Is there a difference in hippocampal cerebral blood volume between patients with early Alzheimer's disease versus mild memory loss of other etiologies?

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A. Study Purpose and Rationale

This study will determine whether patients with mild memory loss who go on to develop Alzheimer's disease show a difference in cerebral blood volume across hippocampal subregions, compared to patients with mild memory loss who do not develop Alzheimer's disease.

Memory failure is one of the most common complaints of the elderly, and may represent normal aging or disease. Memory localizes to several areas of the brain, particularly the hippocampus. The hippocampal circuit is composed of four subregions of distinct neuronal populations: dentate gyrus, entorhinal cortex, subiculum, and CA subfields, each of which is targeted by different causes of memory loss. For example, patients with Alzheimer's disease show selective loss of neurons in the entorhinal cortex, even during the earliest stages of disease.[1]

Alzheimer's disease can only be diagnosed after death, through pathologic examination of the brain. During life, a "probable" diagnosis of Alzheimer's disease may only be made clinically, through medical, neurologic, and neuropsychologic tests. However this diagnosis can only be made sensitively once the dementia is rather severe and the patient experiences dysfunction in many spheres of life. In elderly patients with mild memory loss, it would be useful to attribute the memory loss to normal aging or disease, and then diagnose the disease and treat the disease as early as possible. Early diagnosis may be critical; for example in Alzheimer's disease treatment with donepezil may slow disease progression, and early treatment may afford patients a better quality of life.

Theoretically, an MRI technique that measures brain metabolism and cell loss with fine spatial resolution may assist in the determining the cause of memory loss, specifically for Alzheimer's disease. A surrogate measure for chronic brain metabolism, brain blood volume, may be measured by performing T1-weighted MRIs, using a gadolinium chelate as an intravascular contrast agent, then generating cerebral blood volume maps.[2] CBV maps of healthy elderly without memory loss and AD patients are currently being generated and evaluated for signal differences across hippocampal subregions. However even if a difference is detected, it is unknown whether this difference is part of the early or late pathophysiology of AD. To address this question, the study described here will be performed. This study will look for a difference in CBV in the entorhinal cortex of patients with mild memory loss who go on to develop AD compared to patients with stable mild memory loss who do not develop AD. It will also be powered to detect differences between CBV in other hippocampal subregions between patients with early AD versus patients with normal memory loss of aging. In this way, it will be determined whether decreased CBV in specific hippocampal subregions is part of the early pathophysiology of AD.

B. Study Design and Statistical Analysis

[1] Braak H, Braak E. Evolution of the Neuropathology of Alzheimer's disease. Acta Neurol Scand Suppl 1996; 165: 3-12.

[2] Kuppusamy K, Lin W, Cizek GR, Haacke EM. In Vivo Regional Cerebral Blood Volume: Quantitative Assessment with 3D T1-weighted Pre- and Postcontrast MR imaging. Radiology 1996; 201: 106-112.

This study will be performed as a nested case-control study. We will begin with a cohort of elderly patients with mild memory loss. The patients will be drawn from the Washington Heights and Inwood Community Aging Project (WHICAP) run by Dr. Richard Mayeaux at the Sergievsky Center of Columbia University. WHICAP is a longitudinal, community-based cohort study of approximately 2000 persons >65 years residing in Washington Heights and Inwood.[3] Patients in this study receive yearly medical, neurologic, and neuropsychiatric battery of tests, and are followed for the development of dementia.

One of the tests performed is the Selective Reminding Test, which is specific for hippocampal dysfunction.[4] Patients with a memory slope < - 0.2 over the past 3 years, but with a prior horizontal or positive memory slope, will be eligible for the study. These subjects have new-onset memory loss, but otherwise do not meet the criteria for Alzheimer's disease. Other exclusion criteria will include any central nervous system disease, psychiatric disease, or substance abuse. Subjects with treated hypertension, diabetes, or hypothyroidism will not be excluded. There are approximately 150 patients in WHICAP who will be eligible for the study.

All subjects will receive MRIs on the Phillips 1.5 tesla magnet in the Neurological Institute. As chronic metabolism is being measured by CBV maps, subjects will be instructed simply to relax and close their eyes. A sagittal scout image will be acquired, allowing selection of slices that are perpendicular to the long axis of the hippocampus. The two sets of 3D T1-weighted images will be acquired with the following parameters: (TR= 20 ms; TE= 6ms; flip angle 25 degrees; in-plane resolution= 0.86x0.86 mm). The first image will be acquired before intravenous injection of Omniscan, a gadolinium chelate, and the second image will be acquired 4 minutes after Omniscan injection, for optimal visualization of cerebral macro and microvasculature.

Image analysis will be performed on a Linux workstation using image display and analysis software (MEDx.) All imaging processing will be performed by an investigator blinded to subject identity. A standard slice will be selected just anterior to the lateral geniculate nucleus, where all hippocampal subregions are visible. The investigator will generate a cerebral blood volume map by subtracting the post-gadolinium image from the pre-gadolinium image, then dividing this difference by the pixel value of the sagittal sinus (post- pre), thereby generating relative CBV maps for each subject. Using standard anatomical atlases, the subregions of the hippocampus will be selected, and average signal of the regions of interest will be calculated and recorded as the CBV.

Patients will be followed, as per normal protocol in the WHICAP study, continuing to receive yearly neurologic, psychiatric, and neuropsychologic tests. Results of these tests are reviewed at weekly conferences, and patients' diagnoses are updated yearly. All of the clinicians who administer and score these tests and make the diagnosis of AD will be blinded as to subjects' CBV values.

For the purposes of this study, patients will be followed for 3 years, during which time it is expected that 30% of patients with mild memory loss will develop Alzheimer's disease.[5] At the end of 3 years, patients will be divided into two groups and a nested case-control analysis will be performed. Mean CBV for each of the four hippocampal subregions will be determined in AD patients versus non-AD patients, and unpaired t-tests will be performed to determine significance of any difference.

It is likely that only ½ of eligible subjects will choose to enroll, so based upon a total number of subjects 75, and a standard deviation for CBV of 0.54%, the detectable effect, with 80% power and

[3] Tang M, Stern Y, Bell K, Mayeux R. The APOE-(epsilon 4) allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. JAMA 1998; 279 (10): 751-755.

[4] Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974; 24 (11): 1019-1025.

[5] Jacobs DM, Sano M, Dooneief G, Marder K, Bell KL, Stern Y. Neuropsychological detection and characterization of preclinical Alzheimer's disease. Neurology 1995; 45 (5): 957-962.

P<0.01 is 0.5%. Setting P < 0.01 allows four comparisons to be performed, with the appropriate overall P value < 0.05, for each of the entorhinal cortex, dentate gyrus, CA subfields, and subiculum.

C. Study Procedure

All procedures in this study are performed solely for research purposes. However, there are two classes of actions performed in this study. One set includes the yearly medical, neurologic, and neuropsychologic tests performed for the WHICAP study, of which subjects are already members, have already consented to, and are familiar with. Our ancillary study will not affect subjects' participation in WHICAP whatsoever.

Procedures which are specific to this study include intravenous line placement, intravenous injection of Omniscan, a gadolinium chelate used as a contrast agent, and magnetic resonance imaging. The amount of time required for the procedure will be 1½ hours, of which 1/2 hour will be used for further explaining the procedure, familiarizing the patient with the imaging environment, including magnet and head coil, and obtaining consent, 1/2 hour will be used for inserting the intravenous line and properly positioning the patient on the MRI bed, and ½ hour will be used for obtaining images, removing the intravenous line, and monitoring the subject. The subject's participation in the study will be limited to the day when they are approached over the telephone for interest in the study and the day of imaging. The patients may experience mild pain when the intravenous line is inserted and other side effects as explained in "Medical Device", may experience some side effects of Omniscan, as explained below in "Study Drugs," and may experience mild back pain or claustrophobia while the MRI is performed.

D. Study Drugs

In this study, all patients will receive intravenous Omniscan, a gadolinium chelate used as an MRI contrast agent. Gadolinium is a metal salt which stays within the blood vessels and alters magnetic signal, allowing the vasculature to be better visualized. It has been used millions of times since its approval for clinical use in 1988 and is routinely used for head MRIs – 5 million doses were given in the United States in 1998.[6] It is supplied in one of four forms, which differ only in the elements bound to gadolinium. It is excreted by the kidneys, with a half-life approximately one hour.

Omniscan will be administered intravenously, which is standard clinical use. Fifteen mL will be given as a bolus injection over one minute, which is also standard clinical dose and administration time. Side effects of Omniscan include a self-limited nausea, occurring in 1.6% of patients, and hives, occurring in 0.7% of patients.[6] These hives resolve without treatment over several hours. There is one reported fatality from a severe allergic reaction to Magnevist (a different gadolinium chelate), however non-fatal reactions have occurred to all of the gadolinium chelates. These severe allergic reactions tend to occur more frequently in patients with asthma or history of severe allergic reactions, either to gadolinium or other substances, so patients with these characteristics will be excluded. To treat any unforeseen side effects, a crash cart will be in place in the MRI suite, and a physician will be present at all times.

E. Medical Device

Intravenous line: In this study, an intravenous line is necessary to deliver the contrast agent Omniscan into the intravascular space. All patients will have an 18 gauge intravenous line placed by a physician participating in the study. Intravenous lines are widely used in every hospital- side effects include mild pain upon insertion, extravasation of injected fluid, bruising, bleeding, and very rarely, infection. The line will be removed after the study is complete (after approximately one hour). Because

[6] Runge VM. Safety of Magnetic Resonance Contrast Media. Topics in Magnetic Resonance Imaging 2001; 12 (4): 309-314.

these patients are otherwise healthy and ambulatory, and because the line is in place for a relatively short period of time, the risk of these side effects is very small.

Magnetic Resonance Imaging: In this study, MRI imaging is necessary to visualize the brain. By placing patients in a strong magnetic field, and by exciting and recording relaxation of the spin of hydrogen atoms, MRI detects tissue density. There are no known intrinsic health risks of exposure to magnetic fields. However, certain patients may have exogenous metal devices implanted in their bodies (such as pacemakers, aneurysm clips, joint replacements) which are affected by the high magnetic fields: these subjects will be excluded from the study. This will be ascertained by careful verbal and written questioning, performed both over the phone and before entering the MRI hatch, using a questionairre that is standard in the clinical MRI suite at Milstein Hospital. Furthermore, patients will be instructed to remove all metal items from their body before entering the MRI hatch.

Brain MRI involves reclining on a horizontal bed, resting the head in a padded container, inserting ear plugs (to help drown out the noise from the machine), and having an open, plastic head coil pulled over the head. Then the patient's head is moved into the center of an open cylinder (the magnet), and he is instructed to remain still over the next 30 minutes while the images are taken. Some patients experience a sore back from lying horizontal for 30 minutes, and others may feel claustrophobic or anxious, due to the noises and the unfamiliar environment. Patients will always be in voice contact with the researchers, and if patients desire it, a researcher will stay in the MRI room with the patient while the image is taken. The study may be stopped at any time, based on the subject's wishes. After the first image is taken, a researcher will enter, inject the gadolinium, then exit, and the second image will be taken. Overall, the patient will be in the magnet for 30 minutes or less.

F. Study Questionnaires

Standard MRI safety questionnaire from Milstein Hospital MRI suite.

G. Study Subjects

a. Inclusion criteria

- Participant in WHICAP study
- >65 years old
- Mild memory loss, as determined by memory slope <-0.2 over the past 3 years on the Selective Reminding Test.

b. Exclusion criteria

- Central Nervous System Disease (including dementia, Alzheimer's disease, Parkinson's disease, etc.)
- Psychiatric Disease (past or current.)
- Current Substance Abuse.
- Any condition which precludes MRI (pacemaker, metal implants, claustrophobia.)
- Any condition which predisposes patients to allergic reaction to gadolinium (asthma, past anaphylactic reaction.)

Vulnerable population: These patients are elderly, but non-demented, only suffering from mild memory loss. Only patients who understand the risks and benefits of the procedure will be allowed to participate. Subjects' caregivers or partners will be encouraged to attend the experiment, but the patient alone will be the only person giving consent.

Many subjects will be Spanish-speaking only. If this is the case, an investigator fluent in Spanish will be present at all times, and the consent will be written in Spanish.

H. Recruitment of Subjects

After each WHICAP patient's yearly medical, neurologic, and neuropsychologic exams, the results are discussed at a weekly multidisciplinary conference, where a diagnosis is made. During their visits, WHICAP participants are approached by their physician as to their interest in participating in this and other research studies. WHICAP participants who express interest in participating in MRI studies and who meet study criteria, will be approached by a phone call, wherein an investigator will explain the experiment in detail, explain how and why the subject was chosen, answer any questions the subject may have, then invite the subject to participate.

I. Confidentiality of Study Data

Patients will be assigned a randomly-generated study number. MRI images will be referred to only using this number. A sheet of paper linking study numbers to demographic information will be stored in a locked file cabinet, accessible only to investigators.

J. Potential Conflict of Interest

None of the investigators or the University has a proprietary interest in the procedure under investigation, nor stands to benefit financially from the results of the investigation.

K. Location of the Study

MRI images will be taken in the MRI suite in the basement of the Neurologic Institute. MRI images will be analyzed in the Presbyterian Hospital, Taub Institute, 18th floor.

L. Potential Risks

Risks of the study derive from intravenous line insertion, Omniscan injection, and MRI.

From the intravenous line, patients may experience pain, bruising, bleeding, fluid extravasation, and infection.

From the Omniscan injection, participants will experience a 1.6% risk of self-limited nausea, and 0.7% risk of self-limited hives. There is also a much smaller risk of severe allergic reaction or anaphylaxis. A crash cart will be in place in the MRI suite, and a physician will be present at all times.

There are no long-term health risks from MRI, and no cumulative effects. Patients may experience back pain from lying horizontal and still for ½ -1 hours, and patients may experience claustrophobia or anxiety.

As there is no current diagnostic test or treatment for mild memory loss, by participating in this study, patients are not losing any effective standard of care.

M. Potential Benefits

Participants are not expected to benefit directly from participation. The ultimate benefit of this research to society, is to better understand changes in the brain that occur with aging and disease that impair memory.

N. Alternative Therapies

There are no alternative therapies.

O. Compensation to Subjects

Subjects will receive $100 cash at the conclusion of the study. This compensation will be given whether or not the subject completes the study.

P. Costs to Subjects

Medical costs a subject incurs as a result of participating in this study are the subject's responsibility. The great majority of subjects are expected to incur no costs, however if a subject experiences a rare side effect, such as infection or anaphylactic reaction, he must cover these costs.

Q. Minors as Research Subjects

This study does not include minors.

R. Radiation or Radioactive Substances

This study does not include radiation or radioactive substances.