HOW MAGNETIC RESONANCE SPECTEROSCOPY CHANGES CAN DETECT EARLY ALZHEIMER'S?

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ABSTRACT

Background and purpose: Alzheimer's disease is one of the most common causes of dementia in elderly. Alzheimer's disease and vascular dementia together accounts for more than 50% of dementia in elderly. The early stage of Alzheimer's disease is known as the mild cognitive impairment (MCI) which is as the gradual impairment in cognitive functions with relatively intact daily life activities.

Purpose: To detect the role of MRS in the prediction of MCI (early Alzheimer's disease) to allow early prevention of the disease before conversion of MCI to AD.

Patients and Methods: This study included 40 patients (27 males and 13 females) with age ranged from 50 to 69 years (mean age = 59.8 years). They were divided into two main groups, the first group pre-Alzheimer's (MCI) included 20 patients, and the second group (control group) included 20 patients. All patients underwent MRI and MRS using 1.5 T system.

Results: In our study, males were relatively more affected by than females. The mean age of MCI was 56.3 years. The most common symptom was memory dysfunction followed by psychological changes. The NAA/Cr ratio was significantly lower in MCI than control group in the hippocampal, temporal regions. Regarding mI/Cr ratio, it was significantly higher in MCI than control group. Finally the Cho/Cr ratio also was significantly higher in MCI than control group in the same areas respectively.

Conclusions: Mild cognitive impairment is the early stage of Alzheimer's disease. MRI and MRS are promising tools for the detection of early structural and functional changes occurring in MCI patients before the appearance of dementia manifestations.

INTRODUCTION

Alzheimer's disease (AD) represents 50-70% of all dementia cases in elderly population. Aging process is one of the major causes of the disease as it affects about 30% of elderly population above the age of 85 years. At the time of clinical presentation of dementia, significant irreversible brain changes is already present, and this what makes the diagnosis of AD at its early stage is highly essential. *(1)*

Most of the elderly develop mild course of a gradual cognitive deterioration, typically in memory, over their life span, but this degree of deterioration is minor and in most of the cases does not compromise the individual's life activities. *(2)*

Mild cognitive impairment (MCI) is known as abnormal cognitive state, but it does not meet the full criteria for the diagnosis of dementia. According to the new guidelines most of the published papers consider Alzheimer's disease (AD) involves not only dementia's state but also the pre-dementia phase or the MCI. *(3)*

Cognitive impairment (MCI) usually starts in middle age and increasing during older ages. Regarding the incidence rates of MCI, it was about 31.9% in people elderly above 60 years. But it is known that some population with MCI may remain stable or even return to normal over time. *(2)*So the challenge for radiologists and neurologists is the early diagnosis of MCI to allow early treatment and close follow up, trying to prevent the more neurological deterioration. *(4)*

Recent studies tried to assess the structural and functional abnormalities of the grey and white matter occurring in Alzheimer's dementia and MCI to provide the sufficient information about how to detect the disease

early enough before irreversible damages.[5]

MR spectroscopy is one of the non-invasive techniques that allow early detection of several naturally occurring compounds and metabolites within the human brain. These metabolites can detect structural and biochemical abnormalities in the brain of the demented patients [6]

These changes in the brain metabolites include variations in the NAA, choline, myo-inositol and creatine levels. Regarding the NAA, it is a free amino acid, detected in the brain within the cell bodies of the neurons. Its function is not clearly identified, but it is believed that it acts as cellular osmolite. Also it is considered a storage form of aspartate, and a precursor of N-acetyl-aspartate-glutamate. NAA is the most important marker for the health of neurons. So in cases of the disruption of mitochondrial energy and metabolism there is drop in the NAA concentration. [7]

The myo-inositol is one of the cyclic sugars required for cell growth and it is also has been considered as a glial cell marker. In MCI, reduced NAA combined with an elevated myo-inositol is thought to reflect the pathological neuronal loss combined with the replacement through gliosis. [8]

Creatine (Cr) is the marker of energy metabolism, it is present as a complex peak that is formed of creatine and phosphocreatine compounds. Creatine is involved in energy metabolism via the Creatine kinase reaction generating ATP. Another finding reported in MCI is the increase in the myo-inositol concentration, as well as its relation to the creatine. [9]

The Choline is an MRS marker which gives an idea about the products of cell membrane phosphotidyl choline breakdown and degeneration. Elevated Choline peak in MCI reflects cell membrane turnover due to neuro-degenerative process. [8]

PATIENTS AND METHODS

This study was included two groups the first group included patients with cognitive impairment admitted to neurology department in Mansoura University Hospital. It included 20 patients (13 males and 7 females), the age ranged from 50 to 69 years. We compared this group to another normal control group formed also from 20 normal individuals of similar age group.

All patients underwent scanning with 1.5 T MRI systems Signa HDe GE Healthcare Milwakee Wis Medical System and/or Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B (Siemens Medical system Inc., Erlangen, Germany. A Standard head coil was used for radiofrequency transmission and reception of the MR signal and restraining foam pads were used to minimize head motion. A scout sequence was run on each subject to help in slice positioning, then T1-weighted (T1W) and T2-wighted (T2W) images sets were acquired in the axial, sagittal and coronal planes. The T1W sequence was (time–to-repetition "TR"=500msec, field of view =4cm, matrix =256x256 slices, acquisition time =9:47 minutes). The T2W sequence was in axial, sagittal and coronal planes with fast spin echo (FSE) multiplaner sequence with flow compensation (TR=3530 msec ,TE=81and 70 msec, flip angle=90,sclice thickness 5mm, field of view=24cm, matrix=256x160 slices, acquisition time=10:35 minutes).

All subjects underwent multi-voxel 1H-MR spectroscopy. All MR spectroscopic examination was performed by using multi-voxel MR spectroscopy package. T1-Weighted images in the sagittal and coronal planes were obtained for localizing the 1MR spectroscopy voxels. 1MR spectroscopy voxels were placed over the hippocampus and temporal areas. A time-to-echo (TE) of 144 m sec and TE of 35 m sec was chosen to quantify the different metabolites (NAA, MI, Cr and Cho). The NAA/Cr, MI/Cr and Cho/Cr ratios were then determined for the hippocampus, temporal and parietal areas.

STATISTICAL ANALYSIS

Data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version

17.0 to obtain

Descriptive data:

Descriptive statistics were calculated in the form of:

1. Mean.
2. Standard deviation (±SD).
3. Minimum and maximum.

Analytical statistics:

In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests:-

1- Student's t-test:-Used to compare between mean of two groups of numerical (parametric) data.

2- ANOVA (analysis of variance):- Used to compare between more than two groups of numerical (parametric) data.

For continuous non- parametric data, Mann-Whitney U- test was used for inter-group analysis and Pearson correlation coefficient ® test was used correlating different parameters. Inter-group comparison of categorical data was performed by using chi square test (X2-value), Wilcoxon signed rank test was used for two values within the same group.

Some investigated parameters were entered into a logistic regression model to determine which of these factors is considered as a significant risk factor and identify its odds ratio.

The sensitivity and specificity maternal lipid profile to diagnose RDS of their neonates were examined at different cutoff points using ROC curve analysis to determine the best cutoff point as well as the diagnostic power of each test.

A P value <0.05 was considered statistically significant (S). And a P value <0.0001 was considered highly significant (HS) in all analyses.

RESULTS

The MCI group included 20 patients (13 males and 7 females), the age ranged from 50 to 69 years and the mean age was 59.8 years.

Clinically, memory disorders by different degrees were the main clinical complaint and it was present in all the patients. Followed by Behavioral and psychological changes

Table (1): showing the clinical presentation of the MCI patients.

Psychological changes	*Behavioral changes*	*Memory dysfunction*	
13	***16***	***20***	**No**
65%	%80%	100 %	**%**

Table (2): The differences in the MRS changes between MCI patients and control group.

P value	Control group	MCI group	Region of interest
			A-NAA/Cr
<0.0001	**1.81±0.23**	**1.52±0.19**	**1-Hippocampus**
<0.0001	**1.62±0.09**	**1.14±0.211**	**2-Temporal**
			B-MI/Cr
<0.001	**1.22±0.19**	**1.64±0.16**	**1-Hippocampus**
<0.001	**1.09±0.21**	**1.61±0.15**	**2-Temporal**
			C-Ch/ Cr
<0.001	**1.12±0.15**	**1.39±0.91**	**1-Hippocampus**
<0.001	**0.96±0.12**	**1.42±0.19**	**2-Temporal**

As regards the MRS changes, in this study the NAA/Cr ratio was significantly higher in control group than MCI patients in the hippocampal and temporal regions.

The MI/Cr ratio was significantly higher in MCI patients than control group in the hippocampal and temporal regions.

While the Cho/Cr ratio was also significantly higher in MCI patients than control group in the hippocampal and temporal regions.

Case 1

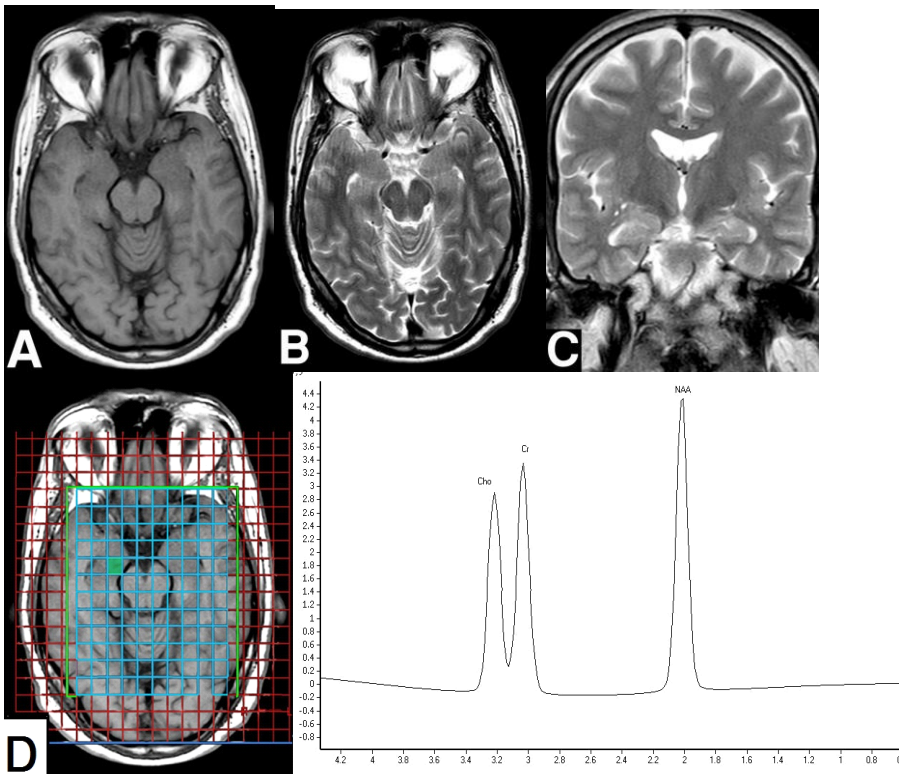

Figure A and B: axial T1WI, axial T2WI showing normal appearance of the hippocampus and ventricular system.

Figure C: coronal T2WI showing normal appearance of the hippocampus and ventricular system.
Figure D: Normal MRS of the right hippocampal region using multi-voxel technique with short TE (35msec).

Case 2

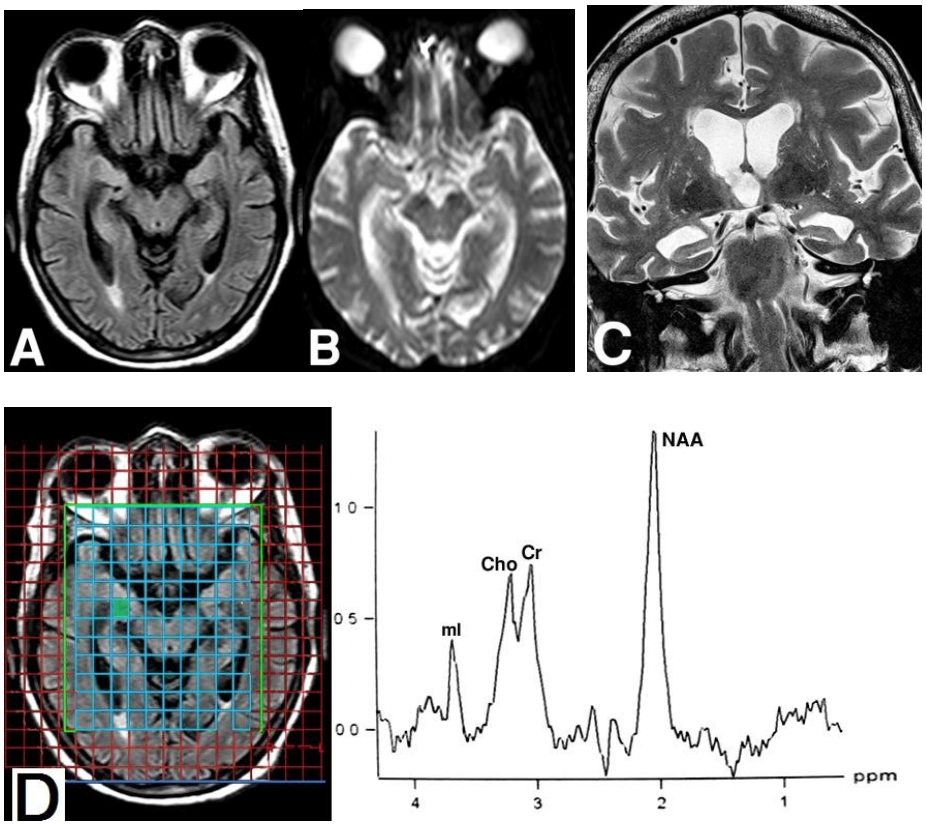

Figure A and B: axial T1WI, axial T2WI showing mild hippocampal atrophy.
Figure C: coronal T2WI showing normal appearance of the hippocampus and ventricular system.
Figure D: Showing the MRS changes in the right hippocampal region using multi-voxel technique with short TE (35msec) in the form of reduced NAA, elevated Cho and mI peaks

DISCUSSION

Alzheimer's dementia is the most common neurodegenerative diseases associated with aging and accounting for 60-70% of age-related dementia cases. In the year 2000 nearly 25 million individuals all over the world above the age of 60 were diagnosed with dementia, more over this number is expected to extend beyond 80 million by (2040). MCI is frequently considered the prodromal stage of AD, to the extent that MCI has been referred to as early-stage of AD (or the pre-Alzheimer's stage), and clinical manifestations of AD is now subdivided into the stage of MCI and the subsequent stage of AD dementia. ***(10).***

In the present study, the mean age of MCI patients was 50 to 69 years and the mean age was 59.8 years. This is in agreement with **Katz et al (2012)** [(11)], they reported that, the incidence of conversion of MCI into dementia especially AD increases with age. This was also in agreement with **Olazarán ei al., (2011)** [(12)] they studied about 176 patients and their study found that the percent of MCI was 46% and their ages were around 56 years. Also they found that after 1 year follow up 9.9% of the patients (8 patients) suffering from MCI progressed to Alzheimer's dementia during this time. Also there have been many researches that repeatedly connected major risk cognitive decline and dementia with the older age and lower level of education

Regarding the sex prevalence, in the current study, the MCI patients were (20)

patients, 13 males (65%) and 7 female (35%). The Reports of the association between the gender of the patients and MCI and/or dementia have been controversial. So there is also no strong agreement regarding the effect of gender on MCI occurrence; however, some recent researches find possible connection with male gender [13]

A large population-based study that was conducted by **Petersen et al., (2010)** [14] stated that the incidence of MCI was slightly higher in male than female gender.

As regards the clinical evaluation of the patients included in this study, all of them suffered from memory disorders in different degrees, and this was in agreement with the study carried out by **Grinberg et al., (2013)** [15] they mentioned that cognitive complaint (memory dysfunction) is a major and consistent finding in the affected patients with dementia and MCI.

The changes in the neuronal activity during the pathogenesis of MCI are associated with important changes in the brain metabolites. Brain metabolism can be measured accurately with magnetic resonance spectroscopy. Using (1H) proton MRS, many brain metabolites can be evaluated and measured. This includes N-acetyl aspartate (NAA), myo-inositol (mI), creatine (Cr), choline (Cho). [16]

In the present study, MCI patients showed lower NAA/Cr ratio and higher mI/Cr as well as Cho/Cr ratios than the control group. These differences were significant statistically in all areas of interest that included the hippocampus and temporal. Our study results are in agreement with many other 1H MRS studies which revealed that the changes mentioned before are due to two major pathological processes including the loss of neuronal integrity as well as the acceleration of neuronal gliosis. So the myo-inositol and the myo-inositol to creatine ratio show significant increase in cognitive impairment. Also the neuronal degeneration marker the choline and the choline to creatine ratio are elevated in MCI than in control group as a result of the ongoing neuro degeneration process. For the neuronal integrity marker NAA and the NAA to creatine ratio, they showed significant reduction when compared to the control group.

Our results are in agreement with **Graff-Radford and Kantarci, (2013)** [16] they reported that patients with cognitive impairment showed significant decrease in the NAA ratio when compared to the age-matched healthy control individual. Decreased NAA/Cr ratio was also detected in the areas of interest including the temporal lobe and the hippocampal region as a result of accumulation of pathological amyloid plaques and neurofibrillary tangles during the pathogenesis of the disease and this can be correlated to the degree of the severity of the neuro-degeneration. Therefore, reductions of the NAA levels reflect the loss of the healthy neuronal cells and deteriorated neuronal function of the remaining cells.*(17)*

Our results of increased myo-inositol level which is considered the gliosis marker are in agreement with **Fayed et al., 2017** *(18)* **and Shih et al., 2017** *(19)* these studies showed similar results of abnormally elevated myo-inositol levels in MCI patients especially in the affected anatomical locations.

Finally, it must be mentioned that MRI including MR spectroscopy should be combined with other clinical and laboratory methods as well as the pattern of brain atrophy in the patients with Pre-Alzheimer's disease so that we can reach the accurate diagnostic level. *(17).*

CONCLUSIONS

- Mild cognitive impairment (MCI) is considered the early stage of Alzheimer's disease.
- If untreated MCI may unfortunately progress to dementia state.
- Combined clinical, radiological and laboratory investigations allow early diagnosis, better treatment and follow up of those patients.

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