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NEURORADIOLOGICAL MANIFESTATIONS OF TUBERCULOUS MENINGITIS

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ABSTRACT

Introduction: Tuberculous meningitis (TBM) represents the most severe form of extra pulmonarytuberculosis [1].The early and exact diagnosis of TBM is important but difficult due to time consuming definitive microbiological procedures [2].Neuroimaging is an important initial investigation in tuberculous meningitis[3].This study was conducted to evaluate the neuroradiological findings in patients with tuberculous meningitis, as a useful modality for itsearly diagnoses and prompt treatment. **Materials and methods:** A consecutive series of 100 patients diagnosed with TBM admitted to the PIMS neurology ward were studiedbetween 15thMarch 2013 and 14thApril 2014. Cranial imaging results were obtained by non-contrast enhanced CT brain (NECT) and MRI brain with contrast. **Results:** The mean age was 34.86 ± 17.56 years with a female preponderance (55%). On admission, 72% were in MRC stages II or III. The in-hospital mortality was 16%. NECT was obtainedin all the patients and was abnormal in 67% of the patients. The most common CT findings were hydrocephalus (58%), edema (24%) and infarcts (5%). MRI was obtained in 62% of the patients and was abnormal in 87% of these cases. Out of these patients hydrocephalus (60%), tuberculomas (53%), leptomeningeal involvement (45%)and infarcts (13%)were the most frequent signs. Tuberculomas were almost always multiple involving both the supracortical and infracortical regions. In 10% patients with a normal NECT, MRI revealed positive findings. **Conclusion:** Neuroimaging techniques are a handy tool in the early diagnosis of TBM. MRI is particularly helpful in defining findings, such as hydrocephalus, tuberculomas, leptomeningeal involvement, or infarcts.

INTRODUCTION

Tuberculosis captain of the men of death with its various forms is still a challenging problem in Pakistan [4]. Tuberculous meningitis (TBM) also known as meningeal tuberculosis is the most common presentation ofneurotuberculosis [5] and a serious disease of worldwide importance. It is one of the most lethal forms of tuberculosis, seen in 5 to 10% of extra pulmonary tuberculosis (TB), and accounts for approximately 1% of all TB cases[6].The case fatality rate of untreated TBM is almost 100% and a delay in treatment may lead to permanent neurological damage, therefore prompt diagnosis is needed for the timely initiation of antituberculous therapy [7]. The early and exact diagnosis of TBM is difficult due to non-specific symptoms (5) and time consuming definitive microbiological procedures [8]. Diagnosis is often based on the clinical features and cerebrospinal fluid (CSF) findings. TBM is characterized by a broad spectrum of manifestations, posing a diagnostic challenge and requiring a high index of clinical suspicion. TBM tends to present sub acutely, over a period of variable duration that ranges in literature from weeks to months but in majority of patients there is a history of vague non-specific symptoms of duration of two to eight weeks prior to meningeal irritation. These prodromal symptoms are constitutional and include malaise, fatigue, anorexia, fever and headache. CSF routine examination shows a lymphocytic pleocytosis with reduced glucose levels (<60mg/dL) and raised proteins (>45mg/dL). CSF culture for mycobacterium tuberculosis or CSF smear remain the reference standard for diagnosing CNS TB, however these are time-consuming investigations and can be negative in 15-75% of cases [8]. Modern neuroimaging is a cornerstone in the early diagnosis of CNS tuberculosis and may prevent unnecessary morbidity and mortality due to treatment delay. Contrast-enhanced MR imaging is generally considered as the modality of choice in the detection and assessment of CNS tuberculosis [8]. However, the efficacy and utility has not been fully evaluated and validated. The specific findings of the disease on imaging studies are tuberculomas, inflammatory exudates at basal cisterns (basal meningitis), meningeal enhancement, hydrocephalus, brain abscess, cerebral oedema, calcificationand infarcts (due to vasculitis) [3, 9, 10]. These characteristic findings can be more accurately identified by magnetic resonance imaging (MRI) brain which can be useful for early diagnosis, prognosis and also for follow-up[2, 11]. MRI brain provides high definition ofinfratentorial lesions and the early cerebral changes of TBM, but data regarding the diagnostic sensitivity and specificity are limited.

This study was carried out to evaluate the utility of neuroimaging techniques particularly MRI brain in the early diagnosis of TBM, with an aim to initiate immediate therapy to reduce the high mortality and morbidity associated with the disease.

MATERIALS AND METHODS

This was a prospective, interventional study carried out at the PIMS hospital, Islamabad from 15th March 2013 to 14th April, 2014. A consecutive series of 100 patients diagnosed with tuberculous meningitis (TBM) admitted to the neurology department were studied. 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 unconscious patients from their next of kin). Patients above the age of 13 years with diagnosis of TB meningitis were included in the study. The diagnosis of TBM was made on the basis of clinical and lab parameters. The clinical parameters included any two of: fever, constitutional symptoms (malaise, vague ill health), meningeal irritation and altered mental and behavior changes for more than 2 weeks coupledwith the typical CSF findings of TBM i.e., predominantly lymphocytic pleocytosis (raised WBC count with predominant lymphocytes), low sugar (<60% of blood glucose) and high protein concentration (>45mg/dl). 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 CSF routine examination, patients with CNS malignancy and pregnancy. CSF for AFB culture was sent for most of the patients but that data was not included in this trial due to the time-consuming nature of the test. MRC staging was done for all patients at the time of admission in addition to detailed history and examination. An urgent NECT brain scan was done before lumbar puncture for all the patients on admission and reported by radiologist. Hydrocephalus, edema and infarcts were observed. An MRI scan of the brain with contrast was performed during hospital stay or on outpatient basis for all the available patients and subsequently reported by radiologist. Hydrocephalus, meningeal enhancement, tuberculomas, and infarcts were evaluated. Tuberculomas were also classified according to their number and location. In-hospital outcome in terms of mortality and survival was recorded for all patients during 2 weeks of hospital stay.

Data Collection & Statistical analysis:

Data was collected on a 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. Significance was set at $p<0.05$.

RESULTS

The baseline characteristics of study population are shown in Table- I. The mean age was 34.86 ± 17.56 years with a female preponderance (55%, 55 out of 100). 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.

TABLE I: BASELINE CHARACTERISTICS

Age Mean		34.86 ± 17.56 years
		(range 13-80 years)
Gender	Male	45%
	Female	55%
MRC stage	MRC stage I	28%
	MRC stage II	58%
	MRC stage III	14%

NECT was obtained in all the patients and was abnormal in 67%. The most common CT findings were hydrocephalus (58%), edema (24%) and infarcts (5%) shown in Table-II and Figure-I.Some patients had a combination of the findings.

TABLE II: RADIOOGICAL FEATURES OF TBM ON NECT BRAIN

NECT Brain findings	Normal	33%
	Hydrocephalus	58%
	Edema	24%
	Infarcts	5%

FIGURE I: RADIOLOGICAL FEATURES OF TBM ON NECT BRAIN
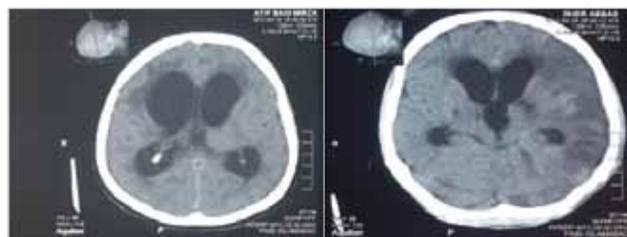
A) Axial CT scan without contrast shows ventricular dilatation and acute hydrocephalus with periventricular seepage.
B) Axial CT scan without contrast shows hydrocephalusand left middle cerebral artery infarction (ischemia)
MRI brain with contrast was obtained in 62% of the

patients and was abnormal in 87% of these cases. MRI brain could not be done in 38% of the patients. Out of these patients hydrocephalus (60%), tuberculomas (53%), leptomeningeal enhancement (45%) and infarcts (13%) were the most frequent signs shown in Table III and Figure II.

TABLE III: RADIOLOGICAL FEATURES OF TBM ON MRI BRAIN with contrast

MRI Brain findings	Normal	12.9%%
	Hydrocephalus	60%
	Tuberculomas	53%
	Leptomeningeal	45%
	enhancement	
	Infarcts	13%

FIGURE II: RADIOOGICAL FEATURES OF TBM ON MRI BRAIN with contrast

A) Axial T1-weighted contrast enhanced MRI scan shows a solitary ring-enhancing lesion (tuberculoma) in the right thalamus (supratentorial) with hydrocephalus and meningeal enhancement.
B) Axial T1-weighted contrast enhanced MRI scan shows a solitary ring-enhancing lesion (tuberculoma) in the left cerebellar hemisphere (infratentorial).
C) Axial T1-weighted contrast enhanced MRI scan shows dense meningeal enhancement especially of the basal meninges with hydrocephalus.
D) Axial T1-weighted contrast enhanced MRI scan-showsmultiple nodular and ring-enhancing infratentorial lesions (tuberculomas).
E) Axial T1-weighted contrast enhanced MRI scan showsmultiple nodular-enhancing supratentorial lesions (tuberculomas).
F) Coronal FLAIR MRI scan shows multiple hyperintense signal cortical areas consistent with ischemic areas/ infarcts.
Tuberculomas were almost always multiple (82.4%). In most of the patients (64.7%) tuberculomas occupied both the supracortical and infracortical regions. 17.6%(6 out of 34)of the patients had a solitary tuberculoma. 20.5 % patients out of these had supratentorialtuberculomaswhile14.7% had infratentori-altuberculomas either in the brainstem or cerebellum shown inTable IV and Figure II. In 10% patients with a
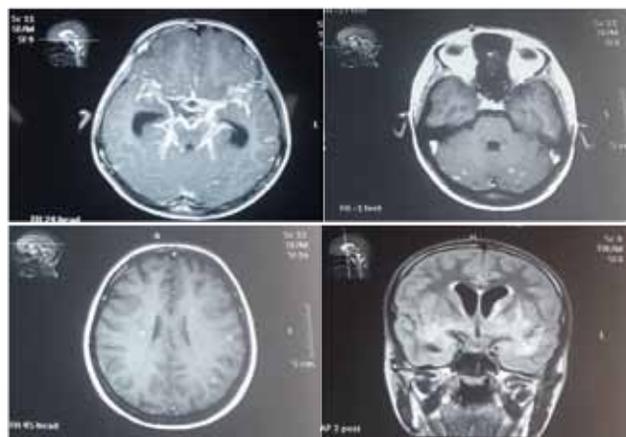
normal NECT, MRI revealed positive findings.

TABLE IV: CLASSIFICATION OF TUBERCULOMAS

Number of tuberculomas	Solitary	17.6%
	Multiple	82.4%
Location of tubcerculomas	Supratentorial	20.5%
	Infratentorial	14.7%
	Both supratentorial and Infratentorial	64.7%

DISCUSSION

Tuberculous meningitis (TBM) is the most common form of central nervous system tuberculosis. It is very difficult to diagnose and high index of suspicion is necessary for early diagnoses and treatment [12]. The definitive micro-biological diagnosis of TBM depends on demonstrating M. tuberculosis by smear or culture of the CSF [13, 14]. However, this process is time-consuming. According to the current available literature CSF culturecan be nega-tive in 15-75% of cases [8]. Treatment delay due to delayed diagnosis is often associated with permanent neurological damage and high fatality [7, 14], therefore early recognition is of paramount importance as the clinical outcome depends upon the stage at which therapy is initiated. Current antituberculous drugs are highly effective when treatment is initiated early, before the onset complications. TBM is the most common cause of chronic meningitis in developing countries and a major public health problem of the third world coun-tries like Pakistan. The pathophysiology of TBM is the basis of its typical neuroradiological findings [15, 16]. The pathogenesis involves seeding of the meninges or brain parenchyma by tuberculous bacilli, resulting in the formation of small subpial or subependymal foci of metastatic caseous lesions termed Rich foci. The Rich focus then increases in size until it ruptures into the

subarachnoid space causing meningitis. Rich foci deeper in the brain parenchyma causetuberculomas. A dense exudate infiltrates the cortical or meningeal blood vessels, producing inflammation, obstruction, or infarction. Basal meningeal exudate accounts for the cranial nerves dysfunction and obstruction of basilar cistern leading to obstructive hydrocephalus. These lesions produce typical neuroradiological findings which can aid in the diagnosis of TBM. The mean age of patients was 34.86 ± 17.56 years which is near to the results by Qureshi et al (14) and Salekeen et al(4),but higher than in earlier studies [17, 18]. This study showed a female preponderance (55%) which is similar to Qureshi et al (14) while other studies (17,18) have found a minor male predominance. Majority of the patients presented in MRC stage 2 which is in accordance with most of other studies [4]. The delayed presentation of TBMappears to be multifactorial and is probably attributable to the low socioeconomic and educational levels of most of our patients, especially those from remote urban areas who have false myths and believe in spiritual healing, leading to the general practice not to seek medical assistance until the terminal stages of the disease. Cranial imaging is useful in diagnosing TBM and in predicting its complications [19, 20]. Serial scans also have a prognostic value [2]. Some studies comparing CT to MRI have indicated MRI as a superior diagnostic imaging modality [21-23].In this study,NECT brain was obtained in all the patients prior to lumbar puncture, as its less time consuming and the facility is available round the clock even in emergency. CT brain was abnormal in 67% of the patients. MRI brain with contrast was done in 62% of the patients. Some of the patients were too critical for the MRI scan, some had expired while some were lost to follow up and did not return with the scan. However out of the 62 patients in whom MRI scans were done 87% had radiological findings. MRI showed even more findings in cases where CT scan results were suspicious especially in case of meningeal enhancement or tuberculomas. In this study 10 patients had normal CT scans of the brain, while the MRI scans of these patients revealed findings suggestive of TBM such as meningeal enhancement, tuberculomas and infarcts. MRI has higher efficacy for detectingtuberculomas, basal enhancement and infarction in TBM. Therefore, clinicians should use neuroradiological techniques to obtain clues for TBM in addition to patient history and clinical and CSF findings. Imaging facilities such as MRI and the use of contrast can aid in increased and early case detection. Hydrocephalus is a common complication of TBM, and was seen in 60% cases in this study whichis in accordance with most of the other studies.24-25In literature most of the hydrocephalus associated with TBM is non-communicating type but communicating hydrocephalus has also been seen in

some studies. To the best of our knowledge none of the local studies in Pakistan have reported the frequency of both types of hydrocephalus in TBM[14, 15]. The reported frequency of hydrocephalus varies from 12% to 77% in patients with TBM in various case series [1,13, 22, 24-26] Hydrocephalus is reported to be much frequent in children than in adults [27]. Tuberculomas were detected in 33 of the patients in this study (53%). Tuberculomas are common forms of CNS TB and result from parenchymal rich foci [10]. Tuberculomas are frequently multiple [10, 29, 30].In this study tuberculomas were multiple (82.4%) in patients withtuberculomas and solitary in 17.6% of the cases. Tuberculomas were located on both sides of the tentorium. The location of solitary lesions was supra or infratentorial, mostly in the basal ganglia/thalami and cerebellar hemispheres. Tuberculomas either showed a hypointense core with rim enhancement or were nodular with diffuse enhancement. However, the former pattern was more common. Meningeal enhancement was seen in 45% of the cases. It was mainly around the basal cistern. However diffuse and focal meningeal enhancement was also observed. Ischemia/infarcts were observed in 13% of the patients. The cerebral infarction in TBM has been reported as a major cause of long-term morbidity in some studies [31].Previous studies reported the incidence of infarction in TBM as ranging from 13% to 53% [31-33]. The fact that most of the available patients had been screened using MR scans, additional findings such as tuberculomas and infarcts were detected and the duration of therapy was modified accordingly. The study was limited by the fact that patients were screened only at the start of the treatment, and there was no set protocol for follow up of patients who develop these complications during the course of treatment. A more detailed study would be required to analyze such cases. Neuroradiological findings such as tuberculoma, meningeal enhancement, or hydrocephalus, are helpful for the diagnosis of TBM in the early stages in while microbiological results are awaited [34, 35]. MRI and CT scanning are also critical in predicting the outcome and in evaluating the complications of the disease that require neurosurgical intervention. Moreover, MRI may provide specific findings associated with TBM, and, if available, it should be performed for all patients in the early stage of the disease to detect specific signs related with poor outcome.

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