Family's inherited condition links prion diseases, Alzheimer's

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(PhysOrg.com) -- A laboratory connection between Alzheimer's disease and brain-wasting diseases such as the human form of mad cow disease has moved into the clinic for what is believed to be the first time, manifesting itself in the brains of patients with a rare inherited disorder.

In three cases from an Illinois family, researchers at Washington University School of Medicine in St. Louis report that brain regions harmed by an inherited form of Creutzfeldt-Jakob disease (CJD) also have amyloid plaques identical to those found in the same brain areas in Alzheimer's patients.

The finding adds to other, earlier evidence suggesting that the misfolded protein believed to cause CJD, known as a prion, appears to play a role in the Alzheimer's disease process.

"This interplay between amyloid and the prion protein raises questions about whether these diseases are really all that different, and whether there are common pathways involved in both conditions that can provide an avenue for new treatments," says lead author Nupur Ghoshal, M.D., Ph.D., an investigator at Washington University's Alzheimer's Disease Research Center (ADRC).

Ghoshal's research, published in Archives of Neurology, began with the autopsy of a patient who died from inherited CJD more than two decades ago after being followed clinically by senior author John C. Morris, M.D., now the Harvey A. and Dorismae Hacker Friedman

Distinguished Professor of Neurology and director of the ADRC. The autopsy revealed not only the expected brain changes inflicted by CJD but also amyloid brain plaques, even though the patient was younger than the age at which Alzheimer's typically occurs.

CJD and other spongiform encephalopathies rapidly plunge patients into dementia, causing death in a few months to years. They have been associated with rare genetic mutations typically found in a handful of ethnic groups that includes some Jewish sects and some Eastern European lineages. In recent decades, sporadic cases of CJD-like diseases have been associated with consumption of brain and spinal tissues from cows with a brain-wasting condition called mad cow disease . These cases helped spur development of a theory that a misfolded protein known as a prion causes inherited and transmissible forms of diseases like CJD.

Healthy organisms normally make the prion protein, which in its regular configuration contributes in a yet-to-be-identified way to the function of nerve cells. Researchers believe misfolded copies of the prion protein can cause other nearby copies of the protein to misfold, triggering a harmful chain reaction that leads to conditions like CJD.

Ghoshal's analysis showed that the amyloid detected in the initial CJD patient's autopsy was the same type found in the brains of patients with Alzheimer's. The amyloid appeared in regions of the brain most often harmed by CJD and Alzheimer's disease.

With help from the National Prion Disease Surveillance Center and the archives of the neuropathology division at Barnes-Jewish Hospital and the School of Medicine, she then tracked down and analyzed brain tissue samples from two other members of the same family who died from inherited CJD. They also had deposits of the same form of amyloid in the same brain regions.

Ghoshal considered other possible explanations for the presence of amyloid besides CJD. Amyloid deposits may naturally accrue in healthy aging brains, but that type of buildup normally doesn't appear until age 65 or over, and all three patients were younger than this when they died. Amyloid has also been linked to traumatic brain injury, but none of the patients had experienced such an injury.

"This all becomes very interesting in light of several recent discoveries that have suggested CJD and Alzheimer's have important links," Ghoshal says. "For example, a genetic risk factor for inherited CJD was recently linked to increased risk of Alzheimer's disease."

A recent Yale study suggested that the amyloid plaques of Alzheimer's disease only harm brain cells if the prion protein is present at synapses, the junctures where two nerve cells communicate. Ghoshal recommends further study of patients with inherited and spontaneous CJD to clarify the links between the two diseases and develop new approaches to treating them.

More information: Ghoshal N, Cali I, Perrin RJ, Josephson SA, Sun N, Gambetti P, Morris JC. Codistribution of amyloid beta plaques and spongiform degeneration in familial Creutzfeldt-Jakob disease with the E200K-129M haplotype. *Archives of Neurology*, Oct. 2009.

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