease in $A\beta_{40}$ in the CSF, but a significant increase in $A\beta_{42}$, which suggests that the brain plaques were dissolving, Dr. Siemers said.

A phase III trial of the antibody is set to begin in 2009, Dr. Siemers said at the meeting sponsored by the Alzheimer's Association. ■