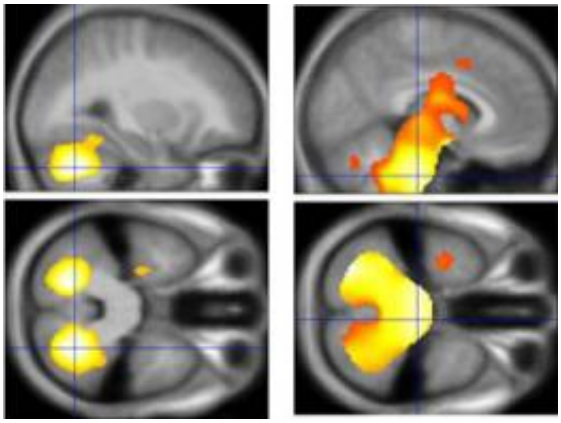
Brain abnormalities seen in children with severe form of diabetes

July 12 2012, By Jim Dryden



Brain scans identified regions of significantly reduced gray matter (right column) and white matter (left column) in young people with Wolfram syndrome. The brainstem and the cerebellum were particularly affected. (TAMARA HERSHEY, PHD)

(Medical Xpress) -- Children with a rare syndrome that includes a form of insulin-dependent diabetes have brain abnormalities that appear to set the stage for cognitive problems later in life, according to new research at Washington University School of Medicine in St. Louis.

The scientists studied children with Wolfram syndrome, which causes insulin-dependent diabetes in childhood. The disorder also causes hearing and vision loss and kidney problems. As patients get older, they can develop cognitive difficulties and dementia, and more than half die

before their 30th birthday.

Earlier case studies had used imaging to identify brain abnormalities, but scientists had assumed those changes occurred late in the disease process when Wolfram's patients got older. The new findings suggest, however, that some changes in the brain occur early in childhood.

The study is published in the online journal *Public Library of Science (PLoS) One*.

"This work strongly suggests that brain changes occur very early in the disease," says first author Tamara Hershey, PhD. "The Wolfram gene is important throughout the body — in the heart, retina, pancreas and so on. The pancreas is affected very early in development eventually leading to diabetes, so it stands to reason that other organs like the brain may also be affected at an early age, even before a child experiences any cognitive problems."

Wolfram syndrome results from mutations in a single gene called WSF-1, which was first identified in 1998 by the late M. Alan Permutt, MD, a former professor of medicine and of cell biology and physiology. He later developed an animal model of the disorder.

In 2010, Permutt organized the world's first clinic exclusively for patients with Wolfram syndrome. The initiative drew children worldwide to St. Louis for testing and evaluation. Another clinic was held last year, and a third will take place this summer at St. Louis Children's Hospital.

Hershey, a professor of psychiatry, of neurology and of radiology, focuses on the neurological aspects of Wolfram syndrome. She leads the scientific efforts of the interdisciplinary clinic, along with Bess A. Marshall, MD, associate professor of pediatrics, who is the clinic's

medical director. Nearly a dozen Washington University faculty members evaluate patients at the Wolfram clinic as part of studies to better understand the syndrome.

For the new study, Hershey obtained brain scans of Wolfram patients ages 5-25 and other young patients who only had type 1 diabetes, along with healthy controls in the same age range. The study represents the first time that scientists have attempted to measure and statistically quantify brain differences in patients with Wolfram syndrome.

“These individuals are intact cognitively, and some of them are very smart, high-functioning kids,” she says. “But we have been able to detect significant differences in the size of certain brain structures, leading us to believe that some of these differences must happen during brain development.”

In particular, Hershey’s group has identified changes in the brainstem and the cerebellum. They also found that the skulls of these children tended to be smaller than would have been expected, based on their ages at the time of the study. The investigators also detected differences in the thickness of the brain’s cortex, particularly in parts of the cortex related to vision.

“We were able to pinpoint those regions of the brain that are most affected in terms of size — the brainstem and the cerebellum,” she says. “And we also used a type of imaging called diffusion tensor imaging that allowed us to measure the integrity of white matter pathways in the brain. Again, we found evidence that the brainstem and the cerebellum white matter were affected in patients with Wolfram syndrome, compared to those with type 1 diabetes only and healthy controls.”

Wolfram syndrome is very rare, affecting an estimated one in 770,000 children. Before these comprehensive research clinics were established,

most of what scientists knew about the brains of patients with the disorder had come from clinical exams of adult patients or autopsies of patients with Wolfram's.

Hershey believes that by conducting annual MRI scans and continuing to track patients with Wolfram syndrome over time, it may be possible to distinguish changes that occur during brain development from those that occur due to degeneration related to the disorder.

More information: Hershey T, Lugar HM, Shimony JS, Rutlin J, Koller JM, Perantie DC, Paciorkowski AR, Eisenstein SA, Permutt MA. Early brain vulnerability in Wolfram Syndrome. *PLoS One*, July 11, 2012. dx.plos.org/10.1371/journal.pone.0040604.

Provided by Washington University School of Medicine in St. Louis