

Review Article

Tubercular Meningitis in Children: An Update

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Introduction:

Central nervous system (CNS) tuberculosis (TB) accounts for approximately 1% of all of disease caused by *Mycobacterium tuberculosis* but kills and disables more sufferers than any other form of tuberculosis. Tubercular meningitis (TBM) is the most common form of CNS tuberculosis which causes substantial morbidity and mortality in adults and children. The worldwide prevalence of TB in children is difficult to assess because data are scarce and poorly organized. The available reports grossly underestimate the true incidence. The developing world has 1.3 million cases of TB and 40,000 TB-related deaths annually among children younger than 15 years. In these countries, 10-20% of people who die of TB are children. TBM complicates approximately 1 of every 300 untreated primary TB infections.¹ Early diagnosis and treatment is very important as if treated early, most patients recover completely, but if the disease progress untreated, death and disability are very common despite microbiological cure.² The diagnosis and management of TBM challenges physicians throughout the world. This article is

targeted to discuss about the update of clinical characteristics, investigations and treatment of TBM.

Clinical Manifestations

TBM is a disease of young children with 40% patients under 2 years of age and 70% under 5 years at the time of presentation.¹ The clinical presentation of TBM is non-specific, especially in the early stages of disease. Most patients present with a vague ill health lasting 2-8 weeks prior to the development of meningeal irritation. These nonspecific symptoms include malaise, anorexia, fatigue, fever, myalgias and headache. Children with TBM often present with neck stiffness, seizure and abdominal symptoms such as nausea and vomiting. The neurological picture is mostly the result of combined effect of increased intracranial pressure and infarction.² A history of contact is identified in approximately 50 to 60% of children. A close association with disseminated tuberculosis is seen in pediatric age. Cranial nerve palsies occur in 20-30% of patients. The sixth cranial nerve is most commonly affected. Vision loss due to optic nerve involvement may occasionally be a dominant presenting illness. Ophthalmoscopic examination may reveal papilloedema and choroid tubercle.^{3,4}

Table-I

*Consensus tuberculous meningitis diagnosis*⁵

Clinical entry criteria

- Symptoms and signs of meningitis including one or more of the following: headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy.

Tuberculous meningitis classification

Definite tuberculous meningitis

- Patients should fulfill criterion A or B:

A) Clinical entry criteria plus one or more of the following: acid-fast bacilli seen in the CSF; *Mycobacterium tuberculosis* cultured from the CSF; or a CSF positive commercial nucleic acid amplification test.

B) Acid-fast bacilli seen in the context of histological changes consistent with tuberculosis in the brain or spinal cord with suggestive symptoms or signs and CSF changes, or visible meningitis (on autopsy).

Probable tuberculous meningitis

- Clinical entry criteria plus a total diagnostic score of **10 or more points** (when cerebral imaging is not available) or **12 or more points** (when cerebral imaging is available) plus exclusion of alternative diagnoses. At least 2 points should either come from CSF or cerebral imaging criteria.

Possible tuberculous meningitis

- Clinical entry criteria plus a total diagnostic score of **6-9 points** (when cerebral imaging is not available) or **6-11 points** (when cerebral imaging is available) plus exclusion of alternative diagnoses. Possible tuberculosis cannot be diagnosed or excluded without doing a lumbar puncture or cerebral imaging.

Not tuberculous meningitis

- Alternative diagnosis established, without a definitive diagnosis of tuberculous meningitis or other convincing signs of dual disease.

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Table-II

Diagnostic criteria for classification of definite, probable, possible, and not tuberculous meningitis ⁵

Clinical criteria (Maximum category score=6)	
Symptom duration of more than 5 days	: 4
Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks	: 2
History of recent (within past year) close contact with an individual with pulmonary tuberculosis or a positive TST or IGRA (only in children <10 years of age)	: 2
Focal neurological deficit (excluding cranial nerve palsies)	: 1
Cranial nerve palsy	: 1
Altered consciousness	: 1
CSF criteria (Maximum category score=4)	
Clear appearance	: 1
Cells: 10–500 per μ l	: 1
Lymphocytic predominance (>50%)	: 1
Protein concentration greater than 1 g/L	: 1
CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2.2mmol/L	: 1
Cerebral imaging criteria (Maximum category score=6)	
Hydrocephalus	: 1
Basal meningeal enhancement	: 2
Tuberculoma	: 2
Infarct	: 1
Pre-contrast basal hyperdensity	: 2
Evidence of tuberculosis elsewhere (Maximum category score=4)	
Chest radiograph suggestive of active tuberculosis: signs of tuberculosis=2; miliary tuberculosis=4	2/4
CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS	: 2
• AFB identified or <i>Mycobacterium tuberculosis</i> cultured from another source—ie, sputum, lymph node, gastric washing, urine, blood culture	: 4
• Positive commercial <i>M tuberculosis</i> NAAT from extra-neural specimen	: 4

TST=tuberculin skin test. IGRA=interferon-gamma release assay. NAAT=nucleic acid amplification test. AFB=acid-fast bacilli.

Table-III

Comparison of the presenting clinical variables independently predictive of tuberculous meningitis in five published studies ⁶

Study	Kumar et al, 1999 India	Youssef et al, 2006 Egypt	Thwaites et al, 2002 Vietnam	Moghtaderi et al, 2009 Iran
Age group	Children (1 month-12 year)	Children and adult (5 months to 56 year)	Adults (16- 70 years)	Older children and adults (9-80 years)
Variables predictive of tuberculous meningitis	History of illness > 6 days CSF lymphocytes > 50% of total white cells Optic atrophy Abnormal movement Focal neurological deficit	History of illness > 5 days CSF lymphocytes > 30% of total white cells CSF white cell < 1000 Clear CSF CSF protein > 100 mg/dl	History of illness \geq 6 days CSF lymphocytes \geq 10% of total white cells CSF white cell < 750 Age < 36 years Total WBC of blood < 15000/cu mm	History of illness > 5 days CSF lymphocytes > 70% of total white cells CSF white cell < 1000/HPF Age > 30 years

Staging: Outcome of TBM relates closely to the stage of disease at the time treatment is begun. Apart from having prognostic value in the individual patient, staging is also important when treatment modalities in different studies are compared. The British Medical Research Council introduced a three-stage classification system in 1948. During the 1970s this staging was modified to include the Glasgow Coma Scale (GCS) and more recently 'refined' to improve prognostic accuracy. The refined MRC scale is as follows.

Stage 1: GCS score of 15/15 with no focal neurological sign.

Stage 2a: GCS score of 15 with no neurological deficit or a GCS score of 13-14 with or without neurological deficit

Stage 2b: GCS score of 10-12 with or without neurological deficit

Stage 3: GCS score <10. ²

Investigation:

The diagnosis of TBM can be difficult. Most important is CSF study. In this section we will discuss how the conventional and advanced investigations help in the diagnosis of TBM.

CSF study: Characteristic CSF findings of TBM include the following : (i) lymphocytic-predominant pleiocytosis. Total white cell counts are usually between 100 and 500 cells/ μ L. Very early in the disease, lower counts and neutrophil predominance may be present, (ii) elevated protein levels, typically between 100 and 500 mg/dL, (iii) low glucose, usually less than 45mg/dL or CSF: plasma ratio <0.5. ⁶ Atypical CSF findings have been described, including normal CSF glucose, protein, cell count, or a neutrophil predominance. Rare cases of culture-proven TBM with no other CSF abnormalities have also been reported. ⁷

AFB staining: Definitive diagnosis of TBM depends upon the detection of the tubercle bacilli in the CSF, either by smear examination or by bacterial culture. Standard staining techniques are Ziehl-Neelsen, Kinyoun, or auramine-rhodamine. These can detect approximately 100 AFB/ml of CSF. ² The ZN stain is a faster method of diagnosis but a single sample has low sensitivity, on the order of 20%–40%. Several daily large volume (10–15 mL) lumbar punctures are often needed for microbiologic diagnosis; sensitivity

increases to >85% when four spinal taps are performed. ³

Culture: The gold standard for the diagnosis of TBM is the growth of *M. tuberculosis* from the CSF, but 4 to 8 weeks are required for cultures to become positive and up to 45% of patients with presumed TBM have negative CSF cultures. There is a variety of culture media used which include egg-based (Löwenstein-Jensen-LJ, Petragnani, American Trudeau Society, and Ogawa), agar-based (Middlebrook 7H10 and 7H11) and liquid media (Middlebrook 7H9, Kirchner, BioFM and Dubos). Due to the slow growth of the organism (40 to 60 days), this exam is useful only from an epidemiological point of view. The BACTEC radiometric method has been used for several years for rapid isolation of bacteria. Recently, the BACTEC method has been used for the isolation of *M. tuberculosis* in CSF specimens. Studies have demonstrated several advantages of using the method, including higher yield and more rapid isolation of *M. tuberculosis*. The time required for isolating *bacteria* is average 15 days. ^{8,9}

ADA: CSF Adenosine Deaminase activity (ADA) is a marker of cell-mediated immunity. It was found that ADA values less than 4 U/L excludes TBM and greater than 8 U/L are suggestive of TBM. CSF ADA \geq 10 U/L has >90% sensitivity and specificity of diagnosing TBM. However, false-positive ADA can be found in patients infected with HIV, cryptococcal meningitis, lymphomatous meningitis, and cytomegalovirus disease. ^{10,11} Thus it is not recommended as a routine diagnostic test for TBM.

NAA: Commercial nucleic acid amplification (NAA) assay can confirm TBM (specificity 98%) but cannot rule it out (sensitivity 56%). ² The sensitivity of CSF microscopy and culture falls rapidly after the start of treatment, whereas mycobacterial DNA may remain detectable within the CSF until one month after the start of treatment. So because of its high specificity, a positive NAA test is regarded as a definitive test in patients with suspected TBM, and offers particular value in patients who have previously received treatment. ¹²

Xpert MTB/RIF assay: The Xpert MTB/RIF is a new fully automated diagnostic molecular test that simultaneously detects the presence of multidrug resistant tuberculosis (MTB) and rifampicin resistance in specimens, using nested real-time (sensitivity 67-85%, specificity 94-98%). The advantages are the ease of use for inexperienced staff and rapid turnover

time (about 2 h). Its ability to detect rifampicin resistance within 2 h may lead to an important improvement in the management of Multidrug resistant TB (MDR-TB). The World Health Organization (WHO) has recently endorsed the implementation of the Xpert MTB/RIF assay for national tuberculosis programmes in developing countries.¹³

MT: The result of the tuberculin skin test for the diagnosis of tuberculosis varies according to age, vaccination with BCG, nutritional status, HIV infection, and technique of administration.¹⁴ Additionally, a positive tuberculin skin test does not differentiate M tuberculosis infection (which is a common event in tuberculosis endemic areas) from active disease. The diagnostic utility of skin testing being positive for CNS tuberculosis varies from 10-50%.^{2,15}

Other immunological tests available are interferon gamma release assay (IGRA), ELISA etc. Pretreatment peripheral blood INF- γ enzyme-linked immunospot (ELISPOT) response has not shown any advantage over conventional bacteriological diagnosis in adults but has not been evaluated in children.² A systematic review of commercially available antibody detection concluded that such tests have no role in the diagnosis of extrapulmonary tuberculosis.¹⁶

A complete blood count should be performed, and the erythrocyte sedimentation rate should be determined. Blood count show leukopenia and/or normal WBC count, but leukocytosis and neutrophilia have been reported in some patients with TBM. There may elevated ESR. The serum glucose level should be measured; this value is a useful comparison with the glucose level measured in the CSF. In addition to this, serum electrolyte, liver function test and renal function test should be done which may show hypernatraemia due to development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in about 45%.¹⁷

Neuroimaging: Neuroimaging is very important in diagnosis of TBM. Cranial computerized tomography (CT) and more recently MRI are extremely helpful in diagnosing and managing TBM and its complications.¹⁸ Classic CT triad of TBM consists of basal meningovascular enhancement, obstructive hydrocephalus and cerebral infarction, most commonly of the basal ganglia. One study found that combination of hydrocephalus, basal enhancement and infarction is 100% specific and 41% sensitive for the diagnosis of childhood TBM. although the authors suggested pre-contrast hyperdensity in the basal cisterns as the best predictor of TBM.^{19,20}

Magnetic resonance imaging (MRI) is the imaging test of choice for visualizing abnormalities associated with TBM. It shows diffuse, thick, meningeal enhancement. Contrast enhanced MRI is generally considered as the modality of choice. It is useful for assessment of the location of lesions and their margins, as well as ventriculitis, meningitis and spinal involvement (sensitivity 86%, specificity 90%). The T2-weighted MRI imaging has been shown to be particularly good at demonstrating brainstem pathology; diffusion-weighted imaging (DWI) is best at detection of acute cerebral infarcts due to TBM. Tuberculoma is best evaluated in MRI. The appearance of a solid caseous tuberculoma is that of an isointense or mildly hyperintense brain lesion with marked surrounding low density that demonstrates vasogenic oedema. Marked rim enhancement is always present after contrast administration. A hypointense centre indicates liquefaction and abscess formation.² Tuberculous abscesses are larger than tuberculomas (often >3 cm in diameter), solitary, thin walled, and often multiloculated.²¹ DWI in tuberculous abscesses has shown restricted diffusion with low apparent diffusion coefficient (ADC) values, probably a result of the presence of intact inflammatory cells in the pus. Unfortunately these radiological features are not specific for tuberculoma. The differential diagnosis of solid tuberculoma includes toxoplasmosis and cerebral tumours, while cystic tuberculomas cannot be differentiated from pyogenic brain abscess and neurocysticercosis on usual imaging alone.^{2,22}

A large lipid, lactate peak has been used to identify tuberculomas by magnetic resonance spectroscopy (MRS). Serial transcranial doppler ultrasonography (TCD) with blood flow velocity and pulsatility index measurements, can be efficiently utilized to prognosticate outcome in tuberculous meningitis related vasculopathy.²³

Air encephalography is the most reliable way of determining the level of CSF obstruction. If in lateral skull x-ray, air in the basal cistern and lateral ventricles indicates communicating hydrocephalus but air only at the level of basal cistern indicates noncommunicating hydrocephalus.²

Treatment

Antimicrobial therapy: TBM is a medical emergency and treatment should be initiated as soon as the condition is suspected because delay is associated with death and disability. Therefore empiric treatment

should be started as soon as TBM is suspected clinically.² The recommended treatment regimen for presumed drug susceptible TBM consists of two months of daily Isoniazid(INH), Rifampicin(RIF), Pyrazinamide (PZA), and either Streptomycin (SM), or Ethambutol (EMB), followed by 10 months of INH and RIF.²⁴

INH is considered the most critical of the first-line agents due to its excellent CSF penetration and high bactericidal activity. CSF penetration of INH is about 90 to 95%.⁷ While RIF penetrates the CSF less freely (5%–25%). However, the high mortality of TBM due to RIF-resistant strains has confirmed its importance. PZA has excellent penetration into the CSF (95%–100%) and is a key drug in reducing the total treatment time for drug-susceptible TBM. Hence, if PZA cannot be tolerated, the treatment course for TBM should be lengthened to a total of 18 months.⁴

INH kills most of the rapidly replicating bacilli in the first 2 weeks of treatment, with some additional help from SM and EMB. Thereafter, RIF and PZA become important because they “sterilize” lesions by killing organisms; RIF kills low or non-replicating organisms and PZA kills those in sites hostile to the penetration and action of the other drugs.⁴

The 4th drug: There are no data from controlled trials to guide choice of the fourth drug. Most authorities recommend either Streptomycin or ethambutol, although neither penetrates the CSF well in the absence of inflammation, and both can produce significant adverse reactions. SM should not be given to those who are pregnant or have renal impairment and resistance is relatively common worldwide. While EMB- induced optic neuropathy is a concern, especially when treating comatose patients, although at the standard dose of 15 - 20 mg/kg, the incidence is less than 3%.²⁵

The British Thoracic Society (BTS), the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS) acknowledge the scarcity of evidence from controlled trials regarding the choice of the fourth drug in the intensive phase. The BTS recommend streptomycin or ethambutol while the IDSA/ATS favor ethambutol,^{3,24} So, treatment should best be started with INH, RIF, and PZA. The addition of a fourth drug is left to the choice of the local physicians and their experience, with little evidence to support the use of one over the other.

Some researchers advocate ethionamide, particularly in South Africa. Ethionamide penetrates healthy and inflamed meninges, but can cause severe nausea and vomiting.²⁵

Duration: Evidence concerning the duration of treatment is conflicting. The duration of conventional therapy is 6-9 months, although some investigators still recommend as many as 24 months of therapy. In the national guideline of Bangladesh for treatment of tuberculosis in children, the recommended duration is 12 month.²⁶ WHO recommendation for duration is 12 months.²⁷ Recently, in a study it has been shown that short course intensified treatment (6 months INH, RIF, PZA, Ethambutol for HIV uninfected and 9 months for HIV infected patients) is safe for drug susceptible cases.^{28,29}

Table-V
First-line treatment regimens for tuberculous meningitis in children WHO and UK recommendations²⁸

Antituberculosis drugs	Daily dose in children	Duration
Isoniazid	10–20 mg/kg (maximum 500 mg)	12 months
Rifampicin	10–20 mg/kg (maximum 600 mg)	12 months
Pyrazinamide	15–30 mg/kg (maximum 2 g)	2 months
Ethambutol	15–20 mg/kg (maximum 1 g)	2 months

Table-V
National Guideline(Bangladesh) for treatment of TBM²⁶

Drug	Daily dose and range (mg per kg body weight)	Duration
Isoniazid (H)	10 (5-15) [maximum 300mg]	12 months
Rifampicin (R)	15 (10-20) [maximum 600mg]	12 months
Pyrazinamide (Z)	35 (30-40) [maximum 2000mg]	2 months
Streptomycin (S)	15 (12-18) [maximum 1000mg]	2 months

Corticosteroids: Adjunctive corticosteroid increases the survival of patients, improve symptom and seizure control and reduce tuberculoma size and peri-lesional

oedema. One possible explanation for the survival benefit is that the anti-inflammatory effects of corticosteroids reduce the number of severe adverse events (9.5% versus 16%), particularly hepatitis. Since there are no controlled trials comparing corticosteroid regimens, treatment choice should be based on those found to be effective in published trials. One recommended regimen for severe TBM is intravenous dexamethasone for four weeks (1 week each of 0.4mg/kg/day, 0.3 mg/kg/day, 0.2mg/kg/day, and 0.1 mg/kg/day followed by four weeks of tapering oral dexamethasone therapy .³⁰ WHO recommendation is dexamethasone 0.6mg/kg/day intravenous initially and then orally. It is recommended to reduce the dose weekly to stop over 6-8 weeks.²⁸ Oral prednisolone can also be given as adjunctive therapy at the dose of 2mg/kg/day for six weeks.²⁶

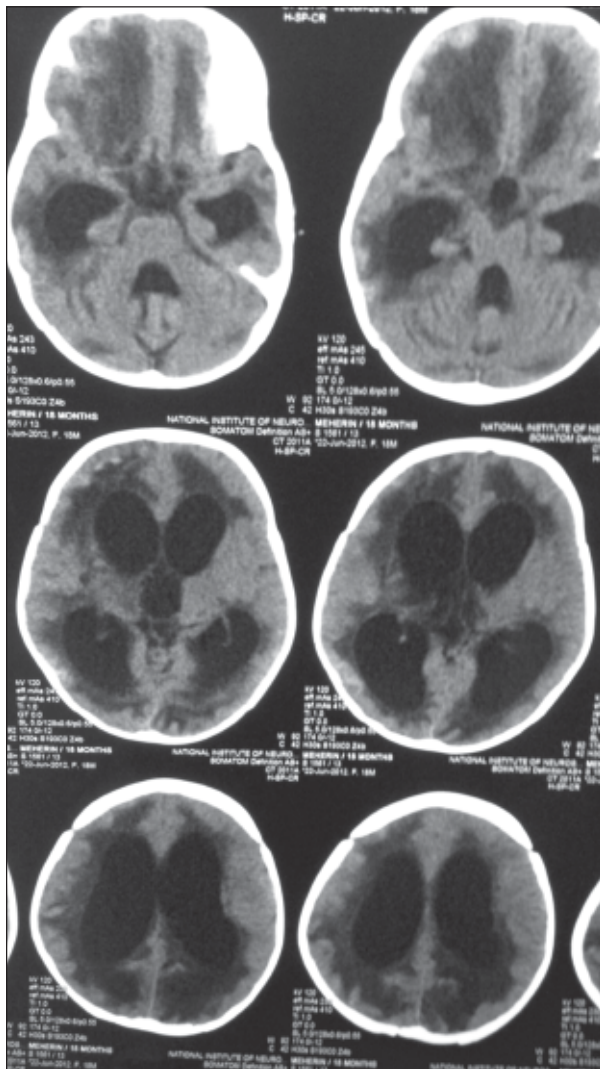


Fig-1: CT scan of brain showing communicating hydrocephalus in a case of Tubercular Meningitis

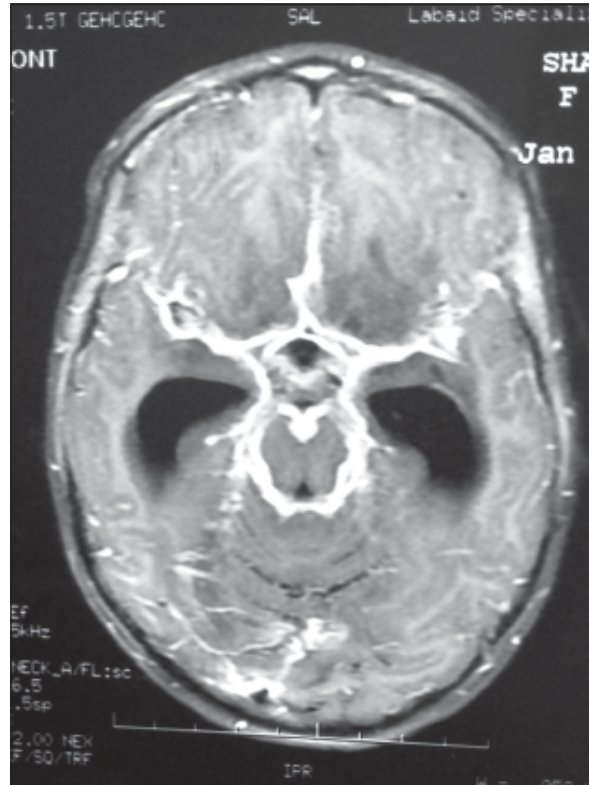


Fig- 2: MRI of Brain showing basal cistern enhancement i on contrast enhanced T1-W image in case of TBM

MDR TBM: TBM resistant to INH and RIF is described as MDR . No controlled trials have been published for the treatment of MDR TBM. Clinicians of patients with MDR-TBM are left to extrapolate from guidelines for the treatment of pulmonary MDR-TB. The World Health Organization recommends for pulmonary MDR-TB the use of a minimum of four agents to which the *M. tuberculosis* strain has known or suspected susceptibility including use of any first-line oral agents to which the strain remains susceptible, an injectable agent (i.e., an aminoglycoside or capreomycin), a FQN, and then adding other second-line agents as needed for a total of at least four drugs.²⁷

Role of other drugs: Ischemic brain damage is the most important reason for the permanent neurological sequelae in TBM. Aspirin is used in this cases due to antithrombotic , anti-ischemic and anti-inflammatory properties . However, in adult Aspirin showed significant reduction in mortality at 3 month while in children it showed no significant improvement in mortality and morbidity at 6 months.^{31,32} Another drug is **Thalidomide** which is an immunomodulatory agent. In two case series of tuberculomas and

tubercular abscess and blindness due to optic arachnoiditis showed dramatic clinical and neuroradiological improvement after low dose of thalidomide. However, caution should be taken as it produces serious side effects.³² **Fluoroquinolones** could represent highly effective fourth drugs and are an essential component of treatment regimens for multidrug-resistant cases. **Vitamin D** supplementation may play role in TBM as in few studies it has been seen that there is an association between tuberculous meningitis and low sunshine hours 3 months before disease. It suggests a possible role for low vitamin D in bacterial dissemination.²⁸

Fluid Management in TBM: Hyponatraemia is common in TBM and has been related to stage of disease, cerebral perfusion pressure and clinical outcome. It may result from syndrome of inappropriate ADH (SIADH) or cerebral salt wasting (CSWS). Patients with SIADH are euvolaemic or hypervolaemic and need fluid restriction while CSWS is associated with hypovolaemia and requires fluid replacement. A positive fluid balance in TBM is important as there is risk of stroke. In addition diuretic treatment of hydrocephalus should be initiated only once the patient's hydration status has normalized.²

Conclusion: TBM is a devastating disease. Despite undeniable advances in the investigation in recent years, most of the problems that pediatricians and neurologists face have been solved by the uniform definition of TBM. Still some challenges are yet to solve. Most important are consensus regarding the 4th drug and MDR TBM treatment. Therefore, new studies in children are urgently suggested. In the meantime, when treating a child with suspected TBM, the most aggressive attitude is to be used both for diagnosis and for therapy.

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