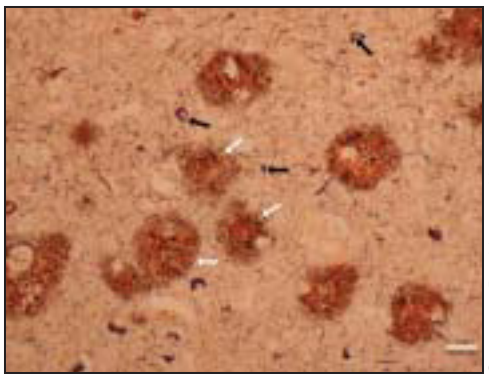

Courtesy Dr. Vahram Haroutunian

Brains of patients taking both insulin and oral hypoglycemic drugs had fewer plaques (white arrows) than those of nondiabetics, but equal neurofibrillary tangles (black).

Insulin Tied to Fewer Plaques in AD

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 β 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: Although epidemiological studies confirm a significantly increased risk of Alzheimer's and other dementias in subjects with diabetes, their brains generally appear less physically ravaged by the disease, Michal Schnaider Beeri, Ph.D., said at the International Conference on Alzheimer's Disease.

"Medication might be one explanation for this apparent discrepancy between [epidemiological] and neuropathology studies," said Dr. Beeri of the Mount Sinai School of Medicine, New York.

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 according to use of diabetic medications. Of the 124 subjects with diabetes, 49 were on insulin only, 28 were on oral diabetes medications only, 18 were on a combination of agents, and 29 weren't on medications. The groups were compared with each other and with those without diabetes.

The researchers saw no significant links between medication and the presence of tau neurofibrillary tangles. But they found a strong interaction between medication and amyloid β_{42} plaques—a diagnostic hallmark of Alzheimer's—in the hippocampus, amygdala, and entorhinal cortex.

The link between diabetes drugs (like insulin) and fewer plaques echos the effects of both on insulin neurobiology.

DR. BEERI

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. Diabetics 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, diabetics not on medications, and those on only oral agents, Dr. Beeri said.

The largest differences were 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 ratings for subjects in the other two groups. Those who had taken combination therapy also had significantly fewer plaques than did those who took no medications, as well as those who took only insulin.

These relationships remained significant even after controlling for age at death, sex, dementia severity, fasting glucose level at last admission, and apo E4 status. There were no significant changes when subjects with other comorbidities were excluded.

"The results suggest insulin combined 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, which was presented by the Alzheimer's Association. "Insulin and insulin sensitizers (oral hypoglycemics) target organs at the periphery but also seem to have an effect on the brain, [suggesting] the possibility of therapeutic targeting of insulin signaling pathways of the brain for reducing amyloid β–associated neuropathology of Alzheimer's." ■