Increase of brain atrophy rate in patients with a known date of onset of Alzheimer's disease: A marker of disease progression

Y. Endo[1], H. Rusinek[1], S. De Santi[2], D. Frid[1], W-H. Tsui[2], S. Segal[2], A. J. Convit[2], M. J. de Leon[2]

[1]Radiology, New York University School of Medicine, New York, NY, United States, [2]Psychiatry, New York University School of Medicine, New York, NY, United States

Introduction

MRI studies have indicated that increased volume loss occurs both globally throughout the whole brain as well as regionally within medial temporal lobe (MTL) structures in patients with Alzheimer's disease (AD) relative to cognitively normal individuals. Previous investigators have focused on the rate of brain atrophy by comparing serial MRI scans and measuring the amount of volume loss (1-5). However, very few have looked at how the atrophy rate may change with progression of AD (1), and no one, to our knowledge, has analyzed the relationship between the rate of brain atrophy and the time from onset of AD. This study investigates how the rate of atrophy in the whole brain and the MTL may change during AD. We show that the atrophy rate within the MTL assumes a positive linear correlation with the number of years since the onset of AD.

Methods

Among subjects evaluated in our AD core center, we selected those with at least 2 MRI scans and with known time of onset of sporadic, or non-familial, AD. We were able to establish the time of onset as the midpoint between the date at which the subject was last evaluated as normal or only mildly impaired and the date at which the subject first fulfilled the standard criteria for the diagnosis of AD (6). Baseline and follow-up coronal T1-weighted MRI GRE sequences with TR 35 ms, TE 9ms, NEX=1, FA 60˚, 256 x 192 matrix, 1.3 mm slice thickness, and 18 cm FOV were coregistered and were decomposed into interior *I* and border *B* regions (5,7). The regions of interest (ROI) of the left and right MTL were constructed as boxes centered around the left and right hippocampi, respectively, with the width and height of each box equal to one quarter of the intracranial width and height to account for variability in the size of the brain (Figure 1). The anterior and posterior limits of the MTL ROIs were defined as the anterior and posterior margins of the hippocampi, respectively. The whole brain ROI was defined as the set union $I \cup B$. For each of the three ROIs for each subject, the annual atrophy rate was calculated as the baseline minus follow-up brain ROI volume, divided by the baseline volume and the number of years between the two MRI scans. In order to determine whether duration of AD influenced the rate of atrophy within the left and right MTL as well as the whole brain, the length of disease was calculated as the number of years the two MRI scans were performed after each subject was diagnosed with AD. For those subjects who were normal or only mildly impaired at the time of the scans but were later diagnosed with AD, the duration of disease was assigned a negative number.

Results

18 AD subjects (5 men and 13 women) fulfilled the inclusion criteria for the study. Their average age at the time of onset of AD was 75.1 +/-8.6 and the duration of disease at the time of the two MRIs ranged from –2.9 to +4.2 years. In a multivariate linear regression analysis using age, gender, education level, and duration of AD as predictors of the brain atrophy rates, only the duration of AD was significantly correlated with the atrophy rate in the left MTL (R^2=0.58, p=0.001) and the right MTL (R^2=0.30, p=0.03). Figure 2 illustrates the relationship between the duration of AD and the atrophy rate in the left and right MTL. The duration of AD was not a significant predictor of global brain atrophy rate.

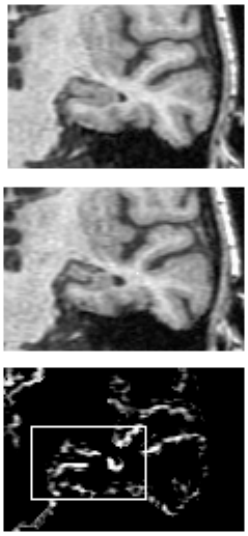

Fig 1. Baseline (top), follow-up (middle) and difference (bottom) images of the brain of a subject with AD. Bottom image also shows the box outlining the left MTL.

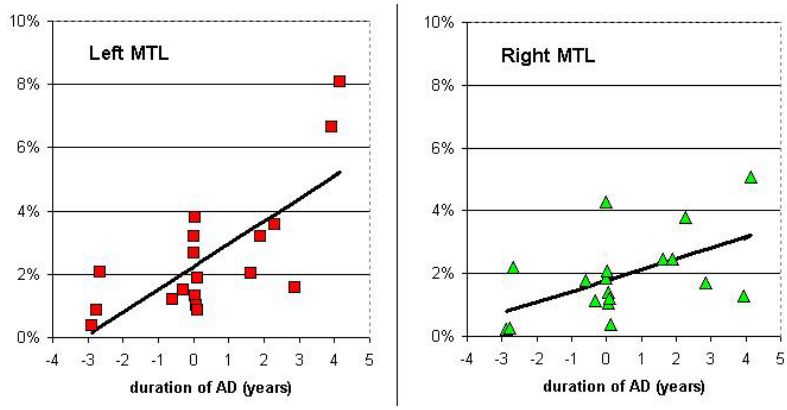

Fig 2. Annual atrophy rate in the left and right MTL in relation to the duration of AD. The mean atrophy rate at the time of diagnosis (disease duration = 0) was 2.2% per year for the left MTL and 1.8% per year for the right, with annual acceleration of 0.73% per year^2 for the left MTL and 0.34% per year^2 for the right.

Discussion

Our study presents novel evidence that volume loss within certain areas of the brain accelerates during the course of AD. Subjects who had been diagnosed with AD for a longer period showed a greater annual rate of atrophy within the MTL, with an estimated 0.5% per year increase in the rate bilaterally for each additional year the subject survives with AD. Our results are consistent with other studies that have also found structures within the MTL to be more vulnerable to atrophy in AD compared to the brain as a whole (3,4). The model of an accelerated atrophy further emphasizes the need for early therapy. Pharmacotherapy, even if effective in arresting further brain loss, is unlikely to improve cognitive function if substantial tissue loss has already occurred.

References

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