Hippocampal Atrophy May Predict Alzheimer's

BY SUSAN BIRK

CHICAGO — Volumetric reduction of the hippocampus has emerged as a promising noninvasive imaging biomarker for prodromal and early stages of Alzheimer's disease.

The hippocampus was the site of the most dramatic changes in patients with single-domain mild cognitive impairment (memory loss), compared with normal controls. This part of the brain is therefore one of the most significant regions of interest for the early diagnosis of Alzheimer's disease (AD), said Dr. David S. Karow of the University of California, San Diego (UCSD), Medical Center.

Dr. Karow, a radiology resident, and his colleagues analyzed baseline MRI and fluorodeoxyglucose positron emission tomography (FDG-PET) images of the cohort of patients. All the patients were participants in the multicenter Alzheimer's Disease Neuroimaging Initiative, which is funded by the National Institutes of Health and by industry.

The finding of hippocampal volume reductions could help pave the way for the development of an objective, noninvasive test for early AD that would enable physicians to prescribe medications sooner to slow the disease's progression, Dr. Karow said in an interview. "The data we have gives us confidence that hippocampal volume is very promising for the diagnosis of early AD.... If you were going to pick one region as a noninvasive biomarker, whether it's for mild AD, mild cognitive impairment, or single-domain cognitive impairment, it's likely that the hippocampus is the region to monitor."

The study revealed significant metabolic as well as structural reductions in the hippocampus, but volumetric reductions were more pronounced, he said.

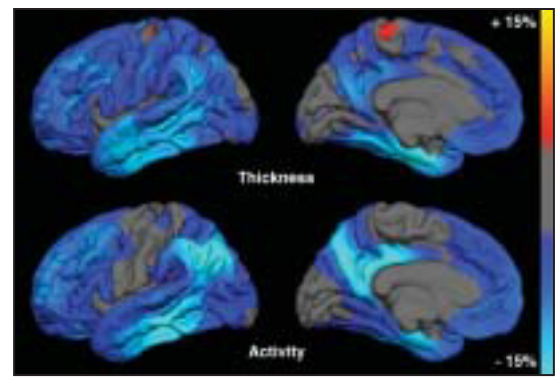
The findings support a model of AD characterized by a process of downstream deinnervation, in which volume loss in regions of the mesial temporal lobe—the hippocampus in particular—leads to loss of activity in other regions.

In this study, the posterior cingulate cortex surfaced as the region of greatest early metabolic change without structural change. "This region is not the initial site of pathology, but because it's linked neurochemically to the mesial temporal lobe, you'll see metabolic changes there first," he said. According to the model of AD, once these regions have been deprived of chemical and electrical input, atrophy will ultimately follow, Dr. Karow said.

He noted that, to his knowledge, the study is the first in AD research to combine data from both PET and MRI images, and to look at the relationship between metabolic and structural changes using a region of interest (ROI)-based approach across the whole brain. He presented the findings at the annual meeting of the Radiological Society of North America, and won the Trainee Research Prize for this work.

The researchers analyzed data from PET and MRI images for 80 normal controls, 156 patients with mild cognitive impairment (MCI), 69 patients with single-domain mild cognitive impairment (SMCI), and 68 patients with AD. Forty-five regions of interest were identified using FreeSurfer, 3-D reconstruction and segmentation software that assessed average differences in the volume/thickness and metabolic activity of these regions. Effect sizes for each group of patients were then calculated for each region.

Hippocampal volume reductions in SMCI patients averaged 9.5%, compared with controls. This group of patients also exhibited mean morphometric reductions of 6.2% in the entorhinal cortex, 5.5% in the amygdala, and 4.1% in the parahippocampal cortex. Compared with controls, volumetric losses in these structures were greatest for patients with mild AD, followed by MCI and then SMCI patients.



COURTESY DR. DAVID S. KAROW

Maps show average differences in activity and thickness between the diagnostic groups.

The largest metabolic differences among SMCI patients were declines of 4.2% in the entorhinal cortex, 3.3% in the posterior cingulate cortex, and 3.1% in the hippocampus, compared with controls.

Although the study revealed regions of the brain with greater metabolic reductions than atrophy in the SMCI, MCI, and AD groups, the magnitude of these changes was not as dramatic as the structural changes taking place in the hippocampus, Dr. Karow said. In terms of effect size, ROIs in the mesial temporal lobe, including the entorhinal cortex, and, in particular, the hippocampus, stood out as the most important in all three groups of patients, compared with controls.

Dr. Karow reported that neuroradiologists at UCSD have used the findings to create an imaging protocol that employs a commercial version of the brain imaging software used in this study. The protocol generates an automated segmentation of the patient's brain and compares the volume size of the hippocampus and the temporal horn of the lateral ventricle against normal volumes.

Hippocampal volume in patients with AD is typically at least two standard deviations below normal, and volume of the temporal horn of the lateral ventricle is typically two standard deviations above normal, noted Dr. Karow.

He disclosed that he has no financial conflicts of interest related to this study. Dr. Karow's coinvestigators included his mentors Anders Dale, Ph.D., and Dr. Carl K. Hoh. Dr. Dale is a founder of CorTechs Labs Inc., which developed the commercial version of the FreeSurfer software, called NeuroQuant; he holds equity interest in the company and serves on its scientific advisory board. Dr. Karow said the terms of this arrangement were reviewed and approved by UCSD in accordance with its conflict of interest policies.

Dr. Karow, the FreeSurfer-based methods also hold potential for the diagnosis of different types of dementia and behavioral disorders, as well as for clinical evaluations of medications, including those designed to slow AD progression. ■

Alzheimer Pathology May Belie Dementia Status

BY MARY ANN MOON

In some patients who die at very old age, the brain might show the classic pathologic features of Alzheimer's disease even though the patient did not exhibit dementia, according George M. Savva, Ph.D., of the University of Cambridge, and his associates.

The Cognitive Function and Ageing Study (CFAS) "confirms earlier reports of considerable overlap in the burden of neuropathological features of Alzheimer's disease between groups of the oldest old persons with dementia and those without dementia," said Dr. Savva.

The brain donors were subjects who had participated in the CFAS when they were aged 70-100 years, undergoing periodic evaluations for dementia with the Mini-Mental State Examination, the Geriatric Mental State Examination, and interviews. A subgroup of 426 subjects donated their brains to the study upon their deaths. In all, 243 had a diagnosis of dementia at the time of death; the rest had been determined to be free of dementia.

The prevalence of moderate or severe neuritic plaques and of neurofibrillary tangles rose with increasing age at death, even in those who had not had dementia. In contrast, the prevalence of cortical atrophy corresponded with dementia diagnoses, the investigators said (N. Engl. J. Med. 2009;360:2302-9).

"Neuropathological validation of the diagnosis of Alzheimer's disease, based on confirmation of the presence of these changes, has a different meaning in the oldest old, because the same burden of pathological features may be found in persons who do not have dementia," wrote Dr. Savva and his colleagues who reported no relevant conflicts of interest. ■

Statins May Decrease Rate of Dementia by More Than 50%

BY MICHELE G. SULLIVAN

VIENNA — Statin treatment may reduce the risk of later dementia by more than 50%, a national Finnish study has determined.

"Disturbances in cholesterol metabolism have previously been linked to dementia development," Dr. Alina Solomon wrote in a poster presented at the International Conference on Alzheimer's Disease. However, she noted not all studies have concluded that statins confer a protective effect against dementia onset.

Dr. Solomon, of the University of Kuopio, Finland, and her colleagues examined this question using data from the national FINRISK study, a large, population-based survey of cardiovascular risk factors in Finnish citizens. The survey began in 1972 and is conducted every 5 years. The substudy of FINRISK included data on 17,257 citizens who were included in the 1997 and 2002 cohorts and who were at least 60 years old in 1995, when statins became available in Finland.

By the study's end at 2007, 1,551 subjects had developed dementia and 15,706 had not. Of those who developed dementia, 18% had taken at least 1 year of statin therapy, while 37% of those without dementia had taken a statin—a significant difference.

No significant associations were found between dementia and the use of other cholesterol-lowering medications, Dr. Solomon said, suggesting that "the effect of statins in dementia is partly independent of their cholesterol-lowering effect."

Those who developed dementia also had significantly higher baseline total cholesterol and baseline systolic and diastolic blood pressure. But a multivariate regression model controlling for age, gender, education, weight, cholesterol, and blood pressure still found that statins conferred a 57% risk reduction for dementia over the study period.

The finding does not prove that statins prevent dementia, but it does suggest further studies should explore the idea, focusing on statin types, dosages, and duration of treatment, Dr. Solomon said at the meeting, which was sponsored by the Alzheimer's Association. None of the researchers had any potential conflicts to declare. ■