Role of DWI and MRS in diagnosis of Alzheimer’s and pre-Alzheimer’s disease

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ABSTRACT

Background and purpose: Alzheimer’s disease (AD) is a major cause of dementia in elderly affecting about 30% above the age of 85 years, while mild cognitive impairment (MCI) is the impairment in cognitive functions with intact daily life activities which is described as the preclinical phase of AD.

Purpose: To evaluate the role of DWI and MRS in prediction of pre-Alzheimer’s patients and differentiating them from those with AD.

Patients and methods: This study included 37 patients (24 males and 13 females) with age ranged from 50 to 73 years (mean age = 61.6 years). They were divided into two main groups, the first group pre-Alzheimer’s (MCI) included 24 patients, and the second group (AD) included 13 patients. All patients underwent DWI and MRS using 1.5 T system.

Results: In our study, males were more commonly affected by the two diseases, the mean age was 61.6 years and memory dysfunction followed by depression was the most common clinical symptom. Regarding DWI study, there were statistically higher ADC values in AD (0.97 and 0.94) than in MCI (0.90 and 0.79) in the hippocampal and temporal regions respectively. The NAA/Cr ratio was significantly higher in MCI (1.74 and 1.58) than in AD (1.41 and 1.05) in the hippocampal, temporal regions respectively. Regarding mI/Cr ratio, it was significantly higher in AD (1.51 and 1.47) than in MCI (1.10 and 1.11). The Cho/Cr ratio also was significantly higher in AD (1.27 and 1.38) than in MCI (1.02 and 0.99) in the same regions respectively. From the ROC curve analysis the NAA/Cr ratio was the most sensitive and specific in both regions.

Conclusions: Mild cognitive impairment is a term used to describe the pre-Alzheimer’s stage. Later, most of MCI patients develop Alzheimer’s dementia. The combination of DWI and MRS is promising tool for the detection of early structural changes occurring in MCI patients before the full manifestation of dementia syndrome starts to appear. Clinical significance: DWI and MRS help in early prediction, follow-up, and treatment of patients with pre-Alzheimer’s disease.

1. Introduction

Most of the elderly individuals follow a mild course of a gradual cognitive decline, typically in memory, but this degree of decline is minor and does not compromise a person’s ability to function. While fewer population go through life with virtually no cognitive decline, these individuals are regarded as aging successfully. On the other hand the cognitive decline in the elderly is due to the pathological aging of the brain resulting in dementia, and its most common type, Alzheimer’s disease [1].

Cognitive impairment (MCI) is defined as cognitive aging but without dementia. It usually starts in middle age and accelerates in old age. Regarding the incidence rates of MCI, it was about 31.9% in people older than 60 years with the incidence of the MCI has shown to be increased every 5 years. Also, MCI is considered as preclinical dementia, and the prevention of it is important clinically [2].
Nowadays, the challenge for neuroradiologists is the early diagnosis of this disorder in the pre-dementia state. This early diagnosis would identify who are targeted by treatment and close follow-up, trying to prevent the more neurological deterioration. Although the mild cognitive impairment (MCI) has been considered as an intermediate step between the normal state and Alzheimer’s disease (AD), not all MCI patients develop AD at the similar rate and even some patients never convert to AD [3].

Alzheimer’s disease (AD) accounts for 50–70% of all dementia cases in elderly population, and age is a main risk factor as the disease affects about 8% of the elderly above 65 years and 30% above the age of 85 years. At the time of clinical presentation of dementia, irreversible brain damage is already present, and this makes the diagnosis of AD at early stages of the disease an urgent prerequisite [4].

More studies tried to assess the structural and functional abnormalities of the gray and white matter occurring in Alzheimer’s dementia, and to detect whether the multimodal MRI evaluation can provide the sufficient information about how to differentiate between AD and the other types of dementia [5].

The main advantage of DWI is its ability to observe minor changes occurring at the microscopic level. The cellular microscopic barriers can normally restrict the Brownian motion of the water molecules within the tissue. But after breakdown of these structures, measurable difference in the diffusion of water molecules is observed by DWI and several studies suggest they even proceed the macroscopic atrophy [6].

MR spectroscopy is a non-invasive technique that allows the detection of naturally occurring metabolites in the human brain. These metabolites can detect structural alteration and biochemical abnormalities in the brain of demented subjects and may help in the differential diagnosis and early detection, monitoring disease progression, and evaluation of therapy [7].

One common finding that was reported in the MRS changes as associated with AD in the recent literatures is a decrease in the NAA and its ratio to the creatine. Multiple observations suggested that disruption of mitochondrial energy and metabolism leads to reversible drop in the NAA concentration [8].

On the other hand the myo-inositol is a cyclic sugar alcohol which is thought to be as a glial cell marker. In AD, a decreased NAA combined with an increase in mI is thought to reflect the pathological neuronal loss combined with the replacement through gliosis [9].

Creatine (Cr) is the marker of energy metabolism via the Cr kinase reaction generating ATP. In literatures, in AD the increase in the mI concentration, as well as its ratio to the creatine is suggested [10].

The high choline level as an MRS marker in AD patients may be a consequence of membrane phosphatidyl choline catabolism produced to provide free choline for the chronically deficient acetylcholine production in the [11].

2. Patients and methods

This study was conducted on patients with cognitive impairment and dementia admitted to neurology department in Mansoura University Hospital. It included 37 patients (24 males and 13 females), and the age ranged from 50 years up to 73 years. The mean age was 61.6 years.

Clinically, the patients suffered from memory disorders by different degrees. While, depression, anxiety and behavioral changes are the most clinical symptoms.

All patients underwent scanning with 1.5 T MRI systems Signa HD GE Healthcare Milwaukee 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, and then T1-weighted (TIW) and T2-weighted (T2W) image sets were acquired in the axial, sagittal and coronal planes. The T1W sequence was time–to–repetition “TR” = 500 ms, field of view = 4 cm, matrix = 256 × 256 slices, acquisition time = 9:47 min. The T2W sequence was in axial, sagittal and coronal planes with fast spin echo (FSE) multiplanar sequence with flow compensation (TR = 3530 ms, TE = 81 and 70 ms, flip angle = 90, slice thickness 5 mm, field of view = 24 cm, matrix = 256 × 160 slices, acquisition time = 10:35 min).

Diffusion weighted echo planar images were acquired in the axial plane (TR = 3200 ms, TE = 94 ms, FOV = 230 mm × 230 mm, 20 slices, slice thickness 5 mm with 1.5 mm gap, matrix size = 128 m × 128 mm).

The apparent diffusion coefficient (ADC) was obtained for the hippocampal, temporal, parietal, and frontal regions by 5 mm-sized manually defined roi at the regions of interest.

All subjects underwent multi-voxel 1H-MR spectroscopy. All MR spectroscopic examinations were 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, temporal and parietal areas. A time–to–echo (TE) of 144 ms and TE of 35 ms 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.

Water suppression of the dominant water signal by CHESS technique, outer volume fat suppression as well as magnetic shimming were performed automatically for all patients at the beginning of MRS examination. Curve fitting was done automatically for all obtained spectra. Post processing of the spectroscopic data consisted of frequency shift and phase and linear baseline corrections after Fourier transformation. These processes were automatic.

3. Statistical methods

Data were tabulated, coded and then analyzed using the computer program SPSS (Statistical package for social science) version 17.0 to obtain the following:

Descriptive data:

Descriptive statistics were calculated in the form of the following:

1. Mean.
2. Standard deviation (±SD).

Analytical statistics:

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

- ANOVA (analysis of variance): Used to compare between more than two groups of numerical (parametric) data.
- Inter-group comparison of categorical data was performed by using chi square test ($X^2$-value).

The sensitivity and specificity of ADC, mI/Cr, Ch/Cr and NAA/Cr to differentiate between MCI and AD were examined at different cutoff points using reciprocal operative curve (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.
4. Results

Our study included 37 patients, and they were divided according to the clinical examination followed by DWI and MRS into two main groups: the first group 24 patients with MCI and the second group 13 patients with Alzheimer’s disease. The mean age of Alzheimer’s disease (63.77 ± 5.99 years) is higher than that of MCI patients (57.78 ± 5.15 years). Also males were more commonly affected by the two diseases.

Clinically, memory disorders by different degrees are present in all the patients. While depression is the most common symptom, it was present in 41.6% of the patients included (suffering from both diseases). Anxiety affected 25% while behavioral changes affected 41.6% of the patients (see Tables 1 and 2).

It shows that AD patients (0.97, 0.94, 0.89, 0.92 and 0.83) had higher ADC value than MCI patients (0.9, 0.79, 0.82, 0.76 and 0.8) in the hippocampus, temporal, parietal, occipital and frontal regions with statistically significant differences.

As regards the MRS changes, in this study the NAA/Cr ratio was significantly higher in MCI patients (1.74, 1.58, and 1.59) than in AD patients (1.4, 1.05 and 1.79) in the hippocampal, temporal and parietal regions respectively. The ml/Cr ratio was significantly higher in AD patients (1.51, 1.47 and 1.47) than in MCI patients (1.1, 1.11 and 1.14) in the same regions, while the Cho/Cr ratio was significantly higher in AD patients than in MCI patients in the same regions.

5. Discussion

Alzheimer’s disease is the most common neurodegenerative diseases associated with aging and accounting for 60–70% of age-related dementia cases. In 2000, approximately 25 million people worldwide over the age of 60 were diagnosed with dementia; also this number is expected to reach over 80 million by 2040 and earlier diagnosis of AD is widely considered an important research goal for researchers. 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 are now subdivided into the stage of MCI and the subsequent stage of AD dementia [12].

In the present study, the mean age of MCI patients was 57.78 ± 5.15 years, and that of AD was 63.77 ± 5.99, and this was in agreement with Katz et al. [13]. They reported that, the incidence of dementia especially AD increases exponentially with age, and the highest incidence of the disease was between 60 and 80 years. The mean age of AD was higher than that of MCI, as the MCI represents the pre-dementia/pre-Alzheimer stage in most of cases. This was in agreement with Olazaran et al. [14] who studied 176 patients and they found 46.0% had MCI, and 10.2% had dementia at baseline. But after 1 year follow-up, 8 of their MCI patients (9.9%) showed progression to Alzheimer’s dementia.

Regarding the sex prevalence, in the current study, the MCI patients were 24, 16 males (66.6%) and 8 females (33.3%). The AD patients were 13, 8 males (61.5%) and 5 females (38.5%). The reports of the association between the gender of the patients and MCI and/or dementia have been controversial. A population-based prospective study was conducted by Petersen et al. [15] found that the incidence of MCI was higher in men than in women.

As regards age and sex in Alzheimer’s disease, the current study was in agreement with Rizzi et al. [16] and they reported that in the old ages, the incidence of AD is higher among males, while in very old ages, usually above 85, women may have slightly greater possibility to develop dementia than men. Another study was carried out by Mielke et al. [17] who reported higher incidence of AD in males than in females until age 78, after which females showed higher incidence than males.

As regards the clinical presentation of our patients, all of them were suffering from memory dysfunction in different stages, and this was in agreement with Grinberg et al. [18] who reported that, for the diagnosis of dementia, the first complaint is usually the cognitive complaint (memory dysfunction), while depression was the second common symptom. These findings were in agreement with Becker et al. [19] who reported that depression is a major symptom in the patients suffering from MCI. Depression and cognitive impairment/dementia usually co-exist and this makes it challenging to determine whether the depression is within the causal pathway leading to dementia or it is a consequence of the disease. Both theories are supported in the literature, suggesting that, there is no definitive answer for this question [20].

Regarding the diffusion MR imaging, in the current study, there was increase in the ADC values in AD patients with statistically significant differences when compared to the MCI patients in the hippocampus, temporal, frontal, occipital and parietal regions.

Table 1
The differences in the ADC value between MCI patients and AD.

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>MCI</th>
<th>AD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC HP</td>
<td>Mean ±SD</td>
<td>0.90</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>ADC T</td>
<td>Mean ±SD</td>
<td>0.79</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>ADC F</td>
<td>Mean ±SD</td>
<td>0.82</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>ADC P</td>
<td>Mean ±SD</td>
<td>0.76</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>ADC OCC</td>
<td>Mean ±SD</td>
<td>0.80</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2
The differences in the MRS changes between MCI and AD.

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>MCI</th>
<th>AD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-NAA/Cr</td>
<td>1-Hippocampus 1.41 ± 0.21</td>
<td>1.74 ± 0.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2-Temporal 1.05 ± 0.15</td>
<td>1.58 ± 0.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>3-Parietal 1.79 ± 0.08</td>
<td>1.59 ± 0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>B-ml/Cr</td>
<td>1-Hippocampus 1.51 ± 0.15</td>
<td>1.10 ± 0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2-Temporal 1.47 ± 0.13</td>
<td>1.11 ± 0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3-Parietal 1.51 ± 0.13</td>
<td>1.14 ± 0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-Ch/ Cr</td>
<td>1-Hippocampus 1.27 ± 0.8</td>
<td>1.02 ± 0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2-Temporal 1.38 ± 0.17</td>
<td>0.99 ± 0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3-Parietal 1.36 ± 0.08</td>
<td>1.02 ± 0.11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Zhang et al. [21] have studied 26 patients with MCI, 26 patients with AD and 18 normal controls. They reported higher ADC values from MCI patients compared to those of the normal control group in the hippocampus. They explained that the increased water diffusivity in AD and MCI occurs due to the disruption of the intracellular cytological skeletal framework due to neurofibrillary tangle formation. Neuronal loss also accompanies neurofibrillary changes, and the resultant expansion of the extracellular space would also be expected to cause an elevation of ADC in MCI patients than in normal control and in AD patients than those having MCI. Finally, glial activation was also associated with amyloid plaque formation, and that inflammatory process also resulted in expansion of the extracellular spaces, and subsequently causing a higher ADC value in both MCI and AD.

In the present study, higher ADC values were obtained also in the temporal lobes and these results were in agreement with the finding that the temporal lobe was one of the earliest structures that were involved in development of pathological changes in MCI and AD [21].

In addition, Reginold et al. used diffusion tensor imaging and tractography to reconstruct white matter tracts based on restricted diffusion of water molecules along myelinated axons and they found that there is significant disruption of tracts that can be detected as increased mean diffusivity (MD, degree of water diffusivity) in both MCI and AD.

**Case 1.** (A) Coronal FLAIR MR image showing mild bilateral hippocampal atrophy in mild cognitive impairment (MCI) case; (B–E) showing ADC values in the hippocampal, temporal, frontal, occipital and parietal regions respectively. (F) MRS changes in MCI case in the right hippocampal region in the form of decreased NAA, and minimal increase in Cho and ml peaks.
sion), increased axial diffusivity (AxD), increased radial diffusivity (RD) or decreased fractional anisotropy (FA, directional diffusion) in the temporal lobe white matter in patient with AD [22].

As regards MRS, the changes in neuronal activity during the progression of AD are associated with significant changes in the brain metabolites. Brain metabolism can be measured accurately with MRS. Using proton (1H) MRS, numerous metabolites related to brain functions can be detected, including N-acetyl aspartate (NAA), myoinositol (mI), creatine (Cr), and choline (Cho). NAA is the only metabolite present within neural cell body, axons and dendrites, so it is considered to be the marker of neuronal viability and function, while mI on the other hand, has higher concentration within the glial cells and thus it is often taken as a marker for gliosis [23].

In the present study, AD patients showed lower NAA/Cr together with higher mI/Cr and Cho/Cr than patients with MCI. The differences were statistically significant in all the studied areas (hippocampus, temporal and parietal). Our results are in agreement with other 1H MRS studies which showed that, the glial activation marker mI or the ratio of mI to creatine (mI/Cr ratio) and the membrane integrity marker Cho or the Cho: Cr ratio are elevated in MCI and AD. The neuronal integrity marker NAA or the NAA:Cr ratio tends to be decreased in patients with MCI and AD [7]. The decrease in the NAA level or NAA/Cr ratio was reported in several other studies on patients with MCI whom latter on developed AD and in patients with probable AD. Increased mI has been reported in patients with MCI and AD. In one 1H MRS study, Cho/Cr ratios longitudinally increased in patients with MCI that progressed to AD [11].

Our results are in agreement with Graff-Radford and Kantarci [24] who reported that AD patients had significant reduction in

Case 2

(A) Coronal FLAIR MRI image showing significant brain and bilateral hippocampal atrophy in Alzheimer’s disease (AD) case. (B–E) Showing ADC values in the hippocampal, temporal, frontal, occipital and parietal regions respectively (being higher than those in the MCI case in the different regions). (F) MRS changes in an AD case in the right hippocampal region in the form of significant decreased NAA, and elevated mI and Cho peaks.
the NAA levels when compared with age-matched healthy controls and also when compared with MCI patients and this was the most common 1H-MRS finding in AD. Reduced NAA/Cr ratios have been also shown in the posterior cingulate gyrus, temporal, occipital, parietal and frontal lobes.

These results are consistent with most of the in vitro studies that were done on the postmortem brains of AD patients, and these studies also showed that NAA reduction correlated with the severity of the neuro-pathologic findings, such as the pathological amyloid plaques, the neurofibrillary tangles, and the presence of the apolipoprotein E genetic markers. Therefore, reduction in the NAA levels may reflect either a loss of the neuronal cells or neuronal function or even both of them [7]. Increased ml has also been reported in several anatomic locations in AD, and this was an indicative of the increased glial cell content in AD if compared to MCI patients. Increased ml has been reported most frequently in the posterior cingulate gyrus, temporal, parietal, frontal white matter and occipital lobes [10].

Finally, it should be mentioned that neuro-radiologists have made a great effort since the initial use of MRI in AD imaging to assess changes in brain anatomy, specifically the brain shrinkage and regional changes in white matter. However these efforts should be combined with DWI, tractography using diffusion tensor imaging, MRS as well as the clinical and biochemical methods to reach accurate diagnostic level [25,26] (see Cases 1 and 2).

Limitations of the study:

– Some degree of irritability of the elderly patients.
– Longtime of examination.

6. Conclusions

• Mild cognitive impairment (MCI) is a term used to describe symptomatic patients who do not meet the criteria for dementia.
• The majority of individuals with MCI develop dementia in the near future.
• The multimodality MRI including DWI and MRS are promising tools for the detection of micro- and macro-structural changes occurring in brain, before the full manifestation of dementia starts to appear. This early diagnosis allows better treatment and follow-up of those patients.

Conflict of interest

We have no conflict of interest to declare.

References