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NEURORADIOLOGY IN TUBERCULOUS MENINGITIS- DIAGNOSTIC SIGNIFICANCE AND PROGNOSTIC VALUE.

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ABSTRACT

Introduction: Tuberculous meningitis (TBM) is the most common and belligerent form of CNS TB. Prompt definitive diagnosis of TBM is arduous due to tedious microbiological procedures. This study was conducted to evaluate the neuroradiological findings in patients with TBM as a modality for early diagnoses and predicting prognosis.

Materials and methods: A successive series of 100 patients diagnosed with TBM admitted to the PIMS neurology ward were studied between March 2013 and April 2014. Cranial imaging results were obtained by non-contrast enhanced CT brain (NECT) and MRI (magnetic resonance imaging) brain with contrast. MRC staging on admission and in-hospital mortality were recorded. **Results:** The mean age was 34.86 ± 1.76 years with a female preponderance (55%, 55 out of 100). On admission, 72% were in MRC stages II or III. The in-hospital mortality was 16%. NECT was obtained in all the patients and was abnormal in 67% of the patients with hydrocephalus (58%), edema cerebral (24%) and infarcts (5%) being the commonest findings. CT infarct had the highest mortality rate of 60%. MRI was obtained in 61% of the patients and was abnormal in 88.5% of these cases. Hydrocephalus (61%), tuberculomas (54%), leptomeningeal involvement (46%) and infarcts (13%) were the most frequent radiological signs on MRI. Mortality was significantly associated with infarcts but not with tuberculomas. **Conclusion:** Neuroimaging techniques are a handy tool in the early diagnosis of TBM. MRI is particularly helpful in defining findings such as infarcts and tuberculomas and in predicting mortality and morbidity.

KEYWORDS: CNS TB; TBM; NECT; MRI brain; prognosis; mortality; MRC staging.

INTRODUCTION

Tuberculous meningitis (TBM) is the most common yet belligerent form of CNS tuberculosis with invasion and involvement of the meninges and the underlying brain parenchyma.^[1] It constitutes 1% of all cases of TB with a case fatality rate of almost 100% in untreated cases, as the disease is complicated by hydrocephalus, brain edema, infarction, tuberculomas and brain abscess, to name a few.^[2] The global disease burden has a considerable magnitude with approximately 9 million affected in 2013 with an estimated mortality of 1.5 million.^[3] A delay in treatment precludes a precarious outcome, as the disease stage at which antimicrobial therapy is started is the single most important predictor of prognosis.^[4] Early and definitive diagnosis of TBM is difficult due to the subacute presentation with nonspecific clinical manifestations. The diagnosis of TBM cannot be confirmed or excluded on the basis of clinical findings. Microbiology is time consuming and has a low sensitivity in TBM whether it is acid-fast

bacillus smear or culture.^[4,5,6] Cerebrospinal fluid (CSF) biochemistry and cell count is helpful for diagnosis and requires clinical correlation.^[7] CSF culture for mycobacterium tuberculosis remains the gold standard for diagnosing CNS TB. However it is a time-consuming investigation with poor sensitivity and can be negative in 15-75% of cases.^[6] Studies have suggested a better yield with serial larger volume taps, which again is cumbersome.^[8] Neuroimaging studies, both CT scan and MRI are of vital importance in the early diagnosis of CNS tuberculosis and may prevent excessive morbidity and mortality due to treatment delay and subsequent neurological sequelae.^[9] Contrast enhanced MR imaging is generally considered as the modality of choice in the assessment of patients with CNS tuberculosis. However, its efficacy and utility has not been fully evaluated in clinical trials. The specific findings of the disease on imaging studies are tuberculomas, basal meningitis, meningeal enhancement, hydrocephalus, brain abscess, cerebral edema, calcification and infarcts.^[9-11] These

characteristic findings can be more accurately identified by MRI brain which can be useful for early diagnosis, prognosis and also for follow-up.^[12-14] MRI brain provides a better view of infratentorial lesions. Modalities like diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences aid in screening the subtle, early cerebral changes of infarcts complicating TBM.^[15] However, data regarding the diagnostic sensitivity and specificity and prognostic implications of neuroimaging in TBM are limited. This study was carried out to evaluate the diagnostic and prognostic value of neuroimaging techniques i.e. CT brain and MRI brain in TBM, in terms of predicting disease morbidity and mortality.

MATERIALS AND METHODS

This was a single-center, prospective, observational, descriptive study conducted via consecutive, non-purposeful sampling at the Department of Neurology, PIMS hospital, Islamabad over 13 months i.e. from 15th March 2013 to 14th April, 2014 after approval from the hospital ethical committee. A series of 100 patients diagnosed with tuberculous meningitis admitted in succession to the neurology ward were enrolled without delay. This study was an independent project of the department and was not funded by any pharmaceutical organization. Informed consent was obtained from all patients (and in case of obtunded or comatose patients from their next of kin). Patients above the age of 12 years with diagnosis of TB meningitis were included in the study. The diagnosis of TBM was established on the basis of clinical and lab parameters as well as a favorable, therapeutic response to antitubercular therapy at 2 weeks. The clinical parameters included any two of: fever, constitutional symptoms, symptoms and signs of meningeal irritation and altered mental state for more than 2 weeks. The lab parameter employed in this study was a CSF biochemistry and cell count typical of TBM i.e. a lymphocytic-predominant pleocytosis (100-500 WBCs with lymphocytic-predominance), hypoglycorrhachia (<60% of blood glucose) and high protein concentration (>45mg/dl).^[4] CSF analysis was performed using SysmexXN/1000 2013 analyzer. CSF acid-fast bacillus smear was performed in all cases but wasn't employed as diagnostic tool. CSF for AFB culture was sent for most of the patients but that data was not included in this trial as the aim of this study was to validate the diagnostic utility of neuroradiology and not microbiology. Key exclusion criteria included patients with CSF positive for Gram staining or culture

of other organisms on lab analyses, patients with clinical features and CSF typical of pyogenic meningitis (predominant neutrophilic leukocytosis) on routine examination, patients with CNS malignancy and pregnancy. BMRC (British Medical Research Council Scale) staging of TBM was done for all patients at the time of admission in addition to detailed history and examination. MRC was used as the scale to assess disease severity and morbidity in this study.

An urgent NECT brain scan was done before lumbar puncture for all the patients on admission and reported by radiologist. An MRI scan of the brain with contrast, DWI and ADC sequences was performed during hospital stay or on out-patient basis for all the available patients and subsequently reported by a radiologist within a week. These scans were evaluated for various radiological manifestations of TBM like hydrocephalus, cerebral edema, infarct and tuberculomas. In-hospital outcome in terms of mortality was recorded for all patients during 2 weeks of hospital stay. MRC at the time of admission and in-hospital mortality were used to define prognosis. All patients were treated with antitubercular therapy and steroids and monitored for clinical improvement.

STATISTICAL ANALYSIS

Data was collected on standard performa and was analyzed by using the statistical software SPSS version 17 (SPSS Inc. Chicago, IL USA). Discrete variables were listed as counts or percentages and continuous variables were listed as means \pm SD. Chi-square test was used for univariate analysis of categorical variables. Multivariate analysis was done using stepwise forward logistic regression. Significance was set at $p < 0.05$. Results were expressed in tabulated form or graphically.

RESULTS

The baseline characteristics of study population are shown in Table I. The mean age was 34.86 ± 1.75 years ranging from 13 -80 years with a female preponderance (55; 55%). The female to male ratio was 1.25:1. At the time of admission, 28% were in MRC stage I, 58% were in MRC stage II while 14% were in stage III. 16% patients expired within 2 weeks of hospital stay and 84% survived. The mean age of the patients who had expired was 34.87 ± 2.21 years with a female preponderance. The baseline characteristics and the gender based distribution is mentioned in Table I

Table I: Baseline characteristics at admission and gender based distribution

Variables		Total n %	Gender Mean ± SD (range)/ n (%)	
			Male	Female
Mean Age (yrs)		34.86±1.75	39.64±1.90 (16-80)	30.94±1.53 (13-80)
MRC Stage	MRC I	28 (28)	12 (12)	16 (16)
	MRC II	58 (58)	28 (28)	30 (30)
	MRC III	14 (14)	5 (5)	9 (9)
Mortality	Died	16 (16)	5 (5)	11 (11)
	Survived	84 (84)	40 (40)	44 (44)

NECT was obtained in all the patients and was abnormal in 67%. The most common CT findings were hydrocephalus (58%), cerebral edema (24%) and infarcts (5%); summarized in Table II. Some patients had a combination of the findings. On univariate analysis patients with normal CT were mostly in MRC stage 1 or 2 (p= 0.00) whereas those with infarction were mostly in stage 3 (p= 0.00). Those with edema and hydrocephalus were mostly in stage 2 (p=0.00 for both). Similarly patients with abnormal CT brain had a higher mortality as compared to those with a normal NECT (p=0.01). CT infarct had the highest mortality (60%; p= 0.00) signifying a higher chance of mortality with infarct. This was followed by edema (33%; p = 0.00) and hydrocephalus (24.0%;p= 0.00). Multivariate analysis however showed only edema to be significantly associated with a higher MRC stage but none of the CT findings were significantly associated with mortality (p>0.05 for all) (Table II).

MRI was obtained in 61% and was abnormal in 88.5% of these cases. MRI brain could not be done in 39% of the patients. Among these patients, hydrocephalus

(61%), tuberculomas (54%), leptomenigeal enhancement (46%) and infarcts (13%) were the most frequent findings; summarized in Table II and illustrated in Figure I. Some patients had a combination of the findings. On univariate analysis patients with normal MRI mostly were in MRC stage 1 or 2 (p= 0.04) whereas those with infarction were mostly in stage 2 or 3 (p= 0.00). Those with leptomenigeal enhancement were mostly in stage 2 (p=0.00). Univariate analysis did not reveal hydrocephalus or tuberculomas to have significant association with MRC stage (p.0.05 for both). Patients with abnormal MRI brain had higher mortality as compared to those with a normal MRI (p=0.04). MRI infarct had the highest mortality (50%; p= 0.00) signifying a higher chance of mortality with infarct. This was followed by leptomenigeal enhancement (21%; p = 0.03) (Figure II). Multivariate analysis however showed none of the findings to be significantly associated with a higher MRC stage (p>0.05 for all). Multivariate analysis for mortality showed infarct to be significantly associated with higher chance of death (p=.00) (Table II) (Figure II)

Table II: Univariate and multivariate analysis for CT and MRI brain findings

Neuroimaging Variables	Morbidity					Mortality					
	MR C I	MR C II	III	OR	ep	Died n (%)	Survived n (%)	OR	Univariate ep	Multivariate ep	
	n (%)	n (%)	n (%)								
CT Brain finding											
Yes	16 (16)	16 (16)	1 (1)	12.38	0.00*	1 (1)	32 (32)	6.16	0.01*	0.87	
Normal	12	42	13			15					

	No	(12)	(42)	(13)				(15)	52 (52)			
Infarct	Yes	0 (0)	1 (1)	4 (4)	19.16	0.00*	0.97	3 (3)	2 (2)	7.58	0.00*	0.05
	No	28 (28)	57 (57)	10 (10)				13 (13)	82 (82)			
Edema	Yes	1 (1)	16 (16)	7 (7)	12.00	0.00*	0.02*	8 (8)	16 (16)	7.05	0.00*	0.06
	No	27 (27)	42 (42)	7 (7)				8 (8)	68 (68)			
Hydrocephalus	Yes	11 (11)	34 (34)	13 (13)	11.01	0.00*	0.98	14 (14)	44 (44)	6.80	0.00*	0.20
	No	17 (17)	24 (24)	1 (1)				2 (2)	40 (40)			
MRI Brain finding												
Normal	Yes	5 (8.1)	3 (4.9)	0 (0)	9.96	0.04*	0.97	0 (0)	8 (13.1)	3.56	0.04*	0.00*
	No	13 (21.3)	36 (59)	5 (8.1)				7 (11.4)	47 (77)			
Infarct	Yes	0 (0)	4 (6.5)	4 (6.5)	18.98	0.00*	0.99	4 (6.5)	4 (6.5)	12.55	0.00*	0.00*
	No	18 (29.5)	34 (55.7)	1 (1.6)				3 (4.9)	50 (81.9)			
Hydrocephalus	Yes	9 (14.7)	23 (37.7)	5 (8.1)	7.52	0.11	0.98	5 (8.1)	32 (52.4)	3.03	0.22	0.82
	No	9 (14.7)	16 (26.2)	0 (0)				2 (3.2)	23 (37.7)			
Basal meningeal enhancement	Yes	5 (8.1)	18 (29.5)	5 (8.1)	10.63	0.03*	0.97	6 (9.8)	22 (36)	6.59	0.03*	0.10
	No	13 (21.3)	21 (34.4)	0 (0)				1 (1.6)	33 (54)			
Tuberculomas	Yes	7 (11.4)	23 (37.7)	3 (4.9)	7.00	0.13	0.98	4 (6.5)	29 (47.5)	2.72	0.25	0.78
	No	11 (18)	16 (26.2)	2 (3.2)				3 (4.9)	26 (42)			

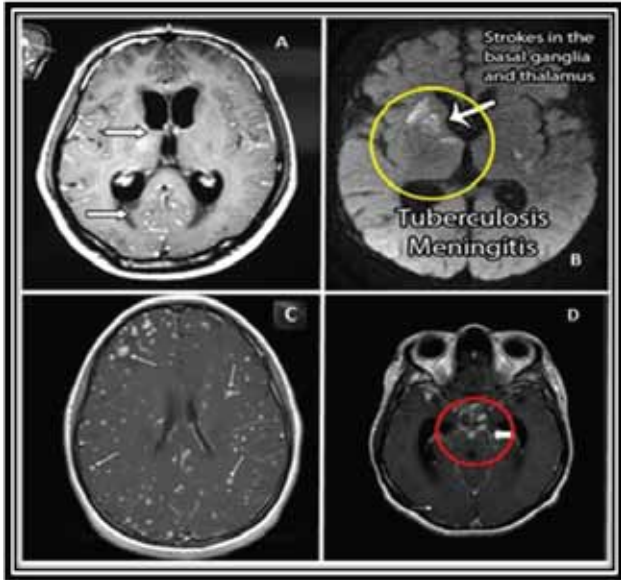


Figure I: MRI Brain in CNS TB

Figure I: MRI Brain in CNS TB: A: Hydrocephalus as shown in MRI brain of one of our patients (No.22) depicted by dilated anterior and posterior horns of lateral ventricles (arrow heads), B: DWI MRI Brain showing restricted diffusion in right sided basal ganglia and thalamus regions in one of our patients (No.35) (arrow head in circle), C: Schematic of MRI Brain T1WI with contrast studded with multiple small tuberculomas (arrow heads)(No.72) D: MRI Brain T1WI with contrast showing basal meningeal enhancement (thick arrow head within circle) in one of our patients (No.83).

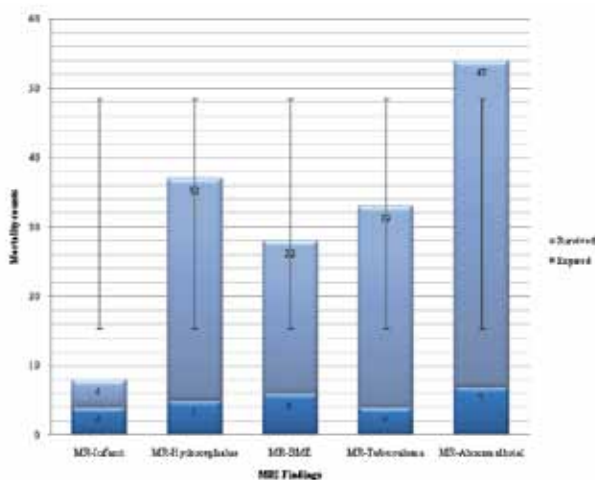


Figure II: MRI Brain findings and distribution of mortality: vertical double capped lines show 1 SD.

DISCUSSION

TBM is the most common cause of chronic meningitis caused by mycobacterium tuberculosis in the developing countries and is a major public health problem due to its permanent neurological sequelae and mortality.^[4] It is the most common and severe form of central nervous system tuberculosis with invasion and involvement of the meninges and the underlying brain parenchyma. The diagnosis of TBM is elusive and high index of suspicion is necessary for early diagnoses. The definitive diagnosis of TBM is dependent on microbiological testing by demonstrating *M. tuberculosis* on smear as AFB or culture of the CSF.^[16,17] CSF acid fast bacillus has a low sensitivity of 20-40%.^[18] CSF culture is a time-consuming procedure. Moreover, CSF culture can be negative in 15-75% of cases.^[6] Treatment delay is often associated with high fatality therefore early recognition is of paramount importance as the clinical outcome depends upon the stage at which therapy is initiated.^[2,17] Current antituberculous drugs are highly effective when treatment commences early, before the onset of complications. The typical neuroradiological findings of TBM appear due to the pathophysiology of TBM which can aid in the diagnosis of TBM.^[19,20] However, the diagnostic value hasn't been fully validated in studies. Moreover, data on the utility of neuroradiology in predicting the outcome of TBM is even more limited. Cranial imaging is useful in diagnosing TBM, predicting its complications and also has a prognostic value.^[14,21-25] Some studies comparing CT to MRI have indicated MRI as a superior diagnostic imaging modality.^[23-25] In this study, NECT brain was obtained in all the patients prior to lumbar puncture, due to easy availability and quick completion. CT brain was abnormal in 67% of the patients. In a review of 289 patients published in the year 2000 CT brain was found to be abnormal in 87% cases.^[26] This difference in radiological yield may be attributed to the fact that they performed both NECT and CT with contrast while we only got the former done. MRI brain with contrast with DWI and ADC was done in 61% of the patients. Out of the 61 patients in whom MRI scans were done 88.5% had radiological findings. This finding is almost comparable to a study in which MRI brain revealed findings in 90% cases.^[27] MRI showed even more findings in cases where CT scan results were suspicious or normal especially in case of meningeal enhancement or tuberculomas as seen in earlier studies.^[27] In this study 10 patients had normal CT scans of the brain, while the MRI scans of these

patients revealed abnormal findings. MRI with contrast has higher efficacy for detecting tuberculomas, basal enhancement and infarction in TBM. Majority of the patients in this study presented in MRC stage 2 which is comparable with most of other studies. [28] The delayed presentation of TBM may be attributed to the poor socioeconomic background and low literacy rate of most of our patients, especially those from remote rural areas who do not seek proper medical assistance until the terminal stages of the disease. However, this just a theoretical assumption and requires proper statistical validation. Ischemia/infarcts were observed in 13% of the patients. Previous studies reported the incidence of infarction in TBM as ranging from 13% to 53%. [29-31] Those patients who had infarcts on CT or MRI brain had greater morbidity reflected by MRC stage of mostly 3. Almost 60% mortality was seen in these patients. Infarcts have been shown to be associated with poor outcome in TBM as shown Wasay et al in their study. [14] MR scans especially DWI sequences were superior in detecting infarcts. The mean age of patients with TBM complicated by infarcts was 35.12 ± 2.18 years (75% males) in our study which was much lower than the mean of age of similar patients in their study i.e. 57 ± 17.6 (56.7% males). They attributed it to Ischemic heart disease while we propose an infection related vasculitis as the etiology which tends to be more common in younger patients. This however, needs validation in a separate study designed to evaluate patients of TBM with infarcts alone. Tuberculomas were detected in 33 of the patients in this study (54%). Tuberculomas are common forms of CNS TB and result from parenchymal rich foci. [10] Tuberculomas are frequently multiple. [10,26,27] In this study 82.4% of these 33 patients had multiple tuberculomas. Patients with tuberculomas were mostly in MRC stage 2. However, mortality was not statistically significant. This is in contrast to older studies; [32] but corresponds to the results of the study by Wasay et al. [14] Hydrocephalus is a common complication of TBM, and was seen in 61% cases in this study which is in accordance with most of the other studies. [32,33] The reported frequency of hydrocephalus varies from 12% to 77% in patients with TBM in various case series. [16,32-34] Patients with hydrocephalus were mostly in MRC stage 2 and had a higher mortality compared to those with normal neuroimaging. In conclusion, patients with infarcts had a worse outcome as compared to those with hydrocephalus or tuberculomas. MRI scans provided additional findings such as tuberculomas and infarcts not identified on CT. This might help in modifying drug regime or duration of therapy by follow up scans and

comparing scans for resolution of findings. This study was limited by the fact that patients were screened only at the commencement of therapy, and there was no set protocol for follow up of patients who develop these complications during the course of treatment or whether initiating prompt therapy conferred a better outcome as we did not study end of treatment outcomes. Neuroradiological findings such as infarcts, tuberculoma or hydrocephalus, are helpful for the diagnosis of TBM in the early stages before a microbiological diagnosis is established. [35-37] MRI and CT scanning are also critical in predicting the outcome and in evaluating the complications of the disease as shown in the study by Wasay et al. [14] Therefore, MRI brain with contrast and DWI sequences should be performed for all patients in the early stage of the disease to detect specific signs related with poor outcome. It may reveal specific radiological findings associated with TBM which contribute to diagnostic certainty.

CONCLUSION

Neuroimaging techniques are a handy tool in the early diagnosis of TBM. MRI is particularly helpful in defining findings such as infarcts and tuberculomas and in predicting mortality and morbidity.

DISCLAIMER

The authors declare that they do not have any conflict of interest.

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Author's contribution:

Sumaira Nabi: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Mazhar Badshah: Study concept and design, data analysis, manuscript writing, manuscript review

Shahzad ahmed: collection, data analysis, manuscript writing, manuscript review

Ali Zohair Nomani: data collection, data analysis, manuscript writing, manuscript review

Irfan Khattak: data collection, data analysis, manuscript writing, manuscript review