New Lesion Found in Alzheimer Brains

In 1906, Alois Alzheimer stood before psychiatrists in Germany and described his studies of a 51-year-old woman who would make his name tragically famous. The woman had had severe memory problems before her death, and when Alzheimer autopsied her brain, he found it riddled with two kinds of lesions: plaques, which are extracellular deposits of a protein fragment now called beta-amyloid, and tangles, intracellular clumps of a protein now known as tau.

These plaques and tangles, observable only in autopsies, currently serve as the only definitive diagnostic markers for Alzheimer's disease, the memory-robbing neurodegenerative disease that afflicts millions of elderly people.

A research group, however, now suggests that Alzheimer missed an equally common brain lesion, as have thousands of scientists since who have examined the brains of people with Alzheimer's disease.

In addition to plaques and tangles, the brains of Alzheimer's patients contain extensive extracellular deposits of a still unnamed protein, Marie L. Schmidt of the University of Pennsylvania School of Medicine in Philadelphia and her colleagues report in the July AMERICAN JOURNAL OF PATHOLOGY.

In shape and size, the new lesions, labeled AMY plaques, often resemble the disease's characteristic amyloid plaques, and they almost never appear in brains devoid of the amyloid plaques.

"When you find amyloid, you seem to find AMY nearby," says study coauthor Virginia M.-Y. Lee. Yet the new lesions are distinct from the amyloid plaques, rarely overlapping in the brain, the investigators report.

Schmidt *et al.*/AMERICAN JOURNAL OF PATHOLOGY

Brain tissue of Alzheimer's disease patient contains amyloid plaques (red) and newly discovered protein deposits (green).

The discovery of AMY plaques was accidental. Having generated antibodies to the components of tangles, Lee and her colleagues unexpectedly found that four of the antibodies did not recognize tau but instead bound to a protein apparently contaminating the tangles.

The researchers then used one of these antibodies to study brains of people who had had typical Alzheimer's disease. In all 32 brains examined, the antibody revealed AMY plaques. Like amyloid plaques, AMY plaques also appeared in the brains of people who had Down's syndrome. Yet in elderly people without dementia, including those with schizophrenia and other neurological diseases, AMY plaques were rare or absent.

How did AMY plaques remain invisible for nearly a century? Lee notes that the traditional dyes used by pathologists do not highlight these brain lesions.

Researchers hope to quickly purify the protein in AMY plaques and identify the gene encoding it. Lee speculates that mutations in that gene may trigger some Alzheimer's disease, much as mutations in the gene for beta-amyloid's precursor protein can.

Instead of causing brain cell death, however, the AMY plaques may merely appear as a byproduct of the destruction that occurs in the disease. Similar debates about tangles and amyloid plaques still rage on.

"Let's not talk about this as a breakthrough yet," cautions Donald L. Price, a neuropathologist at John Hopkins Medical Institutions in Baltimore. *—J. Travis*

Panel urges widespread testing for diabetes

For the first time, an expert committee convened by the American Diabetes Association (ADA) advises that all people age 45 and older get tested for Type 2 diabetes, the more common form of the blood sugar disorder.

If adopted, the change could lead to the identification of millions of people who had no idea they were suffering from this disease. An estimated 15 million people in the United States have adult-onset diabetes, but only about half are aware of their condition. The remainder suffer from vague symptoms or no symptoms at all, yet they may have damaging concentrations of sugar in the bloodstream.

Research has shown that people with Type 2 diabetes typically are diagnosed only after having had the disorder for 7 years. Type 1 diabetes, which usually strikes children and adolescents, can also go undiagnosed for years. A common symptom of both conditions is excessive thirst.

The panel of 17 experts also advises a change in the standard used to diagnose diabetes. Under the proposed guidelines, people with a blood sugar concentration of at least 126 milligrams per deciliter (mg/dl) of blood would be considered diabetic. Under the old standard of 140 mg/dl, as many as 20 percent of newly diagnosed diabetics have already sustained injury to their eyes or kidneys. Untreated, such damage can lead to blindness or kidney failure.

Earlier diagnosis of the disease should prevent or delay such complications, says panel chair James R. Gavin III, the senior scientific officer at the Howard Hughes Medical Institute in Chevy Chase, Md.

"We feel passionately that people need to take diabetes more seriously," Gavin says. "It's a disease that is completely treatable." Type 2 diabetics often control their blood sugar concentrations with diet and regular exercise, he says. In other cases, they must take insulin or other drugs to combat the disease. Type 1 diabetics take daily shots of insulin.

For adults who get good news after a diabetes test, the panel recommends continued vigilance. It says such people should repeat the test every 3 years. That course of action will prevent hidden damage from accumulating if excessive blood sugar concentrations subsequently develop, the panal predicts.

For adults who are at high risk of developing diabetes, the group opts for a more aggressive course of action, recommending a diabetes test before age 45 and at yearly intervals thereafter. Risk factors for Type 2 diabetes include a family history of the disorder, obesity, and uncontrolled high blood pressure, the panel notes.

"We urge that the [panel's guidelines] be widely disseminated and implemented," comments Richard C. Eastman of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Md. The federal Centers for Disease Control and Prevention in Atlanta and the American Diabetes Association (ADA) in Alexandria, Va., have also endorsed the panel's report.

The panel announced the new guidelines June 23 at the 57th Annual Scientific Sessions of the ADA held in Boston. A detailed report written by the panel appears in the July DIABETES CARE. *—K. A. Fackelmann*