ORIGINAL RESEARCH PAPER

Neurology

CLINICAL PROFILE OF PATIENTS WITH TUBERCULOUS MENINGITIS: AN OBSERVATIONAL STUDY

KEY WORDS: Meningitis, Tuberculosis, Tuberculoma, Clinical Features Of Tb Meningitis

Dr. Tejas Deshpande Junior Resident, Department of Respiratory Medicine

Dr. Owez Virani* Junior Resident, Department of Medicine *Corresponding Author

ABSTRACT

INTRODUCTION: The study aims to highlight the different clinical features of tuberculous meningitis encountered at a tertiary centre in India. Not all cases of tuberculous meningitis present with the classical features of the disease and create a diagnostic dilemma.The study tries to assess these various manifestations of TB Meningitis.
AIM: To study the various presentations of patients with tuberculous meningitis in a tertiary care centre.
METHODOLOGY: Prospective observational study was carried out in a tertiary care centre with a final sample size of 71 patients.The clinical features of each of the 71 cases were noted and tabulated.
RESULTS: 49 out of 71 patients presented with typical clinical features of Tuberculous Meningitis. Whereas, remaining 22 out of the 71 cases did not have the classical features.
CONCLUSION: The study highlights that Tuberculous Meningitis manifests as a plethora of symptoms not always forming a spectrum of disease.

INTRODUCTION:

Tuberculous meningitis (TBM) is the most severe type of extra-pulmonary tuberculosis (TB), although it is the least common type (incidence, 5-15%). Approximately 1/3 of the global population is infected with latent TB (1). In 2012, there were ~8.6 million incidences of TB globally, and among these, 1.3 million fatalities occurred (3). The diagnosis of TBM remains challenging due to the nonspecific clinical presentation of patients. The initial differential diagnosis includes other bacterial, viral or fungal infections of the central nervous system (CNS), non-infectious inflammatory diseases of the meninges (including systemic lupus erythematosus) and intracranial malignancy (2). The TBM-induced inflam matory reaction is associated with several complications, including cerebrovascular disease, cranial nerve palsy, hydrocephalus and infarction (4). Rapid diagnosis and therapy are therefore necessary to decrease the high-mo rtality and severe sequelae associated with the disease (4). Due to common characteristics with other diseases and nonspecific clinical presentation, misdiagnosis or delayed diagnosis of TBM results in increased mortality rate (2).

The risk factors of the TBM, including dystrophia, alcoholism, diabetes mellitus and cell-mediated immune mechanism defects, commonly exist in the patients with human immunodeficiency virus (HIV) disease, immunosuppressive diseases, and even in immunocompetent individuals (5). However, alternative factors, including corticosteroid medication, diabetes mellitus and chronic hepatitis and cirrhosis have been associated with the occurrence of TBM in the clinic (6). The World Health Organization suggests treatment between 9-12 months is sufficient for successfully treating TBM (7). The adjuvant prednisolone administration has also proved to be promising in decreasing the mortality of patients with the disease (8).

The diagnosis of TBM should combine clinical manifestations, CSF examination and the effect of anti-TB therapy. Differential diagnosis and trial anti-TB therapy may be of help for diagnosis. Positive CSF smear, CSF culture and biopsy of the brain, or biopsy of meninges are golden standards for the diagnosis of TBM. Early diagnosis and treatment are very important for improving the outcome.

The study aims to highlight the different clinical features of tuberculous meningitis encountered at a tertiary centre in India. In a country with a rigorous national program now targeting to eliminate tuberculosis, the case detection and treatment of Tuberculosis has taken centre stage. Not all cases of tuberculous meningitis present with the classical features of the disease and create a diagnostic dilemma. The study tries to assess these various manifestations of TB Meningitis and in turn reduce this diagnostic dilemma of treating physicians.

AIM:

To study the various presentations of patients with tuberc ulous meningitis in a tertiary care centre.

MATERIALS AND METHODS:

Prospective observational study was carried out in a tertiary care centre with an initial sample size of 82 patients suspected to have Tuberculous Meningitis. The sample was eventually modified to contain only those cases which were proven to have Tuberculous Meningitis. Several diagnostic criteria were used to diagnose the cases including trial of anti-tubercular drugs. The final sample size thus consisted of 71 patients. The clinical features of each of the 71 cases were noted and tabulated.

INCLUSION CRITERIA:

Patients with Tuberculous Meningitis

EXCLUSION CRITERIA:

Patients not willing to participate in the study

SAMPLE SIZE:

71 patients

DURATION OF STUDY:

Two and a half years

DATA COLLECTION TECHNIQUE:

Prospective observational study, in which the clinical features of the cases were noted and tabulated for analysis. The diagnosis was made with the help of various criteria ranging from CSF analysis to the trail of anti-tubercular drugs.

DIAGNOSING TUBERCULOUS MENINGITIS:

The typical features of Tuberculous Meningitis were consid ered as follows:
The initial features of Tuberculous Meningitis form the prodromal phase, which lasts for around 2-3 weeks and is characterized by history of vague ill health, apathy, irritability, anorexia and behavioural changes. Headache, vomiting and fever is noted in around 13-30% of cases in the prodromal phase and heralds the onset of meningitis. Focal neurological deficit and features of raised intra cranial tension may

precede signs of meningeal irritation. Focal or generalized convulsions may occur in 20-30% of patients at some point during the course of the disease and are particularly common in the elderly and children. Underlying mechanisms for this may include hydrocephalus, tuberculoma, cerebral edema and hyponateremia due to Syndrome of Inappropriate Anti-Diuretic Hormone Secretion (SIADH). Cranial nerve palsies can occur in 20-30% of patients, the sixth nerve involvement being the most common. (9,10,11,12)

The various clinical presentations considered as typical used to assess patients include: (12)

SYMPTOMS:
Fever, altered sensorium, seizures, behavioural changes.

Signs: Neck rigidity, papilledema, Abducens nerve palsy, hemiplegia, facial nerve palsy, optic atrophy, decerebration, abnormal movements, oculomotor nerve palsy, choroidal tubercles.

During the last two decades however, with increasing development, the presentations of tuberculous meningitis may have shifted slightly towards those of developed countries which include atypical manifestations(11,13) such as acute meningitic syndrome simulating pyogenic meningitis, progressive dementia, status epilepticus, psychosis, stroke syndrome, locked in state, trigeminal neuralgia, infantile spasm and movement disorders. (9,12,14) The factors responsible for this changing pattern are thought to be related to delay in onset of the primary infection, immunization, problems related to immigrant population and HIV infection. (15,16) These considerations were also kept in mind to categorise features into typical and atypical groups.

Diagnosis of Tuberculous Meningitis was done in the followi ng ways:

CSF ANALYSIS:
Features suggestive of Tuberculous Meningitis were as follows:

1. Leukocyte count between 100 to 500 cells /microliter with predominantly lymphocytic picture, with negative cytology for malignancy.
2. CSF proteins between 100 to 200 mg/dl.
3. Cobweb formation in the sample.
4. Reduced CSF glucose to less than 40% of the serum value.

MICROBIOLOGICAL TESTS:
Features suggestive of Tuberculous Meningitis were as follows:

1. Negative Gram stain, negative India ink stain and sterile culture for bacteria and fungi.
2. Acid fast bacilli in CSF ZN staining.
3. Lowenstein Jensen medium culture of CSF suggestive of Mycobacterium Tuberculosis.

NEUROIMAGING:
Features suggestive of Tuberculous Meningitis were as follows:
CT/ MRI brain revealing thickening and enhancement of basal meninges, hydrocephalus, infarction, edema and mass lesions due to associated tuberculoma or TB abscess.

With the above investigations, neuroimaging was also corre lated with the clinical picture to arrive at a diagnosis. History of previous pulmonary tuberculosis or disseminated tuberc ulosis was taken seriously and favoured the diagnosis of tuberculous meningitis. Concomitant active pulmonary tuberculosis indicated by radiological picture or sputum positivity for acid fast bacilli further confirmed the diagnosis. Evidence of tuberculous lesions elsewhere in the body, like ileocecal junction, lymph nodes, etc. was also checked with local ultrasonography and other required investigations to help in the diagnosis of tuberculous meningitis as a component of disseminated Koch's.

OBSERVATIONS:
Out of the 71 patients enrolled in the study, 49 patients presented with typical features of Tuberculous Meningitis.

The remaining 22 patients presented with non-classical features of Tuberculous Meningitis.

Table 1: Different Presentations of Tuberculous Menin gitis in the study population

Presenting Features	Number of Patients
Typical features (12)	49
Status epilepticus	2
Psychosis	1
Irritability alone	2
Signs of raised ICT without constitutional symptoms	4
Constitutional symptoms alone	9
Blurring of vision alone	1
Comatose or delirious patient	2
Abducens nerve palsy alone	1

The above table indicates that 49 out of the 71 patients included in the study had typical features of tuberculous meningitis as mentioned previously. (12)

The remaining 22 patients however posed a diagnostic dilemma with their atypical features mentioned above. These patients comprised of 2 HIV positive patients, one of which manifested with only vague constitutional symptoms and the other being a case of disseminated Koch's, both of which were diagnosed on neuroimaging with negative stains and microbiological features, with good response to anti-tubercular therapy proving the diagnosis with subsequent improvement in the neuroimaging.

All cases with atypical presentations were confirmed to have tuberculous meningitis with the help of at least one of the modalities mentioned earlier.

DISCUSSION:
The study highlights the atypical presentations encountered at the tertiary care centre and emphasises on the consideration of tuberculous meningitis as a differential diagnosis in such cases as well.

According to the severity of the illness, patients with tuberc ulous meningitis can be categorised into 4 clinical stages (17,18)

Table 2: Clinical staging system for tuberculous menin gitis. (17,18)

Stage	Description
1	Conscious and rational with or without neck stiffness, but no focal neurological signs or signs of hydrocephalus.
2	Conscious but confused or has focal signs, such as cranial nerve palsies or hemiparesis.
3	Comatose or delirious patient with or without dense neurological deficit.
4	Deeply comatose patient with decerebrate or decorticate posturing.

TUBERCULOUS MENINGITIS AND HIV INFECTION:
One of the major causes of re-emergence of TB in the west has been HIV epidemic. The CNS involvement is five times more frequent in HIV seropositive compared to HIV seronegative patients (15,19). Berenguer et al (15) reported that 10 % of 455 patients co-infected with both TB and HIV developed TBM.

Yechoor et al (20) observed that 20 out of 31 patients [65%] identified as definite or probable TBM over a 12 year period were co-infected with HIV. Neurotuberculosis, either alone or associated with other opportunistic infections, was found in 35 of 100 HIV seropositive patients seen over seven years at the National Institute for Mental Health and Neurosciences [NIMHANS] in Bengaluru. (21)

Although HIV infected patients are at an increased risk of TBM, the HIV status does not alter the clinical manifestations, CSF findings and response to therapy. (15, 20, 22, 23) However, CSF examination may frequently be normal in HIV serop ositive subjects with TBM. (16) In such patients radiological clues to the diagnosis of neurotuberculosis include multilo culated abscess, cisternal enhancement, basal ganglia infarction and communicating hydrocephalus, which are not the findings associated with the more commonly encountered CNS lymphoma or toxoplasma encephalitis. Extra-meningeal TB is seen more often [65% to 77%] in patients co-infected with HIV and TB compared to HIV seronegative individuals [9%]. (15.24) Likewise, an associated tuberculoma may be present in more than half of HIV infected patients with TBM. (22) Neurological TB can also be initial presentation of AIDS. (25) Bishburg et al (19) noted that intravenous drug abusers with AIDS were more likely to develop TB of the CNS and TB brain abscesses.

DIFFERENTIAL DIAGNOSES OF TUBERCULAR MENIN GITIS INCLUDE:

1. Partially treated bacterial meningitis
2. Cryptococcal meningitis
3. Viral meningoencephalitis
4. Carcinomatous meningitis
5. Parameningeal infection
6. Neurosarcoidosis
7. Neurosyphilis

CONCLUSION:

The study highlights that Tuberculous Meningitis manifests as a plethora of symptoms not always forming a spectrum of disease. The atypical or uncommon features seen in Tuberculous Meningitis may be seen in other pathologies of the central nervous system, however in countries with espe cially high tuberculosis load, a differential of Tuberculous Meningitis must always be considered.

CONFLICT OF INTEREST: None

REFERENCES:

1. Chin H: Tuberculous meningitis: Diagnostic and therapeutic challenges. Neurol Clin Pract 4: 199 205, 2014.
2. Bartzatt R: Tuberculosis infections of the central nervous system. Cent Nerv Syst Agents Med Chem 11: 321 327, 2011.
3. World Health Organization: Global Tuberculosis Report 2013. http://www.w ho.int/tb/publications/global_report/en/index.html. Accessed January 10, 2014.
4. Christense AS, Andersen AB, Thomsen VO, Andersen PH and Johansen JS: Tuberculous meningitis in Denmark: A review of 50 cases. BMC Infect Dis 11: 47, 2011.
5. Yuchong C, Fubin C, Jianghan C, Fenglian W, Nan X, Minghui Y, Yalin S and Zhizhong Z: Cryptoccosis in China (1985 2010): Review of cases from Chinese population. Mycopathologia 173: 329 335, 2012.
6. Qu J, Zhou T, Zhong C, Deng R and Lü X: Comparison of clinical features and prognostic factors in HIV negative adults with cryp¬tococcal meningitis and tuberculous meningitis: A retrospective study. BMC Infect Dis 17: 51, 2017.
7. World Health Organization: Treatment of tuberculosis guide¬lines. 4th edition. http://whqlibdoc.who.int/ publications/2010/97 892 415 478 33_ eng.pdf.
8. Prasad K and Singh MB: Corticosteroids for managing tubercu¬lous meningitis. Cochrane Database Syst Rev: CD002244, 2008.
9. Tandon PN, Bhatia R, Bhargava S. Tuberculous Meningitis. In: Harris AA, editor. Handbook of clinical neurology [revised series]. Amsterdam: Elsevier Science; 1988.p.195-226.
10. Ramamurthi B, Varadarajan MG. Diagnosis of tuberculomas of brain. Clinical and radiological correlation. J Neurosurg 1961;18:1-7.
11. Kent SJ, Crowe SM, Yung A, Lucas CR, Mijch AM. Tuberculous meningitis: A 30 year review. Clin Infect Dis 1993;17:987-94.
12. Thomas MD, Chopra JS, Walia BN. Tuberculous meningitis. A clinical study of 232 cases. J Assoc Physicians India 1977;25:633-9.
13. Sheller JR, Des Prez RM. CNS Tuberculosis. Neurol Clin 1986;4:143-58.
14. Kocen RS, Parsons M. Neurological Complications of Tuberculosis: Some unusual manifestations. QJM 1970;39:17-30.
15. Berenguer J, Moreno S, Laguna F, Vicente T, Adrados M, Ortega A, et al. Tuberculous meningitis in patients infected with the human immuno de ficiency virus. N Engl J Med 1992;326:668-72.
16. Traub B, Colchester AE, Kingsley DP, Swash M. Tuberculosis of the central nervous system. QJM 1984;3:81-100.
17. Medical Research Council. Streptomycin treatment of tuberculous meningitis: Report of committee on streptomycin in tuberculosis trials. Lancet 1948;1:582-97.
18. Kennedy DH, Fallon RJ. Tuberculous meningitis. JAMA 1979;241:264-8.
19. Bishburg E, Sunderam G, Reichman LB, Kapila R. Central nervous system tuberculosis with the acquired immunodeficiency syndrome and it related complex. Ann Intern Med 1986;105:210-3.
20. Yechoor VK, Shandera WX, Rodriiguez P, Cate TR. Tuberculous meningitis among adults with and without HIV infection. Experience in urban public hospital. Arch Intern Med 1996;156:1710-6.
21. Satishcahndra P, Nalini A, Gourie- Devi M, Khanna N, Santosh V, Ravi V, et al. Profile of neurologic disorders associated with HIV/ AIDS from Bangalore, south India [1989-96]. Indian J Med Res 2000;111:14-23.
22. Dube MP, Holtom PD, Larsen RA. Tuberculous meningitis in patients with and without human immunodeficiency virus infection. Am J Med 1992;93:520-4.
23. Verdon R, Chevret S, Laissy JP, Wolff M. Tuberculous meningitis in adults: review of 48 cases. Clin Infect Dis 1996;22:982-8.
24. Karstaedt AS, Valtchanova S, Barriere R, Crewe- Brown HH. Tuberculous meningitis in South African urban adults. QJM 1988;91:743-7.
25. Whiteman M, Espinoza L, Post MJ, Bell MD, Falcone S. Central nervous system tuberculosis in HIV infected patients: Clinical and radiographic findings. AJNR Am J Neuroradiol 1995;16:1319-27.