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Volumetric and visual rating of magnetic resonance imaging scans in the diagnosis of amnestic mild cognitive impairment and Alzheimer's disease

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Abstract

Background: In the diagnosis of Alzheimer's disease (AD), structural magnetic resonance imaging (MRI) scans have been used primarily to exclude non-Alzheimer's causes of dementia. However, the pattern and the extent of medial temporal atrophy on structural MRI scans, which correlate strongly with the pathological severity of AD, can be used to support the diagnosis of a degenerative dementia, especially AD, even in its early predementia stage.

Methods: Elderly subjects (n = 224) were diagnosed with either no cognitive impairment (NCI), amnestic mild cognitive impairment (aMCI), or AD. Hippocampal and hemispheric gray matter volumes were measured on structural MRI scans, and a new visual rating system was used to score the severity of medial temporal atrophy (VRS-MTA) of the hippocampus (HPC), entorhinal cortex, and perirhinal cortex on a coronal image intersecting the mammillary bodies.

Results: Although both VRS-MTA scores and HPC volumes distinguished between subjects with NCI, aMCI, and AD, subjects with aMCI and NCI could be better distinguished using right VRS-MTA scores, in comparison with right HPC volumes. VRS-MTA scores were more highly correlated with episodic memory and Clinical Dementia Rating scores. A combination of left sided VRS-MTA scores and left sided hippocampal volume was the most predictive measure of diagnostic classification.

Conclusion: VRS-MTA is a clinically convenient method or distinguishing aMCI or AD from NCI. As compared with volumetric measures, it provides better discriminatory power and correlates more strongly with memory and functional scores.

Keywords: Alzheimer disease; Dementia; Volumetric analysis; Visual rating; Brain MRI; Medial temporal atrophy; Diagnosis; Cognitive impairment; Neuropsychological tests

1. Introduction

Alzheimer's disease (AD), the most common cause of dementia in the elderly population, is a gradually progressive degenerative neurological disorder that is characterized by increasing cognitive and functional impairment, characteristic degenerative pathology, and brain atrophy [1,2]. Approximately one-third of nondemented elderly individuals have neuropathology consistent with that observed in a majority of cases diagnosed with probable AD, yet do

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not manifest the symptoms of the disease during life [3,4]. At present, there is no cure for AD, but an early and accurate diagnosis is potentially important for intervention in this disease, even among cognitively normal, at-risk individuals, before irreversible changes have taken place in the brain [5]. Imaging is currently included in a dementia work-up so as to exclude non-AD etiologies, such as hydrocephalus, brain tumors, subdural hematomas, and strokes, but not to identify and measure the severity of underlying AD neuropathology [4,6−8]. It would seem that limiting use of magnetic resonance imaging (MRI) scans solely for the purpose of excluding diagnoses other than AD, does not optimize the utility of a valuable and widely used imaging resource in the work-up of patients with cognitive impairment. In fact, imaging could be used routinely to support a clinical diagnosis of AD among patients with dementia and amnestic mild cognitive impairment (aMCI), by confirming the presence and severity of AD-like pathology in the brain. MRI could also be used in multicenter clinical trials of pharmacological and nonpharmacological interventions for AD, to ensure that patients in these studies have imaging evidence of AD pathology.

Morphological changes in the brain can be measured using manual, semiautomated, and fully automated volumetric techniques to study whole brain and medial temporal volumes [9−13]. We have expanded the scope and improved the reliability and sensitivity of a visual rating system (VRS) method which assesses the entire medial temporal region [14], separately rating atrophy of the hippocampus (HPC), entorhinal cortex (ERC), and perirhinal cortex (PRC) on a single coronal MRI slice [15,16]. In this study, the capability of VRS for assessing the severity of medial temporal atrophy (VRS-MTA) and volumetric analysis are compared for distinguishing cases diagnosed with no cognitive impairment (NCI), aMCI, and AD among 224 subjects who were enrolled in the Florida Alzheimer's Disease Research Center. The correlation of VRS-MTA scores and volumetric analysis to specific neuropsychological test scores and the Clinical Dementia Rating scale were also evaluated. Finally, VRS-MTA scores and volumetric analysis were combined to determine whether the combination improved diagnostic power.

2. Methods

2.1. Subjects

A total of 224 men and women, 60 to 92 years of age, including English and Spanish speakers, participating in the Florida AD Research Center Clinical Core in Miami and Tampa, Florida, were evaluated in this study. Subjects were recruited from the community (by advertisement and from free memory screening evaluations) and from memory disorder clinics. All subjects or a legal representative provided informed consent as approved by Institutional Review Boards of Mount Sinai Medical Center, Miami Beach, and University of South Florida, Tampa. Subjects were evaluated using: (1) Mini-Mental State Examination (MMSE) [17], a measure of global cognitive status; (2) neuropsychological test battery, following National Alzheimer's Coordinating Center (NACC) protocol [18]; (3) Three Trial Fuld Object-Memory Evaluation (FOME) [19]; (4) Hopkins Verbal Learning Test [20]; and (5) volumetrically acquired structural brain MRI. An MMSE score of $\geq$20 was required to enter the study, so as to ensure that the subjects with dementia would be mildly impaired.

2.2. Diagnosis

Each subject was evaluated independently by a physician and a neuropsychologist, who were experienced in the diagnosis of cognitive impairment or dementia among elderly subjects. These clinicians did not have access to each others' diagnoses, or to any imaging data, before assigning their diagnoses. To standardize the methods with which the independent diagnoses by these two clinicians were reconciled into a consensus diagnosis, an algorithmic diagnosis procedure [21] was used, on the basis of a formula that combined the physician's diagnosis (Phy-Dx) and the neuropsychologist's diagnosis (NP-Dx). The diagnosis of NCI required that both Phy-Dx and NP-Dx were NCI, based on an informant report of "no significant decline in cognition," and no cognitive test scores were 1.5 SD or more below age and education corrected means. The aMCI diagnosis [22] required that both the Phy-Dx and the NP-Dx be aMCI. The Dementia diagnosis met the Diagnostic and Statistical Manual-IV and NACC [18], and a specific diagnosis of AD was based on National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria [23].

2.3. MRI procedures

Structural brain MRIs were obtained on a 1.5 Tesla MRI machine using proprietary 3-D MPRAGE (Siemens, Iselin, NJ) or 3-D FSPGR (General Electric, Milwaukee, WI) sequences to acquire contiguous coronal slices of $\leq$1.5 mm in thickness. Structural MRIs were reconstructed in the coronal plane perpendicular to the anterior commissure−posterior commissure line.

2.4. Visual Rating System

The VRS software was developed to standardize the ratings of atrophy in the HPC, ERC, and PRC structures (Fig. 1) of the medial temporal lobe. All raters using VRS were blind to the subjects' diagnoses and demographic information. Technical details for the VRS have been described previously [15,16]. Briefly, a standard coronal slice, intersecting the mammillary bodies, is used to assess medial temporal atrophy (MTA), separately in the HPC, ERC, and PRC of each hemisphere. Ratings are based on a 5-point scale, with "0" signifying no atrophy, and "4" signifying the most severe atrophy. MTA ratings for each hemisphere are