Diabetes-Related Alzheimer's Set to Increase

BY MICHELE G. SULLIVAN

VIENNA — The rising tides of Alzheimer's disease and obesity could join in the next 40 years to create a flood of dementia associated with type 2 diabetes.

The outlook may be dire, researchers said at the International Conference on Alzheimer's Disease. If the trends in child and adolescent obesity continue unabated, by 2040 one-third of the 81 million expected Alzheimer's cases worldwide may be a direct result of obesity-driven diabetes, Mary Haan, Ph.D., said at the meeting.

"We need to identify the contributions to this increase in dementia and figure out how to decrease this burden," Dr. Haan said. "In the setting of diabetes and Alzheimer's, this means we need to think about intervening earlier in the process and treating across the life span. Our focus should be prevention, which is probably more effective when begun at younger ages."

Dr. Haan is the primary investigator on the Sacramento Area Latino Study on Aging (SALSA), a prospective cohort study that has been ongoing since 1997. SALSA consists entirely of Mexican Americans, whose high rates of type 2 diabetes, metabolic syndrome, and hypertension create an ideal population in which to study the impact of these disorders on cognition.

At the meeting, Dr. Haan of the University of California, San Francisco, presented 9 years of follow-up data on this group of 1,789 men and women (mean baseline age 72 years). At study entrance, 33% of the group had type 2 diabetes and 40% had a body mass index of more than 25 kg/m^2. More than half had metabolic syndrome.

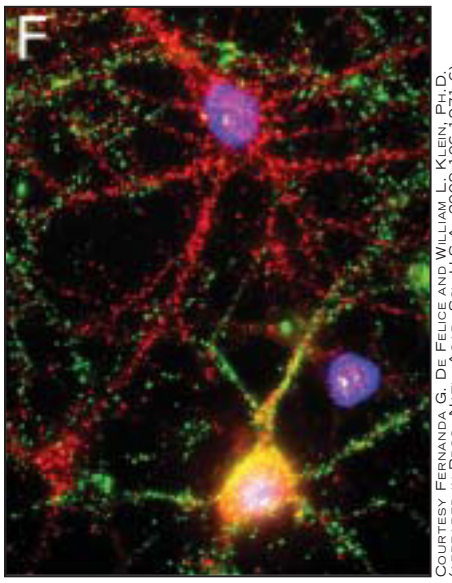
Over 9 years, 158 incident cases of dementia or nondementia cognitive impairment developed. After controlling for age, gender, girth, diabetes treatment, fasting insulin, and C-reactive protein, Dr. Haan said the presence of diabetes at baseline more than doubled the risk of dementia or cognitive impairment. "This translates into a population attributable risk of 19%," she said. "Nineteen percent of all these dementia cases were the direct result of type 2 diabetes."

When carried forward in accordance with projected increases in obesity, the 19% figure means that by 2040, 24 million cases of dementia could be directly tied to type 2 diabetes, she said. However, "there are no randomized controlled trials that support the notion that we should be treating [cognitive impairment] with an antidiabetic drug," she said. Instead, the most effective method is probably to prevent obesity and insulin resistance—the two factors that most strongly influence the development of diabetes.

Suzanne Craft, Ph.D., agreed. "The concern is this current epidemic of diabetes associated with insulin resistance, in conjunction with a rapidly aging population, foreshadows an epidemic of Alzheimer's." And although it makes sense to investigate the impact that diabetes treatment might have on cognition, an incredibly effective intervention already exists.

"Exercise is the most potent insulin-sensitizing agent we have," said Dr. Craft, a geriatrician and Alzheimer's researcher at the Veterans Administration Puget Sound Health Care System, Seattle. "A single bout of aerobic exercise improves insulin sensitivity for 24 hours. It's much more potent than any medication. Caloric restriction also lowers hyperinsulinemia and improves insulin sensitivity."

A large body of work now suggests that insulin resistance increases the risk of Alzheimer's by multiple mechanisms, Dr. Craft said. Far from being active only in the periphery, insulin readily crosses the blood-brain barrier and binds to receptors located throughout the brain. Once in the brain, insulin interacts with amyloid beta in several ways, increasing its intracellular clearance through insulin degrading enzyme and apparently even protecting neurons from the protein's toxic effects.



COURTESY FERNANDA G. DE FELICE AND WILLIAM L. KLEIN, PH.D. (APPEARED IN PROC. NATL. ACAD. SCI. U.S.A. 2009;106:1971-6)

Memory loss in Alzheimer's may be tied to loss of insulin receptors (red).

"This has been known for some time, but recent research has shown that amyloid beta may have its own independent effects on insulin signaling," Dr. Craft said. A series of experiments by William L. Klein, Ph.D., concluded that soluble oligomers of amyloid beta can remove insulin receptors from the dendritic plasma membranes of hippocampal neurons. The study concluded that insulin receptor signaling downregulated the oligomeric binding sites. The addition of rosiglitazone potentiated this effect, suggesting that insulin-sensitizing agents may have some role in cognitive protection (Proc. Natl. Acad. Sci. U.S.A. 2009;106:1971-6).

"Insulin appears to mitigate many of the negative effects of amyloid and regulates its clearance, while beta amyloid appears to reduce insulin signaling. So high levels of insulin in the brain can induce a brain insulin-resistance by removing the insulin receptors from the nerve cell membranes," Dr. Craft said.

She recently investigated insulin's effect on memory in a group of 33 patients with Alzheimer's or mild cognitive impairment and 59 elderly controls. The patients received placebo or five escalating doses of intranasal insulin, which travels directly into the central nervous system along the olfactory and trigeminal vasculature. Cognition was tested 15 minutes after each treatment. "We saw a 50% improvement in memory compared to baseline with the highest dose," Dr. Craft said (J. Alz. Dis. 2008;13:323-31).

Insulin also affects vascular function in the brain. "It's very well known that insulin resistance is accompanied by peripheral vascular dysfunction, but the understanding that this may also manifest in the brain is very new and potentially important."

In insulin resistance, there is a downregulation of the phosphoinositide-3 (PI3) kinase pathway, which mediates vascular relaxation. But the mitogen-activated protein (MAP) kinase pathway, which mediates vasoconstriction, is driven by high levels of insulin and does not downregulate with insulin resistance. "You get a reduction in vasodilation and hyperactivation of vasoconstriction," Dr. Craft said. "This imbalance is thought to underlie many of the vascular dysfunctions associated with insulin resistance."

She saw this in a recent study of 196 brains (71 with dementia). The brains were divided into four groups: normal, diabetic without dementia, diabetic with dementia, and dementia without diabetes (Arch. Neuro. 2009;66:315-22).

"We saw a surprising pattern when we looked at plaques and tangles: The brains of the patients with dementia but no diabetes had a high load, as anticipated, but the brains of diabetic patients with dementia had a plaque load that was similar to the normal controls."

The patients with both dementia and diabetes did, however, show high levels of microvascular lesions, which were absent in the other groups. "The volume of the lesions is small, so they are almost certainly not directly responsible for the cognitive impairment, but this finding may point to some broader based vascular dysfunction," Dr. Craft said. ■

Prediabetes Associated With Accelerated Brain Aging

BY MICHELE G. SULLIVAN

VIENNA — Markers of metabolic dysfunction are associated with changes in brain volume and cognition, suggesting that these prediabetic conditions accelerate brain aging, according to researchers who undertook a study of more than 2,000 subjects.

Subjects with these markers—hyperinsulinemia, hyperglycemia, and insulin resistance—had decreased total cerebral volume equivalent to 6 years' worth of structural brain aging, Dr. Zaldy S. Tan said at the International Conference on Alzheimer's Disease.

"These changes were seen even among nondiabetics," said Dr. Tan, suggesting that metabolic dysregulation might affect the brain long before diabetes becomes clinically apparent.

Dr. Tan, of Harvard Medical School, Boston, and his colleagues based the study on data extracted from the Framingham Heart Study Offspring Cohort. This group consists of 5,124 men and women who are the children of the original Framingham cohort. They have undergone up to eight examinations since their cohort was established in 1975; exams are conducted every 4-6 years.

Dr. Tan and his colleagues focused on 2,518 participants who had attended the seventh examination cycle, were free of stroke and clinical dementia, and had undergone volumetric brain MRI and cognitive testing. Their mean age was 63 years; 269 had diabetes.

The researchers correlated MRI and cognitive measures with diabetes, fasting glucose levels, hemoglobin A_{1c}, fasting insulin, and homeostatic model assessment–estimated insulin resistance (HOMA-IR). The models controlled for age, sex, education, stroke risk factors, ApoE4 status, and homocysteine, C-reactive protein, and interleukin-6 levels.

No correlates were found between metabolic dysfunction and hippocampal volume, but total cerebral brain volume was inversely correlated with diabetes, HbA_{1c}, fasting insulin level, and insulin resistance. "These changes were equivalent to 6 years of structural brain aging, and persisted even among those without diabetes," Dr. Tan said.

He also found an inverse correlation between executive function and diabetes, fasting glucose, HbA_{1c}, fasting insulin level, and insulin resistance, in patients with and without diabetes.

Visual memory was inversely related to fasting insulin and insulin resistance, but there were no significant relationships between measures of metabolic dysfunction and verbal memory.

Two proposed mechanisms account for the association of diabetes and structural brain volume. Diabetes is a known vascular risk factor and might induce cerebrovascular brain injury, and eventual structural and cognitive brain aging. But even before diabetes arises, altered insulin levels in the brain also might exert a negative effect.

The conference was sponsored by the Alzheimer's Association. ■