

# Role of MRI in Evaluation of Ring Enhancing Lesions of Brain in Correlation with MR Spectroscopy

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## Abstract-

### Introduction:

Ring enhancing lesions of the brain though common on neuroimaging are always challenging for radiologists to diagnose because of their varied etiologies. MRI plays a significant role in the early detection and advanced techniques like MR Spectroscopy increase the chances of successful diagnosis by differentiating infectious lesions from non-infectious lesions.

### Objectives:

1. To establish a differential diagnosis of the various ring enhancing lesions on conventional MRI.
2. To study the characteristic imaging findings of various ring enhancing lesions on MRI.
3. To study the role of MR spectroscopy in the evaluation of various ring enhancing lesions in the brain with a single voxel proton MR spectroscopy.

**Material and Methods:** A prospective observational study was conducted in the Radiology department of a tertiary hospital for a duration of 2 years which included 44 patients. MRI along with MRS was performed on these patients.

**Results:** Among 44 patients, various ring enhancing lesions (REL's) detected on MRI were tuberculomas (20, 45%) which were the most common followed by, NCC (8, 18%), abscesses (6, 14%), metastases (5, 11%), primary brain tumors (3, 7%) and toxoplasmosis (2, 5%).

On MR spectroscopy, Choline peak was observed in 20 (45%) cases, Lipid peak was present in 31 (70%) cases, Lactate peak in 27 (61%) cases reduced NAA peak in 7 (16%) cases and amino acids in 6 (14%) cases. Choline/creatine ratio of <1 was seen in 10 (23%) of the NCC cases, Choline/creatine ratio of >1-2 was seen in 20 (45%) of the NCC cases, Choline/creatine ratio of >2 was seen in 9 (20%) of the NCC cases

**Conclusion:** In this study, MRI and MRS played a pivotal role in successful diagnosis of various ring enhancing lesions which helped in the initiating the treatment among these patients accordingly.

**Keywords:** Choline, Magnetic Resonance Imaging, Metabolites, MRI, MRS, Ring Enhancing Lesions, Tuberculoma.

### Introduction:

One of the most typical neuroimaging abnormalities are ring-enhancing lesions (REL'S). They can have a variety of etiologies.<sup>1</sup> The symptomatic presentation of these lesions is often non-specific and hence it is difficult to reach the final diagnosis.<sup>2</sup> These lesions can be detected using computed tomography and magnetic resonance imaging (MRI) that are widely available.<sup>3</sup> MRI helps in early detection of these lesions which are visually demonstrated using contrast between grey-white matter junction differentiation, tumor ischemia and infarction, edema, multiple sclerosis plaque, infection, abscess and hemorrhage. For the detection and diagnosis of both infectious etiologies, such as intracranial abscesses, and non-infectious lesions, such as primary intra parenchymal neoplasms, demyelination, lymphoma, and cerebral metastases, Magnetic resonance spectroscopy is an essential technique.<sup>4</sup>

By measuring the amount and ratio of tissue metabolites including lipid, choline, amino acids, N-acetyl aspartate, etc. during a standard MRI scan, MR spectroscopy (MRS) can determine the potential nature and characteristics of these lesions. These lesions are situated either superficially or deeply inside the brain parenchyma, in the sub-cortical region, and at the gray-white matter interface.<sup>4</sup>

### Objectives:

1. To establish a differential diagnosis of the various ring enhancing lesions on conventional MRI.
2. To study the characteristic imaging findings of various ring enhancing lesions on MRI.

3. To study the role of MR spectroscopy in the evaluation of various ring enhancing lesions in the brain with a single voxel proton MR spectroscopy.

### Materials and Methods:

This study was conducted in Radiology Department of Raja Rajeswari Medical College and Hospital during the period July 2021 to July 2023.

### Study design and study subjects:

A prospective study was conducted on 44 patients referred to the department of Radio diagnosis, RajaRajeswari Medical College and Hospital with clinically suspected ring enhancing lesions of brain. They were subjected to radiological evaluation by MRI. Ethical committee approval was obtained. Informed consent, thorough clinical history and clinical examination was done on patients before MRI examination.

### Inclusion criteria

All cerebral ring enhancing lesions detected on contrast MR studies and all patients with incidentally diagnosed ring enhancing lesion by CT.

### Exclusion Criteria

Patients having history of claustrophobia, metallic implants insertion, cardiac pacemakers and metallic foreign body in situ.

### Ethical statement:

Ethical approval for the study was sought and obtained from the health research and ethics committee of RajaRajeswari Medical College and Hospital. The data obtained was treated with utmost confidentiality.

### Statistical analysis

All the data collected was entered and compile into excel sheet and was analyzed using SPSS software version 26. Data was presented using frequency and percentages. The graph was plotted by the MRI machine software, and the peak amplitude of choline, lipid, lactate, reduced NAA and amino acids in the ring enhancing lesions were recorded. The choline/creatinine ratio were calculated and associated with the type of lesion the patients exhibited.

### MRI and MRS technique:

All the 44 patients were subjected to MRI on Philips MRI ACHIEVA of 1.5 tesla field strength. Conventional spin echo sequences, axial T1, T2 and FLAIR: Coronal T2; Sagittal T1; Post contrast axial, coronal and sagittal; DWI; T2 GRE Single voxel spectroscopy was performed at TE of 144. The voxel is placed on the lesion so that it covers the maximum area of the lesion in a single voxel. We used PRESS and T1 post contrast sequence as localization sequence with 5 mm thickness. Spectroscopy was avoided in small lesions close to the bone. Special sequences such as CISS 3D, VENBOLD were used as and when required.

### Results:

**Table 1: Demographic details among the study subjects**

| Variable              | Frequency | %  |
|-----------------------|-----------|----|
| <b>Age (in years)</b> |           |    |
| <b>0-10</b>           | 7         | 16 |
| <b>11-20</b>          | 10        | 23 |
| <b>21-30</b>          | 12        | 27 |
| <b>31-40</b>          | 6         | 14 |
| <b>41-50</b>          | 5         | 11 |
| <b>51-60</b>          | 3         | 7  |
| <b>&gt;60</b>         | 1         | 2  |

| Gender |    |    |
|--------|----|----|
| Male   | 31 | 70 |
| Female | 13 | 30 |

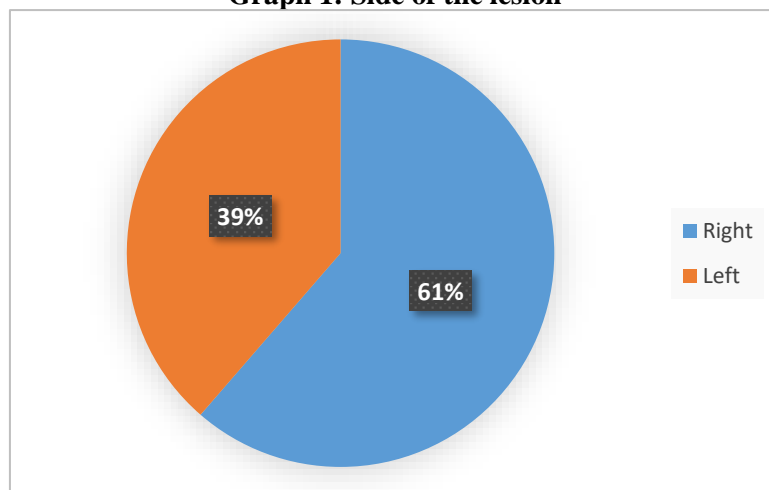
Among 44 patients included in the study, majority were males (70%) and most common age group in the study was between 21-30 years (12, 27%). Only one case (2%) belonged to >60years age group (table 1).

**Table 2: Various Ring enhancing lesions on MRI**

| Ring enhancing lesion | Frequency | Percentage |
|-----------------------|-----------|------------|
| Tuberculoma           | 20        | 45         |
| Neurocysticercosis    | 8         | 18         |
| Abscess               | 6         | 14         |
| Metastasis            | 5         | 11         |
| Primary brain tumor   | 3         | 7          |
| Toxoplasmosis         | 2         | 5          |

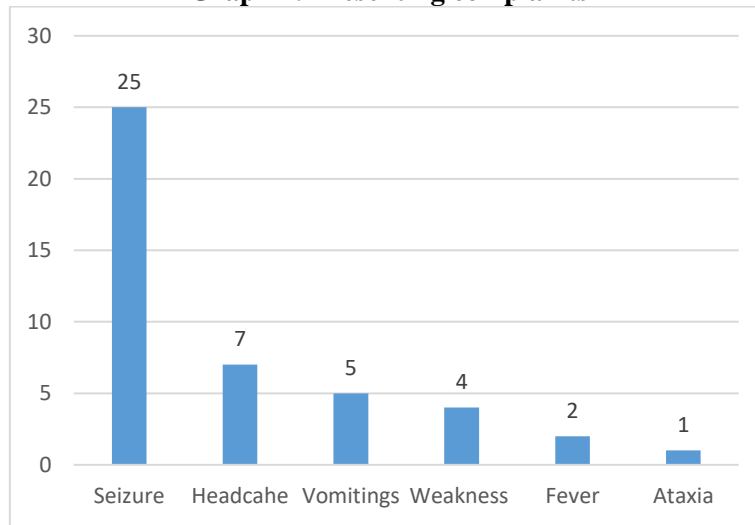
Various ring enhancing lesions (REL's) detected on MRI were tuberculomas (20, 45%) which were the most common followed by, NCC (8, 18%), abscesses (6, 14%), metastases (5, 11%), primary brain tumors (3, 7%) and toxoplasmosis (2, 5%). (Table 2).

**Graph 1: Side of the lesion**



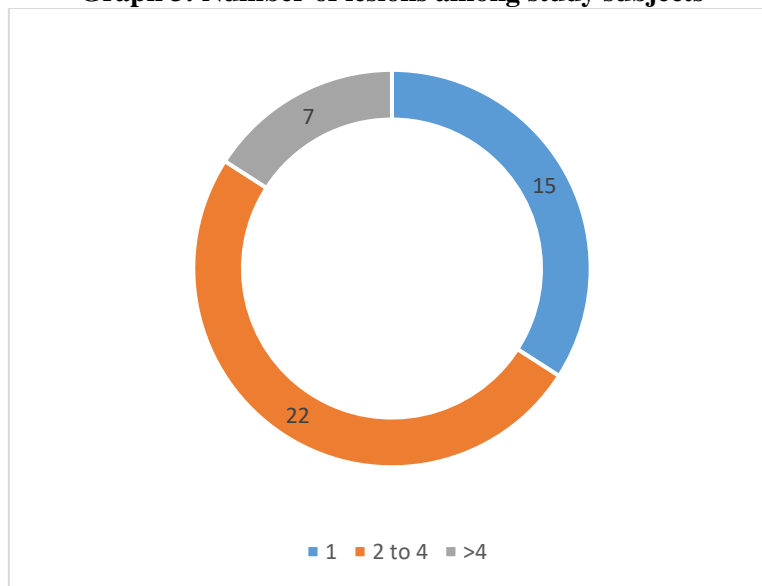
REL's were common on the right side (27, 38%) (Graph 1).

**Graph 2: Presenting complaints**



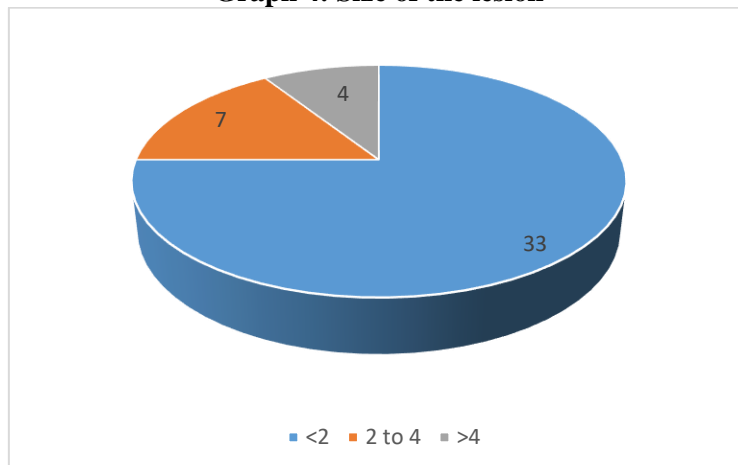
Majority in the study presented with seizures (25,57%). (Graph 2)

**Graph 3: Number of lesions among study subjects**



22 (50%) of them presented with 2-4 lesions. (Graph 3)

**Graph 4: Size of the lesion**



Majority 33 (75%) of them showed RELs < 2cm. (Graph 4)

**Table 3: Metabolite peaks according to various REL's**

| REL                        | Metabolite peak |                 |                 |                |                |
|----------------------------|-----------------|-----------------|-----------------|----------------|----------------|
|                            | Choline         | Lipid           | Lactate         | Reduced NAA    | Amino acids    |
| <b>Tuberculoma</b>         | 4 (20%)         | 20 (100%)       | 10 (50%)        | 3 (15%)        | 0 (0)          |
| <b>NCC</b>                 | 8 (100%)        | 0 (0)           | 6 (75%)         | 1 (12%)        | 0 (0)          |
| <b>Abscess</b>             | 0 (0)           | 6 (100%)        | 6 (100%)        | 0 (0)          | 6 (100%)       |
| <b>Metastasis</b>          | 5 (100%)        | 2 (40%)         | 3 (60%)         | 1 (20%)        | 0 (0)          |
| <b>Primary brain tumor</b> | 3 (100%)        | 1 (33%)         | 1 (33%)         | 1 (33%)        | 0 (0)          |
| <b>Toxoplasmosis</b>       | 0 (0)           | 2 (100%)        | 1 (50%)         | 1 (50%)        | 0 (0)          |
| <b>Total</b>               | <b>20 (45%)</b> | <b>31 (70%)</b> | <b>27 (61%)</b> | <b>7 (16%)</b> | <b>6 (14%)</b> |

On MR spectroscopy, Choline peak was observed in 20 (45%) cases, Lipid peak was present in 31 (70%) cases, Lactate peak in 27 (61%) cases reduced NAA peak in 7 (16%) cases and amino acids in 6 (14%) cases. (Table 3).

**Table 4: Choline/creatinine ratio in ring enhancing lesions of the brain.**

| REL                        | Choline/creatinine ratio | Frequency (%) |
|----------------------------|--------------------------|---------------|
| <b>NCC</b>                 | <1                       | 10 (23)       |
| <b>Tuberculoma</b>         | >1-2                     | 20 (45)       |
| <b>Primary brain tumor</b> | >2                       | 9 (20)        |

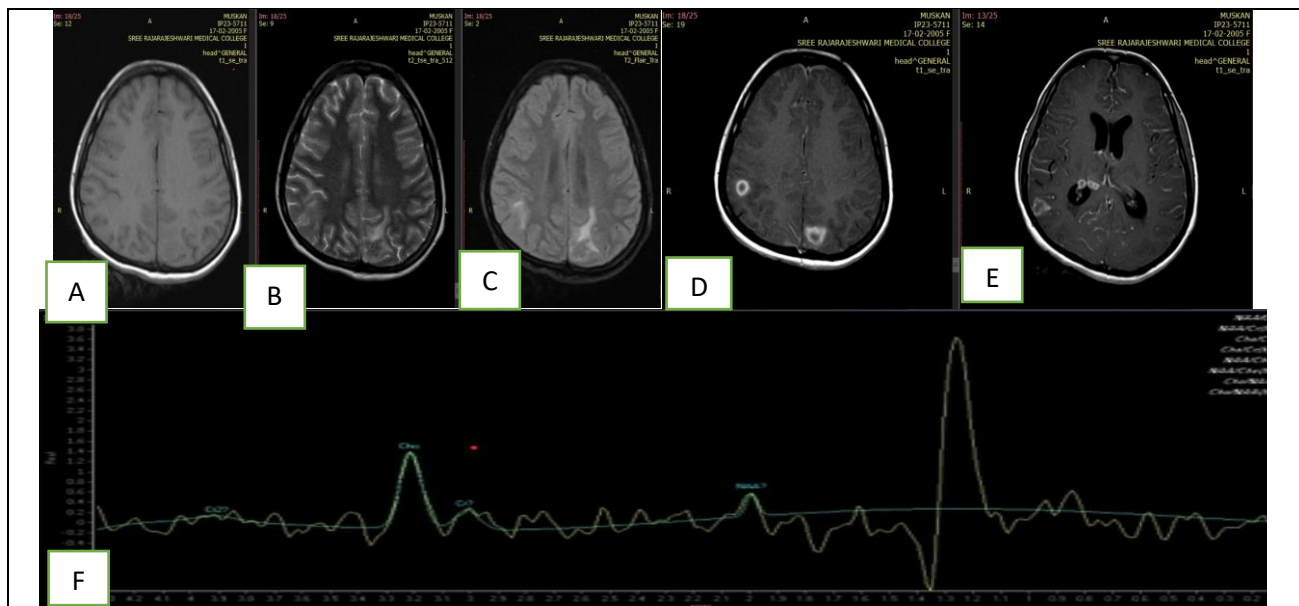
Choline/creatinine ratio of <1 was seen in 10 (23%) of the NCC cases, Choline/creatinine ratio of >1-2 was seen in 20 (45%) of the tuberculoma cases, Choline/creatinine ratio of >2 was seen in 9 (20%) of the primary brain tumor cases. (table-4).

**Characterization of REL's:**

**Tuberculoma:**

One of the cases in the study who was an 18 year old female who presented with fever since 15 days along with weakness. On performing MRI brain plain along with contrast, multiple ring enhancing lesions with perilesional edema are noted involving right parietal, left temporal lobe, left occipital lobe and posterior horn of right lateral ventricle near the choroid plexus, largest lesion measures 14 x 12 mm. Similar ring enhancing lesion is noted arising from choroid plexus

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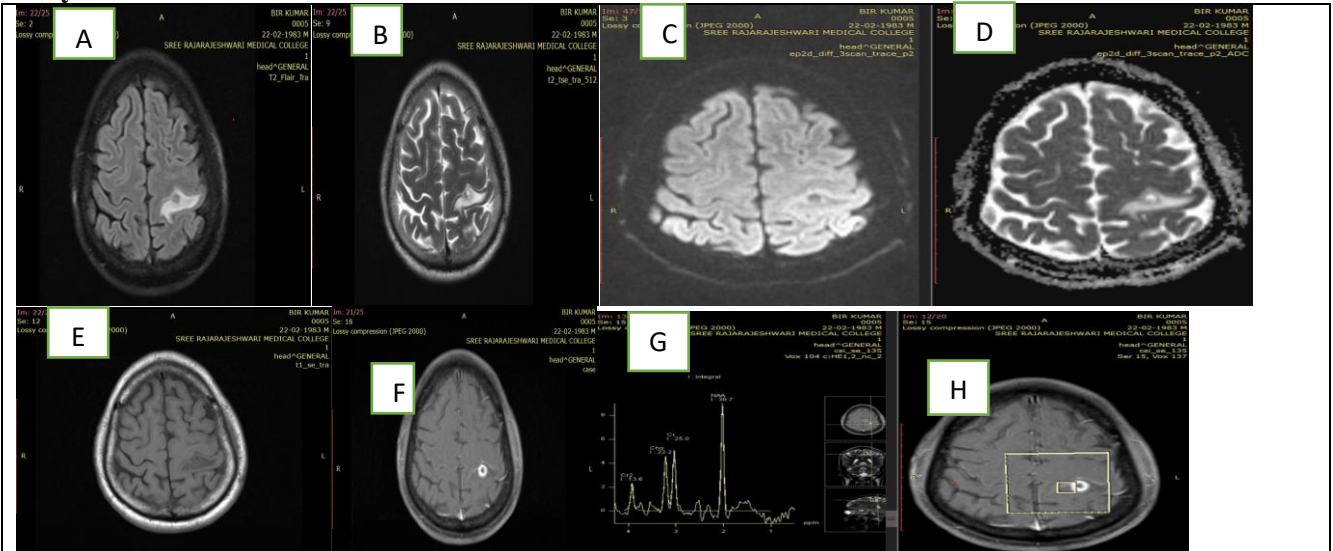


**Figure 1: Case presentation of tuberculoma: Figure A to E- Multiple ring enhancing lesions with perilesional edema are noted involving right parietal, left temporal lobe, left occipital lobe and posterior horn of right lateral ventricle near the choroid plexus. Figure F-MR spectroscopy showing lipid/lactate peak.**

choroid plexus, largest lesion measures 14 x 12 mm. Similar ring enhancing lesion is noted arising from choroid plexus

of posterior horn of right lateral ventricle. On MR spectroscopy lipid and lactate peak was observed (Figure 1). Final diagnosis of caseating type of tubercular granuloma was made.

### Neurocysticercosis:

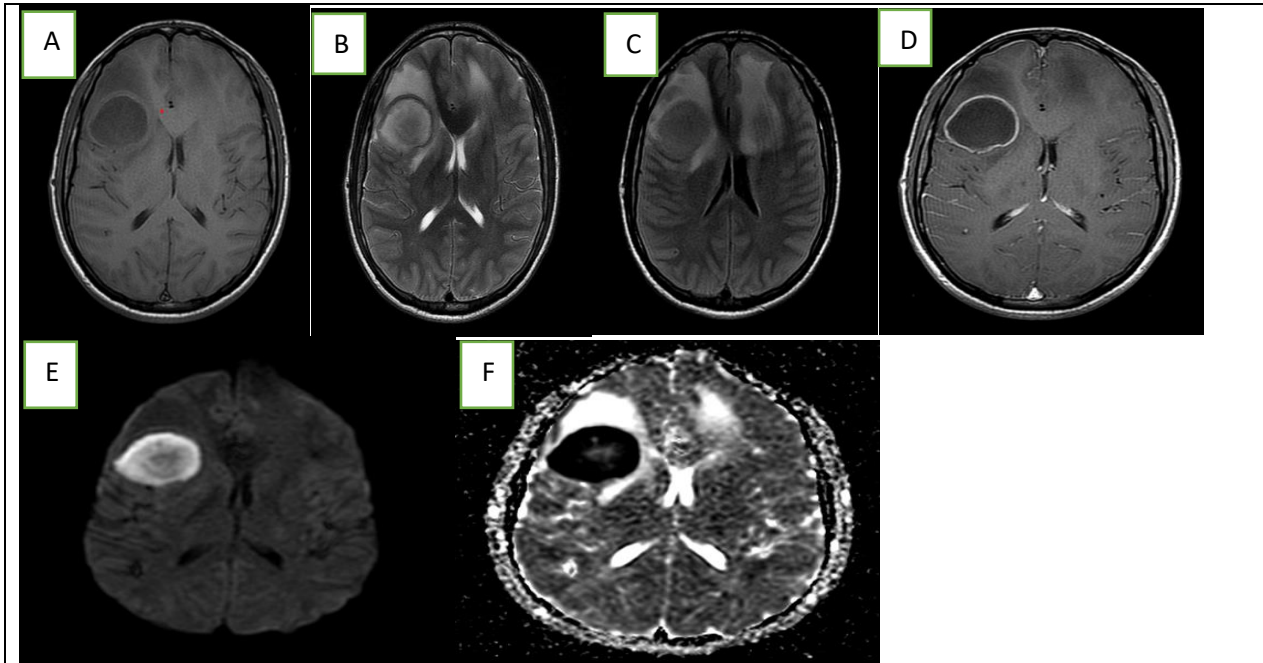


**Figure 2: Case presentation of Neurocysticercosis: Figure A-H:** Multiple (4 in number), well-defined, small, ring enhancing, round to oval lesions are noted in the right frontal white matter in the parafalcine region, left high parietal white matter and anteroinferior aspect of right cerebellar hemisphere on the medial aspect.

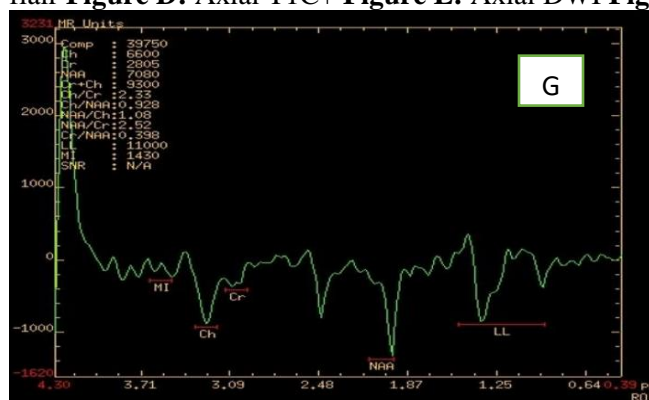
One of the cases in the study who was a 40 years old male presented with seizures. On performing MRI plain and contrast, multiple (4 in number), well-defined, small, ring enhancing, round to oval lesions are noted in the right frontal white matter in the parafalcine region, left high parietal white matter and anteroinferior aspect of right cerebellar hemisphere on the medial aspect; largest measuring 9.8 x 8 mm (AP x TR) in the left high parietal white matter were noted.

Peripherally the lesion appears T2/FLAIR hypointense and T1 hyperintense with central area of hyperintensity on T2/FLAIR and hypointensity on T1 with perilesional edema appearing hyperintense on T2/FLAIR. There was no blooming on SWI and no diffusion restriction on DWI. Central hyperintense foci are noted on T1 with corresponding hypointensity of T2 sequence within the lesions, showing post contrast enhancement. On MR spectroscopy, lipid lactate peak was seen. Small T2 hyperintensities are noted in bilateral basal ganglia – s/o VR spaces. A final diagnosis of neurocysticercosis was made (Figure 2).

**Brain abscess:**

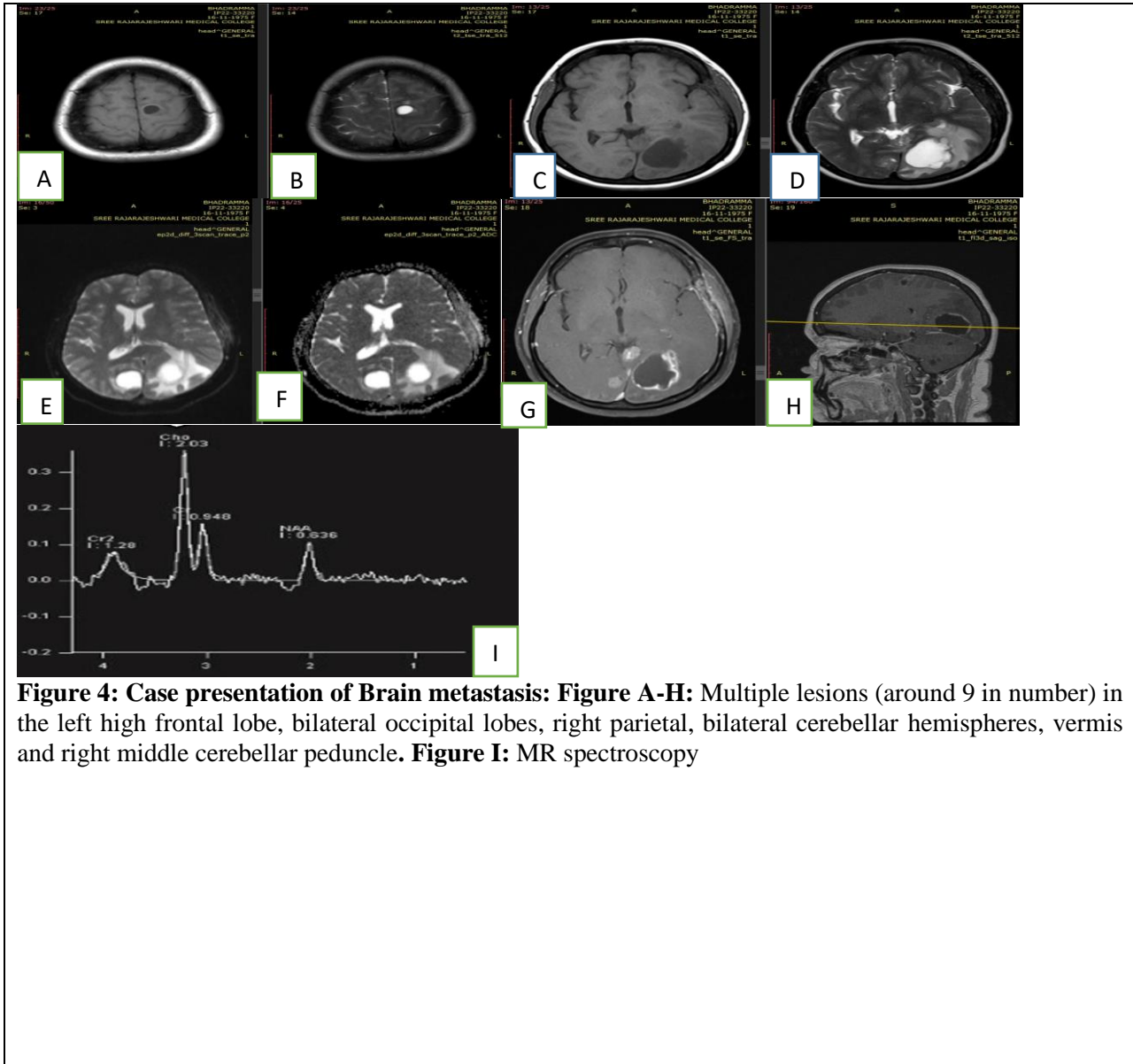


**Figure 3:** Case presentation of Brain abscess: **Figure A:** Axial T1 **Figure B:** Axial T2 **Figure C:** Axial flair **Figure D:** Axial T1C+ **Figure E:** Axial DWI **Figure F:** Axial ADC.



**Figure G:** MR spectroscopy

On performing MRI in one of the cases of the brain abscess in this study, MRI showed well-defined round intra-axial lesions, T1 hypointense and T2 hyperintense in the right frontal subcortical white matter. The lesions had a thick wall with dual rim sign best seen on T2WI, ring enhancement in post-contrast T1. The lesions showed true restricted diffusion on DWI images (low signal on ADC). There was important perilesional edema (Figure 3).

**Brain metastasis:**

**Figure 4: Case presentation of Brain metastasis: Figure A-H:** Multiple lesions (around 9 in number) in the left high frontal lobe, bilateral occipital lobes, right parietal, bilateral cerebellar hemispheres, vermis and right middle cerebellar peduncle. **Figure I:** MR spectroscopy

This was the case of a 47 year old female which presented with c/o headache, vomiting and giddiness. It was a known case of left breast carcinoma since 4 years. On performing MRI, multiple lesions (around 9 in number) were noted in the left high frontal lobe, bilateral occipital lobes, right parietal, bilateral cerebellar hemispheres, vermis and right middle cerebellar peduncle. These lesions appeared T1 and FLAIR hypointense, T2 heterogeneously hyperintense with surrounding perilesional edema. There was no evidence of diffusion restriction.

On post contrast study, these lesions showed ring enhancement with few of them showing enhancing solid component. Few areas within the lesion showed foci of blooming (s/o hemorrhage). The largest lesion was noted in the left occipital region measuring 3.6 x 2.4 cm. The lesion was causing effacement of occipital horn of left lateral ventricle. Mass effect was noted in form of midline shift of 3.9mm to right side. Multiple lytic lesions were noted in the calvarium, largest in the left parietal bone. On whole spine screening, multiple altered signal intensities in S2, L5, L1 and T7 vertebrae were noted. A final diagnosis of metastasis was made.

**Discussion:**



Ring enhancing lesions are common on neuroimaging and can be easily detected on conventional MRI but arriving at a specific diagnosis becomes challenging because the REL's with different etiologies appear similar on conventional MRI.<sup>5</sup> MRS is an advanced technique which plays a potential role in successful diagnosis by differentiating neoplastic from non-neoplastic lesions and also in differentiating infectious REL's with different etiologies.<sup>6</sup>

In this study, among 44 patients included in the study, majority were males (70%) and most common age group in the study was between 21-30 years (12, 27%). Only one case (2%) belonged to >60years age group. This was consistent with a study by Rajasree et al.<sup>7</sup> in which majority i.e., 20% belonged to 21-30years age group and males were predominant (66%) in their study. Similarly, Archana et al.<sup>8</sup> reported highest incidence of REL's in 21-30years age group (25%) and among males (70%). In a study by Elsadway et al.<sup>9</sup> 60% were males which was similar to this study.

Majority in the study presented with seizures (25,57%) followed by headache (7, 16%) and vomiting (5,11%). This was consistent with a study by Seth S et al.,<sup>10</sup> where seizures (80%) was the most common presentation, followed by headache (28%) and vomiting (18%). A study by Elsadway ME et al.<sup>9</sup> stated that majority of the patients experienced headache, although these symptoms tend to vary amongst individuals. In a study by Patil et al.<sup>11</sup> patients most commonly presented with seizures (82%), neurological deficit (34%), headache (64%), vomiting (52%), weakness (48%) and fever (46%) which was in accordance to this study.

In this study, among 44 patients, various ring enhancing lesions (REL's) detected on MRI were tuberculomas (20, 45%) which were the most common followed by, NCC (8, 18%), abscesses (6, 14%), metastases (5, 11%), primary brain tumors (3, 7%) and toxoplasmosis (2, 5%). This was similar to Rajasree et al.<sup>7</sup>, Bava JS et al.,<sup>12</sup> and Mirchandani S et al.,<sup>13</sup> in which tuberculomas were the commonest whereas in a study by Patil et al.<sup>11</sup> NCC was the commonest (38%), followed by tuberculomas (32%) which was little different from this study.

In this study, REL's were common on the right side (27, 38%). Patil et al.<sup>11</sup> reported 36% of lesions on the right side of brain which was in concordance to this study.

In this study, 22 (50%) of them presented with 2-4 lesions and majority 33 (75%) of them showed RELs < 2cm.

This was similar to a study by Patil et al.<sup>11</sup> in which majority (48%) had 2-4 lesions and 66% had less than 2 cm size of lesions.

On MR spectroscopy, Choline peak was observed in 20 (45%) cases, Lipid peak was present in 31 (70%) cases, Lactate peak in 27 (61%) cases reduced NAA peak in 7 (16%) cases and amino acids in 6 (14%) cases. In a study by Patil et al.<sup>11</sup> Choline peak was observed in 64%, Lipid in 56%, Lactate in 52%, reduced NAA peak in 32% and amino acids in 14% of the patients which was comparable to this study.

In a study by Rajasree et al.<sup>7</sup> the highest peak was observed for choline in 66% patients, which was prevalent in patients diagnosed with neurocysticercosis which was similar to this study.

In this study, Lipid peak was 100%, lactate was 50% choline peak was 20%, reduced NAA was 15% in the cases of tuberculoma, Choline peak was 100%, lactate peak was 75% and reduced NAA peak was 12% for the cases of NCC. Jayasundar R et al.<sup>14</sup> concluded that presence of lipid can be used for differentiating tuberculomas from both non-specific Intracranial granulomas and NCC.

Lipid, lactate and reduced AA peak was 100% for the cases of abscesses. Choline peak was 100%, lactate peak was 60% and lipid peak was 40% for the cases of metastasis. Choline peak was 100%, lactate peak was 33% and lipid peak was 33% and reduced NAA peak was 33% for the cases of primary brain tumor. Lipid peak was 100% and lactate peak was 50% and reduced NAA peak was 50% for the cases of toxoplasmosis. These findings were consistent with a study by Rajasree et al.<sup>7</sup>

In a study by Mishra et al.<sup>15</sup> Lactate and AAs with or without other metabolites were observed in 25 of 29 cases of abscesses on MRS whereas in this study it was 100%; lactate peak was 100% and choline peak was 75% in their study which was almost similar to this study.

Choline/creatine ratio is most frequently used to differentiate low and high-grade tumours. A choline/creatine ratio >2.0 is considered as a strong indicator of high-grade neoplasm.<sup>16,17</sup> In this study, Choline/creatine ratio of <1 was seen in 10 (23%) of the NCC cases and Choline/creatine ratio of >1-2 was seen in 20 (45%) of the tuberculoma cases. This finding was consistent with that of Patil et al.,<sup>10</sup> Kumar et al.<sup>18</sup> and Gupta et al.<sup>19</sup> In this study, Choline/creatine ratio of >2 was seen in 9 (20%) of the primary brain tumor cases. This was similar to Patil et al.<sup>11</sup> and Rajasree et al.<sup>7</sup>

## Conclusion:

MRI is the most accurate way to characterize cerebral ring-enhancing lesions. In this study, among 44 patients, various ring enhancing lesions (REL's) detected on MRI were tuberculomas (20, 45%) which were the most common followed by, NCC (8, 18%), abscesses (6, 14%), metastases (5, 11%), primary brain tumors (3, 7%) and toxoplasmosis (2, 5%). These lesions were common in 21-30years age group and among males. Majority presented with 2-4 lesions with size < 2cm and on the right side of the brain. On MRS, Choline/creatine ratio of <1 was seen in 10 (23%) of the NCC cases, >1-2 was seen in 20 (45%) of the tuberculoma cases and >2 was seen in 9 (20%) of the primary brain tumor cases. Thus MRI played a crucial part in this study by recommending the right diagnosis based on typical imaging findings and the characterisation of various ring-enhancing lesions was aided by MRS.

**REFERENCES:**

1. Omuro AM, Leite CC, Mokhtari K, Delattre JY. Pitfalls in the diagnosis of brain tumours. *Lancet Neurol* 2006;5:937-48.
2. Reiche Werner, Schuchardt Volker, Hagen Thomas, IlyasovKamil A, Billmann Johannes, Weber Johannes. Differential diagnosis of intra-cranial ring enhancing cystic mass lesions—role of diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI). *Clin Neurol Neurosurg*. 2010;112(3) :218–225
3. Cunliffe CH, Fischer I, Monoky D, Law M, Revercomb C, Elrich S, Kopp MJ, Zagzag D. Intracranial lesions mimicking neoplasms. *Archives of pathology & laboratory medicine*. 2009 Jan 1;133(1):101-23.
4. Bulakbasi N. Clinical applications of proton MR spectroscopy in the diagnosis of brain tumours. *Spectroscopy* 2004; 18(2):143-153
5. Smirniotopoulos JG, Murphy FM, Rushing EJ, Rees JH, Schroeder JW. Patterns of contrast enhancement in the brain and meninges. *Radiographics*. 2007;27(2):525-51
6. Poosarla R. *Role of MRI in the Evaluation of Ring Enhancing Lesions in Brain in Correlation with MR Spectroscopy* (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).
7. Rajasree D, KUMAR TL, Vijayalakshmi K. Role of Magnetic Resonance Spectroscopy in the Evaluation of Ring Enhancing Lesions of the Brain. *Journal of Clinical & Diagnostic Research*. 2020 Oct 1;14(10).
8. Archana R, Kumar PS, Kishore A. Role of MRI in evaluation of ring enhancing lesions of brain in correlation with MR spectroscopy. *Amino Acids*. 2018;3:7-5.
9. Elsadway ME, Ali HI. Verification of brain ring enhancing lesions by advanced MR techniques. *Alexandria journal of medicine*. 2018 Apr 19;54(2):167-71.
10. Seth R, Kalra V, Sharma U, Jagannathan N. Magnetic resonance spectroscopy in ring enhancing lesions. *Indian pediatrics*. 2010 Sep;47:803-4.
11. Patil YP, Patel CR, Kuber RS, Sekhon RK. Characteristics of Ring enhancing lesions in brain in correlation with MRI and MR spectroscopy. *Int J Heal Clin Res*. 2021;4(1):120-7.
12. Bava JS, Sankhe A, Patil S. Role of MR spectroscopy in evaluation of various ring enhancing lesions in brain. *Int J Sci Res*. 2016;5(7):1512-14.
13. Mirchandani S, Dave J, Dave AN. Role of MRI & MR spectroscopy (metabolic mapping) in characterisation of ring enhancing lesions in brain. *J Dent Med Sci*. 2019;18(5):55-60
14. Jayasundar R, Singh VP, Raghunathan P, Jain K, Banerji AK Inflammatory granulomas: evaluation with proton MRS NMR Biomed. 1999 May;12(3):139-44.
15. Mishra AM, Gupta RK, Jaggi RS, Reddy JS, Jha DK, Husain N, Prasad KN, Behari S, Husain M. Role of diffusion-weighted imaging and in vivo proton magnetic resonance spectroscopy in the differential diagnosis of ring-enhancing intracranial cystic mass lesions. *Journal of computer assisted tomography*. 2004 Jul 1;28(4):540-7.
16. McKnight TR, von demBussche MH, Vigneron DB, Lu Y, Berger MS, McDermott MW, et al. Histopathological validation of a three-dimensional magnetic resonance spectroscopy index as a predictor of tumor presence. *J Neurosurg*. 2002;97(4):794-802.
17. Brandao LA, Castillo M. Adult brain tumors: Clinical applications of magnetic resonance spectroscopy. *Neuroimaging Clin N Am*. 2013;23(3):527-55.
18. Kumar A, Kaushik S, Tripathi RP, Kaur P, Khushu S. Role of in vivo proton MR spectroscopy in the evaluation of adult brain lesions: our preliminary experience. *Neurology India*. 2003 Oct 1;51(4):474.
19. Gupta RK, Pandey R, Khan EM, Mittal P, Gujral RB, Chhabra DK. Intracranial tuberculomas: MRI signal intensity correlation with histopathology and localised proton spectroscopy. *Magnetic resonance imaging*. 1993 Jan 1;11(3):443-9.