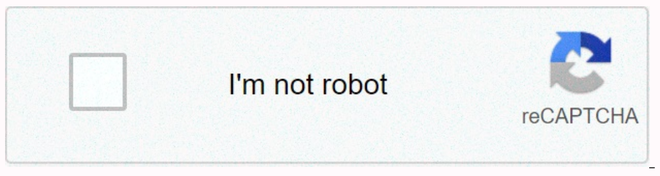


Continue

# Tb meningitis guidelines

Click on the image for details. NI FEATURE: TRAVEL THROUGH EONS - COMMENT YEAR : 2018 | Volume : 66 | Issue : 6 | Page : 1550-1571 Tuberculous meningitis: Challenges in diagnosis and management: Lessons learned from Prof. Dastur's article published in 1970 Manish Modi1, Manoj Kumar Goyal1, Anumiti Jain1, Suhalika Singhal Sawhney1, Kusum Sharma2, Sameer Vyas3, Chirag Kamal Ahuja3 1 Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh, India2 Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India3 Department of Radio Diagnostics and Imaging, Postgraduate Institute of Medical Education and Research, Chandigarh, India Date of Web Publication28-Nov-2018 Correspondence Address: Dr. Manish ModiDepartment of Neurology, Postgraduate Institute of Medical Education and Research, Chand igarh IndiaSource of Support: None, Conflict of Interest: NoneCheckDOI: 10.4103/0028-3886.246224 It is about five decades since Dastur et al., published his groundbreaking work on pathology of tuberculous meningitis (TBM). Although most of their findings find relevance in today's time, there is an important difference; These findings can now be replicated in the course of life using modern technology. In this article, we review Professor Dasturs and colleagues' groundbreaking words, analyze their findings, interpret how they revolutionized our understanding of TBM and highlight their relevance in today's day. We also discuss challenges in the management of TBM, which we continue to face today and the various options required to overcome these challenges. Keywords: Antituberculous treatment, challenges, complications, tuberculosis, tuberculous meningitis Key Message: Recent image modalities enable radiologists and treating physicians to diagnose tuberculous meningitis (TBM) with a reasonable degree of safety at an early stage, thereby enabling the initiation of an early treatment for TBM. All these image findings are in congruence with the findings clearly described in the gross pathology of Professor Dastur and his colleagues. This article describes how this article revolutionized our understanding of TBM and its relevance in modern times. How to quote this article:Modi M, Goyal MK, Jain A, Sawhney SS, Sharma K, Vyas S, Ahuja CK. Tuberculous meningitis: Challenges in Diagnosis and Management: Lessons learned from Prof. Dastur's article published in 1970. Neurol India 2018;66:1550-71 How to quote this URL:Modi M, Goyal MK, Jain A, Sawhney SS, Sharma K, Vyas S, Ahuja CK. Tuberculous meningitis: Challenges in diagnosis and management: Lessons learned from Prof. Dastur's article published in 1970. Neurol India [serial online] 2018 [quoted 2020 December 10];66:1550-71. Available from: Nec minus a phlegmone et abcessu quam hujasmodi meningitis et tuberculis, cefaloteltaler et incurabilesoriuntur(Sometimes headache, fatal incurable, follow abscesses and swellings in the envelopes of the brain, as well as plaques and tubercles of these membranes)Willis, 1672. [1] First described by Willis in the 17th century, tuberculous meningitis (TBM) is the most severe form of tuberculosis (TB). TB in all forms remains a challenging clinical problem and a public health problem of significant importance and size, worldwide. It continues to be a worldwide burden, with most new active cases occurring in underdeveloped countries. [2] According to World Health Organization (WHO) statistics, five countries, viz., India, China, Pakistan, Indonesia and South Africa, account for over 70% of the global disease burden. [3] Mycobacterium tuberculosis (MTB) causes approximately 10.4 million new cases of tuberculosis and 1.5 million deaths annually, with an additional 0.4 million deaths in people infected with human immunodeficiency virus (HIV). Patients who are converging with HIV are more than 20 times more likely to develop tuberculosis compared to non-infected individuals. [3] Although tb in the central nervous system accounts for 5-10% cases of extrapulmonary TB and only 1% of all cases of tuberculosis, it is responsible for more deaths than any other form of tuberculosis, due to the inherent seriousness of this disease. [4] Nearly five decades ago, Dastur and colleagues in their groundbreaking paper had highlighted the gross pathological changes in 100 patients with TBM, who succumbed to this disease. The work of Professor Dastur and colleagues continues to be very relevant in modern times. The landmark paper by Dastur et al.,[5] gave us an insight into pathophysiology and pathological changes of CNS TB, which are replicated in the present day by advanced imaging techniques. With the use of magnetic resonance imaging (MRI), more so that the newer sequences such as magnetization transmission (MT), gradient recalled echo (GRE), susceptibility-weighted (SW), diffusion weighted (DW) and liquid curb inversion recovery (FLAIR) images, The cause and extent of the disease, its underlying pathophysiology, complications and the favorable or negative response to treatment can now be measured with almost the same precision during life as that reported in post mortem samples of Dastur et al. [5] A careful interpretation of the data from Dastur et al., suggests that the majority of patients had one or more life-threatening complications in the form of hydrocephalus, infarctions, severe arachnoiditis, including spinal arachnoiditis and tuberculomas, corresponding to stage 3 of the Medical Research Council (MRC) staging [Table 1]. [5],[6] As almost all cases analyzed by Dastur et al., had advanced TBM, it is reasonable to expect that the findings presented by them may not be clear in some patients, especially those at an early stage of TBM. In these patients, magneticization transmission (MT) MRI imaging detects the earliest signs of meningitis in the form of hyperintense signal changes on T1 weighted MT sequences, conventional echo sequences for spin can be normal. [7] The usual places of basal meningeal improvement include interpeduncular fossa, pontine, perimesencephalic and suprasellar cisterns, and Sylvian cracks [Figure 1]a. The degree of improving exudates varies from a thin layer to a thick sheet [Figure 1]b, as evidenced by Professor Dastur and colleagues. In more advanced cases, as described by Dastur et al., these exudates may block the flow of CSF (cerebrospinal fluid) producing hydrocephalus, which can communicate (dilatation of all ventricles) [Figure 1] c mainly due to basal exudates, or non-communicative either due to narrowing of the cerebral aqueduct or obstruction to the CSF current at the level of the foramen of Lushka and Magendie, through various mechanisms. All these pathological findings can now be revealed during life with available image modalities. While contrast enhanced computed tomography (CECT) scanning is the imaging modality of the choice to establish the diagnosis of TBM in an emergency setting, MRI provides a much more objective information about the degree of exudate, degree of hydrocephalus, associated periventricular ooze as well as other complications such as the development of infarctions and borderzone encephalitis (BZE). The latter was a phenomenon described by Dastur et al., which occurs in the form of localized necrosis of the underlying cerebral parenchyma in relation to infiltrative exudates [Figure 2]a, [Figure 2]b and [Figure 2]c, [Figure 3]a and [Figure 3]b.Table 1: British Medical Research Council (MRC) criteria for assessing disease severityClick here to see Figure 1 : Pathological and radiological correlation in a patient who succumbed to tuberculous meningitis. (a) Post-mortem brain that shows opaque opinions with thick exudates at the base of the brain. (b and c) Contrast enhanced computed tomographic scanning showing thick reinforcing exudates at the base of the brain in basal cisterns (white arrows) in the same patient while he was alive. Also note the dilatation of ventricles suggesting hydrocephalusClick here to see Figure 2: Border zone encephalitis (BZE) affecting the brain stem of a patient with tuberculous meningitis. (a and b) Note hyperintense signal changes (white arrows) on T2W MRI (T2 weighted magnetic resonance) images involving pons and left temporal lobe; (c) Axial section on the level of pons in the post-mortem brain of the same patient that shows diffuse necrosis of almost whole pons that are suggestive of BZE (white arrow)Click here to displayFigure 3: Border-zone encephalitis (BZE) affects the left peri-Sylvian region of TBM. (a) Intensive hyperintense signal changes (white arrows) seen on T2W MRI (T2 weighted magnetic resonance) image involving left temporo-parietal region (white arrows). Also note the dilatation of temporal horn on the right side and an infarction in the left thalamus; (b) Gadolinium improved MRI image of the brain showing thick reinforcing exasates on the left crack and basal cisterns (white arrows)Click here to seeDastur et al., noted gross compression and narrowing of major arteries (especially the middle cerebral arteries) due to meningovasculitis at the base of the brain with resulting ischemia (mainly in basal ganglionic and thalamus regions) in almost 50% of children and 33% of adults. With the use of new MRI sequences, these changes can be seen during life as areas with diffusion limitation on DWI [Figure 4]a and [Figure 4]b. Complications such as optochiasmatic arachnoiditis [Figure 5]a, [Figure 5]b and [Figure 5]c, as well as spinal arachnoiditis and tuberculomas [Figure 6]a and [Figure 6]b can be documented with precision of contrast enhanced MR. Figure 4: Infarction in a patient with tuberculous meningitis. (a) Diffusion weighted magnetic resonance imaging showing an infarction in the left putaminal, thalamus and temporal regions (white arrows). (b) Gadolinium enhanced magnetic resonance imaging showing thick reinforcing exudates in the left Sylvian crack that envelop the middle brain artery (white arrows) in the same patientClick here to see Figure 5: Optochiasmatic arachnoiditis in a patient with tuberculous meningitis. (a and b) Gadolinium enhanced magnetic resonance imaging of the brain showing plate and ring-enhancing lesions (white arrows) involving sellar and suprasellar, as well as the left medial temporal areas. (c) Autopsy section (coronary) of the same patient showing organized thick exudates with fibrosis affecting the pituitary and left temporal regions (white arrows)Click here to showFigure 6: Tuberculomas in a patient with tuberculous meningitis. (a) T2 weighted axial magnetic resonance imaging of the brain showing multiple hyperintense lesions; notice the central hypointensity (T2 abbreviation) in most lesions suggesting tuberculomas. (b) Gadolinium enhanced magnetic resonance imaging of the brain showing multiple ring-promoting lesions (white arrows)Click here to seeTo summarize, newer image modalities have given radiologists and treating physicians the opportunity to diagnose TBM with a reasonable degree of safety at an early stage, thereby providing an early treatment of TBM. All these image findings are consistent with the findings clearly described in the gross pathology of Professor Dastur and his colleagues. This clinician-pathology-radiological correlation has given an edge to clinicians to establish an early diagnosis of TBM and in the treatment of the condition. Despite the availability of descriptive literature on the pathological findings of TBM for more than 5 decades, mainly due to the groundbreaking work of Professor Dasturs and colleagues, the morbidity and mortality of TBM continues to be unacceptably high. Reported mortality rates, according to the MRC phase at the presentation stage, are 4% in grades 1, 11% in grades 2 and 50% in grade 3 of a study from northern India[4] and 20% for grade 1, 30% for grade 2 and 50% for stage 3 of a study from Currently, the major challenges for successful management of TBM are an early diagnosis of TBMA effective treatment of TBMHandling complications.A. Early diagnosis of TBM:This continues to be the biggest challenge in TBM due to the following reasons:A1: and varied clinical symptomatologyA2: Poorly sensitive diagnostic laboratory parameters. A1. and varied clinical symptomatologyThe clinical symptomatology of TBM is often not specific. A prodromal period of nonspecific constitutional symptoms (irritability, anorexia, weight loss or sleep disorders in children; and fatigue, loss of appetite, weight loss and night sweats in adults) can last from a few days to several weeks in a majority of patients. This is especially true in the underdeveloped world where rampant abuse of quinolons and other antibiotics often suppresses the first symptomatology of TB. The typical duration of symptoms in TBM is usually of a few weeks and months, although some of the diagnostic criteria require a minimum duration of 5 days only. [9] The typical symptoms include headache, fever, vomiting, meningism, neurological deficits and altered mental status. Photophobia is less common than headache and neck stiffness. In children, vomiting and convulsions are more common than in adults. The classic triad of meningitis, that is, fever (adults: 60-75%, children: 67%), headache (adults: 50-80%, children: 25%) and vomiting (adults: 40-80%, children: 98%) may not be present in all patients. Neck stiffness is usually absent during the early disease. [4],[10] To overcome the challenges arising from the varied symptomatology, a high index of suspicion and performance of appropriate examinations (cerebrospinal fluid [CSF] analysis and neuro imaging) is required to squeeze the diagnosis especially in the early stages of TBM. Various diagnostic algorithms have been proposed by Ahuja et al.,[11] and Marais et al.,[9] (including the modified algorithm of Ahuja et al.,[12]) for a unified case definition of TBM specifically for research purposes, where particular TBM has been defined in only cases where Mycobacterium has been isolated from csf by some of the available microbiological techniques. A2. Poorly sensitive diagnostic laboratory parameters 9TBM is a paucibacillary disease; thus CSF microscopy using Ziehl Neelsen stain [which can confirm the diagnosis quickly through demonstration of acid-fast bacilli (AFB)] has a very low sensitivity (0-20%).[ 13] The results of the culture of MTB are notoriously slow to achieve, with conventional solid media (Lowenstein-Jensen media) giving results only after 10-35 days. [14] To overcome this challenge, many new diagnostic techniques have become available in recent years. These have shortened the lag period to establish the diagnosis of TBM and have improved sensitivity while retaining a good specificity. Currently, several floating cultural systems, including the BACTEC MGIT 960 system (Becton Systems, Sparks, Md) and MB/BacT system (BioMérieux, Durham, N.C) are available, providing positive results in a shorter period of time with the added benefit of providing drug susceptibility testing (DST) of MTB at the same time. [15] Commercial NAATs (nucleic acid amplification tests) have shown potential as rapid rule-in diagnostic tests for TBM, With high specificity (98%), but a low sensitivity (56%).[ 16],[17] A recent review has shown the promise that multiplex polymerase chain reaction techniques (PCR) offer, which have better sensitivity compared to the commercial NAATs (sensitivity 71-94%, specificity 88-100%). Recent NAATs show promising results by increasing the sensitivity and specificity of detection of MTB, as well as to assess resistance in a short period of time. However, these tests require specialized laboratory settings with strict quality control. [18],[19]Xpert MTB/RIF (Cepheid, Sunnydale, CA, USA; an automated diagnostic test that can identify Mycobacterium tuberculosis [MTB] DNA and resistance to rifampicin [RIF]) is the last approved diagnostic test for TUBOSE by who (World Health Organization) in 2010. The main advantages of this test are that the technique can be easily learned, the machine can be used in decentralized settings, the processing time is only 2 hours, and the closed disposable cartridge system reduces the risk of contamination. [20] The sensitivity of Xpert MTB/RIF in a large Vietnamese study was 59.3% [(n = 108/182 (95% confidence interval (CI) 51.8; 66.5)], which is (significantly but only slightly) lower than for mycobacteria growth indicator tubes (MGIT) culture [66.5% (n = 121/182), (95% CI 59.1; 73.3)]. However, the specificity was comparable to that reported for other commercial NATs [99.5% (95% CI 97.2; 100)]. An important advantage of Xpert MTB/RIF is that it can detect rifampicin (RIF) resistance within two hours. In the study above, four patients with RIF resistance (n = 4/109, 3.7%) was identified by Xpert, of which 3 were confirmed to have suffered from multi-drug resistance (MDR) TBM. [21] These figures are too small to draw robust conclusions on the positive or negative predictive value of rifampicin resistance testing of Xpert MTB/RIF. However, since rifampicin resistance is associated with a very high mortality rate in TBM, it is recommended that a positive result for rifampicin resistance, in the context of a clinical picture suitable for resistant TB, should prompt clinicians to consider immediate second-line treatment. Xpert MTB/RIF has the ability to improve the creation of an early diagnosis of TBM, and in particular to open the field for clinical trials that research treatment optimization for patients with MDR-TBM. It is relevant to note that Dastur et al., reported evidence of TB elsewhere in the body (especially in the lungs and lymph nodes) in almost all of the autopsy bodies. With an important trace from this discovery, we analyzed 70 tbm patients [(either determined (n = 26) or probable (n = 44)] with whole-body FDG PET (flouro-deoxy glucose positron emission tomography) and found signs of TB elsewhere in the body in 66 (94.3%) of patients. FGD-PET showed signs of lung involvement in 62 (88.6%) and lymph nodes involvement in 61 (87.1%) patients [Figure 7]. Therefore, if there are doubts about the diagnosis, additional body image in the form of chest X ray, a calculated tomographic (CT) image of the chest and abdomen, and if necessary, a whole body FDG PET, can help make a decision on the start of ATT. Taken together, it is reasonable to conclude that newer techniques such as Xpert MTB/RIF, NAATs, multiplex PCR for MTB as well as whole body FDG-PET have the potential to help establish an early diagnosis of TBM and thus, in helping to change the management of TBM completely. Figure 7: Whole body Flouro-deoxyglucose positron emission tomography (FDG-PET) in a patient of tuberculous meningitis. (a) The maximum intensity projection (MIP) image shows increased trace recording in supraclavicular, mediastinal and upper abdominal regions (black arrows). (b) FDG eager ring strength lesion (Standarized recording value [SUV] max ~1.5 × 1.1 cm) involves left cerebral peduncle. (c) FDG avid (SUVmax 12) mediastinal lymph nodes (white arrows). (d) FDG avid gastro-hepatic lymph nodes (black arrows)Click here to displayB. Effective treatment of TBM Drug regimens recommended for the treatment of TBM is derived from short-term lung TB treatments. However, the current algorithms for the treatment of TBM have ignored an important fact, it will want the brain to be considered a distinctive space, and thus the dosage and duration of the therapeutic regimen for TBM should be established with respect to pharmacokinetic (PK) and pharmacodynamic (PD) evidence. Even today, the optimal drug dosage and correct duration of treatment for TBM have not been unequivocally established by large clinical trials. The challenges of effective treatment of TBM are still related to:B1. Medicines, doses and duration of antituberculous therapy (ATT)B2. Treatment of multi-drug resistance (MDR) TBM. B1. Medicinal products, doses and duration of ATTThe first-line anti-TB agents recommended for the treatment of TBM include rifampicin (RIF), isoniazid (H), pyrazinamide (PZA), ethambutol (EMP) and/or streptomycin (S). Among the first-line medicines used in TBM, RIF, EMP and streptomycin have poor penetration over the blood-CSF barrier. [22] Currently, who recommends a 2-month treatment with 4 first-line medications in the intensive phase, followed by a continuation phase of at least rifampicin and isoniazid for 4-10 months. [2] However, as mentioned earlier, there are no data from randomised controlled trials to form the basis of these recommendations. Some authors have advocated for a longer course of treatment for up to 2 years or even more, while others have suggested that short-term RIF-based regimens for 6 to 9 months may be sufficient. [23],[24] 24] Treatment of TBM varies from place to place. The current guidelines in the UK suggest treatment with rifampicin, isoniazid, pyrazinamide and a fourth agent (streptomycin, ethambutol or prothionamide) for the first two months followed by rifampicin and isoniazid for 10 months for uncomplicated cases of TBM (including cerebral tuberculomies without meningitis). ATT should be given for 18 months if PZA is not part of the first treatment regimen. The American Thoracic Society recommends initiating isoniazid treatment (INH 10mg/kg/day up to 300 mg/day), rifampicin (RIF 10-20mg/kg/day up to 600 mg/day), pyrazinamide (PZA 15 mg/kg/day up to 2 gm/day) and ethambutol (EMB 20mg/kg/day up to 1.2 gm/day). After the first 2 months, INH and RIF continue alone for another 7-10 months, even if the optimal duration of treatment is not defined. [25] Recently, several studies have shown that high doses of RIF in TBM regimens are associated with higher levels in CSF and improved survival, although these studies have only registered a small number of patients. [26] There is also a lack of data on the use of fluoroquinolones in TBM, which remains an attractive option, as they are active against MTB, are well tolerated, have extensive safety data, have relatively little resistance to MTB and have a good penetration in CSF; clinical use has, however, shown inconsistent results. [26],[27]Together, it is clear that there are still doubts about the optimal doses, regimen and duration of ATT in TBM, and thus large randomized trials are the need for the hour to solve these problems. B2. Treating MDR TBMDrug-resistant tuberculosis is a growing problem globally. Resistance to rifampicin is associated with a very high mortality rate in TBM, a finding that emphasizes the importance of including rifampicin in successful treatment regimens. [28] Globally, approximately 20% of the isolates in TB are resistant to at least one antituberculous drug, and 7% are resistant to the least isoniazid. [29] Isolated resistance to isoniazid with or without resistance to streptomycin is found more often in high-burdening environments. Isoniazidresistens has been associated with increased mortality due to TBM, especially in those infected with human immunodeficiency virus (HIV). [30] An adverse outcome can be prevented from using pyrazinamide throughout the treatment period. [RRR] MDR-TBM (resistance to at least rifampicin and isoniazid in multi-drug resistance tuberculous meningitis) is very deadly. Most patients die within two months of starting treatment. [28] Mdr-TBM management is still far from satisfactory mainly for two reasons. Firstly, early detection of drug resistance is limited by the lack of rapid diagnostics. Thus, the timing of an adjusted treatment plan for drug-resistant TBM is based on the available and sensitivity results are often too late to prevent neurological disability or death. Secondly, due to the lack of good detection techniques, there are no studies evaluating the optimal regimen for resistant TBM. It is relevant to mention that recent diagnostic techniques (Xpert MTB/RIF, multiplex PCR, liquid based culture medium) have shown promise of detection of MDR/DR in the early stages of TBM. Whole genome sequencing of MTB can help define drug resistance-related genes and can help with rapid diagnosis of MDR TB and better treatment of patients. [31],[32] However, large studies remain to validate their routine use. If found successful, these methods can reveal MTB strains that are resistant to rifampicin at an early stage and open the field for studies focusing on second-line treatment for resistant TBM.D. Handling complicationsThe optimal management of complications of TBM such as optochiasmatic arachnoiditis, spinal arachnoiditis, vasculic infarctions, tuberculomas (especially paradoxical as well as persistent lesions) and hydrocephalus, remains to be defined. The paradoxical response (it will want clinico-radiological deterioration after the start of the start) is often reported. This can be observed in all tissues, but most often in the lungs, lymph nodes and brain. [33] In the brain, the paradoxical response often occurs in the form of the appearance of new

tuberculomas or enlargement of existing tuberculomas, when ATT is started (usually within 1-4 months after the start of ATT). It can be accompanied by exacerbation of symptoms or the appearance of signs of a place occupying lesion. This paradoxical response is considered to be more related to increased immune response rather than a manifestation of drug resistance. When other causes of exacerbation (such as drug resistance or the development of new infarctions) are excluded, these patients should be administered by continuation of ATT and administration of high-dose systemic corticosteroids. Some authors have suggested the implication of a more aggressive immunomodulation with drugs. The proposed therapies for various complications are: C1. Use of immunomodulatory drugsC2: Treatment of stroke and vasculitisC3: Surgical treatment of complications. C1: Medical therapy including the use of immunomodulatory drugs:The various options used to treat these complications include a longer duration of treatment, the introduction of second line ATT, the use of high-dose steroids for a longer duration, the use of immunomodulatory drugs such as thalidomide, levamisole, adjuvant interferon gamma therapy and administration of intrathecal hyaluronidase, etc., In our personal experience of >50 patients, the use of thalidomide (at a dose of 2 mg / kg body weight) for 4-6 months in patients with TBM suffers from various sequels (such as optochmatic arachnoiditis, a paradoxical increase in the size of tuberculomas, an increase in the size and number of lesions, and has resulted in an improvement in the clinical condition of patients and has resulted in radiological dissolution of the lesions in > 70% of patients, who had already received >2 months of ATT and steroids. Some recently published studies in a small number of patients have also shown dissolution of lesions using thalidomide. [34] It is relevant to mention that robust scientific evidence for the use of some of the above options is lacking, and thus the need for properly conducted large multicenter studies to provide guidelines for better treatment of these patients cannot be emphasized. C2. Tuberculous vasculitis and strokeThe poor result from TBM mainly reflects the extent of ischemic damage to the brain as a result of inflammation, necrosis and thrombosis of blood vessels involved in meningovasculitis. The most common clinical manifestation of TBM-related stroke is hemiplegia, which is more common in young children than in adults, and in patients with advanced disease, which had been highlighted by Dastur et al. [5] No adjunct therapy has consistently reduced the incidence of stroke or altered the course of hemiplegia in TBM. Corticosteroids did not significantly affect the number of new infarctions seen on CT or MRI, or the extent of residual hemiplegia in children or adults. [8] Only aspirin can help reduce the incidence of stroke, but its role must be confirmed in larger studies. [35] C3. Surgical management of hydrocephalus The mainstay in the management of TBM with hydrocephalus is CSF diversion. Surgical management can be planned according to the Vellore grade at the presentation [Table 2]. Grade I patients can be monitored for medical treatment, but early surgery has shown a better result. Grade II patients definitely show improvement in early surgery. Some authors have advocated for a short period of external ventricular drainage (EVD) before shunt surgery in Class III patients, but direct shunt surgery is better. An EVD is recommended for grade IV patients followed by the installation of a CSF diversion in the form of a shunt in only those patients who have shown an improvement after installing an EVD. [36] However, some authors have found a good result in 20% of Grade IV patients who have undergone shunt surgery without the installation of a previous EVD. [37] In the above context, it is important to note that while previous studies[38] showed 100% mortality in Grade IV hydrocephalus, a recent study[37] found a mortality rate of 60% in stage IV hydrocephalus. Lower mortality in this study was attributed to an early shunt surgery in addition to the institution of ATT, steroids and supportive care. Table 2: Modified Vellore Grading SystemClick here to showNew, more and more interest has been generated in endoscopic CSF diversion procedures for TBM. The endoscopic third ventriculostomy (ETV) is not a preferred procedure in hydrocephalus, at least theoretically, as it is usually of an communicative type in TBM. however, there are several reports of the use of ETV in hydrocephalus due to TBM. The success rate for ETV is reported to range from 68% to 77% in patients in various studies. The experience of a surgeon well versed in endoscopic procedures determines the success rate, as TBM exudates and scarring cause difficulty recognizing the anatomical landmarks on the floor of the third ventricle, thereby inhibiting efforts to perform a successful third ventriculostomy. Patients with a longer duration of symptoms and those who have received at least four weeks of ATT are more likely to benefit from ETV. [39] An early diagnosis and an early start to antituberculous treatment in a suspected case of TBM save lives. A high index of suspicion in patients with a meningitis syndrome of more than a 5-day duration, especially in endemic regions, is fundamental to the diagnosis of TBM. TBM is a paucibacillary disease; Therefore, the conventional Ziehl Neelsen staining of the CSF sample is usually negative. The use of newer modalities such as MGIT BACTEC and Xpert MTB/RIF has improved sensitivity to more than 50% in a few series. Nucleic acid amplification techniques such as multiplex PCR have improved sensitivity to 80% in some series, but are not readily available. A negative Xpert MTB/RIF does not exclude TBM. Isolation of Mycobacterium should be tested in each patient by each available method, both to confirm the diagnosis and to determine drug sensitivity. Evidence of tuberculosis elsewhere in the body is present in most cases of TBM. Therefore, all efforts should be carried out to check for signs of TB of other organs such as lung, lymph nodes, adrenal glands, gastrointestinal tract, genitourinary tract, etc., by a thorough clinical and radiological examination (including a chest X-ray, WHOLE BODY CT scan and even an entire body PET CT, where facilities are available). In Professor Dastur's series of autopsies, a combination of basal exudates, hydrocephalus, border zone encephalitis and parenchymale tuberculomas was characterized by TBM. Radiological signs of this combination in a patient with fever encephalopathy are almost diagnostic of TBM, especially in endemic countries. Evidence of other findings on imaging such as opto-chiasmatic arachnoiditis, spinal arachnoiditis and vasculating infarctions also favors the diagnosis of TBM. Treatment should be started early, preferably before neurological deterioration. Isoniazid, rifampicin and pyrazinamide are the main ingredients of the treatment regimen and should be used whenever possible. An interruption of treatment in the intensive phase of treatment increases the risk of death. Patients can deteriorate despite initial treatment, due to the presence of a paradoxical response. This is the consequence of increased immunological response, resulting in progressive fibrosis and arachnoiditis, which causes an increase in the size of the tuberculoma or the appearance of new tuberculomas and exudates, with an increase in the severity of the brain This can lead to sudden deterioration in a patient who initially responded well to treatment. This situation does not guarantee escalation of ATT or the start of other line processing. Anecdotal reports have suggested the use of high-dose steroids (including pulses of intravenous methylprednisolone), thalidomide and even immunodepremtic drugs to reduce inflammatory response related harm. Increased intracranial pressure due to hydrocephalus is a major challenge. Early CSF diversion in shunt surgery gives a better result in patients with TBM with hydrocephalus. Financial support and sponsorshipNil.Conflicts of interestAutorer declares that they have no conflict of interest. They have no source of funding. [Additional file 1] 1.Ruhrah J. The story of tuberculous meningitis. With Library Hist J 1904;2:160-5. 2.Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: Estimated incidence, prevalence and mortality by country. WHO monitoring and monitoring project. JAMA 1999;282:677-86. 3.WHO. Global tuberculosis control: WHO report 2016. Report. Geneva: World Health Organization, 2016. 4.Modi M, Sharma K, Prabhakar S, Goyal MG, Takkar A, Sharma N, et al. Clinical and radiological predictors of outcomes in tubercular meningitis: A prospective study of 209 patients. Clin Neurol Neurosurg 2017;161:29-34. 5.Dastur DK, Lalitha VS, Udani PM, Parekh U. Brain and meninges in tuberculous meningitis – Coarse pathology in 100 cases and pathogenesis. Neurol India 1970;18:86-100. 6.Medical Research Council Streptomycin in tuberculosis trials committee. Streptomycin treatment of tuberculosis meningitis. Lancet 1948;2:582-97. 7.Gupta RK, Kathuria MK, Pradhan S. Magnetization transmit MR imaging in CNS tuberculosis. Am J Neuroradiol 1999;20:867-75. 8.Thwaites GE, Nguyen DB, Nguyen HD, Quy HT. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. In 2004, 100,000 people were discharged. 9.Marais S, Thwaites G, Schoeman JF, Torok ME, Misra UK, Prasad K, et al. Tuberculous meningitis: A uniform case definition for use in clinical research. Lancet Infect Dis 2010;10:803-12. 10.Udani PM, Dastur DK. Tuberculous encephalopathy with and without meningitis: clinical characteristics and pathological correlation. J Neurol Sci 1970;10:541-61. 11.Ahuja GK, Mohan KK, Prasad K, Behari M. Diagnostic criteria for TBM and their validation. Tuber Lung Dis 1994;75:149-52. 12.Sharma S, Goyal MK, Sharma K, Modi M, Sharma M, Khandelwal N, et al. Cytokines play a role in the pathogenesis of tuberculous meningitis: A prospective study from a higher care center in India. J Neurol Sci 2017;39:131-6. 13.Garg RK. Tuberculosis of the central nervous system. Postgrad Med J 1999;75:133-40. 14.Sharma K, Sharma M, Singh S, Modi M, Sharma A, Ray P, et al. Real-time PCR followed by analysis of high-resolution melting curve: A quick and pragmatic approach for screening multidrug-resistant extrapulmonary Tuberculosis 2017;106:56-61. 15.Koh W, Ko Y, Kim C, Park KS, Lee NY. Rapid diagnosis of tuberculosis and multidrug resistance using a MGIT 960 system. Ann Lab Med 2012;32:264-9. 16.Sharma K, Appannanavar SB, Modi M, Singh M, Sharma A, Varma S. Role multiplex polymerase chain reaction using IS6110 and Protein b for diagnosing additional lung tuberculosis: northern India. Indian J Pathol Microbiol. 2015;58:27-30. 17.Sharma K, Sharma A, Singh M, Ray P, Dandora R, Sharma SK, et al. Evaluation of PCR using Protein b primers for rapid diagnosis of tuberculous meningitis. Neurol India 2010;58:727-31. [PUBMED] [Full Text] 18.Sharma K, Modi M, Kaur H, Sharma A, Ray P, Varma S. rpoB gene high resolution melting curve analysis: A quick approach for the diagnosis and screening of drug resistance in tuberkuless meningitis. Diagn Microbiol Infect Dis 2015;83:144-9. 19.Modi M, Sharma K, Sharma M, Sharma A, Sharma N, Ray P, et al. Multi targeted loop-mediated isothermal reinforcement (LAMP) for rapid diagnosis of tuberculous meningitis. Int J TB Lung Ds 2016;20:625-30. 20.Evans CA. GeneXpert - a game-changer for tuberculosis control? PLoS Med 2011;8:e1001064. 21.Nhu NT, Heemskerk D, Thu do DA, Chau TT, Mai NT, Nghia HD, et al. Evaluation of GeneXpert MTB/RIF for the diagnosis of tuberculous meningitis. J Clin Microbiol 2013;52:226-33. 22.Donald PR. Cerebrospinal fluid concentrations of antituberculosis agents in adults and children. Tuberculosis (Edinb) 2010; 90:279-92. 23.Jullien S, Ryan H, Modi M, Bhatia R. Short course vs long-term course antituberculous treatment in tuberculous meningitis. Cochrane Library 2016;9:CD012091. 24.Donald PR, Schoeman JF, Van zyl LE, De Villiers JN, Pretorius M, Springer P. Intensive short course chemotherapy in the management of tuberculous meningitis. Int J Tub Lung Ds 1998;2:704-11. 25.American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America: Treatment of Tuberculosis. Am J Respir Crit Care Med 2003;167:603-62. 26.Ruslami R, Ganiem AR, Dian S, Apriani L, Achmad TH, van der Ven AJ, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled Phase 2 study. Lancet Infect Dis 2012;13:27-35. 27.Heemskerk AD, Bang ND, Mai NTH, Chau TTH, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. N Eng J Med 2016;374:124-34. 28.Thwaites GE, Lan NT, Dung NH, Quy HT, Oanh DT, Thoa NT, et al. Effect of antituberculosis drug resistance to response to treatment and outcome in adults with tuberculous meningitis. J Infect Dis 2005;192:79-88. 29.WHO. Multidrug and comprehensive drug-resistant TB (M/XDR-TB) 2010 global report on monitoring and response. Report. Geneva, Switzerland: World Health Organization; 2010. Report no.: ISBN 978 92 4 159919 1. 30.Tho DQ, Torok ME, Yen NT, Bang ND, Lan NT, Kiet VS, et al. Influence of antituberculosis drug resistance and Mycobacterium tuberculosis lineage on associated tuberculous meningitis. Antimicrob Agents Chemovel 2012;56:3074-9. 31.Sharma K, Verma R, Advani R, Chatterjee O, Solanki HS, Sharma A, et al. Entire genome sequencing of mycobacteria tuberculosis isolates from extrapulmonary sites. OMICS 2017;21:413-42. 32.Tho DQ, Torok ME, Yen NT, Bang ND, Lan NT, Kiet VS, et al. Influence of antituberculosis drug resistance and mycobacterium tuberculosis lineage on the outcome of HIV-associated tuberculous meningitis. Antimicrob Agents Chemovel 2012;56:3074-9. 33.Smith H. Paradoxical reactions during chemotherapy of tuberculosis. J Infect 1987;15:1-3. 34.Keddie S, Bharambe V, Jayakumar A, et al. Clinical perspectives on the use of thalidomide for central nervous system tuberculosis. Eur J Neurol 2018;25: . 35.Misra UK, Kalita J, Maurya PK. Stroke in tuberculous meningitis. J Neurol Sci 2011;303:22-30. 36.Mathew JM, Rajshekhar V, Chandy MJ. Shunt surgery for patients of poor grade with tuberculous meningitis and hydrocephalus: Effect of response to external ventricular drainage and other factors on long-term outcome. J Neurol Neurosurg Psychiatry 1998;65:115-8. 37.Savardekar A, Chatterji D, Singhi S, Mohindra S, Gupta S, Chhabra R. The role of ventriculoperitoneal shunt placement in patients with tubercular meningitis with hydrocephalus in poor neurological grade: A prospective study in the paediatric population and review of literature. Childs Nerv Syst 2013;29:719-25. 38.Palur R, Rajshekhar V, Chandy MJ, Joseph T, Abraham J. Shunt surgery for hydrocephalous in tubercular meningitis: A long-term follow-up study. J Neurosurg 1991;74:64-9. 39.Chugh A, Husain M, Gupta RK, Ojha BK, Chandra A, Rastogi M. Surgical outcome of tuberculous meningitis hydrocephalus treated by endoscopic third ventriculostomy: Prognostic factors and postoperative neuroimaging for functional assessment of ventriculostomy. J Neurosurg Pediatr 2009;3:371-77. [Figure 1], [Figure 2], [Figure 3], [Figure 4], [Figure 5], [Figure 6], [Figure 7] [Table 1], [Table 2] 2]