Refractive Index As Surrogate Biological Marker Of Tumefactive And Other Form Of Multiple Sclerosis And Its Superiority Over Other Methods
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Citation

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Abstract
Large plaques of Multiple sclerosis (MS) or tumefactive multiple sclerosis is difficult to distinguish from Glioma, metastasis or lymphoma. Values of Apparent Diffusion Coefficient (ADC) are overlapping and no specific discrimination could be made. Like MS, Proton MR spectroscopy shows increased peak of Choline and low NAA peak in glioma, lymphoma and metastasis as well. Refractive index (RI value) can distinctly distinguish MS from the above mentioned diseases and prediction rate is high. A special software and RI and color coded palette were created to generate RI and color coded portray or mapping superimposed over the T2 weighted image in a DICOM Editor.

ABBREVIATIONS:
MS- Multiple Sclerosis
ADC- Apparent Diffusion Coefficient
MRS- Proton MR Spectroscopy
NAA- N Acetyl Aspartate
CR- Creatine
Cho- Choline
MI- Myoinositol
ANN-Artificial Neural Network
RI- Refractive Index

INTRODUCTION
Multiple Sclerosis (MS) can be considered as one the devastating demyelinating diseases involving the central nervous system in a bizarre manner. It may be of benign or a disabling type involving the white matter exclusively. It is regarded as inflammatory disease affecting the myelin sheath of the nerve fibers (1,2). MRI is considered as surrogate to pathological process of MS (2). Break down of the surveillance component of the autoimmune system results in attacking both healthy and damaged cells with destruction of the normal healthy cells in the process. This process may be permanent or temporary causing mild, moderate and severe form of MS (3,4,5). Sometimes the large plaques as tumefactive MS mimics a brain tumor, metastasis or lymphoma and causes a diagnostic problem (6,7).

Discrimination of brain tumors and this type of pseudotumoral lesions by conventional MR imaging (MRI)
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is highly challenging (8). Intention of this research was to justify the diagnostic validity of MR Spectroscopy (MRS), Apparent Diffusion Coefficient (ADC) values and Refractive index (RI) of various forms of MS lesions predicted by Artificial Neural Network (ANN).

A brain tissue has both physical and chemical state. Physical state is denoted by Refractive index (RI) and ADC value (apparent diffusion coefficient), and chemical state by MR Spectroscopy (MRS). If the discriminating ability of RI, ADC value and MRS are combined together they will complement one another and diagnostic accuracy may be improved. Conventional MRI alone fails to differentiate between malignant brain lesion and benign tumefactive plaques accurately as it is unable to characterize the tissue (or lacks biological specificity).

ANN was used to check the prediction accuracy after proper training of the various dataset of RI values, concentration of Choline, Creatine, Choline Creatine and Choline NAA (N Acetyl Aspartate ratio) and ADC values determined after examination of the patients.

According to the McDonald criteria for MS (9,10), the diagnosis requires structural changes due to the demyelinating lesions distributed in time and space. MRI has a significant part in the diagnosis of MS, since MRI can display multiple lesions which are clinically occult, and MRI can show new lesions in follow up studies. MS is typically distributed in the white matter myelin sheath and is helpful in differentiating them from vascular lesions. MS plaques involve corpus callosum, temporal lobes, brain stem, cerebellum and spinal cord (11).

Enhancement of the lesions after Gadolinium depicts only the damaged blood-brain barrier and signal abnormality of the effected tissue seen on routine sequences without providing any diagnostic information about the disease (12,13).

Multivoxel or Single voxel one dimensional proton MR spectroscopy (MRS) can discriminate the lesions to some extent by studying the chemical environment of the lesions by increasing the diagnostic accuracy from 49% to 79%(14). Major metabolites are NAA, Choline, Creatine, Lactate, Lipid (7). It was noted that the amplitude of total creatine in normal and pathological brain remains constant and was considered as reference value. In MS Choline peak and lipid lactate peaks increase with increased Choline creatine and Choline NAA ratio and lowering of Creatine: NAA ratio (15).

Increased choline and lactate and low NAA (N Acetyl Aspartate) peaks are the speciality of MS in MRS (15,16). Sometimes high choline peak and diminished Choline NAA ratio may mimic glioma or a metastatic lesion and very difficult to discriminate between the two (17).

Physical status of the tissue can be recognized by RI which is a vital marker of living tissue. RI can exclusively distinguish various tissues (18,19). It relies on of water and solid parts like protein and lipid/ phospholipid of tissue.

The method to determine the RI of brain tissue and various brain lesions matching with the T2 value of external referencing solutions of known RI from the T2 mapping was described by Biswas and Luu (20) (Figure 1). T2 relaxation value and RI could be related as follows:

\[ \text{RI} = - (0.0003 \times \text{T2}) + 1.3338 \] à equation 1.

A RI shade could be created from this equation and RI map from the T2 weighted image could be generated.

**Figure 1**
External reference of known RI, T2 mapping and T2 shade creation (With kind permission from Reference 20)

Some other physical activity of the neural tissue can be taken into account. ADC value based on the Brownian movement of water and solute across the cell membrane (21,22). These values change in various disease state including tumor-like condition from the normal state and an apparent idea of the brain tissue integrity can be appreciated ( Figure 2) (22).
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Figure 2
A: Diffusion weighted image B, C: ADC mapping D: color coded ADC mapping of Tumefactive MS

MATERIALS AND METHODS:
After taking proper institutional ethical permission, 58 patients of various ages ranging from 13 to 77 years with both the genders were examined in a 3 Tesla GE Signa HDxt (Table 1).

Table 1

<table>
<thead>
<tr>
<th>TYPE OF PATIENTS</th>
<th>NUMBER TOATL - 58</th>
<th>AGE years</th>
<th>SEX Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>34</td>
<td>13-77</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Epidermoid cyst</td>
<td>6</td>
<td>36-64</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>LOW GRADE GLIOMA</td>
<td>7</td>
<td>49-81</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>5</td>
<td>56-77</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>67</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>METASTASIS</td>
<td>5</td>
<td>56-83</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Axial, Coronal and sagittal T1, T2, FLAIR, Diffusion weighted image (DWI) were performed routinely along with Post gadolinium MRI using T1 Fat saturated images (TR: 500-700, TE: 10, slice thickness: 5 to 6 mm) using 0.1 mmol/kg Gadolinium. Diffusion weighted images were performed considering the b value 0, TR: 3300 - 3500, TE: 94 - 118).

Signal intensity of the plaques in T2 weighted images were also determined as region of interest after loading the image in a DICOM editor.

Proton MRS was done routinely in all the patients. Both multi voxel and Single voxel Spectroscopy were performed with voxel size between 8mm x 8mm x 8mm to 10mm x 10mm with TR- 9602 and TE-110 to 144ms. TE of 35 ms was used occasionally to check the Lactate peak. Particular emphasis was placed on the Choline: creatine, Choline: NAA, creatine: NAA ratio, Choline, NAA and MI peak amplitude considering creatine as the reference peak.

The apparent diffusion coefficient (ADC) map was created by the software of the scanner on a pixel-by-pixel basis. Color coded ADC mapping were available as well (Figure 2).

Determination of RI shade:
T2 relaxation value could be determined by implementing a multi echo train acquired during a spin echo scan using various TE and generating a T2 map (distribution of T2 values) of the brain by the software of the scanner. Referencing solutions were prepared from biopsy materials of known histopathological diagnosis with known RI determined by Abbey Refractometer (20). A T2 map of the brain with referencing solutions kept out side of the skull (as external references with known RI) (Figure 1) were generated and T2 values of brain tissues and referencing solutions were tabulated. A T2 shade was prepared and relationship of T2 value and RI from external referencing solutions was established (20) as mentioned earlier:
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Figure 3
A: T2 weighted image B: RI mapping of brain C: RI shade generation D: False color shade.

RI= - (0.0003 X T2) + 1.3338. \text{ Equation 1}

A RI shade was created from this equation. A false color coded shade was created (Figure 3) assigning various light and deep shades of red as high RI value and blue and white as low RI value.

From the algorithm, a software was created so that running the program on a T2 weighted image RI map and color coded image could be generated in the DICOM Editor. T2 weighted image of unknown etiology could be assessed by creating a RI and color coded image running the software for RI shade and palette of color coded shade in the DICOM editor.

RESULTS:

RI of gray matter is 1.3952 and that of white matter is 1.4102 (Table 2). Any change of RI values of gray matter and white matter from the normal range was taken as abnormal (Table 2). A MS plaque has refractive index ranging from 1.3421 to 1.3612. In case of malignancy RI value was found to be more than 1.4259 and RI value below 1.3952 was found to be benign. Low grade Glioma has RI of 1.4331 and that of Glioblastoma is 1.4446. T2 value and corresponding RI value were tabulated as well (Table 2). Signal intensity of T2 weighted images could be determined from the Region of Interest (ROI) in the DICOM editor.
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Table 3
Signal intensity (T2W image) and RI values

<table>
<thead>
<tr>
<th>SIGNAL INTENSITY ms</th>
<th>RI VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1408</td>
<td>1.3333</td>
</tr>
<tr>
<td>1345</td>
<td>1.335</td>
</tr>
<tr>
<td>905</td>
<td>1.3434</td>
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<tr>
<td>896</td>
<td>1.3436</td>
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<td>761</td>
<td>1.3441</td>
</tr>
<tr>
<td>676</td>
<td>1.3451</td>
</tr>
<tr>
<td>608</td>
<td>1.3576</td>
</tr>
<tr>
<td>562</td>
<td>1.3762</td>
</tr>
<tr>
<td>511</td>
<td>1.3871</td>
</tr>
<tr>
<td>390</td>
<td>1.4123</td>
</tr>
</tbody>
</table>

A linear relationship is noted between 1/signal Intensity and RI value and (Figure 4)

\[
\text{RI value} = (0.0089) \times 1/\text{signal intensity} + 1.3127
\]

Figure 4
Relationship between RI and 1/signal intensity

Calculation of measured ADC map

Inbuilt software of the MRI machine determined the ADC value from the diffusion weighted MR image and map of Apparent Diffusion coefficient (b=0 and or 1000 s/mm2). (22). ADC values were also depicted in table 4.

Table 4
ADC VALUES

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ADC</th>
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<tbody>
<tr>
<td>CSF</td>
<td>300</td>
</tr>
<tr>
<td>CSF</td>
<td>320</td>
</tr>
<tr>
<td>CSF</td>
<td>330</td>
</tr>
<tr>
<td>MS</td>
<td>145</td>
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<tr>
<td>MS</td>
<td>135</td>
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<td>MS</td>
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<td>MS</td>
<td>75</td>
</tr>
<tr>
<td>MS</td>
<td>73</td>
</tr>
<tr>
<td>gray matte</td>
<td>76</td>
</tr>
<tr>
<td>gray matte</td>
<td>76</td>
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<td>gray matte</td>
<td>78</td>
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<td>gray matte</td>
<td>80</td>
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<tr>
<td>w matter</td>
<td>70</td>
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</tr>
<tr>
<td>glioma</td>
<td>156</td>
</tr>
<tr>
<td>glioblasto</td>
<td>142</td>
</tr>
</tbody>
</table>

Choline, Creatine, NAA, MI peak amplitude, Choline creatine ratio and creatine NAA ratio of various patients
were tabulated in the table 5.

**Table 5**

**SPECTROSCOPIC DATA**

<table>
<thead>
<tr>
<th>T1W</th>
<th>T2W</th>
<th>CR</th>
<th>GABA</th>
<th>CHOL</th>
<th>T2HPO</th>
<th>LAC</th>
<th>CHOL/CREAT</th>
<th>NAA</th>
<th>CHOL/NAA</th>
<th>GLY</th>
<th>GABA/CREAT</th>
<th>SI</th>
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</table>

**DISCUSSION:**

**EXAMINATION OF THE LESIONS:**

In the materials and methods section the relationship between RI and T2 value was mentioned, which can be recapitulated:

\[
RI = - (0.0003 \times T2) + 1.3338.
\]

As mentioned earlier a program along with RI shade and a false color palette was created from the above equation and from various algorithm. T2 weighted image of unknown etiology could be assessed by generating a RI and color coded image in the DICOM editor after running the software for RI shade and color coded palette.

Mass like plaques are shown in Figure 6 in T1,T2 weighted, Flair and post contrast images in axial, sagittal and coronal scan. Corpus callosum and para ventricular white matter is involved. Multivoxel MRS shows high peak of Choline and a Choline-creatine ratio and no appreciable change in the Choline NAA ratio. Lipid and lactate peaks are unremarkable.

The Color coded RI map shows blue and white shades overlaying the mass like plaques representing low RI values. RI map depicts the RI of the plaque ranging from 1.3421 to 1.3534. As the values are less than 1.3952 benign lesions can be predicted confidently.

**Figure 8**

A and D: T2W axial image showing para ventricular white matter plaques B,C and E,F: RI and color coded images showing plaques with RI of low value.

Similarly, mass like plaques shown in Figure 7 and 8 suspecting MS in MRI were confirmed by RI and color coded map in the DICOM editor.

**Figure 6**

Figure 7
Same patient of Figure 6. Large MS plaques in the para ventricular white matter in: A: T2W B: RI C: Color coded mapping D: Sagittal E: Coronal F: Color coded mapping

Multivoxel MRS is equivocal in discriminating demyelinating from malignant lesions as both of them have high choline peak and increased Choline Creatine and low Creatine NAA ratio.

Figure 9
A, D: T1 Fat saturated contrasted Glioblastoma B, E: Multivoxel Spectroscopy C: T2 W image E: RI mapping showing high RI value of the margin of the lesion and low RI value of perilesional edema

Figure 9 depicts a lesion in the fronto-parietal lobe with T1 and Flair hypointense and T2 hyperintense central component. Post contrast study shows hyperintense peripheral margin. MRS shows typical high choline peak, Choline creatine ratio and increased lipid peak. RI map shows high RI values (1.4578 to 1.4592) in the peripheral component and low RI value of 1.3761 with blackish shade in the central disintegrated and liquefied component. A diagnosis of Glioblastoma could be made. T2 W image of a left parietal lobe mass lesion (Figure 10) shows red colored infiltrating peripheral component with degenerated bluish white central component (10C). RI map shows grayish white peripheral component and blackish central component (10D).

Figure 10
A: T2 weighted image of a Glioblastoma B: Single voxel spectroscopy C, D: Color coded and RI image generated in the DICOM editor

Artificial Neural Network (ANN) (Palisade Neural Tool 7), a nonlinear modeling Probabilistic Neural Network technique (23, 24) was implemented to assess and make virtual pathological prediction from the data obtained from MRI, various components of MRS, ADC value and other laboratory data (RI) (Table 6). The ANN with extraordinary data processing uniqueness, nonlinearity, learning and generalization capability was used to characterize the disease (24). Thus there are 10 input nodes or independent numeric variables. The network consists of a single hidden layer with 10 nodes (24). It has 8 output nodes of different types of tissue (such as CSF, gray and white matters) and diseases (or types of lesions). These diseases were targeted for prediction. Output nodes are regarded as Dependent variables (25).
Table 6
Training and testing of the dataset by the ANN before prediction

<table>
<thead>
<tr>
<th>Node</th>
<th>Name</th>
<th>Value</th>
<th>Value</th>
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</tbody>
</table>

Figure 11
Prediction of MS by ANN in respect to RI values after training and testing.

Table 6 shows various dataset of 10 input nodes (independent variables) and 8 output nodes (Disease or tissues, CSF). Neural tool trains and tests at the same time (Figure 12).

Figure 12
Statistics of the ANN when RI values is considered for prediction of the disease.

Figure 13
Prediction in respect to ADC as independent numerical value after training and testing of the net (Table 6)
Figure 14
Prediction in relation to Spectroscopic data (Cho/Cr ratio)

It was evident that the prediction of MS was 100% (Figure 11) when RI values were regarded as independent numerical values (in the extreme right of the table). Figure 12 depicts the statistical aspect of the prediction by RI. On the contrary prediction is (20 to 60%) in the context of ADC values or Choline creatine ratio depicted in Figure 13 and 14 respectively.

SUMMARY:
Sometimes tumefactive MS or other type creates difficulty to distinguish from metastasis or glioblastoma. ADC with overlapping values and even proton MRS are not worthy for the accurate diagnosis. RI shade and color coded mapping of the T2 weighted image can diagnose MS accurately (100%). RI appears to be superior to ADC value and MRS in this regard which has immense importance in managing the patients. RI renders noninvasive insight into the local biophysical change that are associated with underlying pathologic changes in multiple sclerosis.

ACKNOWLEDGEMENT
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