ORIGINAL ARTICLE

Stages of Tuberculous Meningitis: a Clinicoradiologic Analysis

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Abstract

Objective: To determine the frequencies and percentages of various clinicoradiologic variables of tuberculosis meningitis (TBM) with reference to British Medical Research Council (BMRC) staging of the disease.

Study Design: A case series.

Place and Duration of Study: Department of Neurology, Jinnah Postgraduate Medical Centre, Karachi, from October 2010 to September 2011.

Methodology: The study included 93 adult patients with the diagnosis of tuberculous meningitis (TBM) at the study place. Patients were divided in three groups according to British Medical Research Council (BMRC) staging of TBM. Different clinical and radiological findings were analyzed at different stages of the disease. Data was analyzed using SPSS (Statistical Package of Social Sciences) version 11.0.

Results: A majority of patients were found to be in stage-II disease at the time of admission. History of illness at the time of admission was more than 2 weeks in 50% of stage-I patients but around 80% in stage-II and stage-III patients. Neck stiffness was the most commonly reported finding in all stages. Cranial nerve palsies were higher in stage-III (75%) than in stage-II (43%) and in stage-I (24%) patients. Hydrocephalus and basal enhancement was the most frequently reported radiographic abnormalities.

Conclusion: Duration of illness and cranial nerve palsies are important variables in the diagnosis of TBM stages and if TBM is suspected, empiric treatment should be started immediately without bacteriologic proof to prevent morbidity and mortality.

Key words: *Tuberculous meningitis. British Medical Research Council (BMRC) stages. Clinicoradiologic variables. Hydrocephalus. Neck stiffness. Basal enhancement.*

INTRODUCTION

In 2009, there were an estimated 9.4 million cases of tuberculosis globally, equivalent to 137 cases per 100,000 populations. Most of the estimated number of cases in 2009 occurred in Asia (55%) and Africa (30%).[1]

Pakistan ranks eighth on the list of the 22 tuberculosis high-burden countries in the world, according to the World Health Organizations Global Tuberculosis Control Study 2009.[1]

The incidence of CNS tuberculosis generally reflects the incidence of tuberculosis in the community. About 10% of patient who have tuberculosis anywhere in body develop CNS disease.[2] Central nervous system involvement is the most devastating form of tuberculosis. High mortality and morbidity are due to delayed diagnosis due to variable clinical and neuroimaging manifestations.[3] It is often diagnosed when brain damage has already occurred.[4,5]

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Unfortunately, there is no single diagnostic method that is both sufficiently rapid and sensitive. Cerebrospinal fluid (CSF) profile of tuberculous meningitis (TBM) mimics CSF profile of long list of infectious and non-infectious meningeal processes. Several case series have established CSF staining sensitivities of < 20%[6] while culture studies have the sensitivity between (25 – 70%).[7] Similarly, the sensitivity of commercially available nucleic acid amplification assays for TBM was reported to be 56% in one systematic review, and the negative predictive value and positive predictive value were just (44%) and (35%) respectively.[8] A history of infection with or exposure to tuberculosis may or may not be present, and evidence of active tuberculosis is present in less than 50% of cases.[9]

The outcome of tuberculous meningitis (TBM) is influenced by the clinical stage of disease at the start of treatment.Various studies have shown that the presence of cranial neuropathy was associated with poor outcome.[10] Stroke occurring due to infectious vasculitis in TBM independently predicts a poor outcome of tuberculous meningitis.[11]

The specific findings of the disease on imaging studies are tuberculomas, inflammatory exudates at basal cisterns, hydrocephalus, and vasculitis leading to infarcts. These characteristics findings can be more accurately identified by magnetic resonance imaging (MRI) which can be useful for diagnosis, prognosis and also for follow-up.[12] MRI provides high definition of

infratentorial lesions and the early cerebral changes of TBM, but data regarding the diagnostic sensitivity and specificity are limited.

This study will analyze the frequency and percentages of various clinical and radiologic features of tuberculous meningitis at different clinical stages of the disease.

METHODOLOGY

The study was carried out at the Department of Neurology, Jinnah Postgraduate Medical Centre, Karachi. Ninety three (93) patients (males 50 and females 43) were included in this study who presented with the compatible clinical picture of subacute to chronic meningitis i.e., fever, headache, altered mental status with or without neurological deficits for more than 7 days at the time of admission and typical CSF picture of lymphocytic pleocytosis (20 – 500 cells per cubic mm) with increased CSF protein and decreased CSF glucose concentration. They were considered to have tuberculous meningitis when they fulfilled any one of the following criteria: (i) positive AFB staining and/or CSF culture and/or PCR assay for mycobacterium tuberculosis; (ii) history of contact with tuberculosis patient during last 2 months; (iii) evidence of tuberculosis anywhere else in the body i.e., gastrointestinal or pulmonary involvement etc.; (iv) patients with one or more of the following radiological features on MRI brain contrast study i.e. hydrocephalus and/or basilar enhancement and/or tuberculoma formation.

Patients with neutrophil predominant CSF picture, with positive CSF India ink staining or cryptococcal antigen assay, having current or past history of any malignancy, with history of organ transplantation or taking immunosuppressive drugs and patients who did not give meaningful clinical response to empiric anti-tuberculous treatment after 4 weeks as determined by improvement in at least one stage upward were excluded from this study.

Patients who met the above mentioned inclusion criteria for tuberculous meningitis (TBM) were sub-grouped in the following three groups on the basis of British Medical Research Council contemporary clinical criteria for the severity of TBM.[11] This grading system is reproducible across different levels of clinical expertise and across different disciplines of healthcare workers and is, therefore, a more reliable grading system. Stage-I is alert and patient oriented without focal neurological deficits. Stage-II is a patient with Glasgow coma score (GCS) of 14 to 11 with focal neurological deficits. Stage-III is a patient with Glasgow coma score of 10 or less, with or without focal neurological deficits.

Finally, frequencies and percentages for selected clinicoradiologic variables like duration of illness, papilloedema, cranial nerve palsies, signs of meningeal irritation, hydrocephalus, meningeal enhancement, tuberculomas, radiographic infarction and chest X-ray were calculated among different BMRC stages of TBM to assess their importance in the diagnosis of TBM.

Data was analyzed using SPSS (Statistical Package of Social Sciences) version 11.0. Clinical characteristics were summarized in terms of frequencies and percentages for categorical variables i.e., age groups, gender, duration of illness (> 2 weeks and < 2 weeks), signs and symptoms.

RESULTS

All patients, according to age were divided into three groups. Among those aged 10 – 19 years, 20% (3 patients) were in stage-I, 46.6% (7 patients) in stage-II and 33.3% (5 patients) were in stage-III. Among those aged 20 – 39 years, 15 patients (26.3%) were in stage-I, 27 patients (47.3%) in stage-II and 15 patients (26.3%) were in stage-III. Among those aged 40 years and above, 3 patients (14.2%) were in stage-I, 10 patients (47.6%) in stage-II and 8 patients (38%) were in stage-III. In all age groups, majority of patients were found to be in stage-II disease at the time of admission.

Females (57.1%, n = 12 patients) outnumbered males (42.9%, n = 9 patients) in stage-I cases, whereas males (59.1%, n = 26 patients) outnumbered females (40.9%, n = 18 patients) in stage-II. Among stage-III cases, males were 53.6% (15 patients) and females were 46.4% (13 patients).

Duration of illness at the time of admission was more than 2 weeks in 52.4% (11 patients) of stage-I patients, 79.5% (35 patients) in stage-II and 89.3% (25 patients) in stage-III patients.

Among different physical findings, neck stiffness was the most commonly reported finding in all stages of disease but its proportion was much lower in stage-III in 17 patients (60.7%) when compared to 16 patients (76.2%) in stage-I and 37 (84.1%) patients in stage-II. Papilloedema was found in 5 patients (23.8%) in stage-I, 16 patients (36.4%) in stage-II and 13 patients (46.4%) in stage-III. Cranial nerve palsies were present in 5 patients (23.8%) in stage-I, 19 patients (43.2%) in stage-II, and 21 patients (75%) in stage-III. These finding revealed that percentage of patients with papilloedema and cranial nerve palsies were much higher in stage-III patients as compared to stage-I and stage-II patients (Table I).

MRI brain contrast studies showed variable findings in terms of tuberculoma(s), miliary tubercles, hydrocephalus, basilar enhancement, and ischaemic infarction. Tuberculomas were single or multiple, and could be seen anywhere in the brain parenchyma. Their percentage was highest in stage-III 39.3% (11 patients) when compared to stage-I, 19% (4 patients) and stage-II 27.3% (12 patients). Miliary tubercles are less than two millimeters in size and are seen as numerous,

round, small, homogenous, enhancing lesions on contrast MRI studies. Their percentage was highest in stage-III 17.9% (5 patients) when compared to stage-I, 0% and stage-II 9.1% (4 patients). Miliary tuberculosis is usually associated with TBM. Hydrocephalus was of the communicating type in majority of patients while meningeal enhancement was most prominent around basilar cisterns. These two radiological abnormalities were reported in more than 50% of all patients with highest percentage in stage-II patients. Chest radiograph was also reported abnormal with unilateral or bilateral upper zone infiltrates in 50% of stage-III cases but in only 23.8% of stage-I cases (Table II).

Table I: Physical findings of patients.

Physical findings	Stage 1 (n = 21)	Stage 2 (n = 44)	Stage 3 (n = 28)
Signs of meningeal irritation (neck stiffness)	16 (76.2%)	37 (84.1%)	17 (60.7%)
Papilloedema	5 (23.8%)	16 (36.4%)	13 (46.4%)
Cranial nerve palsies	5 (23.8%)	19 (43.2%)	21 (75.0%)

Table II: Radiological (MRI brain and X-ray chest) findings of patients.

Radiological findings	Stage 1 (n = 21)	Stage 2 (n = 44)	Stage 3 (n = 28)
Tuberculoma(s)	4 (19.0%)	12 (27.3%)	11 (39.3%)
Miliary tubercles	0 (0%)	4 (9.1%)	5 (17.9%)
Hydrocephalus	9 (42.9%)	32 (72.7%)	15 (53.6%)
Basilar enhancement	6 (28.6%)	26 (59.1%)	16 (57.1%)
Infarction	2 (9.5%)	7 (15.9%)	9 (32.1%)
Chest X-ray	5 (23.8%)	13 (29.5%)	14 (50.0%)

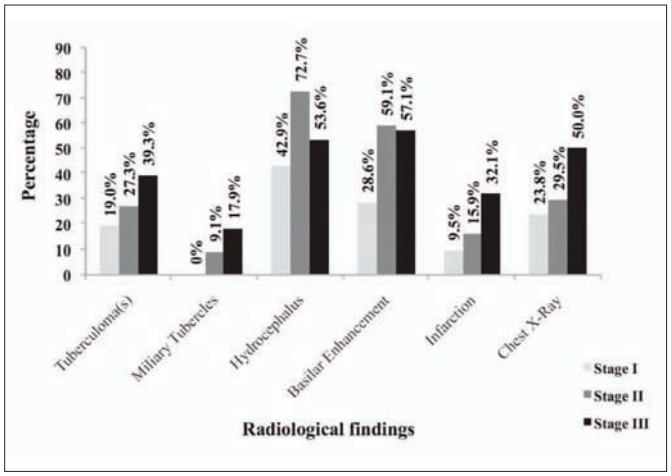

Figure 1: Graphical presentation of radiological (MRI brain and X-ray chest) findings of patients.

DISCUSSION

Tuberculous meningitis (TBM) is the most common form of CNS tuberculosis and is characterized by a slowly progressive granulomatous inflammation of the brain that results in death if left untreated. An early diagnosis, before the onset of coma and focal neurologic deficits, is the greatest contribution a physician can make towards improving outcome from tuberculous meningitis: yet, the diagnosis is often elusive, obscured by non-specific symptoms and signs and insensitive laboratory tests. Any delay in diagnosis is dangerous practice; disease progression is not linear and patients can progress to deep coma over hours following days of mild symptoms.

If TBM is suspected, empiric treatment is started immediately without requiring a bacteriological proof. This is done not only in the developing world but also in more developed countries irrespective of the availability of more diagnostic facilities.[14]

In this study of 93 consecutive patients with treatment responsive tuberculous meningitis, who met the inclusion criteria as mentioned above, we aimed to evaluate the frequencies and percentages of various clinical and radiological features in different stages of the disease on the basis of BMRC contemporary clinical criteria for the severity of tuberculous meningitis.

Majority of patients in this series were found to have stage-II disease at the time of admission followed by stage-III and stage-I patterns respectively. This mode of presentation is not too different from recent studies from Pakistan,[15] which found stage-II pattern at the time of presentation in 50 – 55% of cases. However, Rim Abdelmalek *et al*. also found similar pattern of presentation in 23 out of 29 patients with tuberculous meningitis in Tunisia.[16]

For this study, six clinical and five radiological variables were selected to assess their frequencies and percentages in the diagnosis of tuberculous meningitis in different stages of the disease. Among clinical variables, duration of illness and cranial nerve palsies were found to be important factors in diagnosis of TBM among different stages of the disease. Patients with stage-III pattern were far more likely to have longer duration of illness at the time of admission as compared to those with stage-I and II patterns; however, majority of patients in all stages of disease were found to have signs and symptoms for more than 2 weeks at the time of admission. This phenomenon was comparable to neighbouring study from Kashmir valley where more than 50% of patients were reported 4 weeks after onset of symptoms.[17] Similarly, cranial nerve palsies were reported with increasing percentage in advancing stages of the disease. Sixth, third, second and seventh cranial nerves were found to be involved in descending order in various combinations in different stages of the disease. Verma *et al*. showed that cranial nerves were involved in more than one-third of cases of tuberculous meningitis and 6th cranial nerve was the most commonly affected cranial nerve.[10] However, sixth and third cranial nerve were most frequently reported to be involved in stage-III disease with least common occurrence in stage-I disease. Other studies have also reported cranial nerve palsies in 31% and 22% cases of TBM.[18,19]

Surprisingly, other clinical variables including gender, neck stiffness, papilloedema and focal weakness (stroke) were found to be relatively less important factors to differentiate among different grades of the disease.

Contrast-enhanced MRI is generally considered to be superior to CT scan in detecting and assessing CNS tuberculosis.[20,21] High resolution 1.5 tesla MRI is fortunately available in our institute and MRI contrast studies were carried out in all patients within 48 hours after admission in the ward. The characteristic radiologic findings are non-specific and include basal meningeal enhancement, hydrocephalus, tuberculoma(s) and infarcts; but when correlated with given clinical features these findings may give clue for the diagnosis. Hydrocephalus and basal enhancement were found as the most frequently reported radiographic abnormalities in this series of patients (> 50%). Hydrocephalus was communicating in majority of the patients whereas meningeal enhancement was most commonly found in interpeduncular fossa, pontine cistern and the perimesencephalic and suprascellar cisterns. Similar to cranial nerve palsies, hydrocephalus and basal enhancement were found to be very important variables to differentiate between different stages of the tuberculous meningitis. However, the study by Amin *et al*.,[22] conducted at Shaukat Khanum Memorial Hospital, Lahore, surprisingly found hydrocephalus and vasculitis in less than 10% of their cases.

Interesting aspect of this study is lower percentage of patients with hydrocephalus and basal enhancement in stage-III patients compared to stage-II patients. At the same time there was higher percentage of lacunar and / or territorial MCA infarctions in stage-III patients compared to stage-I and stage-II patients. This study also found multiple and miliary pattern of tuberculoma formation more frequently in advanced stages of the disease (stage-III more than stage-II more than stage-I).

Because BMRC criteria for tuberculous meningitis are based upon clinical features,[13] increased morbidity in advanced stages of the disease in this case series seems more likely to result from mass effect due to tuberculoma(s) formation as well as vasculitic infarction leading to stroke in advanced stages of the disease.

CONCLUSION

High degree of suspicion for TB meningitis is required in endemic regions like Pakistan where one cannot rely on individual clinical and radiological features to reach the diagnosis. However, we suggest to take into account the duration of illness and cranial nerve palsies as important clinical features in patients with compatible clinical picture who have hydrocephalus and/or basal enhancement on MRI studies in any stage of the disease.

REFERENCES

1. World Health Organization. Global tuberculosis control. Geneva: *WHO;* 2009.
2. Murthy JM. Multi-drug-resistant central nervous system tuberculosis. *Neurol India* 2012; **60**:143-5.
3. Cárdenas G, Soto-Hernández JL. The many faces of central nervous system tuberculosis. *Arch Neurol* 2011; **68**:1078.
4. Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. *Lancet Neurol* 2005; **4**:160-70.
5. Van Well GT, Paes BF, Terwee CB, Springer P, Roord JJ, Donald PR, *et al*. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the western cape of South Africa. *Pediatrics* 2009; **123**:e1-8.
6. Rock RB, Olin M, Baker CA, Molitor TW, Peterson PK. Central nervous system tuberculosis: pathogenesis and clinical aspects. *Clin Microbiol Rev* 2008; **21**:243-61.
7. Ken SJ, Crowe SM, Yung A, Lucas CR, Mijch AM. Tuberculous meningitis: a 30-year review. *Clin Infect Dis* 1993; **17**:987-94.
8. Murthy JM. Tuberculous meningitis: the challenges. *Neurol India* 2010; **58**:716-22.
9. Burrill J, Williams CJ, Bain G, Conder G, Hine AL, Misra RR. Tuberculosis: a radiologic review. *Radiographics* 2007; **27**:1255-73.
10. Sharma P, Garg RK, Verma R, Singh MK, Shukla R. Incidence, predictors and prognostic value of cranial nerve involvement in patients with tuberculous meningitis: a retrospective evaluation. *Eur J Intern Med* 2011; **22**:289-95. Epub 2011 Feb 15.
11. Anuradha HK, Garg RK, Agarwal A, Sinha MK, Verma R, Singh MK, *et al*. Predictors of stroke in patients of tuberculous meningitis and its effect on the outcome. *QJM* 2010; **103**:671-8. Epub 2010 Jun 29.
12. Piennar M, Andronikou S, van Toorn R. MRI to demonstrate diagnostic features and complications of TBM not seen with CT. *Childs Nerv Syst* 2009; **25**:941-7.
13. British Medical Research Council. Streptomycin treatment of tuberculous meningitis. *Lancet* 1948; **1**:582-96.
14. Moreira J, Alarcon F, Bisoffi Z, Rivera J, Salinas R, Menten J, *et al*. Tuberculous meningitis: does lowering the treatment threshold result in many more treated patients? *Trop Med Int Health* 2008; **13**:68-75.
15. Zafar SA, Irfan M. Lateral rectus palsy: an important sign in diagnosing tuberculous meningitis. *KMJ* 2011; **3**:10-4.
16. Abdelmalek R, Kanoun F, Kilani B, Tiouiri H, Zouiten F, Ghoubantini A, *et al*. Tuberculous meningitis in adults: MRI contribution to the diagnosis in 29 patients. *Int J Infect Dis* 2006; **10**:372-7. Epub 2006 Jul 12.
17. Wani AM, Mohd Hussain W, Fatani M, Shakour BA, Akhtar A, Ibrahim F, *et al*. Clinical profile of tuberculous meningitis in Kashmir Valley-the Indian. *Infect Dis Clin Pract* 2008; **16**:360-7.
18. Verdon R, Chevret S, Laissy JP, Wolff M. Tuberculous meningitis in adults: review of 48 cases. *Clin Infect Dis* 1996; **22**:982-8.
19. Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, *et al*. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *Lancet* 2002; **360**:1287-92.
20. Jinkins JR, Gupta R, Chang KH, Rodriguez-Carbajal J. MR imaging of central nervous system tuberculosis. *Radiol Clin North Am* 1995; **33**:771-86.
21. Kioumehr F, Dadsetan MR, Rooholamini SA, Au A. Central nervous system tuberculosis: MRI. *Neuroradiology* 1994; **36**:93-6.
22. Amin Y, Shaukat A, Mian BA. Intracranial manifestations of tuberculosis: an imaging study. *Biomedica* 2004; **20**:1-4.