Hippocampal Atrophy May Predict Alzheimer's

BY SUSAN BIRK
Contributing Writer

CHICAGO — Volumetric reduction of the hippocampus is 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. All patients were participants in the multicenter Alzheimer's Disease Neuroimaging Initiative, 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 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," he said.

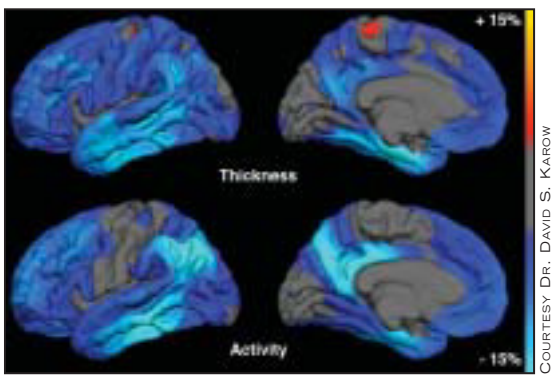
The study revealed significant metabolic as well as structural reductions in the hippocampus, but volumetric reductions were more pronounced, he said.

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 were then calculated for each region.



COURTESY DR. DAVID S. KAROW

Maps show average differences in activity/thickness between diagnostic groups.

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.

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 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 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. ■

Mortality in AD Rises With Long-Term Antipsychotic Use

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Antipsychotics appear to significantly increase the risk of death in patients with Alzheimer's disease, especially if taken for more than 12 months, a randomized controlled trial has determined.

Nursing home patients with Alzheimer's disease (AD) who continued taking the drugs for 1 year were 7% more likely to die than were those who discontinued them, and the mortality difference escalated over the 4-year study. By the end of the trial, just 26% of those taking the drugs were still alive, compared with 53% of those taking a placebo, wrote Dr. Clive Ballard of King's College, London, and his associates (Lancet 2009 Jan. 9 [doi:10.1016/S1474-4422[08] 70295-3]).

The authors did support a limited use of the drugs, particularly in patients with severe dementia-related aggression, geriatrician Karl Steinberg, who is in a group practice in Oceanside, Calif., noted in an interview. But their risks must be carefully considered.

The conclusions seem to support the Omnibus Budget Reconciliation Act of 1987, which mandated gradual dose reductions of antipsychotics in nursing home residents, he added. "This is looking like an increasingly sound idea. We need to keep in mind that the patients for whom we prescribe these medications are suffering from significant dementia and already nearing the end of life, where quality of life should be a major concern."

The trial comprised 165 nursing home residents with AD (mean age 89). At baseline, all of the patients were taking an antipsychotic medication. Most (93%) were taking either risperidone or haloperidol; other agents included thioridazine, chlorpromaine, and trifluoperazine.

Patients were randomized to either continue treatment (83) or discontinue treatment by taking a placebo. Thirty-seven patients did not start treatment, leaving 64 in each treatment group. The 12-, 24-, 36-, and 42-month survival rates were analyzed in the group of those who began taking their study medication, regardless of whether they stopped at any time during the study.

After 12 months, those taking placebo were more likely to survive than were those taking an active agent (70% vs. 77%); the difference was statistically significant. The disparity was magnified as the trial continued. At 24 months, the cumulative survival rate was 71% in the placebo group vs. 46% in the active group; at 36 months, the rate was 59% vs. 30%; and at 42 months, it was 53% vs. 26%.

Death certificates were available for 78%. More deaths of a probable vascular nature occurred in the placebo group; there was no indication that antipsychotics contribute to cerebrovascular deaths.

The reasons for the biggest difference in mortality occurring after the first 12 months of the trial are unclear. "One possible explanation is that the most frail participants who had the most severe dementia … have a high mortality risk regardless of whichever treatment is assigned," they noted. However, "the results are consistent in that patients allocated to discontinue antipsychotics seem to benefit from lower mortality during long-term follow-up than [do] those allocated to placebo."

They noted that up to 60% of nursing home residents with dementia in Europe and North America receive antipsychotic medication, often for extended periods of time, despite data suggesting that the risks outweigh any possible benefit.

"There is clear evidence of a significant increase in adverse events, including parkinsonism, sedation, oedema, chest infections, accelerated cognitive decline, and cerebrovascular events in patients with Alzheimer's treated with antipsychotics," they noted. Alternative treatments include psychological management, memantine, and antidepressants.

The results confirm those in other trials suggesting a link between the drugs and increased morbidity and mortality in dementia patients, said Dr. Marwan Sabbagh in an interview. "This risk was the impetus for the black box warning issued by the FDA for risk associated with antipsychotic use specifically in dementia."

"What makes this more compelling is that … this is objective evidence in a randomized, placebo-controlled study that [AD] subjects taking antipsychotics had demonstrable increases in mortality," said Dr. Sabbagh, chief medical-scientific officer and director of clinical research at the Sun Health Research Institute, Sun City, Ariz.

The study was funded by the U.K. Alzheimer's Research Trust. Dr. Ballard noted financial relationships with many companies that manufacture antipsychotics and Alzheimer's medications. ■