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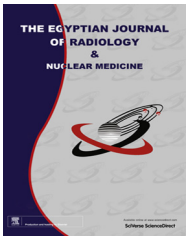

ORIGINAL ARTICLE

In vivo neurobiochemical changes of the posterior cingulate gyrus in patients with Alzheimer's disease detected by multivoxel proton magnetic resonance spectroscopy

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KEYWORDS

Proton magnetic resonance spectroscopy;
Posterior cingulate;
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Abstract *Aim of the work:* To study the neurobiochemical changes in patients with Alzheimer's disease (AD) by multivoxel 1H-MRS.
Materials and methods: Twenty-five patients with probable AD and 12 age- and sex-matched normal controls were subjected to assessment of cognitive functions by the Mini Mental State Examination (MMSE) and imaging with multivoxel 1H-MRS for measuring the NAA/Cho, NAA/Cr, Cho/Cr, MI/NAA and MI/Cr ratios in the posterior cingulate gyrus (PCG) bilaterally.
Results: Patients with AD showed significant decrease in NAA/Cho and NAA/Cr, significant increase in MI/NAA and MI/Cr and non-significant increase in Cho/Cr ratios compared to control. Also, the severity of cognitive impairment was significantly associated with these changes. The NAA/Cho ratio at a cut-off value $\leqslant 1.14$ showed accuracy (94%), the NAA/Cr ratio at a cut-off value $\leqslant 1.40$ showed accuracy (97%), the Cho/Cr ratio at a cut-off value > 1.29 showed accuracy (85%), the MI/NAA ratio at a cut-off value > 0.60 showed accuracy (98%), and the MI/Cr ratio at a cut-off value > 0.83 showed accuracy (97%).

Abbreviations: MMSE, Mini Mental State Examination; 1H-MRS, proton magnetic resonance spectroscopy; AD, Alzheimer's disease; PCG, posterior cingulate gyrus; ACG, anterior cingulate gyrus; MCI, mild cognitive impairment; NAA, N-acetylaspartate; Cho, choline; Cr, creatine; MI, myo-inositol; Lac, lactate

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Conclusion: The multi-voxels 1H-MRS of the PCG is sensitive to biochemical changes in AD. The 1H-MRS peak metabolite concentration ratios may be useful as markers for the progression of AD.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in elderly people. It is a progressive neurodegenerative disease that affects cortical and subcortical structures leading eventually to irreversible loss of neurons, particularly in the cortex (1). In the early stages, the most common symptom is the difficulty in remembering recent events, which is often mistakenly thought to be age-related concerns (2). As the disease advances, symptoms can include confusion, irritability, aggression, mood swings, language problems and long-term memory loss. Patients often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death (3). AD develops for an unknown and variable amount of time before becoming fully apparent, and it can progress undiagnosed for years (4). Patients with AD rely on others for assistance, placing a great burden on caregivers; with eventual social, psychological, physical and economic effects of caregiver's life (5). In developed countries, AD is one of the most costly diseases to the society (6).

Neuroimaging techniques may have an important role in the clinical evaluation of AD for early diagnosis, differential diagnosis and monitoring of disease activity. The proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive imaging modality for biomarkers in AD, which is important for both early diagnosis and evaluating treatment effects. This imaging technique may provide a window into the biochemical changes associated with the loss of neuronal integrity and other neurodegenerative pathology that involves the brain before the manifestations of cognitive impairment in patients who are at risk for AD (7).

The neural network correlates of consciousness are unevenly distributed neuronal aggregates involved in conscious awareness. A critical node in this network is the posterior cingulate gyrus (PCG), which is the backmost part of the cingulate cortex lying behind the anterior cingulate gyrus (ACG), the upper part of the limbic lobe. The cingulate cortex is made up of an area around the midline of the brain. The PCG is commonly affected by neurodegenerative disease. Reduced metabolism in the PCG is an early sign of AD and is frequently present before clinical diagnosis (8). Furthermore, 1H-MRS of the PCG was more sensitive to the biochemical changes in patients with mild cognitive impairment (MCI) and AD than 1H-MRS of other neocortical regions in the brain (9).

With the aim of further contributing to the knowledge of the in vivo neurobiochemical changes of normal aging and AD, we carried out the present study performing multi-voxel 1H-MRS on the PCG of patients with AD and age-matched controls.

2. Materials and methods

2.1. Study participants

This study, performed from March 2012 to August 2013, included 25 patients (15 males and 10 females; age ranged from 64 to 85 years; mean 72.3 ± 10.4 years) referred to the Neurology Department of our institution fulfilling the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (10). The Mini Mental State Examination (MMSE) test was used to evaluate the degree of cognitive impairment (11). Twelve normal subjects (8 males, 4 females; age ranged from 51 to 92 years; mean 71.2 ± 11.4 years) were selected amongst relatives or caregivers of the studied patients and served as the control group. All of them had a clinical history negative for neurological disease, mental disorder, head trauma or other relevant pathologies such as stroke, and scored >26 on MMSE. Illiterate subjects, subjects with physical problems interfering with test interpretation (for example, physically unable to hear or read instructions properly), or subjects with motor deficits affecting writing and drawing skills were ruled out. Additionally, we excluded patients with any metabolic illnesses that affect the cerebral peak metabolite concentration ratios such as diabetes mellitus as it was proved that myo-inositol/creatine (MI/Cr) ratio increases in the brains of patients with diabetes mellitus (12). Neither patients nor controls were taking any medications at the time of examinations. An informed consent from subjects enrolled in the study and/or their caregivers was obtained. An official permission to carry out the study was also obtained from the responsible authorities.

The MMSE is a brief 30-point questionnaire test that is commonly used to screen for dementia. It is also used to estimate the severity and follow the course of cognitive impairment. In the MMSE, any score greater than or equal to 26 points (out of 30) indicates a normal cognition. Below this, scores can indicate severe (⩽9 points), moderate (10–18 points) or mild (19–25 points) cognitive impairment (13). So, patients were further divided into three subgroups according to their points on the MMSE into mild, moderate and severe AD.

2.2. Imaging procedures

Study participants were examined initially with MRI and then with multivoxel 1H-MRS by using 1.5-Tesla MR unit, which had a spectroscopy capability (Signa Horizon SR 120; General Electric Medical Systems, Milwaukee, WI, USA) using a standard quadrature head coil (28 cm quadrature birdcage resonator). The MRI studies comprised the following sequences: multiplanar axial T1-weighted fast spin-echo (T1WFSE) with repetition time/echo time/number of excitations (TR/TE/NEX) of 500/14/2, multiplanar axial T2-weighted fast spin-echo (T2WFSE) with TR/TE/NEX of 4000/126/2, and axial fluid-attenuated inversion recovery (FLAIR) with TR/TE/NEX of 8000/142/1 and inversion time (TI) of 2200 ms (ms).

2.3. 1H-MRS protocol

The 1H-MRS was performed by using two-dimensional multivoxel long-echo (TE of 144 ms) point-resolved spatially