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Gray matter volume abnormalities in type 2 diabetes mellitus with and without mild cognitive impairment☆

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HIGHLIGHTS

- Widespread GM atrophy was found in T2DM patients both with and without MCI.
- MTL atrophy was found with the occurrence of the MCI in T2DM patient.
- MTG atrophy might be associated with an increased risk for MCI in T2DM.

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ABSTRACT

This study sought to evaluate the potential brain gray matter (GM) volume changes that occur with the transition from normal cognition to mild cognitive impairment (MCI) in patients with type 2 diabetes mellitus (T2DM) using voxel-based morphometry (VBM). VBM analyses of brain GM based on magnetic resonance imaging (MRI) data were performed on 28 T2DM patients with MCI, 25 T2DM patients without MCI, 28 MCI patients and 29 healthy controls (HC). Compared with the HC, the T2DM patients both with and without MCI showed significantly decreased total GM volume. Furthermore, the VBM results indicated that the T2DM patients without MCI exhibited extensively decreased GM volume compared with the HC in certain brain regions, including the superior and middle temporal gyrus (MTG), the superior and medial frontal gyrus and the middle occipital gyrus. In addition to more extensive GM atrophy in the aforementioned brain regions, the medial temporal lobe also exhibited GM loss in the T2DM patients with MCI. Furthermore, relative to the patients without MCI, only the left MTG exhibited a lower GM volume in the T2DM patients with MCI, which was positively correlated with the total MoCA score ($r = 0.699$, $P < 0.01$). Finally, relative to MCI, the left MTG atrophy was also found in the T2DM patients with MCI. Our findings suggest that MTG atrophy was associated with an increased risk for MCI in T2DM patients. The brain structural changes in many brain regions may underlie the transition from normal cognition to MCI in T2DM patients.

1. Introduction

Diabetes can result in progressive damage to the central nervous system. Approximately 10.8–17.5% of diabetic patients develop cognitive dysfunction [5], including mild cognitive impairment (MCI) and dementia [4]. It has been reported that type 2 diabetes mellitus (T2DM) is associated with deficits in learning and memory [20], information processing speed, attention and executive function [25]. MCI has attracted increasing research interest as it represents the transitional state between normal aging and Alzheimer's disease (AD) [22]. Previous study has shown that T2DM patients have a significantly increased risk of MCI [10]. It is now widely accepted that MCI is the most important at-risk state

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for AD and may result in elevated mortality in diabetic patients [14,29]. Thus, research on the pathophysiological mechanisms of MCI related to T2DM is crucial for the prompt treatment and improved prognosis of T2DM patients.

Magnetic resonance imaging (MRI) has become a novel and widely used technique to investigate the pathogenesis of various neuropsychiatric disorders. Previous structural MRI studies revealed atrophy of the gray matter (GM) in extensive brain regions on T2DM [8,31], most consistently in the middle temporal gyrus (MTG). However, results for other brain regions are inconsistent. For example, the medial temporal lobe (MTL) was found to be atrophied [12,16], or unchanged [8]. MTG [28] and MTL [9] may play the central role in cognitive decline associated with T2DM. The aforementioned studies mainly focused on non-demented T2DM patients, including both with and without MCI. Thus, this discordance could be due to the cognitive status in T2DM. It is necessary to explore the potential brain GM alterations of T2DM with or without MCI relative to the normal controls.

Voxel-based morphometry (VBM) [2] is a nonbiased and fully automated whole-brain technique for indirect volumetry using voxel-by-voxel analysis. VBM has been widely used in characterizing subtle changes in brain GM structure in a variety of diseases associated with neurological and psychiatric dysfunction, such as AD and MCI [13,15].

The present study divided T2DM patients into non-MCI and MCI groups to explore potential GM volume changes using VBM analysis. In addition, the relationships between potential GM volume changes and cognitive impairment were also investigated.

2. Materials and methods

2.1. Participants

Three age-, gender- and education-matched groups of participants were studied, including 28 T2DM patients with MCI, 25 T2DM patients without MCI and 29 healthy controls (HC). The patients with T2DM were diagnosed using the criteria recommended by the American Diabetes Association (ADA)-2010 [3]. The Beijing version of the Montreal Cognitive Assessment (MoCA) was applied to assess the cognitive situation of each participant as a brief screening tool for MCI [27]. The diagnosis of MCI was based on the criteria established in the 2006 European Alzheimer's Disease Consortium [23], which include complaints of hypomnesis, mini mental state exam (MMSE) score > 24, MoCA score < 26, clinical dementia rating (CDR) $\geq$ 0.5 and normal activities of daily living (ADL) score. We composed a control group of 29 HC with no history or symptoms of diabetes, psychiatric or neurologic disease, and MoCA $\geq$ 26. All of the participants were right-handed and underwent the MMSE to exclude dementia.

All patients underwent clinical and biochemical tests. The MRI scans were performed within the first 24 h after diagnosis. All of the patients were recruited from the general population in Departments of Endocrinology and Gerontology of Southwest Hospital.

Participants with history of known stroke, dementia, alcoholism, head injury, Parkinson's disease, epilepsy, major depression (excluded by the Hamilton depression rating scale) or other neurological or psychiatric illness (excluded by clinical assessment and case history), major medical illness (e.g., cancer, anemia, diabetic ketoacidosis and thyroid dysfunction), white matter hyperintensity lesions on MRI and severe visual or hearing loss were excluded from the study.

This study protocol was approved by the Ethics Committee of Southwest Hospital, Chongqing, China. All participants were advised of the experimental objectives, procedures, and possible risks before MRI scan. Written informed consent was obtained from each participant prior to the study.

2.2. MRI acquisition

All imaging data were obtained using a Siemens 3-T TIM Trio MRI system (Erlangen, Germany) equipped with the standard eight-channel head coil. For each participant, conventional brain T1-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images were obtained to exclude organic disease and white matter (WM) hyperintensity lesions. All MR images were assessed by two experienced radiologists. High-resolution sagittal T1-weighted structural images were acquired using a three-dimensional (3D) magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence with the following parameters: TR = 1900 ms, TE = 2.52 ms, flip angle (FA) = 9°, slice thickness = 1 mm, matrix = 256 × 256, voxel size = 1 × 1 × 1 mm^3 and 176 slices.

2.3. VBM data analysis

The T1 weighted images were processed and examined using the VBM8 toolbox [1] (http://dbm.neuro.uni-jena.de/vbm8/) with default parameters running in the statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm).

The processing steps were briefly presented as follows: (1) All T1-weighted brain structural images were spatially normalized into the identical Montreal Neurological Institute (MNI) coordinate system on a voxel-by-voxel basis [2]. (2) All standardized brain structural images were effectively segmented into GM, WM and cerebrospinal fluid (CSF) using the new Segment and Dartel modules included in SPM8. (3) The segmented, modulated GM images were smoothed with an 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. Global measures of GM, WM and CSF volumes were calculated from the modulated normalized segmented images. The total intracranial volume (ICV) was calculated from the sum of the global measures of the three tissue types.

Voxel-by-voxel comparisons of GM volumes between groups were performed using two-sample t-tests based on the general linear model in SPM8 (age and gender as confounding covariates). We calculated the positive contrasts (HC > T2DM without MCI, HC > T2DM with MCI, T2DM without MCI > T2DM with MCI, MCI > T2DM with MCI) and the negative contrasts. The threshold level for the statistical significance of between-group differences among the three groups was set at $P < 0.05$ using the AlphaSim correction (with a combination of a threshold of $P < 0.001$ and a minimum cluster size of 151 voxels). This correction was conducted using the AlphaSim program in the REST software [7].

2.4. Statistical analysis

2.4.1. Demographic and clinical characteristics analysis

Statistical analysis was performed using the PASW version 18.0 statistical software package (PASW for Windows, Chicago, IL, USA). The differences in demographic and clinical characteristics between patients and controls were analyzed using one-way ANOVA and the two-tailed *t*-test, and Chi-square tests were used for gender differences. A *P*-value less than 0.05 was considered statistically significant.

2.4.2. Total GM volume comparisons

Statistical differences in the total GM volume among the groups were estimated by an ANCOVA model with age, gender, education