Myo-inositol in geriatric patients with cognitive impairment

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Abstract

Background & Objective: Cognitive impairment, in geriatric population, is reported in patients with depression, mild cognitive impairment (MCI), and dementia. MCI is the transitional stage before dementia, with annual conversion rate to dementia of about 20%. Early diagnosis of the underlying cause of cognitive impairment in geriatric patients is crucial for proper management. This could be achieved through proton magnetic resonance spectroscopy. We aimed to study the difference of frontal, posterior cingulate gyrus, and occipital myo-inositol (MI), and myo-inositol/creatine (MI/Cr) ratio between patients with MCI, and cognitive impairment associated with geriatric depression; and study if these metabolites could differentiate between MCI and cognitive impairment associated with geriatric depression.

Methods: Geriatric patients with MCI, and elderly patients with depression associated with cognitive impairment, along with sex and age matched healthy control were evaluated clinically and underwent neuropsychological testing, laboratory tests as well as brain MRI and proton magnetic resonance spectroscopy at baseline. Patients were reevaluated clinically, and neuropsychologically at 12, and 24 months from baseline.

Results: The present study included 62 subjects. Patients with MCI had significantly higher posterior cingulate gyrus, occipital MI/Cr ratio, and frontal MI and MI/Cr ratio than normal controls. No differences were seen between geriatric patients with cognitive impairment associated with depression and those with MCI and healthy control in any of the studied metabolites in the studied brain regions.

Conclusion: Elevated posterior cingulate gyrus, occipital, and frontal MI/Cr ratio, and frontal MI level could help to identify patients with MCI from healthy control, but could not differentiate between MCI and cognitive impairment associated with depression.

Keywords: Mild cognitive impairment, geriatric depression, myo-inositol, magnetic resonance spectroscopy.

INTRODUCTION

The commonest cause of cognitive impairment in geriatric population is Alzheimer’s disease (AD). Worldwide, more than 35.6 million people have AD.1 Mild cognitive impairment (MCI) is the transitional stage prior to dementia.2 Almost, 20% of patients with MCI develop dementia every year.3 Depending on cultural circumstances, the prevalence of depressive disorders among geriatric population range from 10 to 20%.4,5 Depression may be the early presenting feature of AD, at the same time, MCI is reported in about 38% of patients with depression.6 Accordingly, the diagnosis of depression, or MCI could be difficult in the elderly.8

Several neuroimaging tools such as PET or SPECT are helpful to diagnose MCI, Alzheimer’s disease (AD), and other diseases.9,10 However, these tools might not have strong specificity for clinical diagnosis, and the clinical use of these imaging is still limited because of the high costs11, difficulty and scarcity of these investigations,
and at the same time, in most parts of the world, these investigations are still seen as research rather than diagnostic tools. Although MRI is a reasonable tool to evaluate brain volume, and the degree of tissue atrophy in patients with cognitive impairment, it usually misses the identification of early neuropathological changes.\textsuperscript{12,13}

In vivo measurement of early brain metabolite changes that usually occur before structural changes could be accomplished by proton magnetic resonance spectroscopy (\textsuperscript{1}H-MRS). The distinct advantage of MRS is that it requires neither radioactive tracers nor ionizing radiation.\textsuperscript{14} \textsuperscript{1}H-MRS values of certain bioactive molecules are considered as index of tissue viability, integrity, and metabolic turnover in a specific central nervous system (CNS) location.\textsuperscript{15} This technique is useful in the study of focal, diffuse, and heterogenous lesion of the CNS, it is used in presurgical evaluation of epileptic focus, classification, evaluation of recurrence, and radiation necrosis of brain tumor, multiple sclerosis, evaluation of ischemic penumbra of stoke, developmental dysgenesis, head trauma, and metabolic and degenerative diseases of the central nervous system.\textsuperscript{16} \textsuperscript{1}H-MRS has been used for early diagnosis, differential diagnosis, and subsequent monitoring of patients with cognitive impairment, and to measure the effects of pharmacological treatments.\textsuperscript{17,18} Over the past decade, different brain regions have been studied with MRS in MCI patients compared to healthy control especially the posterior cingulate, the hippocampal areas, the posterior white and gray matter, and the frontal areas. The main findings were decreased N-acetyl aspartate (NAA)/creatinine (Cr.) ratio and elevated myo-inositol (MI) concentration in patients with MCI. However, the results for myo-inositol (MI)/Cr. ratio were inconsistent.\textsuperscript{19} MRS studies in depression reported abnormalities in the frontal cortex, occipital cortex, hippocampus, basal ganglia, and anterior cingulate cortex, however, the results were not consistent.\textsuperscript{14} MI is a precursor in the phosphatidylinositol second messenger system, and is predominantly located in glial cells. It is considered as a glial marker; low glial densities are associated with low MI level while gliosis is associated with an increased level.\textsuperscript{20} Previously, it had been suggested that MI may be a robust and sensitive indicator for AD pathology than NAA and could have value as a marker of early brain changes in MCI.\textsuperscript{21} Moreover, frontal, occipital lobes and posterior cingulate gyrus have pathophysiological roles and involved early in cognitive and depressive disorders.\textsuperscript{22-30}

In geriatric population, cognitive decline could be a sign of depression, MCI, or AD. Differentiation between functional (depression) and organic causes of cognitive impairment in geriatric population is challenging, and is essential for early therapeutic intervention. Because of the involvement of frontal, occipital, and posterior cingulate areas in cognitive process, and the robust value of MI for AD pathology, we hypothesized that it is worth to study this metabolite in these brain areas in geriatric patients with MCI, and depression. Our goals were (a) to study the difference of frontal, posterior cingulate gyrus, and occipital myo-inositol (MI), and myo-inositol/creatine (MI/Cr) ratio between patients with MCI, and cognitive impairment associated with depression, (b) to study if these metabolites could differentiate between MCI and cognitive impairment associated with depression.

\section*{METHODS}

This study was a prospective case control study of geriatric patients with cognitive disturbances attending outpatient clinics, Prince Sattam Bin-Abdulaziz University Hospital, Saudi Arabia. Elderly patients with cognitive impairment and/or depression were recruited from neurology and psychiatry clinics during the period from December 2016 to November 2020. Patients with the diagnosis of MCI, or depression were included in the study for further workup. Age and sex matched healthy volunteers were included as a control group. The study was approved by local Institutional Review Board. A written informed consent was taken from the patients or their caregiver. All subjects underwent comprehensive medical evaluations during the first week before starting medication, including medical history, neurological and psychiatric examinations, neuropsychological testing, laboratory tests as well as brain MRI and \textsuperscript{1}HMRS. In order to detect the progression of MCI to probable AD, and to evaluate the outcome of patients with depression clinical evaluation, and neuropsychological testing were performed at baseline and after 12, and 24 months. Subjects were excluded from the study if they had symptoms or signs of cerebral strokes, major neurological diseases that could affect cognitive function, AD, major psychiatric disorders other than depression, comorbid dementia with depression, thyroid dysfunctions, seizures, alcohol or drug abuse or dependence, or any contraindication to MRI. Diagnosis of MCI and depression were made in accordance with
the Diagnostic and Statistical Manual of Mental Disorders fifth edition. Diagnosis of probable AD was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) group criteria. MCI patients who converted to probable AD, and patients with depression who improved during the follow up period were included in the study for further analysis. All subjects were evaluated by Geriatric Depression Scale (GDS) (not validated translated tool), and Montreal Cognitive Assessment Arabic version (MoCA) (validated Arabic translation). Subject with MoCA score of ≥ 26 is considered as having normal cognitive abilities. Regarding GDS, a score > 5 points is suggestive of depression, and a score ≥ 10 points is almost always indicative of depression.

All subjects underwent MRI and 1H-MRS studies on a 1.5-T scanner (1.5 T Philips Ingenia MRI system). Conventional MR images were obtained. 1H-MRS was used to measure MI level and MI/Cr ratio in three brain regions, 1H-MRS voxel of interest measuring 20 × 20 × 20 mm³ was placed in normal appearing left frontal white matter (Figure 1), the second voxel included the right and left PCG (Figure 2), the third voxel included the left occipital cortex (Figure 3).

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 13.0. Descriptive statistics were calculated. Difference between genders was evaluated by nonparametric Chi Squared test. Group differences in age, GDS, MoCA, and metabolite concentrations were evaluated by one-way analysis of variance (ANOVA), Bonferroni post hoc analysis was used. Pearson’s correlation coefficient (r) was employed to analyze the association between the different variables. Values of p ≤ 0.05 were considered to be statistically significant.

RESULTS

The present study included 48 patients with MCI, 32 patients with depression associated with cognitive impairment, and 19 age and sex matched healthy control. 11 patients with MCI

Figure 1. The location of MRS voxel in the left frontal white matter

Figure 2. The location of MRS voxel in the right and left PCG
were excluded (1 death, 4 missing follow up, and 6 not tolerating MRI), of the remaining, 18 patients converted to probable AD during the follow up period. For patients with depression, 7 patients were excluded (2 missing follow up, 2 developed features of probable AD, and 3 not tolerating the MRI). At the end of follow up period, 62 subjects were included (18 patients with MCI, 25 with depression, and 19 healthy control), 35 (56.5%) of them were male. There were no significant age and gender differences between subjects’ subgroups.

GDS, and MoCA scores differed between groups as expected. The highest GDS score was reported among patients with cognitive impairment associated with depression. Regarding MoCA scores, patients’ subgroups had significantly lower MoCA scores compared to normal controls (Table 1).

Frontal lobe showed significantly higher MI, and MI/Cr ratio in patients with MCI than normal controls, while, no differences were reported between depressed patients and healthy control or between depressed patients and MCI patients. The Cr. level was stable among the studied groups.

Occipital lobe and posterior cingulate gyrus MI/Cr ratios were significantly higher in patients with MCI compared to healthy control, and it did not differ between MCI and depressed patients or between depressed patients and healthy controls, at the same time, the MI, and Cr. levels did not differ between the studied subgroups (Table 2).

No significant correlations were reported between GDS and MoCA and the measured metabolites in the studied population in any of the three studied brain areas.

**DISCUSSION**

The present study showed that, elevated PCG, occipital, and frontal MI/Cr ratio, and frontal MI level could differentiate patients with MCI from healthy subjects, but could not differentiate between MCI patients and depressed patients with cognitive impairment or between depressed patients with cognitive impairment and healthy subjects.

Frontal MI level was significantly higher in MCI patients than healthy controls, however

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**Table 1: Demographic, and clinical data of the studied groups**

<table>
<thead>
<tr>
<th></th>
<th>I No. 25</th>
<th>I</th>
<th>II No. 18</th>
<th>II</th>
<th>III No. 19</th>
<th>III</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>Mean (± SD)</td>
<td>64.7 (± 3.1)</td>
<td>64.2 (± 3.4)</td>
<td>63.9 (± 3.3)</td>
<td>0.698</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>No. (%)</td>
<td>14 56</td>
<td>10 56.6</td>
<td>11 57.9</td>
<td>0.310</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>No. (%)</td>
<td>11 44</td>
<td>8 44.4</td>
<td>8 42.1</td>
<td>0.310</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS</td>
<td>Mean (±SD)</td>
<td>10.2 (± 2.4)</td>
<td>2.2 (± 1)</td>
<td>1.7 (± 0.7)</td>
<td>0 vs II P&lt;0.001 I vs III P&lt;0.001</td>
<td></td>
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<tr>
<td>MoCA</td>
<td>Mean (±SD)</td>
<td>21.9 (± 2.1)</td>
<td>21.3 (± 2.2)</td>
<td>27.8 (± 0.9)</td>
<td>0 vs III P&lt;0.001 II vs III P&lt;0.001</td>
<td></td>
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</tbody>
</table>

I = cognitive impairment associated with depression, II = mild cognitive impairment, III = control subjects, GDS = The Geriatric Depression Scale, MoCA = Montreal Cognitive Assessment Arabic version, SD = standard deviation. Significance level is set at P ≤ 0.05.
No significant differences were found between depressed patients with cognitive impairment and either MCI patients or healthy controls. At the same time, no significant differences were found between the studied groups regarding the PCG, and occipital MI levels. In accordance with our results, Watanabe et al. (2010) reported stable MI concentration in patients with MCI in the PCG and occipital lobe. However, the occipital MI level was found to predict the progression of MCI to AD with high specificity. In the study of Siger et al. (2009), MI increases, in MCI patients, primarily in parietal lobe white matter but, during the progression to AD MI increases in both frontal and parietal lobes white matter. In partial contradictory to our results, the PCG MI concentration was significantly increased in MCI patients compared to healthy control in some previous studies. In patients with late life depression, the medial prefrontal cortex MI concentration was not different from healthy control subjects. In drug free depressed patients, there was a trend for higher MI level in the dorsolateral prefrontal cortex compared to healthy control.

In the present study, patients with MCI had significantly higher PCG, occipital, and frontal MI/Cr ratio than control group, while no differences were reported between patients with cognitive impairment associated with depression and patients with MCI or control groups. Moreover, the Cr. levels were stable among the studied groups in the studied areas. In partial accordance with our results, Kantarci et al., (2000) examined metabolic ratios in the left temporal lobe, the PCG, and the medial occipital lobe of MCI patients and reported a significant increase of MI/Cr. ratio in the PCG in patients with MCI compared the healthy control. In other study, it was higher in PCG in patients with MCI compared to healthy subjects, but, the difference was not significant. In the study of Fayed et al. (2008) the MI/Cr. ratio from left occipital lobe and PCG did not differ in patients with depression and cognitive impairment from those with MCI. Previous studies reported no significant differences between MCI patients and healthy subjects regarding the PCG MI/Cr. ratio, and Cr. Concentration. It had been reported that, in patients with late life depression, the frontal white matter MI/Cr. ratio did not differ from healthy control. In non-geriatric depressed patients; the frontal MI/Cr. ratio was not similar across the studies, some reported decreased ratio, one study reported an increased ratio (48), while other one reported no difference. Moreover, creatine which plays...
a central role in maintaining energy stores, is considered to be relatively constant, and it has been used as an internal standard for comparison.50

Patients with MCI had been found to have higher MI/Cr ratio than normal subjects but significantly lower ratio than AD patients, moreover, in a histopathological study of metabolites in MCI, the MI/Cr ratio had been found to be correlated to the neuritic plaques and neurofibrillary tangles, and the MI metabolites change precede NAA changes. The increased MI in MCI patients could reflect early pathological changes including increased inflammatory process which might develop in response to amyloid deposition, and gliosis.51 These pathological changes might precede AD neuronal dysfunction.52,53 In MCI patients atrophy of the temporal region occurs early followed by atrophy of both the frontal lobe, and PCG.54 Moreover, glial activation often anticipating clinical manifestations and macroscopical brain alterations.55 It had been postulated that the increased MI level could reflect an early pathological activation of glial cells, inflammation, and disintegration of white matter fibers52 that could explain the increased MI and MI/Cr levels in our study.

The present study is one of the few studies in Arabic countries that measured MI, and MI/Cr levels in MCI and geriatric depressed patients with cognitive impairment. The inclusion of MCI patients who converted to probable AD and geriatric depressed patients with cognitive impairment who improved during follow up period unmask any uncertainty about the initial diagnosis. This study helps to identify patients with MCI from healthy subjects, but it was limited by some factors including, the relatively small number of patients that might be explained by the few numbers of elderly patients who fulfilled the criteria of inclusion in the study, and long follow up period, at the same time, a considerable number of patients could not tolerate or refuse to do MRI brain. We recommend further study that include other brain area and metabolites with large number of patients which might improve the classification of cognitive impairment in geriatric population.

In conclusion, elevated PCG, occipital, and frontal MI/Cr ratio, and frontal MI level could help to identify patients with MCI from healthy control, but could not differentiate between MCI and cognitive impairment associated with depression.

REFERENCES

DISCLOSURE
Financial support: None
Conflicts of interest: None


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