Insulin Resistance Predicted Early Alzheimer's

BY MARY ANN MOON

FROM THE ARCHIVES OF NEUROLOGY

Insulin resistance in cognitively normal subjects is associated with a pattern of reduced regional cerebral glucose metabolism that is characteristic of mild cognitive impairment and early Alzheimer's disease, according to a study published online Sept. 13.

On PET scanning, subjects with insulin resistance also showed an unusual activation pattern in the brain during a memory encoding task. This coincided with their poorer performance in recalling words, compared with healthy adults who were not insulin resistant.

"Taken together, these results suggest that increased insulin resistance may be a marker of AD [Alzheimer's disease] risk that is associated with reduced regional cerebral glucose metabolism and subtle cognitive impairments at the earliest stage of disease, even before the onset of MCI [mild cognitive impairment]," wrote Laura D. Baker, Ph.D., of the Veterans Affairs Puget Sound Health Care System and the University of Washington, Seattle, and her associates.

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Major Finding: Insulin-resistant adults with newly diagnosed prediabetes or type 2 diabetes showed reduced glucose metabolism in brain regions known to be similarly affected in mild cognitive impairment and early AD. They also showed an aberrant pattern of cerebral activation during a memory-encoding task and had poorer recall, compared with subjects who were not insulin resistant.

Data Source: A study of fluorodeoxyglucose PET scans in 23 subjects with insulin resistance and 6 healthy controls matched for age and education level.

Disclosures: The study was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases and by the U.S. Department of Veterans Affairs. The investigators reported no financial conflicts of interest.

Since insulin resistance is known to cause type 2 diabetes and to raise the risk of Alzheimer's disease, Dr. Baker and her colleagues tested the hypothesis that cognitively normal adults with newly diagnosed prediabetes or type 2 diabetes and insulin resistance would already show abnormal cerebral glucose metabolism in regions known to predict susceptibility to AD.

The study subjects were adults with newly diagnosed, as-yet untreated prediabetes (11 patients) or type 2 diabetes (12 patients) – all of whom had insulin resistance – as well as a control group of 6 adults matched for age and education level who had normal glucose values and no insulin resistance. The subjects underwent PET imaging in a resting state and during a 35-minute memory-encoding task, and were tested for delayed free recall after the scanning was completed.

Insulin resistance was associated with reduced glucose metabolism in the posterior cingulate cortex, precuneus region, parietal cortices, temporal/angular gyri, and anterior and inferior prefrontal cortices. In contrast, no such impairment was seen in the control subjects.

"This pattern of hypometabolism has also been observed in patients with MCI and AD, in middle-aged carriers of the APOE e4 genetic risk factor who do not have dementia, and in presymptomatic adults with the AD-causative presenilin-1 gene," Dr. Baker and her colleagues wrote (Arch. Neurol. 2010 [doi:10.1001/archneurol.2010.225]).

The link between insulin resistance and reduced glucose metabolism was not affected by age, fasting glucose values obtained just before PET scanning, degree of hyperglycemia after oral glucose tolerance testing, or APOE e4 allele status.

In addition, patients with insulin resistance showed a diffuse rather than a more focused pattern of brain activation during the memory encoding task, including activation of areas adjacent to the regions that were activated in the control group. They also showed activation or hyperactivation of areas "not typically engaged in a cognitive task," a finding that has been reported in patients with prodromal or early AD and nonsymptomatic carriers of the APOE e4 allele. This pattern may represent "a compensatory mechanism invoked following dysfunction of the neuroarchitectural network that typically would support a cognitive task," the researchers noted.

Although the insulin-resistant subjects were not cognitively impaired according to current criteria, their recall ability was poorer than that of the control group in the postscanning test. ■

Amyloid Therapies for Alzheimer's May Also Untangle Tau

BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE

HONOLULU – Reearchers are making small steps toward untangling the mysteries of tau – the protein that twists around neurons and destroys cognitive ability in Alzheimer's disease.

The beta amyloid protein, which forms the sticky brain plaques characteristic of the disease, is now considered the "upstream" lesion of Alzheimer's – a prodromal manifestation that appears before the onset of symptoms. The neurofibrillary tangles of phosphorylated tau that appear in both the neuronal cell bodies and dendritic spines occur later and directly correlate with cognitive decline.

In several studies presented at the meeting, which was sponsored by the Alzheimer's Association, scientists gave tantalizing clues to the connection between beta amyloid (Abeta) and tau, and the possible effects of untangling tau's destructive web with immunotherapy.

"Importantly, these studies teach us more not only about tau-targeted therapies, but also about the progression of Alzheimer's disease," William Thies, Ph.D., said at a press briefing on the studies. "It may be that amyloid changes in the brain happen early in the disease and the tau-related changes happen 'downstream,' where they have a more direct effect on cognitive function," said Dr. Thies, chief medical and scientific officer of the Alzheimer's Association.

Dr. Kaj Blennow of the University of Gothenburg (Sweden), discussed a pooled analysis of data collected from two randomized, placebo-controlled studies of bapineuzumab (Janssen and Pfizer Inc.), an antibody to Abeta plaques. The drug is in phase III trials. It induces anti-Abeta antibodies, which have been shown to reduce Abeta plaques.

The subgroup analysis consisted of 46 Alzheimer's patients who were enrolled in either Study 201 (United States) or Study 202 (United Kingdom and Finland). Of these patients, 27 received bapineuzumab and 19 received placebo.

In Study 201, the active group showed a nonsignificant decrease in phosphorylated tau – the kind associated with neuronal death – in cerebrospinal fluid, compared with the control group. In study 202, there were no tau-related treatment effects. When the data were combined, however, Dr. Blennow and his colleagues found a significantly greater decrease in phosphorylated tau in bapineuzumab-treated patients, compared with placebo-treated patients (–9.5 picograms/mL vs. –0.5 picograms/mL). In the pooled data, Dr. Blennow also found a trend toward a decrease in total CSF tau in the active group, compared with the control group.

"These observations suggest that immunotherapy targeting amyloid may also alter neurodegenerative processes that occur later in the disease process and that are more directly associated with loss of function," Dr. Blennow said at the briefing.

Delphine Boche, Ph.D., of the University of Southampton (England), studied the tau effects of another Abeta immunotherapy agent called AN1792, which was pulled from development in 2002 after 6% of the patients who received it developed serious brain inflammation and subsequent brain atrophy.

A number of the patients in the AN1792 trial have since died. Researchers continue to examine their brains to discover other effects of the vaccine, which was designed to reduce brain plaques. Dr. Boche compared samples from the brains of 10 immunized Alzheimer's patients with samples from the brains of 28 nonimmunized patients.

Dr. Boche and her team quantified Abeta-42 – the plaque-forming length of the Abeta peptide – and phosphorylated tau in six brain areas affected by Alzheimer's pathology: the superior and middle temporal gyrus, medial frontal gyrus, inferior parietal lobule, entorhinal cortex, and subiculum and CA1 regions of the hippocampus.

The researchers found that immunized brains had a significantly lower percentage of cerebral cortex covered by Abeta plaque than did the nonimmunized brains (1.4% vs. 5.25%). There was also a significantly lower load of phosphorylated tau in immunized patients in the same regions (0.72% vs. 1.08%).

Dr. Boche also examined neurons to determine whether the tau changes were intra- or extracellular. "The load was significantly lower in the fine dendritic branches compared with the neuron body," she said. "When the Abeta was removed, the dystrophic neurites also disappeared. But there was no significant difference in the level of tau within the nerve body."

Unfortunately, the physiologic changes did not translate into any clinical benefit. "All the vaccinated patients [who are still alive] are still deteriorating despite the treatment," she said.

The final study examined the effect of an active tau immunotherapy on mice engineered to develop neurofibrillary tau tangles. Allal Boutajangout, Ph.D., of New York University, New York, and his colleagues used a monoclonal antibody called PHF1, which recognizes and attacks phosphorylated tau.

Mice that were 2-3 months old received 13 peritoneal injections of the antibody or 13 injections of mouse immunoglobulin G. At 5-6 months old, their behavior was assessed and then they were sacrificed for brain pathology.

The treated mice performed significantly better than the controls on a task that examined balance, general motor coordination, and functional integration. Their brains also showed 58% less tau pathology in the dentate gyrus of the hippocampus—an area important in memory.

Dr. Blennow's study was supported by Janssen Alzheimer Immunotherapy. Dr. Blennow had no relevant financial disclosures, but several of his coauthors are employees of Janssen, Pfizer, or Elan Pharmaceuticals, and own stock in the companies. Dr. Boche's study was sponsored by the Alzheimer's Research Trust; she and her coauthors reported having no financial disclosures. Dr. Boutajangout's study was sponsored by the Alzheimer's Association and Applied Neurosciences. Neither he nor his coauthors reported having any financial conflicts. ■