Hippocampal Atrophy: Biomarker for Early AD?

Hippocampal volume in patients with AD is typically two standard deviations below normal.

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, according to a study of 373 patients.

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), reported 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 in order to slow the progression of the disease, 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," he said. "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."

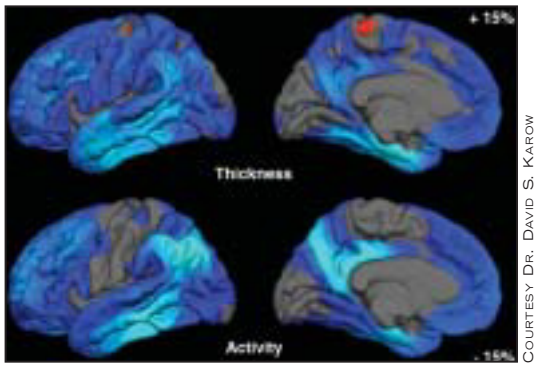
The study revealed significant metabolic as well as structural reductions in the hippocampus, but volumetric reductions were more pronounced, he said.

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, Dr. Karow said.

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, he said.

Dr. Karow 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.

Dr. Karow and his colleagues 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, 3D 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.



COURTESY DR. DAVID S. KAROW

Brain thickness and activity differed in patients with AD (left) compared with controls (right).

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.

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, Dr. Karow noted.

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.

According to Dr. Karow, the FreeSurfer-based methods used in the study 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 the progression of AD. ■

Disparities in Stroke Treatment Seen for Men, Women

BY ROBERT FINN

SAN DIEGO — Women have strokes more often than men, but they are significantly less likely to receive the best available treatment, according to two studies presented at the International Stroke Conference.

In a meta-analysis of 18 studies involving more than 2.3 million men and women who had a stroke, Dr. Archit Bhatt of Michigan State University, East Lansing, determined that women were 30% less likely than men to receive intravenous tissue plasminogen activator (TPA), the most effective treatment known. This difference was statistically significant.

Of the 21,503 patients who received TPA, 63% were male and 37% were female.

The sex disparity persisted even after Dr. Bhatt adjusted for differences in age and other confounders. In the adjusted analysis, women were 23% less likely to receive TPA than men were (Stroke 2009 Feb. 19 [doi:10.1161/STROKEAHA.108.543181]).

"At this point there are no gender-based guidelines to give TPA," Dr. Bhatt noted during a news conference. "So clearly more research needs to be done to understand the barriers to acute stroke therapy in women, so that critical health disparities can be eliminated."

In a separate study, Dr. Louise D. McCullough of the University of Connecticut, Farmington, and her colleagues determined that on average, women arrive at the emergency department 12 minutes later than men do.

In a retrospective analysis of 435 stroke patients, aged 45 years and older, who were treated at a single emergency department, the average man arrived 96.4 minutes after the onset of symptoms, compared with 108.8 minutes for women, a significant difference.

Women were 23% less likely to receive TPA than men were; on average, women arrive at the emergency department 12 minutes later than men do.

Later arrival can have a large impact on treatment and outcome, since TPA must be administered no later than 3 hours after the onset of stroke symptoms.

"The one encouraging thing in our study that we found is that once [women] were in our emergency room, they were treated exactly the same way as men," Dr. McCullough said at the news conference. "They were treated with the same speed, and they were treated at the same rate as men. The problem was they were losing a lot of time getting there."

Although the data did not allow the investigators to determine why women were arriving later, Dr. McCullough offered several hypotheses.

For one thing, women tend to be older than men when they have their stroke.

In addition, a woman may be living alone, having survived her husband, and there may not be anyone available to contact authorities.

Another factor may be that "they don't have the same level of urgency that men have, and it could be they're not identifying their own atypical presentations," Dr. McCullough said.

"I think also women tend to minimize symptoms. We've seen that in heart disease," she added.

Dr. Bhatt and Dr. McCullough both stated that they had no conflicts of interest to disclose. ■