A Study to Assess the Efficacy of Magnetization Transfer Ratio in Differentiating Tuberculoma From Neurocysticercosis

Dr. Ganga Devi Rajapandian[1], Dr. Shivashankar Kumaresan[1], Dr. Babupeter[2], Dr. Priya Muthaiyan[3]

[1]*Associate Professor, Formerly Assistant Professor, Stanley Medical College, Chennai, India,*
[2]*Associate Professor Madras Medical College, Chennai, India,*
[3] *Assistant Professor Stanley Medical College, Chennai, India.*

Abstract
Background: *In Indian patients with acute onset seizures, solitary ring enhancing lesion is the most common imaging abnormality in contrast enhanced CT brain. The two most common cause of these CT-detected lesions are neurocysticercosis (NCC) and tuberculoma. Magnetization transfer ratio obtained using magnetization transfer MR imaging can differentiate tuberculoma from NCC.*
Methods : *The study group included 43 consecutive patients with intra cranial ring enhancing lesions who were referred for MRI Brain. Conventional spin echo, non contrast T1-Weighted (TR 1000, TE 14) axial MR images with and without off - resonance saturation pulse and T2WI were taken for all patients. 3D CISS sequence was taken in axial plane at the site of the lesion. Signal intensity from the rim of the granuloma was obtained with a single pixel from the conventional T1WI (without an off resonance pulse) and MT images (with an off resonance pulse). For each region of interest (ROI), MTR is calculated from the two images using the formula,*
$$MTR = \frac{(Mo - Ms)}{Mo} \times 100$$
where Mo, Ms represent the signal intensity with the saturation pulse off and on, respectively.
Results : *The MT Ratio obtained from the rim of the lesion was tabulated and analyzed using ANOVA method. The Mean MTR was obtained for each group. Mean MTR for tuberculoma was 16.6 +/- 3.1(15.6 –17.56). Innocuous cystic lesions (representing vesicular stage of NCC) showed mean MTR of 10.9 ± 2.8 (9.6 – 12.18). Degenerative NCC showed MTR of 20.8 ± 3.5 (18.7 – 22.9).There were 3 NCC which were hypointense on T2WI which showed a mean MTR which was significantly higher (23.72 ± 3).*
 Conclusions: *MT ratio can be used to differentiate T2 hypointense NCC and Tuberculoma. MT Ratio of Tuberculoma is 16.6 ± 3.1. MT Ratio of T2 hypointense NCC is 23.725 ± 3. Including precontrast MT SE T1 Weighted sequence in our routine MRI Brain protocol for granuloma imaging can help us differentiate T2 hypointense NCC and Tuberculoma, better visualize T2 invisible Tuberculomas and detect presence of associated meningeal disease.*
Keywords: *Tuberculoma, Neurocysticercosis, Magnetization transfer MR imaging, Magnetization transfer ratio, 3D CISS, Scolex.*

I. Introduction

In Indian patients with acute onset seizures, solitary ring enhancing lesion is the most common imaging abnormality in contrast enhanced CT brain (1 - 7). In 1980's ring enhancing lesions were presumed to be tuberculoma and treated with empirical Anti tubercular treatment. A major breakthrough came, when Chandy et al (1989), followed by Rajasekhar et al (1993) found on stereo tactic biopsy and histopathological studies that Neurocysticercosis is the commonest etiology of single enhancing lesion in CT scans(3, 9). The second most common cause of these CT-detected lesions is tuberculoma. Patients with both tuberculosis and NCC have similar clinical and neuroimaging features. Using CECT and conventional MRI Brain, tuberculoma and neurocysticercus granuloma can be differentiated to some extent(3).Various studies have shown that magnetization transfer ratio obtained using magnetization transfer MR imaging can differentiate tuberculoma from NCC(8).

Magnetization Transfer MR Imaging is a technique for improving image contrast in Magnetic Resonance (MR) imaging (11).It is based on application of off-resonance radio-frequency pulses and observing their effects on MR images. There are numerous applications of MT imaging (11, 12, 15, 22, 23, 24). The utilization of magnetization transfer was extended to clinical imaging, including its use with gradient-echo imaging and MR angiography (15, 20, 21). It has also been used with short repetition time (TR) images to detect contrast enhancement and other regions containing short T1 elements, including methemoglobin (11) and lipid. It has been proposed as the reason that adult white matter has high signal intensity on short TR images, even though it has 12% less water than gray matter (11). The magnetization transfer technique enables semi

quantitative characterization of tissue and pathologic entities, which could substantially improve the specificity of MR imaging (11, 12, 13). By measuring the signal intensity with and without application of the pulses, magnetization transfer ratio (MTR) can be calculated. MTRs can be used to detect changes in the structural status of brain parenchyma that may or may not be visible with standard MR technique.

Infections of the central nervous system (CNS) and single CT enhancing lesions (SCTEL) are the major provoking factors in patients with acute onset simple or complex partial seizure(s) with or without secondary generalization.(1,9).Tuberculoma are usually more than 20mm, are associated with midline shift, raised intracranial tension, and progression. (1, 3, 38). Basal meningitis with parenchymal lesions is highly suggestive of tuberculous etiology. Caseating tuberculoma with solid centre are hypo intense with hyper intense rim in T2 Weighted Images (38). Neurocysticercus granuloma are usually less than 20mm, no mass effect, no midline shift, no raised intracranial tension, and no progression. Cyst with dot inside (scolex) is diagnostic of Neurocysticercus granuloma. In Colloid vesicular stage, the cyst is hyper intense in T2WI. Degenerating cyst is hypo intense in T2WI when it mimics tuberculoma. Advanced MRI techniques like Magnetization Transfer Imaging, Apparent Diffusion Coefficient and Magnetic Resonance Spectroscopy are used to differentiate the two lesions.

Magnetization transfer ratio (22) is a quantitative measure of the MT effect on tissues. It is the degree of signal suppression of a given tissue compared with the conventional PD or T1-W image. The MT ratio (MTR) may be simply obtained by collecting a pair of identical images (PD or T1-W), one with and one without MT saturation.

For each region of interest (ROI), MTR is calculated from the two images using the formula:

$$MTR = \frac{(M_o - M_s) \times 100}{M_o}$$

Where M_o, M_s represent the signal intensity with the saturation pulse off and on, respectively. The T2 hypo intense Tuberculoma had the lowest MT ratios relative to T2 isointense / hyperintense Tuberculoma. Pathologically, the hyper intense and isointense (invisible) lesions are the solid granulomas with minimal or no caseation (5). With increased caseation, lesions tend to appear hypo intense on T2-weighted images. The caseation in a tuberculoma is composed predominantly of lipids and amino acids, as has been documented with proton MR spectroscopy (25). Lipids are not known to show MT (26). The presence of lipids as the major macromolecular constituent of the caseating granulomas as compared with noncaseating granulomas is probably responsible for the lower MT ratios in the former. T2 hypo intense tuberculomas have shown much lower MT ratios as compared with gray and white matter, and are prominent on precontrast MT-SE images. T2 hypo intense cysticercus granulomas have a significantly higher MT ratio than do similar-appearing tuberculomas, and are of low visibility, especially when located in the white matter (8). Quantitative MT ratios may help differentiate these similar-appearing infective granulomas and thus aid in the lesion-specific targeting of appropriate therapy. (8)

II. Materials and Methods

The study was started after the approval from the Hospital Ethical Committee. The study group included 43 consecutive patients with intra cranial ring enhancing lesions, were referred to the Barnard Institute of Radiology, Madras Medical College, Chennai for MRI Brain in June 2010 to November 2010. Patients clinically suspected of having intracranial granulomas, who had ring enhancing lesions in Contrast Enhanced Computed Tomography (CECT) or Magnetization Resonance Imaging of Brain were included in the study. All patients with calcified granuloma, patients with a known primary malignancy, patients with claustrophobia and patients with other contraindications for MRI (pacemaker implants, cochlear implants etc) were excluded from the study.

Mr image acquisition:

All patients provided the informed consent for performing additional sequences during imaging. Brief history regarding the nature and duration of illness, treatment history, significant past and personal history is taken from all patients. The study was performed in 1.5 Tesla SIEMENS MAGNETOM SYMPHONY MRI scanner. Conventional spin echo, non contrast T1-Weighted (TR 1000, TE 14) axial MR images with and without off - resonance saturation pulse and T2WI were taken. 3D CISS sequence was taken in axial plane at the site of the lesion. All images were obtained in axial plane with 5mm slice thickness and a base resolution of 192 x 256 matrixes.
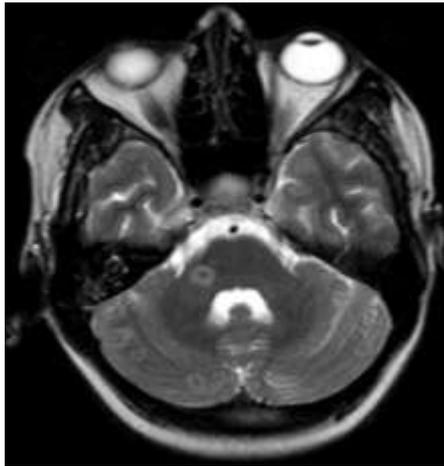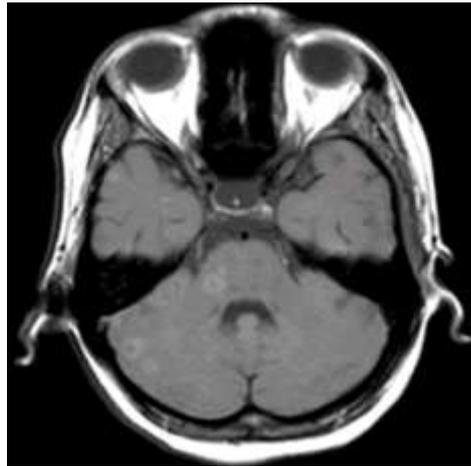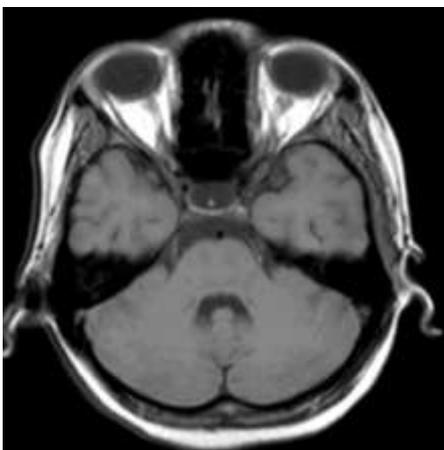
III. Data Analysis

Images were analyzed by two separate radiologists. Signal intensity from the rim of the granuloma was obtained with a single pixel from the conventional T1WI (without an off resonance pulse) and MT images (with an off resonance pulse). For each region of interest (ROI), MTR is calculated from the two images using the formula. Consistency and reliability of the measurements were confirmed by obtaining the values repeatedly.

The final diagnosis of tuberculosis was based on typical CSF features (cellularity and biochemistry), histopathological examination and response to specific treatment.

The diagnosis of Neurocysticercosis was based on the presence of scolex in a cyst in ps3d/ 3d CISS sequence in MR Images. As per the Revised diagnostic criteria for Neurocysticercosis , the presence of multiple cystic lesions with or without scolex on CT or MRI is an Absolute criterion for the definitive diagnosis of neurocysticercosis. Presence of additional findings like infarct, meningeal thickening, basal meningitis were also noted. The MT Ratio from the cortical and deep gray and white matter from frontal, parietal, occipital and temporal regions, head of caudate nucleus and thalamus was also obtained (**Fig 1**).

Fig 1a   **Fig 1b**

Fig 1c   **Fig 1d**

Fig 1 a, b, c, d- MT Ratio from the cortical and deep gray and white matter from frontal, parietal, occipital and temporal regions, head of caudate nucleus and thalamus.

The lesions were grouped as Tuberculoma (**Fig 2**) , degenerative NCC (**Fig 3**). (T2 hypointense / hyperintense) and cystic NCC (T2 hyper intense and follows CSF intensity).
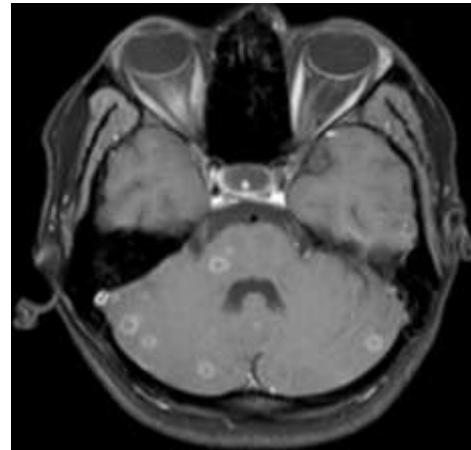
Fig 2a

Fig 2b

Fig 2c

Fig 2d

Fig 2a- T2w MRI Showing Multiple T2 hypointense tuberculoma which have hypointense core with surrounding hyperintense rim

Fig 2c T1 W MT SE image shows the granuloma more conspicuous when compared to T1WI.
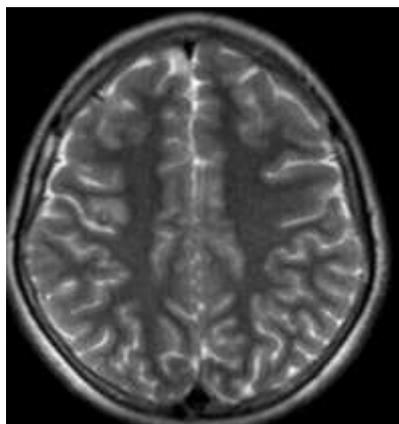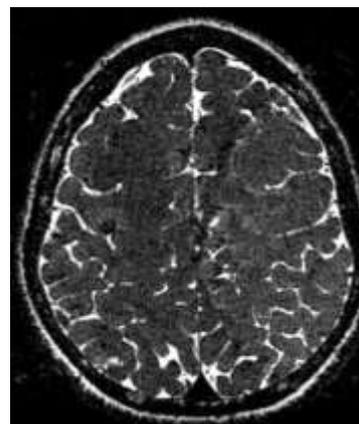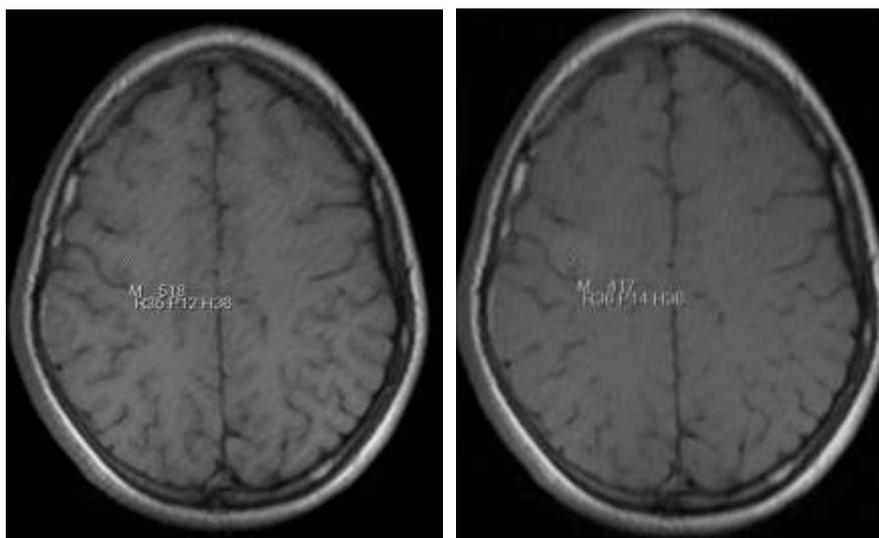**Fig 2d –** T1W Pre and Post contrast showing ring enhancing lesions.

Fig 3a

Fig 3b

Fig 3c

Fig 3d

Fig 3a,b, c,d –Axial T2W, 3D CISS, T1W, T1/MT SE W images at the level of centrum semiovale showing degenerative Neurocysticercosis.

The MT Ratio obtained from the rim of the lesion was tabulated and analyzed using ANOVA method. The Mean MT ratios were obtained for each of the three category with Standard Deviation from the Mean.

IV. Results

A total of 76 granulomas from 43 patients with an age range from 6 to 72 years were analyzed of which 26 patients were men and 17 patients were women. Of these 76 granulomas, 41 were Tuberculomas analyzed in 21 patients and 35 were Neurocysticercous lesions analyzed in 22 patients. Cystic vesicular Neurocysticercus were 21 and degenerating Neurocysticercus were 14. 31 patients had single ring enhancing lesion. Multiple ring enhancing lesions were seen in 12 patients. Histopathological evidence of tuberculosis was present in one patient with Tuberculous abscess in the left middle cerebellar peduncle. The typical radiological features of miliary pulmonary tuberculosis were present in 4 patients. One patient had caries spine. Rest of the patients had positive chest x-ray for pulmonary tuberculosis. 13 patients had solitary lesions in brain and had typical features of tuberculoma in conventional MRI. Follow up after 2 months of treatment showed clinical improvement and reduction in the size of the lesion or the surrounding vasogenic edema.

The MT Ratio of the normal white matter and deep gray matter from healthy controls measured 23.72 ± 2.36 and 17.58 ± 3.52 respectively. The data was taken for comparison with tuberculomas and T2 hypointense cysticercous granulomas. Mean MTR for tuberculoma is 16.6 +/- 3.1(15.6 –17.56).

Descriptives

MTR

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
NCC - VESCICULAR	21	10.9000	2.82981	.61752	9.6119	12.1881	2.90	14.70
NCC - DEGENERATING	14	20.8500	3.57378	.95513	18.7866	22.9134	16.70	28.00
TUBERCULOMA	41	16.5944	3.08239	.48139	15.6215	17.5673	6.00	22.10
Total	76	15.8049	4.60920	.52871	14.7516	16.8581	2.90	28.00

Table 1- Mean MTR of ring enhancing lesions

MTR

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	887.116	2	443.558	45.848	.000
Within Groups	706.236	73	9.674		
Total	1593.353	75			

Table 2- ANOVA tests Showing difference in MTR values between Tuberculous lesions & NCC is statistically significant P value < .05

There were 21 innocuous cystic lesions (representing vesicular stage of NCC) which showed mean MTR of 10.9 ± 2.8 (9.6 – 12.18). 14 lesions with imaging features suggestive of degenerative cysts showed MTR of 20.8 ± 3.5 (18.7 – 22.9). There were 3 lesions which were hypointense on T2WI which showed a mean MTR which was significantly higher (23.725 ± 3).

Dependent Variable: MTR
Tukey HSD

(I) DIAGNOSIS	(J) DIAGNOSIS	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
NCC - VESCICULAR	NCC - DEGENERATING	-9.95000*	1.07318	.000	-12.5175	-7.3825
	TUBERCULOMA	-5.69439*	.83466	.000	-7.6913	-3.6975
NCC - DEGENERATING	NCC - VESCICULAR	9.95000*	1.07318	.000	7.3825	12.5175
	TUBERCULOMA	4.25561*	.96281	.000	1.9522	6.5591
TUBERCULOMA	NCC - VESCICULAR	5.69439*	.83466	.000	3.6975	7.6913
	NCC - DEGENERATING	-4.25561*	.96281	.000	-6.5591	-1.9522

*. The mean difference is significant at the .05 level.

Table 3 - Post Hoc Tests, When multiple comparisons are made, the mean difference between the ratio of the three groups is significant.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
							Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)			Lower	Upper
MTR	Equal variances assumed	16.373	.000	-1.634	74	.106	-1.71439	1.04911	-3.80480	.37602
	Equal variances not assumed			-1.562	49.727	.125	-1.71439	1.09758	-3.91925	.49047

Table 4 -T-Test, showing the group allocation is correct.

V. Discussion

MTR was calculated from the rim of the lesion. In the study of Rakesh Gupta et al (8), it is stated there was no significant difference between the MT ratios in the core and the rim of Tuberculous lesions. Mean MTR of tuberculoma in our study was 16.6 ± 3.7. Using MT Ratio of 16.6 ± 3.7 (12.9 − 20.3), the sensitivity for detecting tuberculoma was 78%, specificity was 73% and positive predictive value was 78%. In addition, Tuberculomas were better seen in precontrast MT SE images compared to T1WI and T2WI especially T2 hypointense Tuberculomas. More lesions were detected on precontrast MT-SE images, since few lesions did not enhance after contrast injection. Contrast enhancement due to disruption of the blood-brain barrier depends on the activity of the lesion and inactive lesions may not enhance after contrast administration (8). Two study patients also had basal meningitis. In precontrast MTSE images, parenchymal hyper intensity along the surface of brain stem was visible. On contrast, there was enhancement of the basal meninges and cisternal tuberculoma.

35 Neurocysticercus lesions were analyzed in 22 patients. The size of the lesion ranged from 8mm to 15.5mm. Intra ventricular cysts were larger in size. Demonstration of scolex within a cyst in CT/MRI is considered the absolute criteria for the diagnosis of Neurocysticercosis as per the revised diagnostic criteria of NCC. 3D CISS images demonstrate the cyst wall and scolex due to inherent high contrast resolution of the sequence. Degenerating NCC cysts show hypo intense center with hyper intense rim in MT images. There were 21 cystic lesions (representing vesicular stage of NC) which showed MTR of 10.9 ± 2.8 (9.6 − 12.18). There were 3 granuloma which were hypointense on T2WI which showed MTR which was significantly higher (23.725± 3). 14 lesions with imaging features suggestive of degenerative cysts showed MTR of 20.8 ± 3.5 (18.7 − 22.9)

The difference in the MTR values of tuberculous & NCC lesions is illustrated by box chart in **figure 4**
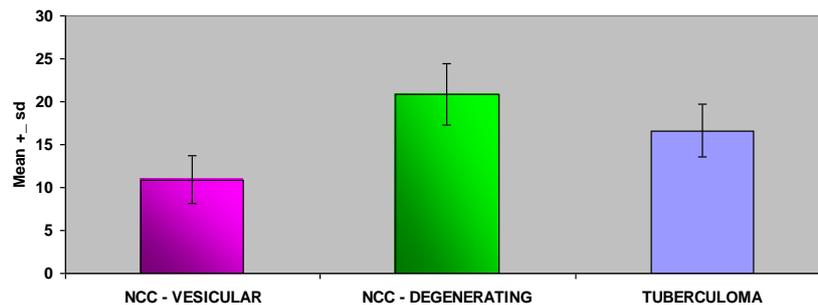
Fig 4- Efficacy of MTR in differentiating tuberculous lesions versus NCC

According to the study of Rakesh Gupta et al, the tuberculous lesions with a hypointense core on T2-weighted images had MT ratios of 23.8 ± 1.76 in the rim and 24.2 ± 3.1 in the core. In our study, the mean MTR was 16.6 ± 3.7 for Tuberculoma. There are several key parameters in the off-resonance saturation transfer technique that can alter the quantitative and qualitative MTC. The principle determinants being the base sequence used, characteristics of the saturating pulse (pulse type, power, duration, time between pulses, duty cycle i.e. number of pulses per TR, bandwidth, its effective flip angle), offset frequency of the saturating pulse, and field strength. All of these characteristics alter the degree of saturation and Magnetization transfer ratio obtained and must be known before quantitative comparisons can be made between clinical studies. (22). So, machine parameters could be the reason for the variability of MTR measured in both studies.

In 1998, Kathuria MK et al (28) measured the magnetization transfer ratio (MTR) in different stages of neurocysticercosis. The visibility of a lesion on MT-SE sequence was dependent on its MTR and its location at a particular site (cortical gray matter, white matter, or deep gray matter). The difference in MTR of the lesion and the surrounding brain parenchyma decides the resulting contrast and visibility of the lesion Innocuous cystic lesions, which were hyperintense on T2-weighted images, did not show any MT (MTR = 5.10+/-1.2), whereas degenerating T2 hyperintense lesions showed MTR of 26.40±2.7. Nondegenerating and degenerating scolices showed an intermediate MTR of 21.7± 3.3 and 15.0±4.5, respectively.

VI. Limitations of the study

The total number of the lesions analysed include 41 tuberculoma and 35 Neurocysticercus. A total of 107 tuberculomas in seven patients were analyzed in the study by Rakesh Gupta et al (8).The no of lesions enrolled in this study were less than the previous study conducted. This could account for the wide confidence interval noticed in this study. Magnetization transfer ratio obtained for white and grey matter as well as tuberculoma and NCC in our study were less than the previous studies. This is probably due to technical and machine parameters. Hence MTR has to be standardized for each machine and MTR between two different studies cannot be compared. Histopathalogical results are available for only one lesion.

VII. Conclusion

MT ratio can be used to differentiate T2 hypointense NCC and Tuberculoma. MT Ratio of Tuberculoma is 16.6 ± 3.1 and MT Ratio of T2 hypointense NCC is 23.725. T2 invisible Tuberculomas are better visualized in MT images. Hence disease load can be better assessed using MT images. Presence of associated meningeal disease can be demonstrated using precontrast MT SE Images in Tuberculoma. Including precontrast MT SE T1 Weighted sequence in our routine MRI Brain protocol for granuloma imaging can help us differentiate T2 hypointense NCC and Tuberculoma, better visualize T2 invisible Tuberculomas and detect presence of associated meningeal disease.

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