

CT Perfusion Dynamics of Intracranial Tuberculomas

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ABSTRACT

Aims: To study perfusion characteristics of intracranial tuberculomas and analyze changes with anti tubercular treatment.

Materials and Methods: Nineteen patients of histologically proven intracranial tuberculomas were included in the study of which 9 were not on antitubercular treatment and ten were on antitubercular treatment (6 patients on treatment for less than 2 months and 4 were more than 6 months). All patients underwent CT perfusion (CTP) and CTP parameters like rCBV and rCBF were obtained from entire lesion, center and capsule of lesions and compared.

Results: CTP parameters like rCBF and rCBV were significantly low in all the three ROIs in the group not on treatment compared to that of on treatment ; rCBF and rCBV of entire lesion ($p=0.018$ and $p=0.005$ respectively), capsule ($p=0.045$ and $p=0.010$ respectively) and center of the lesion ($p=0.020$ and $p=0.009$ respectively). Tuberculomas on antitubercular treatment of more than six

months showed reduced rCBF and rCBV in entire lesion ($p=0.01$ & $p=0.01$ respectively), capsule ($p=0.04$ & $p=0.03$ respectively) and center ($p=0.08$ & $p=0.05$ respectively) compared to those on treatment for less than two months. Similarly tuberculomas on treatment for six months did not show significant difference in rCBF and rCBV compared to tuberculomas who were not on treatment. Tuberculomas on treatment for less than two months showed statistically increased rCBF and rCBV in entire lesion ($p=0.01$ & $p=0.04$ respectively), capsule ($p=0.03$ & $p=0.01$ respectively) and center ($p=0.03$ & $p=0.01$) compared to those not on treatment.

Conclusion: Intracranial tuberculomas not on treatment and those on treatment for around six months show low perfusion and tuberculomas on treatment for less than two months show high perfusion. These findings suggest that serial perfusion profiles of tuberculomas on treatment could possibly be seen as surrogate markers of response to treatment.

Keywords: Brain, Central nervous system, Tuberculoma

INTRODUCTION

Tuberculomas constitute about 5-40% of all intracranial space occupying lesions [1]. Neuroimaging techniques like Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) play important roles in the diagnosis of central nervous system tuberculosis including tuberculoma. Routine imaging features of tuberculoma are non specific [2-4].

Advanced MR imaging techniques like diffusion weighted imaging, MR spectroscopy, Magnetization Transfer imaging and MR perfusion imaging have improved the sensitivity and specificity in the diagnosis of intracranial tuberculoma [5-8]

Earlier investigation using MR perfusion technique in tuberculoma revealed altered perfusion parameters. However, the lesions were presumed to be of tubercular aetiology in lieu of histological verification of the lesions [8]. Recent MR perfusion studies are promising in differentiating intracranial ring enhancing tuberculomas from ring enhancing metastases [9,10].

CT Perfusion (CTP) is an established method in the evaluation of hyper acute and acute ischemic strokes of brain. The results of CTP observations are comparable to those of MR perfusion and diffusion images [11,12]. The present study uses CT perfusion technique in histologically proven tuberculomata to understand the pathophysiology and its therapeutic implications.

MATERIALS AND METHODS

After obtaining permission from the institute (NIMHANS, Bangalore), a prospective study was conducted in the year 2005 and 2006 in the Department of Neuroimaging and interventional radiology with following design:

Inclusion Criteria

1. The treatment naïve tuberculomas selected after CT guided stereo-tactic biopsy.
2. Patients on antitubercular treatment after CT guided stereo-tactic biopsy.

Exclusion Criteria

1. Paediatric patients were excluded from the study.

Informed consent was obtained in all patients

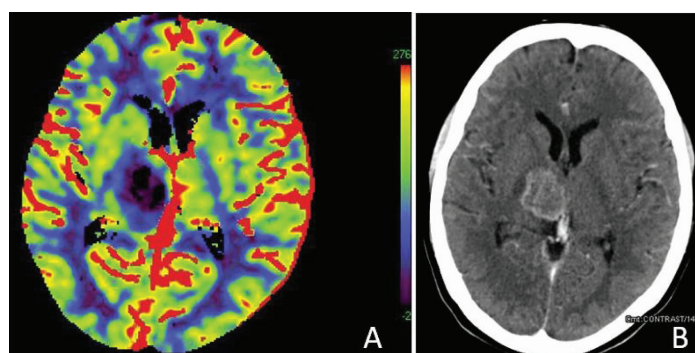
There were 19 patients in the study; nine patients were not on antitubercular treatment and ten were on antitubercular treatment at the time of study. In ten patients who were on antitubercular treatment at time of study six were on treatment for less than two months and four were more than six months. There were 13 females and six males in the age group of 17-56 y (Mean 32.93). All patients underwent plain and contrast enhanced CT scan of brain. In case of multiple tuberculomas, largest supratentorial lesion was selected for CTP evaluation.

CT Perfusion Imaging Technique and Data processing

Patients were advised fasting for 6 h prior to the CT perfusion study. An 18G cannula was introduced into the antecubital vein. Once the position of cannula was confirmed in situ, a non-enhanced CT of brain was performed to identify the axial sections demonstrating the lesion. Subsequently dual-slice dynamic CT bolus tracking perfusion studies using a multi-detector CT scanner was performed. The first slice was selected at the level of the maximum cross-sectional diameter of the mass lesion as seen on initial plain CT and the second slice was 10mm cranial to the first. The slice thickness was 10mm

with a matrix size of 512 x 512. Fifty ml of 65% iodinated contrast agent was injected through an 18G cannula into the antecubital vein using a pressure injector at the rate of 6ml / second. Following a delay time of 4 seconds, a total of 40 images were acquired at a rate of one image / sec.

The image data was transferred to a workstation with Siemens MV 300 post processing software. Perfusion images were created with reference to superior sagittal sinus away from the bone. Irregular shape regions of interest (ROI) were drawn in the following regions: a) entire lesion, b) capsule of the lesion c) center of the lesion and d) within 1-2cm adjacent to the lesion. The CTP parameters from each of these ROIs were compared with perfusion parameters from ROIs in contra lateral normal-looking brain parenchyma and cerebral haemodynamic parameters such as relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV) and relative time to peak (rTTP) were obtained using deconvolution method. Colour maps also generated as shown in [Table/Fig-1a,b, 2a,b].



[Table/Fig-1a,b]: rCBF (A) color map of tuberculoma without treatment in right thalamus showing low perfusion with corresponding contrast CT image (B)

STATISTICAL ANALYSIS

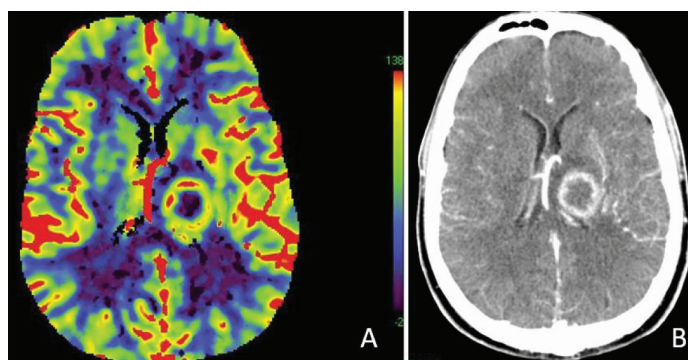
Mean and standard deviations of these parameters were calculated in all patients. Paired Student t-test was performed to obtain statistical significance between two groups of patients. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The CT imaging features of these tuberculomas are given in [Table/Fig-3]. CT perfusion parameters are given in [Table/Fig-4,5]. [Table/Fig-6] shows mean and standard deviation of perfusion parameters of both the groups.

Case No.	No. of lesion	Plain CT	Enhancement pattern	Calcification	Location
1	1	isodense	ring	No	Rt. parietal
2	1	isodense to hyperdense	Ring	No	Rt basal ganglion
3	1	isodense	Ring	No	Rt frontal
4	2	isodense	ring	No	Bil. frontal
5	1	isodense	ring	No	Rt basal ganglia
6	1	isodense	ring	No	Lt parietal
7	1	isodense	ring	No	Lt frontal
8	2	isodense	ring	No	Lt parietal & Lt cerebellar
9	1	isodense	ring	No	Lt parietal
10	1	isodense	ring	No	Lt thalamic
11	1	isodense	ring	Peripheral specks	Rt frontal
12	1	isodense	ring	No	Lt thalamic
13	2	isodense	ring	No	Midbrain and Rt insula
14	2	isodense	ring	Peripheral specks	Bil. frontal
15	1	isodense to hyperdense	ring	No	Rt. basal ganglia
16	1	isodense	ring	No	Rt. centrum semiovale
17	1	isodense to hyperdense	ring	No	Lt. parietal
18	1	isodense	ring	No	Rt. frontal
19	2	isodense	ring	No	Rt. cerebellar and Lt. parietal

[Table/Fig-3]: CT characteristics of the lesions



[Table/Fig-2a,b]: rCBF (A) colour map of tuberculoma on treatment in left thalamus showing high perfusion with corresponding contrast CT image (B)

Contrast enhanced CT scan of brain showed single lesion in 14 patients and multiple lesions in five patients. The lesions in all the patients were isodense on plain CT and showed ring-enhancement on contrast studies. CTP parameters like rCBF and rCBV were significantly low in all the three ROIs in the group not on treatment compared to that of on treatment; rCBF and rCBV of entire lesion ($p=0.018$ and $p=0.005$ respectively), capsule ($p=0.045$ and $p=0.010$ respectively) and center of the lesion ($p=0.020$ and $p=0.009$ respectively). Tuberculomas on antitubercular treatment for more than six months showed reduced rCBF and rCBV in entire lesion ($p=0.01$ & $p=0.01$ respectively), capsule ($p=0.04$ & $p=0.03$ respectively) and center ($p=0.08$ & $p=0.05$ respectively) compared to those on treatment for less than two months. Similarly tuberculomas on treatment for six months did not show significant difference in rCBF and rCBV compared to tuberculomas who were not on treatment. Compared to tuberculomas not on treatment, tuberculomas on treatment (for less than two months) showed statistically increased rCBF and rCBV in entire lesion ($p=0.01$ & $p=0.04$ respectively), capsule ($p=0.03$ & $p=0.01$ respectively) and center ($p=0.03$ & $p=0.01$). [Table/Fig-7,8] shows scatter and bar diagram of tuberculomas in entire lesion and capsule of the lesion.

DISCUSSION

CNS involvement in tuberculosis is common. The usual manifestations include acute and chronic meningitis, granulomata, encephalopathy and abscess. Tuberculoma is the focal granulomatous form, encountered in about 10%-40% of CNS tuberculosis [10]. Histologically, the mature tuberculomas are composed of

Case no.	Age (years/sex)	Whole			Center			Capsule			Periphery		
		rTTP	rCBF	rCBV	rTTP	rCBF	rCBV	rTTP	rCBF	rCBV	RTTP	rCBF	rCBV
1	36/f	1.11	0.95	1.09	0.98	0.08	0.2	1.03	1.76	1.78	1.1	0.93	1.05
2	22/f	0.85	0.73	1.06	1.25	0.06	0.2	0.89	0.16	0.38	0.65	3.07	2.46
3	32/f	1.11	1.14	1.2	1.09	0.14	0.12	1.11	1.7	1.76	0.91	0.43	0.53
4	17/f	0.96	0.76	0.96	0.82	0.09	0.17	0.89	1.7	1.93	1.17	0.42	0.45
5	40/f	1.49	0.72	0.75	1.98	0.18	0.37	1.05	1.93	1.89	1.26	0.32	0.39
6	50/m	0.89	0.79	0.77	0.72	0.52	0.42	0.9	1.19	1.15	0.9	1.21	1.03
7	40/m	1.04	0.63	0.77	0.88	0.08	0.28	1.08	1.41	1.37	0.91	0.64	0.76
8	28/f	0.9	1.37	1.28	0.68	0.18	1.19	0.87	2.2	1.9	0.99	1.07	1.13
9	30/m	1.01	1.05	1.04	1.02	0.11	0.07	1	1.08	1.02	0.99	0.85	0.69

[Table/Fig-4]: CT perfusion parameters of Tuberculoma without treatment (TWT)

Case No.	Age (years/sex)	Rx history	Whole			Center			Capsule			Periphery		
			rTTP	rCBF	rCBV	rTTP	rCBF	rCBV	rTTP	rCBF	rCBV	RTTP	rCBF	rCBV
10	56/f	2 mth	0.96	3.68	3.58	0.9	3.11	3.38	0.91	4.18	3.72	0.66	1.58	1.19
11	20/f	1.5 mth	1	2.66	3.16	1.2	1.06	1.77	1.01	3.4	4.74	0.9	0.58	0.7
12	31/m	1 mth	0.79	5.07	3.91	1.05	0.4	0.42	0.76	7.17	5.58	0.57	3.27	1.83
13	37/m	1 mth	1.04	4.25	4.14	1.04	3.47	3.18	1.02	5.05	4.39	1.04	0.2	0.2
14	17/f	2 mth	0.98	1.61	2.38	1.35	0.61	1.12	0.85	2.07	2.7	1.12	0.36	0.35
15	22/f	2 mth	0.98	1.42	1.54	0.91	1.41	1.84	1.11	1.26	1.35	0.9	1.84	1.57
16	35/f	6 mth	1.21	1.1	1.38	1.59	0.34	0.68	1.13	1.35	1.72	1.07	0.88	0.89
17	31/f	6 mth	1.13	1.71	2.01	1.18	1.04	1.37	1.53	1.62	2.29	2.01	0.04	0.08
18	54/m	6 mth	1.24	0.9	1.12	1.22	0.32	0.59	1.13	1.42	1.73	1.07	0.9	0.85
19	28/f	7 mth	0.86	0.66	0.78	0.85	0.28	0.46	0.82	1.96	1.85	1.06	1.18	1.04

[Table/Fig-5]: CT perfusion parameters of Tuberculoma on treatment (TOT)

	Entire lesion (Mean and SD)		Center		Capsule		Periphery	
	rCBF	rCBV	rCBF	rCBV	rCBF	rCBV	rCBF	rCBV
TWT(n=9)	0.90± 0.24	0.99± 0.19	0.16± 0.14	0.33± 0.33	1.45± 0.60	1.46± 0.53	0.99± 0.83	0.94± 0.62
TOT(n=10)	2.30± 1.53	2.4± 1.22	1.20± 1.16	1.48± 1.07	2.94± 1.97	3.00± 1.49	1.08± 0.96	0.87± 0.56
TOT less than 2 mth(n=6)@	3.11± 1.46	3.11± 0.92	1.67± 1.30	1.95± 1.15	3.85± 2.12	3.74± 1.52	1.30± 1.17	0.97± 0.66
TOT for 6 mth (n=4)#	1.09± 0.44	1.32± 0.52	0.49± 0.36	0.77± 0.40	1.58± 0.27	1.89± 0.26	0.75± 0.49	0.71± 0.43

[Table/Fig-6]: Mean and standard deviation of CT perfusion parameters at various sites of lesion in both groups of patients.

@ and # - subgroups of TOT (n=10)

necrotic caseous center surrounded by a capsule that contains fibroblasts, epithelioid cells, Langhans cells and lymphocytes formed by coalescence of microtuberculomas. In the formation of tuberculoma, initially there is predominant inflammatory reaction with collagen poor capsule and later collagen rich capsule forms with reduction in inflammatory reaction and caseated center due to coagulation necrosis [13].

Three layers are described in tuberculomas. The inner layer is central caseation necrosis with nuclear debris and adjacent inflammatory cells. Hyalinised collagenous tissue forms middle layer and outer layer is of inflammatory cells like lymphocytes and epithelioid [13].

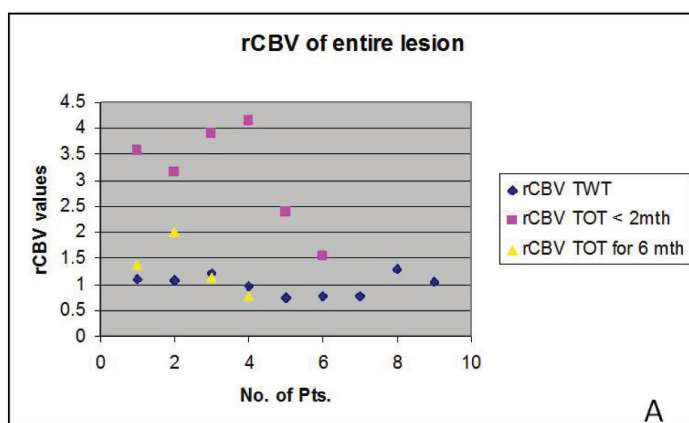
Improved understanding of pathophysiology of a metabolically dynamic lesion such as a tuberculoma may help in better clinical management. Various imaging techniques such as PET, SPECT and MR perfusion have been used in an effort to understand and measure various physiological parameters in many neurological diseases [14-20].

Perfusion imaging is novel method to detect vasculature of tissue and can detect indirectly the metabolic activity of the tissue as perfusion of the tissue changes according to metabolic requirement of the tissue [21].

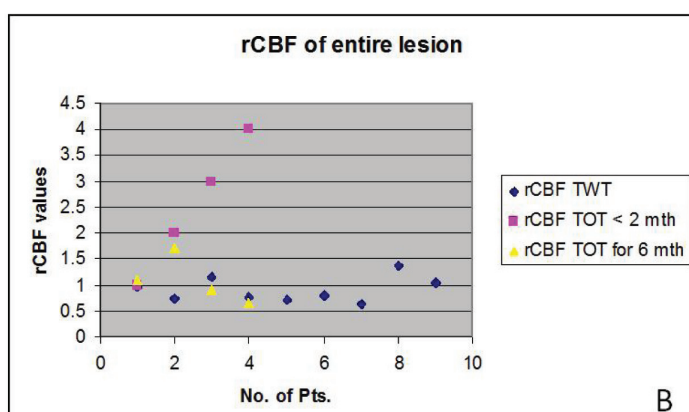
There are only a few pathophysiological studies in CNS tuberculosis using SPECT and MR perfusion imaging techniques [8-10,22].

However, PET is not available at all centers, uses isotopes and lacks resolution. MR is not cost effective and time-consuming. Considering these drawbacks, we performed CT perfusion in our patients.

In an earlier MR perfusion study of tuberculomas, Batra et al., observed increased perfusion similar to that of high grade tumours [8]. Jenkins et al., used CTP and reported changes in time density curve in intracranial tuberculoma with the treatment. They found early appearance of contrast in the lesion compared to normal brain parenchyma. This feature was attributed to the presence of inflammatory granulation tissue. The early wash-in phase was observed even during treatment which the authors explained by the presence of hypervascularity due to neovascularization and loss of auto regulation in the wall of lesion [23]. Recently MR perfusion studies in differentiating tuberculomas from metastasis have shown a cut-off rCBV value of ≥ 3.745 for differentiating ring-enhancing metastases from ring-enhancing tuberculomas [9]. Similar studies in lung lesions have shown significantly high peak height and increased relative flow (RF) in active tuberculoma as compared to inactive tuberculoma [24].



A



B

[Table/Fig-7a,b]: Scatter plot of rCBV (A) and rCBF (B) of entire lesion showing low perfusion in TWT and TOT

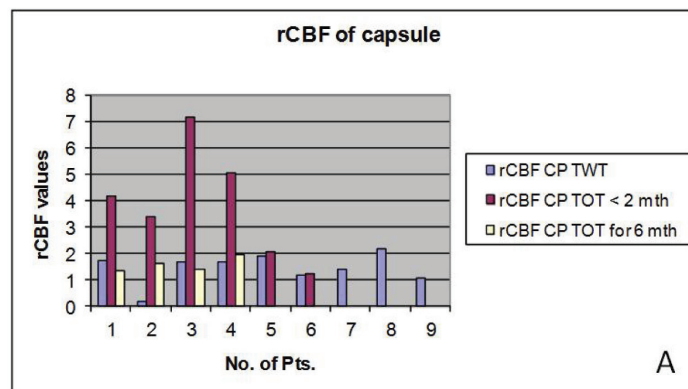
Infective lesions like abscess and toxoplasmosis have reduced perfusion compared to neoplastic lesions as shown by various other studies [25,26]. Thus it becomes clear from all these studies that infective lesions can be differentiated from neoplastic lesions based on perfusion studies.

In the present study we found that CT perfusion parameters were significantly low in treatment naive tuberculomas compared to those on treatment. In the treated group those tuberculomas which were on treatment for more than six months showed low perfusion than those who received treatment for less than two months. However, there was no statistically different perfusion in tuberculomas on treatment for more than six months as compared to treatment naive tuberculomas.

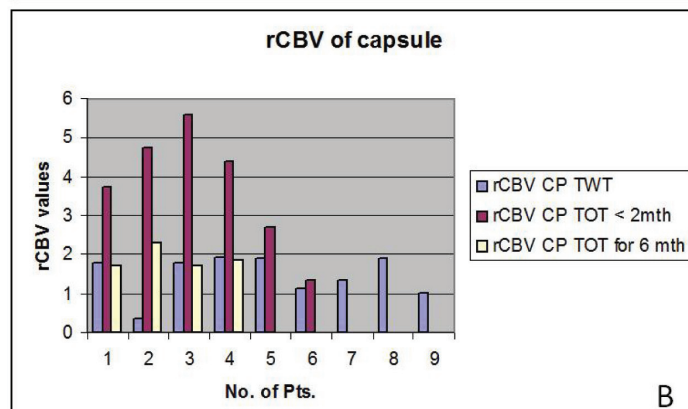
We observed reduced rCBF and rCBV in the capsule and the entire lesion compared to normal brain parenchyma in TWT group of patients. The reduction may be due to the presence of vasculitis in the tubercular granulomatous lesions. Dastur et al., in their important work have demonstrated total or partial vascular occlusion in the lesions. These changes were also noted in the reactive and surrounding edematous zones of tuberculomatous lesions. The core of tuberculomas contains caseation which showed no blood vessels or only ghost of blood vessels [27]. These pathological features explain findings of reduced rCBF and rCBV in our lesions.

On the other hand tuberculomas in TOT (<2 months) patients showed increased rCBF and rCBV parameters in all the three ROIs when compared to normal looking brain parenchyma. This increase may be due to loss of auto regulation in the new vessels developed in the lesion [23].

Jenkins et al., have described changes in micro and macro vasculature of various infective and neoplastic intracranial lesions. They observed that the universal response of cerebral tissue to any injury was coagulation necrosis following which there was reactive granulation repair resulting in reactive hypervascularity with loss of auto regulation [28]. In advanced cases there could be vascular shunting and early venous drainage. In 4-14 days, some of the



A



B

[Table/Fig-8a,b]: Bar diagram of rCBF (A) and rCBV (B) at capsule of tuberculomas without treatment (TWT) and on treatment (TOT)

hypervascularity can be accounted by a true neovascularization of the capsule. Damaged vessels and newly formed vessels in granulation tissue lack tight junction which led to leak of intravascular fluid and contrast into capsule leading to ring enhancement and oedema. These were demonstrated as elevated plateau of time density curve and late wash out phase [28]. These findings are also validated by the fact that there is increased neoangiogenesis with increased expression of vascular endothelial growth factor in the wall of tuberculomas leading to increased rCBV [29].

However, two patients (Cases 14 & 15) of TOT (<2 months) did not show increase in rCBF and rCBV parameters. This may be due to immunologically mediated secondary granulomatous vasculitis (with? vessel occlusion) [30].

The reasons for significant reduction of rCBF and rCBV parameters in patients of TOT (>6 months) compared to patients of TOT (<2 months) may include healing by fibrosis, reactive gliosis and calcification [27].

The tuberculomas showed a corresponding decrease in size in this interval period. The treatment has started the healing process resulting in reduced rCBF and rCBV in our patients. These were in accordance with the study by Jenkins et al., who found an initial hyper vascular phase which gradually returned to isovascular phase on treatment or a hypo vascular phase, attributed to atrophy or atrophy associated with calcification [23].

Similarly with treatment there is decreased neoangiogenesis and cellularity causing decrease in rCBV [29].

CT perfusion as a non-invasive technique uses an intravascular tracer to measure perfusion parameters whereas the traditional Xenon CT and PET measure perfusion by using diffusion tracers. While the two techniques may reflect different physiological mechanisms and the accuracy of flow values obtained by CT perfusion are not fully validated [31], studies have shown that quantitative results of perfusion CT are in agreement with xenon CT [32] and MR technique [33].

We did not use corrected perfusion values as disruption of BBB in enhancing lesions may not adversely affect the rCBF measurement

[34]. CT perfusion involves radiation and the overall effective dose required for dynamic CT is 2.0-3.4mSv which is marginally higher than that required for routine head CT 1.5-2.5mSv [35].

The study group was small and the choice to study after six months of treatment was arbitrary. Jinkins et al., have suggested that the response of tuberculoma to treatment takes eight weeks [23]. Thus the choice of two months was based on this observation. A serial longitudinal study of tuberculomas with treatment till its resolution would perhaps help us to better understand the haemodynamics of tuberculomas and the changes thereof induced by treatment. Further, perfusion parameters would help in identification of tuberculomas which would either respond or resist treatment and also differentiate it from other mimicking lesions.

CONCLUSION

The findings in this study are 1) Intracranial tuberculomas not on treatment and those on treatment for around six months show low perfusion. 2) Tuberculomas on treatment for less than two months show high perfusion. While the temporal and morphological resolution of tuberculomas on treatment have traditionally been the markers of response to treatment, the findings of this study suggest that serial perfusion profiles of tuberculomas on treatment could possibly be seen as surrogate markers of response to treatment. Larger longitudinal studies could address the role of CT perfusion as a non-invasive technique to monitor response to treatment of intracranial tuberculomas.

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