Non-conventional MRI Study in Relapsing Remitting and Secondary Progressive Multiple Sclerosis

Sherif M. Hamdy¹, Maha A. Zaki¹, Dorreya Salem², Ahmed M. Abdelalim¹
Departments of Neurology¹, Radiology², Cairo University

ABSTRACT

Background: Multiple sclerosis (MS) is among the most venerable of neurological diseases and one of the most important by virtue of its frequency, chronicity, and tendency to attack young adults. Aim of the work: Evaluation of the clinical aspects of multiple sclerosis and its correlation with the results of MRS for better diagnosis, selection of treatment and prognosis of patients with multiple sclerosis. Patients and Methods: 50 patients [28 females and 22 males] with definite Multiple sclerosis and 20 healthy controls were subjected to: Thorough Clinical assessment, Routine Laboratory Investigation, Rating Scales including 1-EDSS 2-FSS 3-HDRS 4-MMSE, CSF examination for OCBs, Conventional MRI (including measurement of intercaudate ratio as a measure of central atrophy) and Single Voxel Proton MRS (¹H-MRS). Results: The course of the disease was RRMS in 62% and SPMS in 38% of the patients. A statistically significant higher FSS score was detected in patients with CSF positive for OCBs. Intercaudate ratio (ICR) was significantly higher in patients compared to controls and also in patients with moderate & severe disability (EDSS>3) compared to patients with minimal disability. A statistically significant lower NAA/Cr ratio in patients with MS was found compared to controls. NAA/Cr ratio was significantly reduced in patients with (EDSS>3) compared to patients with minimal disability. The Cho/Cr ratio was higher in the active cases (n=15) compared to the controls. A statistically higher mI/Cr ratio was found in patients compared to controls. Also, mI/Cr ratio was positively correlated to the EDSS scores in patients with SPMS. Patients with (EDSS>3) had a higher number of corpus callosum lesions compared to those with minimal disability. The EDSS score of patients was negatively correlated with NAA/Cr ratio and Cho/Cr ratio and positively correlated with the number of frontal lobe and Corpus callosum lesions. Conclusion: MRS helps better understanding of disease pathology as it could differentiate active from old lesions from resolving activity with treatment. Attention should be paid for patients with EDSS score 3 as this could point towards a sharp turn in the disease course that might necessitate disease modifying therapies at earlier stages. NAA/Cr ratio can serve as a reliable prognostic factor and predictor of conversion from a benign course to a rather aggressive or irreversible course. Cho/Cr is a reliable marker of disease activity even in absence of clinical or conventional neuroradiological evidence for activity. (Egypt J. Neurol. Psychiat. Neurosurg., 2006, 43(1): 479-494)

INTRODUCTION

Multiple sclerosis is the most common demyelinating disorder of the central nervous system and one the most common cause of disability in young adults. There are three main investigations that, because of their high specificity and sensitivity, are valuable in the diagnosis of MS: magnetic resonance imaging (MRI), evoked potentials; and cerebrospinal fluid (CSF) examination. T2 weighted brain MRI is abnormal in about 95% of patients with clinically definite MS.

The initiating cause of multiple sclerosis remains elusive, but the subsequent destruction within the central nervous system (CNS) involves immune mechanisms. In this regard, various subsets of leukocytes, including B lymphocytes, T cells, macrophages, and activated microglia, are found within lesions of MS. It is clear that extensive demyelination occurs in the CNS of individuals with MS. In some cases, demyelination is the result of the loss of myelin-forming oligodendrocytes, but in others oligodendrocyte numbers are relatively preserved and the atrophy originates in myelin. The loss of axons correlates very well with...
progressive disability, and the conversion from relapsing-remitting MS to progressive disease which may be due to the loss of axons beyond a certain threshold. Even in some cases there was loss of axons where the myelin remained intact. Thus, at least in some cases, MS may be a disease that involves an initial axonal injury that leads to inflammation and subsequent demyelination. Diffuse axonal injury in the normal-appearing white matter is already evident by N-acetylaspartate (NAA) spectroscopy in patients with definite MS who do not yet show clinically significant disability (Expanded Disability Status Scale < 2). Others have documented that whole brain NAA is reduced compared with that in normal individuals. Besides the axonal injury, it is now evident that neuronal loss is significant in MS. In MS, MRI-defined volume is reduced by 30%, with an equivalent decrease in the number of neurons demonstrated on histological evaluation, when compared with matched control cases. It is clear that MS is not only an inflammatory demyelinating disease but also a degenerative one that involves axons and neurons.

Conventional MRI is very sensitive for the detection of multiple sclerosis (MS) lesions, but it has relevant limitations, including the inability to differentiate the heterogeneous pathologic substrates of individual lesions and to delineate tissue damage that is known to occur outside macroscopic lesions, i.e., in the normal-appearing white (NAWM) and gray (NAGM) matter. Magnetic resonance spectroscopy can be used to detect the presence of cerebral metabolites and to measure their amount non invasively.

The aim of this work is to evaluation the clinical aspects of multiple sclerosis and its correlation with the results of the non-conventional imaging techniques that can evaluate the lesions quantitatively and qualitatively.

SUBJECTS AND METHODS

This study was conducted on 50 Egyptian patients with Multiple sclerosis and 20 healthy controls (with age & sex matching with patients) recruited from the Neurology outpatient clinic Kasr El-Aini University hospitals or admitted to the Neurology Department, Cairo University in the period from September 2003 and February 2006.

All patients have definite multiple sclerosis according to “McDonald” criteria and its revision. We excluded cases of uncontrolled risk factors. routine laboratory investigation for patients and controls should be normal for inclusion in the study.

Methods:

All patients were subjected to:

1. Thorough Clinical assessment:
   Including detailed history taking and clinical examination according to the Neurology Dept. Cairo University Multiple sclerosis sheet. The following informations were particularly stressed upon:
   a- Course of illness (relapsing remitting or progressive) according to Lubline and Riegold b- Duration of illness c- Mode of presentation (Initial symptom) d- Evidence of activity (Relapse within 1 month or progression) at time of assessment.

2. Rating Scales:
   I. Expanded Disability Status Scale (EDSS)
      The Kurtzke Expanded Disability Status Scale is a method of quantifying disability in MS in eight Functional Systems (FS): Pyramidal, Cerebellar, Brainstem, Sensory, Bowel and bladder, Visual, Mental and Other functions. EDSS scores up to 4.5 refer to people with MS who are fully ambulant. EDSS scores of 5.0 or more are defined by the impairment to ambulation. Patients were also classified to patients with minimal disability (EDSS 3 or less) and patient with moderate or severe disability (EDSS more than 3).
   II. Fatigue Severity Scale (FSS):
      It is a method of evaluating fatigue in multiple sclerosis. It is designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. Essentially, the FSS consists of
answering a short questionnaire that requires the subject to rate his or her own level of fatigue. The obvious problem with this measure is its subjectivity. People with depression alone score about 4. But people with fatigue related to MS average about 5 or more. FSS was performed to all controls to exclude fatigue as one of the inclusion criteria.

III. Hamilton Depression Rating Scale (HDRS):
It was developed to quantify the severity of depressive symptomatology. It is a 21-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. The score is given according to response and physician evaluation. Score from 0 to 9 is considered normal (no depression). A score of 10 or more is considered depression. It was performed to all controls to exclude those with depression.

IV. Minimental State Examination (MMSE):
It is a widely used method for assessing cognitive mental status the patient is given a score out of 30. A score of less than 24 is considered impairment of cognitive functions.

3. Cerebrospinal fluid examination:
Thirty patients underwent CSF examination for 1- Chemistry: total proteins, glucose, and chloride. 2- Cytology: total & differential leukocytic count. 3- Immunology: CSF electrophoresis for oligoclonal bands. CSF was considered positive if it fulfills the following criteria: I- Normal Chemistry II- Pleocytosis<50 cells III- Positive OCB.

4. Neuroradiological assessment:
Magnetic Resonance imaging was performed for patients and control groups on a 1.5 Tesla Philips Intera® Scanner
A) Conventional MR
Conventional MRI was used as a part of the McDonald criteria. The following data was collected from the conventional MRI:

a. Site & number of lesions
b. Intercaudate ratio (ICR) Intercaudate distance (ICD) was defined as the minimum distance between the medial borders of caudate nuclei identified on the axial slices. ICR was defined as ICD divided by the transverse width of the inner table of the skull at the same level. It was calculated as a measure of the degree of brain atrophy. The measurements were performed using DicomWorks® software.

B) Non-Conventional MRI
Single Voxel Proton Magnetic Resonance Spectroscopy (H1-MRS) was performed using the automated SV MRS Package (proton brain examination/SV [PROBE/SV]) (Philips Medical Systems®) for all patients and healthy controls.

Preparations:
Axial T2-weighted images, Coronal T2-weighted images and sagittal T1-weighted images were used to place the VOI in 3 planes with an average volume of 8 ml (20 x 20 x 20 mm). The Lesions were selected from the periventricular region, preferably parietal lobe region for the technical feasibility of adequately avoiding CSF & gray matter signal in this area and to standardize the site for comparison between the patients and controls. Volume of interest (VOI) was carefully placed away from CSF to avoid its signal.

Imaging:
Point resolved spectroscopy (PRESS) pulse sequence was used with the following parameters: repetition time (TR) = 2000 msec, A Short echo time (35msec) was used to study four peaks: N-Acetyl Aspartate at 2.02ppm, Creatine at 3.01ppm &choline at 3.2ppm and myoinositol peak at 3.58ppm taking about 4:56 minutes. All acquisitions and analyses were performed by a single operator with an average total scan time for the whole study about 35 minutes.
Quantitative analysis

Quantitative analysis of each metabolite concentration within VOI and relative ratios was performed by a single operator as follows raw unprocessed spectra were transferred from the scanner to an IBM compatible workstation based on a Microsoft Windows XP platform using FTP (file transfer protocol) protocol through an Ethernet interface. The Java® based MRUI® v2.2 analysis package was used for analysis of the spectra in the following steps: A- Fourier transformation from the raw echo (Figure 2) to the spectrum B- Water suppression: The water signal was suppressed using the HLSVD filter C- Phase & baseline correction: The phase and baseline were corrected so that all the peaks are directed in the positive direction with the start and end of the peaks are the same horizontal line as much as possible. D- Frequency shift Correction of the chemical shift is done by adjustment of the N-acetyl aspartate peak at 2.02ppm and the other curves are adjusted subsequently as shown in figure (1). E- Peak selection & quantification a time-domain package for short time echo quantification was used with the reference metabolite basis set supplied by Ulrike Dydak PhD, University of Zurich, Switzerland.

Creatine was used as an internal reference due to its stability in most pathologies. The following ratios (Naa/Cr, Naa/ch, Cho/Cr and mI/cr) were calculated.

![Figure 1](image)

Fig. (1): The frequency corrected spectrum shows NAA peak at 2.02 ppm, the creatine (Cr) peak at 3.0 ppm, the choline (Cho) peak at 3.2 ppm and the myoinositol (mI) peak at 3.58 ppm.

Statistical analysis

1- The arithmetic mean and standard deviation 2- Student’s "t" test, to test the significance of difference between two means and 3- Pearson’s Correlation tests to detect if change in one variable is accompanied by changes in the other variable 4- Qualitative variables expressed as percentages are compared in different groups using the Mann-Whitney test. The test compares the frequencies in different groups to theoretical values under the null-hypothesis.

RESULTS

The present work included 50 patients [28 females (56%) and 22 males (44%)] with definite multiple sclerosis. The age of the patients ranged from 18 to 43 years with a mean of 30.13±7.63 years. The mean age of male patients (28.33±9.32) was lower than that of the female patients (31.33±6.26). The study included 20 healthy controls subjects who were age and sex
matched with patient group. The age of the healthy control ranged from 18 to 43 years with a mean of 30.39±7.34 years.

The course of the disease was relapsing remitting in 31 patients (62%) and secondary progressive in 19 patients (38%) with a ratio of RRMS to SPMS of 5:3. The RRMS (n=31) patients included 16 males and 15 females with relatively equal proportions whereas in the SPMS (n=19) patients the female patients (n=13) constituted a larger proportion compared to the male patients (n=6). The age of relapsing remitting multiple sclerosis patients in the study ranged from 18 to 43 years with a mean of 29.57±7.42 years compared to that of the secondary progressive multiple sclerosis patients which ranged from 18 to 41 years with a mean of 31.44±8.44 years.

The age of onset of the disease ranged from 16 years to 38 years with a mean of 27.63±6.78 years. The mean age of onset of the disease in male patients was 25.16±7.43 years which was earlier than that of the female patients with a mean of 29.28±5.60 years. The mean age of onset of the disease in (RRMS) was 27.26±6.59 years whereas the mean in the (SPMS) was 28.44±7.53 years.

The duration of illness among patients with multiple sclerosis ranged from 1 year to 8 years with a mean of 2.67±1.90 years. The mean duration of illness in male patients was 3.17±2.41 years and it was statistically significant longer than that of the female patients with a mean of 2.33±1.46 years and the p value was 0.032. The mean duration of illness in the RRMS was 2.28±1.79 compared to the longer duration of illness in the SPMS patients with a mean of 3.56±1.94 years.

Mode of presentation:
27 patients (54%) presented at the disease onset with motor deficit. Ten patients (20%) presented with optic neuritis, eight patients (16%) presented with sensory complaints, three patients (6%) presented with brainstem manifestations and two patients (4%) presented with cerebellar complaints at disease onset as shown in figure (2).

Activity of the disease
Fifteen (30%) patients had evidence of activity at time of assessment. Twelve (80%) were of the RRMS and 3 (20%) were of SPMS type.

Rating Scales:
1. Expanded Disability status scale (EDSS):
The mean EDSS for multiple sclerosis patients ranged from 1.5 to 6.5 with a mean of 3.75±1.40. The male patients EDSS score ranged from 1.5 to 4.5 with mean of (2.95±0.98) which was lower than that of the female patients which ranged from 1.5 to 6.5 with a mean of 4.27±1.41 and the difference was statistically significant p=0.009. Patients who did not need assistance with ambulation and performed their daily activity normally (i.e.: EDSS 4.5 or less) represented the majority of the patients in this study (74%) compared to those with impaired daily activity (i.e.: EDSS 5 or more) which represented 26% of the patients in this study. Means of EDSS score in patients with RRMS and SPMS were (3.45±1.25 and 4.44±1.55) respectively. There was no statistically significant difference between the two groups of patients.

2. Fatigue Severity Scale (FSS):
Fourteen patients (28%) (4 males and 10 females) had fatigue due to disease pathology (FSS>5) with a range of 5.22 to 7 and a mean of 6.16±0.65. Patients with fatigue due to the disease pathology included 9 (64.3%) RRMS patients with a FSS score that ranged from 5.55 to 7 and a mean of 6.21±0.53 and 5 (35.7%) patients with SPMS patients with a FSS score that ranged from 5.22 to 7 with a mean of 6.09±0.89.

3. Hamilton depression scale (HamD):
Twenty six (52%) patients had depression (HamD ≥10) with a score that ranged from 10 to 15 and a mean score of 12.35±1.52. The male multiple sclerosis patients with depression (n=10) constituted a smaller proportion (38.5%) but with a higher mean of 13.00±1.77 compared to the female patients (n=16) who constituted 61.5% and with a mean score of 12.00±1.31. The
depressed multiple sclerosis patients included 19 patients with RRMS with a HamD score that ranged from 10 to 15 with a mean of 12.47±1.62, and 7 patients with SPMS with a HamD score that ranged from 10 to 14 with a mean of 12±1.26. There is no statistically significant difference between the two groups.

4. Minimental State Examination (MMSE):
   The MMSE score of patients with MS ranged from 23 to 30 with a mean of 28.23±1.63. Only one patient with RRMS (2%) had cognitive impairment (MMSE score=23) with the rest of the patients scoring 26 or more (i.e. normal).

Cerebrospinal fluid examination results:
30 patients with definite MS in this study undergone CSF examination for oligoclonal bands (OCBs) 7 patients (23.3%) had positive OCBs & 23 patients (76.7%) had negative OCBs. 4 patients with positive OCBs were males (57%) and 3 were females (43%). A statistically significant higher FSS score (P=0.002) was found in patients with CSF positive for OCBs compared to those without CSF OCBs.

Neuroradiological results:
1. Magnetic Resonance Image results:
   Frontal lobe lesions were found in all patients and ranged from 1 to 11 with a mean of 4.11±3.51. Parietal lobe lesions were found in all patients and ranged from 6 to 24 lesions with a mean of 14.23±7.70. Occipital lobe lesions were found in all patients and ranged from 2 to 8 with a mean of 4.20±2.72. Temporal lobe lesions were found in 28 patients (56%) and ranged from 1 to 5 with a mean of 2.92±1.44. Infratentorial lesions ranged from 1 to 9 with a mean of 3.70±4.01 (Fig. 3). Juxtacortical lesions ranged from 1 to 10 with a mean of 5.03±3.82 (Fig. 3). Corpus callosum lesions were found in 18 patients and ranged from 1 to 7 lesions with a mean of 3.16±2.98.

Intercaudate ratio (ICR):
   The intercaudate ratio in the patients with multiple sclerosis included in this study ranged from 0.09 to 0.16 with a mean of 0.12±0.02 and was higher than the control group which ranged from 0.06 to 0.1 with a mean of 0.08±0.01. Intercaudate ratio was significantly higher in patients compared to controls (P=0.42) (Fig. 4).

2. Proton Magnetic Resonance Spectroscopy (H1-MRS) results:
   The NAA/Cr ratio of the patients in this study ranged from 0.94 to 2.00 with a mean of 1.41±0.27. Whereas in the healthy control the ratio ranged from 1.56 to 3.84 with a mean of 2.69±0.97 (Table 1).
   A statistically significant lower NAA/Cr ratio in patients with multiple sclerosis was found compared to controls (P=0.000). Fig (5) and table (1) NAA/Cr ratio was significantly reduced in patients with moderate & severe disability (EDSS>3) compared to patients with minimal disability (P=0.002) (Table 2).
   The Cho/Cr ratio of patients ranged from 0.57 to 2.58 with a mean of 1.27±0.73 whereas the Cho/Cr ratio in the healthy control subjects ranging from 0.47 to 2.14 with a mean of 0.89±0.40. The Cho/Cr ratio was higher in the active cases (n=15) compared to the controls (P=0.002) (Fig. 6). Mean NAA/Cho ratio of patients ranged from 0.99 to 2.71 with mean of 2.20±1.63 and that of the control group ranged from 1.10 to 3.47 with a mean of 2.47±1.01, with a statistically significant difference in active cases P= 0.001.
   The mI/Cr ratio of patients ranged from 0.80 to 2.07 with a mean of 1.34±0.32 whereas the mI/Cr ratio was lower in the healthy control subjects ranging from 0.47 to 1.20 with a mean of 0.74±0.33. A statistically higher mI/Cr ratio was found in patients compared to controls (P=0.000) (Table 1).
   The intercaudate ratio was significantly higher in patients with moderate & severe disability (EDSS>3) compared to patients with minimal disability (P=0.000).
   Comparison between RRMS (n=31) & SPMS (n=19) patients revealed no statistically significant differences regarding the age, duration
of illness, age of onset of illness, rating scales scores or neuroradiological results including the MRS ratio values (P>0.05).

**Comparison between patients with minimal disability (EDSS≤3) & patients with moderate or severe disability (EDSS>3) revealed (Table 2)**

**Patients with moderate or severe disability (EDSS>3) were significantly**
- Younger than those with mild disability.
- Had a higher number of corpus callosum lesions (P=0.042) compared to those with minimal disability.
- The intercaudate ratio was significantly higher compared to patients with minimal disability (EDSS≤3) (P=0.000).
- NAA/Cr ratio was significantly reduced compared to patients with minimal disability (P=0.002).
- Cho/Cr ratio was also lower compared to patients with minimal disability (P=0.005).
- No statistically significant differences regarding the duration of illness, age of onset of illness, rating scales scores other than EDSS.

**Correlations:**

The Age of patients was negatively correlated with the EDSS scores of patients (r=-0.408, P=0.042*). The duration of illness was positively correlated with HamD scores of patients (r=0.434, P=0.021*).

The EDSS score of patients was negatively correlated with NAA/Cr ratio (r=-0.534, P=0.002**) Fig (7) and Cho/Cr ratio (r=-0.490, P=0.006**) and positively correlated with the number of frontal lobe lesions (r=0.359, P=0.031*) and Corpus callosum lesions (r=0.508, P=0.006**).

FSS score of patients was positively correlated with HamD score of patients (r=0.699, P=0.000**) and Cho/Cr ratio (r=0.399, P=0.029*).

The intercaudate ratio was positively correlated with the EDSS scores of male patients (r=0.639, P=0.30) whereas in the female patients it was correlated with the NAA/Cr ratio (r=0.482, P=0.043*).

The mI/Cr ratio was positively correlated to the EDSS scores in patients with SPMS but not with other patient groups.

![Fig. (2): Percentage of first presenting symptom and sign among patients.](image-url)
Fig. (3): MRI showing different sites of lesions in patients with definite multiple sclerosis in the study (A) Axial T2-weighted image of Patient no.47 showing Infratentorial plaques (B) Axial FLAIR images of patients no.21 showing juxtacortical plaques.

Fig. (4): The intercaudate ratio measurement in a healthy control (left) and patient (right). The ICR was 0.08 in the healthy control and 0.11 in the patient with multiple sclerosis.

Table 1. Comparison of MRS Ratios between patients & controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=50)</th>
<th>Controls (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>1.41</td>
<td>0.27</td>
<td>2.69</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>1.27</td>
<td>0.73</td>
<td>0.89</td>
</tr>
<tr>
<td>mI/Cr</td>
<td>1.34</td>
<td>0.32</td>
<td>0.75</td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>2.20</td>
<td>1.63</td>
<td>2.47</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05). **Highly significant (P < 0.01).
Fig. (5): MRS from a healthy control (A) and Patient no. 9 in the study with multiple sclerosis with EDSS score of 6.5 (B) showing reduction in the NAA peak at 2.02 ppm with a NAA/Cr ratio of 1.01 (markedly reduced) in the patient compared to 2.67 in the control.
Fig. (6): MRS from a healthy control (A) and Patient no. 2 in the study with RRMS multiple sclerosis during a relapse (B) showing reduction in the NAA peak at 2.02ppm with a NAA/Cr ratio of 1.51 and marked elevation of Cho peak with a Cho/Cr ratio of 1.8 and appearance of the lactate & lipid peak at 0.9 ppm.
Table 2. Comparison between patients with (EDSS≤3) & (EDSS>3).

<table>
<thead>
<tr>
<th>Variables</th>
<th>EDSS ≤3</th>
<th>EDSS &gt;3</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.73±8.9</td>
<td>28.05±6.1</td>
<td>0.04*</td>
</tr>
<tr>
<td>Naa/Cr</td>
<td>1.60±0.24</td>
<td>1.30±0.23</td>
<td>0.002*</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>1.51±0.29</td>
<td>1.12±0.35</td>
<td>0.005*</td>
</tr>
<tr>
<td>BCR</td>
<td>0.10±0.01</td>
<td>0.12±0.01</td>
<td>0.000**</td>
</tr>
<tr>
<td>C. callosum lesions</td>
<td>1.72±1.73</td>
<td>4.0±3.26</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

Fig. (7): Scatter diagram showing significant negative correlation between EDSS score & NAA/Cr ratios of patients with multiple sclerosis.

DISCUSSION

Magnetic resonance imaging (MRI) is the gold standard imaging technique for the identification of demyelinating lesions\textsuperscript{20}, but it has relevant limitations, including the inability to differentiate the heterogeneous pathologic substrates of individual lesions\textsuperscript{10} and to delineate tissue damage that is known to occur outside macroscopic lesions, i.e., in the normal-appearing white (NAWM) and gray (NAGM) matter\textsuperscript{21}.

MRI techniques with increased specificity to the heterogeneous pathological substrates of MS-related tissue damage have the potential to increase dramatically our understanding of how MS evolves and, as a consequence, to provide better measures for monitoring the efficacy of treatments\textsuperscript{21}. 
In the CNS, NAA is generally accepted as a neuronal marker as shown by biopsy examinations specific antibodies and clinical studies. Therefore, it is a sensitive marker for reversible neuronal damage or irreversible axonal loss.

De Stefano and colleagues demonstrated a significant correlation between changes in NAA/Cr ratio in NAWM and changes in disability score (measured by EDSS), concluding that axonal damage in NAWM contributes to the chronic disability in MS. This reduction of NAA in early stages may be reversible possibly because production of NAA is reduced in cases of mitochondria metabolism impairment, as occurs in acute MS.

In our study, Patients who scored 5 or more on the EDSS (need assistance to perform their daily activity) had a significantly higher number of lesions in all sites when compared to patients with EDSS scores less than 5. Yet the spectroscopic findings did not vary significantly between the two groups.

But when comparing patients with minimal disability (EDSS≤3) with those with moderate or severe disability, only corpus callosum lesions were significantly higher in those with moderate and severe disability but not other lesions site. Also the intercaudate ratio was significantly higher in the patients with moderate & severe disability.

The spectroscopic findings showed a highly significant lower NAA/Cr ratio in the patients with moderate and severe disability compared to those with mild disability but the Cho/Cr ratio was significantly lower in the patients with moderate and severe disability compared to those with mild disability.

The present work revealed that the differences between patients with mild (EDSS≤3) and those with moderate and severe disability (EDSS≥3) are qualitative rather than quantitative as the higher Cho/Cr ratio among those with mild disability points towards a rather demyelinating pathological process but lower NAA/Cr and higher ICR points towards a rather irreversible axonal and neuronal damage and brain atrophy and building up of permanent disability whether along a relapsing remitting course or during the progressive phase.

On the contrary, the differences between patients who need assistance to perform their daily activity (EDSS>5) and those who don’t (EDSS<5), were rather quantitative and the spectroscopic findings were not different thus it represents a late stage of the same pathology that was evident when patients exceed EDSS scores of 3.

This could point towards a sharp turn in the disease course at EDSS scores more than three and would attract attention towards reconsidering disease modifying therapies at earlier stages than described before.

Despite the differences between the groups of patients with different grades of disability, The NAA/Cr ratio showed a highly significant negative correlation with EDSS scores in all grades of disability and moreover in all other patients groups as males, females, RRMS, SPMS, Active, Non-active, with or without OCBs. The Cho/Cr ratio also showed a significant negative correlation with EDSS scores of patients, a finding that have been confirmed by previous studies.

The present work revealed that, conventional MRI showed only significant positive correlation between number of frontal and corpus callosum lesions and the EDSS scores but not with other lesions site. Also the intercaudate ratio showed significant correlation with EDSS scores in males only but not in other groups. Thus there was inconsistency in the conventional MRI parameters compared to the consistent relation between disability and NAA/Cr ratio among all patients’ groups. Also the conventional MRI failed to differentiate different lesion qualities compared to the MR spectroscopy which could differentiate active from old lesions from resolving activity on treatment. This was in accordance to Zivadinov & Leist, who found that correlations between MRI metrics and clinical measures of disability have presented conflicting results, however, he suggested that MRS measures may prove to correlate better with clinically measured disability.
The correlation between NAA/Cr and disability was found only when measured by EDSS but not with the multiple sclerosis functional composite (MSFC), a finding explained by the fact that EDSS takes in consideration axonal damage which is reflected through permanent disability whereas MSFC takes in consideration the global disease burden and lesion load. Thus NAA/Cr ratio can serve as a reliable prognostic factor and predictor of conversion from a benign course to a rather aggressive or irreversible course long before the patient is wheelchair bound or needing assistance and hence improving the decision of treatment and following up the response.

Demyelination in acute plaques is accompanied by an increased Cho/Cr ratio. Choline was also found to be increased in prelesional NAWM in patients with multiple sclerosis. A decreased NAA/Cho ratio, together with the presence of free lipids and amino acids (resonances at 0.9 to 1.3 ppm at short echo times), indicate active demyelination.

This was in accordance to our result where patients with evidence of activity whether clinical or radiological at the time of assessment, had a significantly higher Cho/Cr ratio & Lower NAA/Cho ratios compared to the patients without evidence of activity and the controls, but not when comparing the non-active patients group with the controls.

In the present work, some patients did not have contrast enhancement in the conventional MRI yet they showed elevation of the choline in their spectra and after administration of pulse methyl-prednisolone based on these findings, there was remarkable improvement and regression of disability.

Narayana et al. also reported a localized increase of Choline in normal appearing white matter which subsequently developed MRI visible plaque at those sites. Thus Cho/Cr ratio can be used in identifying active from stable lesions and predict the conversion of NAWM to lesional white matter. Subsequently it can be used to follow up the response to treatment whether during relapses or disease activity or during the use of disease modifying therapy.

This could be of particular value in the progressive types of MS where there is not enough clinical evidence of disease activity & hence affecting the decision of timing and type of therapy at an earlier stage before disability reaches a late irreversible stage.

Myoinositol is a marker of gliosis which represents permanent damage in lesions of multiple sclerosis the present study revealed that ml/Cr ratio was correlated to the EDSS scores in patients with SPMS but not with other patient groups. Myoinisitol was significantly higher in patients compared to controls It was also positively correlated with the mean time to progressive phase.

In Conclusion

NAA/Cr ratio is a reliable tool in the quantitative assessment of axonal damage that is reflected through permanent disability measured by EDSS. The persistent correlation between NAA/Cr and EDSS in all stages and different patients group makes it a candidate for use in assessment of efficacy of disease modifying therapy.

Cho/Cr is a reliable marker of disease activity even in absence of clinical or conventional neuroradiological evidence for activity. Thus, together with other markers of activity as NAA/Cho ratio and the presence of lipid peak can help in identifying active from stable cases.

REFERENCES


491


الملخص العربي

الانتماءات: دراسة على 50 مريضاً بمرض التصلب المتعدد المكوّن 22 ذكور و 28 نائلاً (تراوحت اعمارهم بين 18 و 41 سنة). تم استخدام المتدفقات البصريّة على 31 مريضاً كانوا يعانون من النوع الطفائي والروفوني 19. وجدت القرارات الإكلينيكية بكمية صور عالية والمدخنة عالية 90% من المرضى في مرحلة الأجهزة العصبية ذات جدوى. وجدت الأعراض المحيطة بمرض السائل الدماغي 22% من المرضى، وجدت التقلبات القلبية عند 22% من المرضى، وجدت التقلبات العقلية عند 4% من المرضى.

وقد أظهرت النتائج ما يلي:

1. تراوح نسبة التأكد من حالات سوء التحول البصري عند 4.13% في 2.54%.
2. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
3. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
4. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.

وقد أظهرت النتائج ما يلي:

1. تراوح نسبة التأكد من حالات سوء التحول البصري عند 4.13% في 2.54%.
2. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
3. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
4. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.

وقد أظهرت النتائج ما يلي:

1. تراوح نسبة التأكد من حالات سوء التحول البصري عند 4.13% في 2.54%.
2. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
3. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
4. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.

وقد أظهرت النتائج ما يلي:

1. تراوح نسبة التأكد من حالات سوء التحول البصري عند 4.13% في 2.54%.
2. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
3. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
4. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.

وقد أظهرت النتائج ما يلي:

1. تراوح نسبة التأكد من حالات سوء التحول البصري عند 4.13% في 2.54%.
2. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
3. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
4. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.

وقد أظهرت النتائج ما يلي:

1. تراوح نسبة التأكد من حالات سوء التحول البصري عند 4.13% في 2.54%.
2. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
3. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
4. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.

وقد أظهرت النتائج ما يلي:

1. تراوح نسبة التأكد من حالات سوء التحول البصري عند 4.13% في 2.54%.
2. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
3. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
4. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.

وقد أظهرت النتائج ما يلي:

1. تراوح نسبة التأكد من حالات سوء التحول البصري عند 4.13% في 2.54%.
2. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
3. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
4. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.

وقد أظهرت النتائج ما يلي:

1. تراوح نسبة التأكد من حالات سوء التحول البصري عند 4.13% في 2.54%.
2. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
3. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.
4. وجدت تأكد التأكد البصري عند 4.13% في 2.54%.