Chapter

Hydrocephalus in Tuberculous Meningitis

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Abstract

Hydrocephalus is a frequent complication of tuberculous meningitis. We present the incidence of hydrocephalus in patients diagnosed with tuberculosis of the nervous system, the therapeutic possibilities and the evolution of these patients. A consensus definition for tuberculous meningitis (TBM) stratified the cases as definite, probable and possible. In various studies, radiological investigations (CT, MRI) can be normal in the initial stages of the disease in approximately 30% of cases, but they do not exclude the possibility of a TBM. The most common radiological changes found in TBM are communicating hydrocephalus (up to 80% of cases), increased basal contrast (50%), cerebral tuberculomas (30%) and cerebral infarcts (10–40%). MRI has been shown to be more sensitive than a CT scan for diagnosed TBM. Communicating hydrocephalus is among the short-term complications of TBM (approximately 80% of cases), being more frequent than non-communicating ones. In these cases, the need to perform a ventriculo-peritoneal unit must be taken into account. Long-term complications are cognitive impairment, epilepsy, stroke, hydrocephalus, myelitis, damage to the hypothalamus or the pituitary gland manifested by obesity, growth disorders and diabetes insipidus. Sequels may occur frequently in TBM such as dementia, epilepsy, neurological deficits, behavioral disorders, blindness and deafness.

Keywords: hydrocephalus, meningitis, tuberculosis, short-term complications, long-term complications

1. Introduction

Tuberculous meningitis is an infection of the leptomeninge caused by *Mycobacterium tuberculosis* and represents one of the three forms of tuberculosis located in the central nervous system, along with tuberculoma and spinal arachnoiditis [1]. It is estimated that 2 billion of the planet's inhabitants are infected with *Mycobacterium tuberculosis*, and 10% of them develop various forms of active tuberculosis. Tuberculous meningitis (TBM) represents 1% of all forms of tuberculosis and 5% of forms of extrapulmonary tuberculosis (**Figure 1**) [2].

The etiological diagnosis of TBM continues to represent a real challenge for the clinician, despite the progress made in the diagnosis of *M. tuberculosis* infection. Modern diagnostic methods, based on molecular biology techniques and gamma

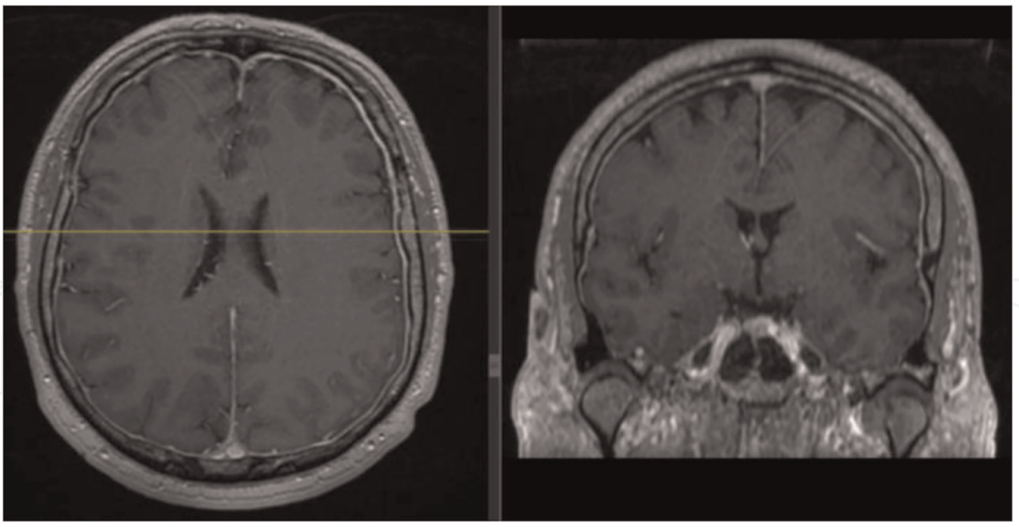

Figure 1.
Axial and coronal contrast-enhanced T1-weighted MRI showing tuberculous meningitis (leptomeningeal enhancement) (courtesy Dr. Bogdan Dobrovat).

interferon release tests, have substantially improved TBM prognosis, although the gold standard for diagnosis remains cerebrospinal fluid culture on special media.

TBM complicates 0.3% of untreated TB infections in children, is more common between 6 months and 4 years. The clinical progression of TBM can be rapid or gradual. Rapid progression is more common in infants and young children [3]. Occasionally, TBM occurs many years after infection.

People at increased risk of TBM are also patients with immunodeficiency caused by aging, malnutrition, HIV/AIDS infection and cancer, but also patients under treatment with biological therapies, such as tumor necrosis factor alpha (TNFα) antagonists [4].

TBM is the most severe form of extrapulmonary tuberculosis (TB), diagnosis remains difficult, and early recognition is crucial for a better prognosis. The mortality rate is high, and sequelae occur frequently in survivors [5]. The optimal treatment has not yet been well established. The increase in the number of TBM cases is also related to the increase in the number of HIV-seropositive patients.

TBM is associated with a multitude of complications such as optochiasmatic and spinal arachnoiditis, tuberculous mass lesion in the brain, periventricular infarcts or hydrocephalus [5, 6]. Among these, hydrocephalus represents a negative predictive factor [5]. Regarding hydrocephalus in patients with TBM, studies have shown that it is found in approximately 80% of children with TBM [3, 7].

Hydrocephalus is one of the most frequent complications of TBM, and its management represents a real challenge for the clinician [8].

2. Pathogenesis

Tuberculosis of the central nervous system in adults is almost always secondary to a latent tuberculosis focus or active pulmonary tuberculosis. In children, TBM is secondary to the primary complex, which disseminates hematogenously in the early stage of evolution, the maximum number of illnesses being recorded in the age group of 1–3 years.

In adults, extraneural tuberculosis foci are represented by miliary, bone, urogenital or serous tuberculosis [9]. The main defensive mechanism of the host that intervenes at the beginning against Mycobacterium tuberculosis is the alternative pathway of complement activation, but once it reaches the CSF the bacteria has every chance to survive because the humoral defense is absent at this level. Two important mechanisms are involved in the immunopathogenesis of tuberculous meningitis: activation of the monocyte/macrophage system and T lymphocytes with the release of cytokines in the CSF; temporary and reversible depression of cellular immunity by decreasing the number of CD4 T lymphocytes, especially in severe forms, independent of immunodeficiency induced by other causes (including HIV infection) [10].

Tuberculous meningitis is a granulomatous meningitis whose main morphopathological aspects are meningeal inflammation with fibrinous exudate and small disseminated tubercles predominantly in the basal cisterns; inflammation of the choroid plexuses and the ventricular and ependymal epithelium (**Figure 2**); inflammation of the cerebral arteries, with the possibility of their secondary thrombosis and the appearance of cerebral microinfarcts. Infarction of small arteries causes symptoms similar to encephalitis; cerebral tuberculomas, with more frequent localization in the brain stem, thalamus and cerebral hemispheres; they behave as expansive intracerebral processes; cerebral edema, of variable degree and extent [9, 10].

In severe forms, severe disorders of CSF hydrodynamics occur, with the consequent appearance of hydrocephalus, both by blocking the aqueduct of Sylvius and the foramen of Lushka, and by decreasing CSF resorption at the level of Pachionii granulations [8, 9]. Due to the accumulation of a large amount of serofibrinous exudate at the base of the brain, compression of the cerebral arteries is also found at this level. The lesions of the choroid plexuses are morphologically identical to those observed in the meninges: fibrin deposits, specific perivascular follicles, obliteration, their fibrous organization leading to cloazonation. One of the consequences of choroid plexites is liquid hypersecretion, the direct consequence of specific exudation. This exudate, as well as the cloazonation, favors the occurrence of internal hydrocephalus, which

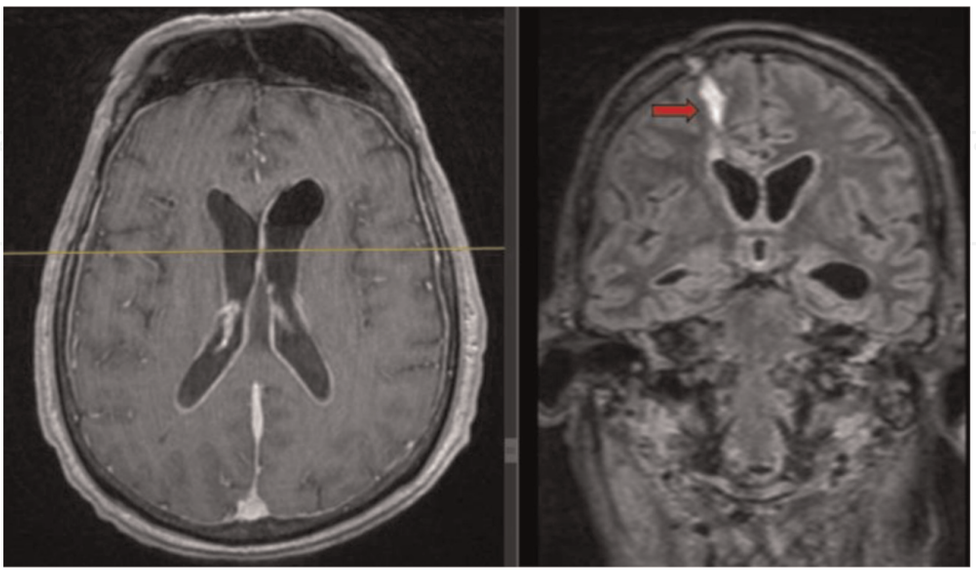

Figure 2.
Axial contrast-enhanced T1-weighted MRI showing tuberculous meningitis (first image). Coronal FLAIR MRI sequence showing postoperative images of an external ventricular drainage in case of tuberculous hydrocephalus. The red arrow marks the place where the external catheter was inserted into the lateral ventricle (the second image) (courtesy Dr. Bogdan Dobrovat).

mainly affects the frontal, temporal and occipital extensions of the ventricles. Arachnoid lesions are mainly located in the basal optochiasmatic region, being responsible for eventual blindness from TBM [9].

3. Clinical characteristics of tuberculous meningitis

Clinical forms of tuberculosis of the central nervous system are represented by

3.1 Intracranial tuberculosis

- Tuberculous meningitis
- Tuberculous meningitis with tuberculous miliary
- Tuberculous encephalopathy
- Tuberculous vasculopathy
- Cerebral tuberculosis
- Cerebral tuberculous abscess.

3.2 Tuberculosis of the spinal central nervous system

- Vertebral tuberculosis with paraplegia
- Tuberculous arachnoiditis
- Spinal meningitis.

Classically, the onset in TBM is insidious (for several weeks), but it can be fulminant in certain cases. A more rapid progression of the disease may occur in young infants in whom symptoms develop only a few days before the onset of acute hydrocephalus, cerebral infarction or seizures.

Clinical manifestations can be divided into three stages, and each stage lasts about 1 week.

3.3 Stage 1 (prodromal stage)

- Lasts 1–2 weeks, consists of non-specific symptoms.
- The child becomes apathetic or irritable, loses interest in playing, has fever, anorexia, vomiting, constipation and weight loss.
- May complain of headache and drowsiness.
- No focal neurological signs.
- Loss or stagnation of developmental stages may occur in children.

3.4 Stage 2—Starts more suddenly

- Signs of meningeal irritation with increased CSF pressure and neck stiffness
- Positive Kernig and Brudzinski signs
- Headache is a cardinal symptom in older children and adults with constant fever.
- Vomiting and constipation can become severe
- Cranial nerve palsies/focal neurological signs
- Lethargy
- Hydrocephalus/Vasculitis
- Some patients have manifestations of encephalitis:
- Disorientation
- Movement disorders
- Speech disorders.

3.5 Stage 3

- Coma sets in quickly
- Irregular high-grade fever and convulsions
- There may be hemiplegia or paraplegia
- Extreme stiffness of the neck, opisthotonus
- Decerebration posture, rigidity
- Deterioration of vital signs, especially the appearance of hypertension
- Death can occur if treatment is started late at this stage.

3.6 Diagnostic categories according to Ogawa (1987)

Confirmed TBM: presence of Koch bacillus in CSF (direct staining, culture) and/or at autopsy
Probable TBM: pleocytosis in CSF, culture negative for bacteria and fungi with one of the following:

- Positive tuberculin test
- Evidence of extra-CNS TB or history of pulmonary TB

- active or significant exposure to TB
- CSF glucose < 40 mg/dL
- CSF proteins > 60 mg/dL [11].

3.7 Diagnostic categories according to Thwaites et al. 2005

Confirmed TBM: Clinical meningitis, abnormal CSF parameters and acid-fast bacilli in CSF (microscopy) and/or positive culture for Mycobacterium tuberculosis.
Probable TBM: Clinical meningitis, abnormal CSF parameters and at least one of the following:

- Suspicion of active pulmonary tuberculosis (chest x-ray)
- BK found in any sample other than CSF.

Possible TBM: Clinical meningitis abnormal CSF parameters and at least 4 of the following:

- History of tuberculosis
- Predominance of lymphocytes in CSF
- Illness lasting > 5 days
- CSF glucose/blood glucose ratio < 0.5
- Alteration of the state of consciousness
- Xanthochromic CSF
- Focal neurological signs [12].

3.8 Classification of tuberculous meningitis

Stage I

- Lack of focal neurological deficit
- Coma score Glasgow 15

Stage II

- Coma Glasgow score 11–14 with focal neurological deficit

Stage III

- Coma Glasgow score 10 or less with or without focal neurological deficit [13].

4. Diagnosis of tuberculous meningitis

The diagnosis of tuberculous meningitis is often a real challenge for the clinician, based in some cases on the clinical aspects and the changes found in the CSF, without bacteriological confirmation. The insidious onset with persistent symptoms for more than 6 days, the presence of neurological manifestations represented by cranial nerve paralysis or peripheral paralysis and the presence of a moderate inflammatory reaction in the CSF are elements that are suggestive for the diagnosis of TBM.

In TBM, the following changes in the cerebrospinal fluid are characteristic:

- pleocytosis, the number of leukocytes is usually between 100 and 500 cells/μL, with a predominance of lymphocytes; at the onset of TBM the number of leukocytes may be lower and neutrophils predominate,
- elevated protein levels, usually between 100 and 500 mg/dL,
- low glucose, usually less than 45 mg/dL or CSF:plasma ratio <0.5 [13].

4.1 CSF examination

- CSF pressure is increased, the color is clear, opalescent or xanthochrome.
- Chloride may be low
- Ziehl–Nelson stained smears can reveal the presence of acid-fast bacilli; they are positive in up to 30% of cases
- CSF culture confirms the diagnosis. The culture is positive in 50–70% of cases, the positive results being related to its volume, it is preferable to collect 5–10 mL of CSF by lumbar puncture [14, 15].
- Antigen detection by polymerase chain reaction (PCR), GeneXpert in CSF and

other useful explorations for the diagnosis of TBM are as follows:

- Immunological tests—the Quantiferon TB Gold blood and CSF test
- Tuberculin intradermoreaction (IDR)—negative in up to 50% of cases
- Cultures of other body fluids can help confirm the diagnosis (pleural fluid, ascites fluid and pericardial fluid)
- Elevated VSH, normal number of leukocytes in the blood with a predominance of lymphocytes;
- The HIV test must be performed in all patients suspected of TBM.
- Gastric lavage in children or sputum examination in adults and older children can reveal tuberculosis bacilli.

- Lymph node biopsy in certain cases to confirm the diagnosis.
- Fundus examination may reveal choroidal tubercles, papillary edema or optic nerve atrophy.

A high index of clinical suspicion is where the patient is in contact with a confirmed case of tuberculosis.

Several studies reveal decreased CSF leukocyte counts and protein levels in HIV-positive patients. CSF examination may even be normal in 5% of HIV-positive patients with TBM [16].

The identification of Mycobacterium tuberculosis in CSF by direct smear or cultures remains the gold standard for confirming TBM, but CSF being a paucibacillary liquid, isolation is only possible in a small number of cases. Moreover, the growth time of the cultures being 3–6 weeks, the diagnosis and the initiation of the treatment can be delayed [14, 17]. For these reasons, the diagnosis of TBM is based in many cases only on the clinical manifestations with slow onset and the neurological signs, associated with the characteristic cytochemical changes in the CSF: moderate inflammatory reaction with a predominance of lymphocytes, low levels of glucose and increased proteins.

The differential diagnosis of TBM is sometimes difficult to make with other forms of meningitis with clear fluid, such as viral meningitis, fungal meningitis, carcinomatous meningitis, partially treated bacterial meningitis, brain abscesses, brucellosis, neurosyphilis and neurosarcoidosis [18]. Meningitis with Cryptococcus neoformans has the same clinical picture and changes in CSF as TBM, but with a delayed evolution (sometimes 2–6 months) and occurs more frequently in immunocompromised people, such as patients with HIV infection [19].

New diagnostic methods of TBM based on the CSF study have been developed to make it more efficient and faster. The BACTEC method allows reducing the time until obtaining a positive culture for M.tuberculosis to 1–3 weeks, and microscopic observed drug susceptibility (MODS) allows the microscopic highlighting of the unique growth characteristics of the Koch bacillus in 5–7 days, also allowing testing simultaneous resistance to antituberculosis medication [20]. Unfortunately, these modern methods are not widely available in all countries.

Nucleic acid amplification (NAA) tests represented by the chain polymerization reaction or M.tuberculosis DNA amplification in CSF ensure a faster diagnosis of TBM, the execution time being 24–48 hours. Being specific, more sensitive and faster than culture, PCR for mycobacteria in CSF constitutes a modern and very useful method in the diagnosis of TBM.

The detection of the IS6110 insertion sequence, used in the initial studies, had a sensitivity between 32–100% and a specificity of 38–100% [21]. Many initial studies conducted to establish the effectiveness of the PCR technique in the detection of M.tuberculosis in CSF used a single target gene, which can cause false negative results. Currently, the multiplex-PCR technique is used, which targets and simultaneously amplifies several genes, such as protein antigen B, MBP64 and IS6110. According to some studies, the sensitivity of this technique is 94.4%, and the specificity is 100% [22].

The Gene Xpert MTB/RIF method is an RT-PCR technique used for the simultaneous detection of M.tuberculosis and sensitivity to rifampicin. It is a quick diagnostic technique, the result being obtained in 2–3 hours. The Gene Xpert technique has a sensitivity of approximately 95% and a specificity of up to 99% for sputum

samples, but the sensitivity in CSF is much lower (approximately 80%) and the specificity is around 97.8%. This is due to the fact that CSF is paucibacillary and the possible presence of substances that inhibit amplification [23].

Molecular diagnostic tests cannot replace direct microscopic bacteriological examination and CSF culture for M.tuberculosis, but they are useful as complementary tests, especially when direct smears are negative. Currently, most experts conclude that commercial NAA tests can confirm TBM but cannot rule it out [22–24].

Another diagnostic method of TBM is the measurement of adenosine deaminase (ADA) activity in CSF. ADA is an element of cellular immunity, its activity being increased in diseases in which cellular immunity is involved, a fact also found in TBM. The sensitivity of ADA varies between 60–90% and the specificity between 80–90%, but the method has not yet been well standardized and is not routinely recommended in the diagnosis of TBM [24, 25]. The detection of M.tuberculosis specific antibodies or antigens in the CSF is a rapid method of diagnosing TBM. The direct detection of cells secreting specific antibodies by the ELISPOT method has a sensitivity of 84% and a specificity of 91.8%, the sensitivity being higher if the test is performed in the first 4 weeks after the onset of the disease [26].

In recent years, two blood tests for in vitro diagnosis of tuberculosis: Quantiferon TB. Gold (Cellestis, Australia) and T-SPOT.TB (Oxford, Immunotec, United Kingdom), based on the pathogenic specificity of ESAT-6 (Early Secretory Antigen Target) and CFP-10 (Culture Filtrate Protein -10) have been developed for clinical use. The cellular immune response is an important component of the immune response regarding M. tuberculosis, the induction of a protective response translating into the synthesis of TH1-type cytokines, especially gamma interferon (IFN-gamma). IFN-gamma detection is the basis of the principle of these two tests. The sensitivity (approximately 89%) and specificity (approximately 98%) are clearly improved compared to those of the PPD skin test [27]. The Quantiferon TB.Gold (QFT-G) test produced by the Cellestis company measures the amount of interferon gamma cytokine released by T lymphocytes after stimulation with ESAT-6 and CFP-10, through a sensitive ELISA technique. QFT-G is a rapid immunological test, with results obtained in 24–48 hours. With its help and in conjunction with clinical, epidemiological data and the CSF examination, it allows a rapid diagnosis, before obtaining a positive culture for M. tuberculosis. QFT-G can be performed from both blood and CSF, a positive result in CSF being a solid argument for the diagnosis of TBM [28].

5. Imaging exploration in TBM

Chest X-ray can be normal in 20–50% of cases; There is usually some evidence of pulmonary tuberculosis (hilar adenopathy, pneumonia or miliary tuberculosis). **Computed tomography (CT**) and **nuclear magnetic resonance (MRI**) of the brain are normal in the early stages of the disease, but as TBM progresses they may show increased basal contrast, communicating hydrocephalus, signs of cerebral edema, one or more clinically silent tuberculomas, most often in the cerebral cortex or thalamic regions [29, 30].

In various studies, MRI has been shown to be more sensitive than a CT scan, but cerebral CT is easier to perform in children, MRI requiring general anesthesia in small children. A CT scan may initially be normal in nearly 30% of cases, which does not

initially exclude the possibility of a TBM [31]. Common neuroimaging findings seen in TBM are outlined below:

Communicating hydrocephalus—80%; basal meningeal enhancement—75%; cerebral infarctions—8–44%; tuberculomas—8–31% [29, 30].

Thwaites performed computed tomography in 60 cases of tuberculous meningitis and found hydrocephalus in 87% of cases in children compared to 12% in adults [32]. In children, this complication appears after 6 weeks of infection. Vascular infarcts were found in 28% of cases, most of them being located in the territory of the middle cerebral artery. Severe prognosis is associated with basal and periventricular exudate [33].

The performance of the magnetic resonance images is due to the intravenous use of gadolinum. Hyperdensity in the basal cisterns is a good predictor for tuberculous meningitis [33, 34]. Both imaging methods give suggestive information on when neurosurgical intervention for hydrocephalus should be performed.

Imaging differences were also noted depending on the age group and the association or non-association of HIV infection.

In the statistics of Thwaites, the presence of basal exudate in 82% of cases and hydrocephalus in 77% of patients is reported in adults who underwent cerebral magnetic resonance [34]. During treatment, 74% of patients develop tuberculoma, most cases being asymptomatic. Children and adults with tuberculous meningitis and HIV infection have less hydrocephalus and basal exudate, and more frequent infarcts, increased convolutions, and multiple lesions compared with patients without HIV [35–37].

Patients with HIV infections more frequently develop cerebral atrophy [35, 36].

6. Classification of TBM

In 2010, a new consensus definition was proposed, the criteria for defining TBM being applicable regardless of patients' age or HIV status. According to these criteria, patients are stratified as definite, probable and possible tuberculous meningitis [38].

1. **Clinical Criteria** include

   - symptoms duration > 5 days (4 points)
   - symptoms suggestive of TB (> 1 of the following): weight loss/low weight gain; night sweats; cough> 2 weeks (2 points)
   - cranial nerve palsy (1 point)
   - altered consciousness (1 point)
   - focal neurologic deficit (excluding cranial nerve paralysis) (1 point);
   - a close contact with a person confirm with TB or positive tuberculin test or Quantiferon TB Gold/ElI-SPOT TB positive test (2 points).

   The maximum score of clinical criteria is 6.

2. **The criteria regarding the CSF examination** are represented by

    - clear CSF (1 point);
    - the number of cells between 10–500/μL (1 point);
    - lymphocytic predominance with lymphocytes > 50% (1 point);
    - protein concentration > 1 g/l (1 points).
    - absolute CSF glucose <2.2 mmol/L (1 points).

    The maximum score is 4 points.

3. **The radiological criteria are based on the existence of the most frequently encountered changes in MTB:**

    - hydrocephalus (1 point);
    - basal meningeal hyperdensity (2 points);
    - basal meningeal thickening (2 points);
    - tuberculomas (2 points);
    - cerebral infarcts (1 point)
    - pre-contrast basal hyperdensity (2 points).

    The maximum score for this section is 6 points.

4. **The presence of extraneuraxial TB increases the probability of the diagnosis of MTB and includes**

    - radiographically detectable pulmonary tuberculosis (2 points);
    - miliary TB (4 points);
    - CT or MRI suggestive for TB outside the central nervous system (2 points);
    - fast-identified bacilli or M. tuberculosis cultivated from another source (e.g., sputum, ganglia, gastric lavage, urine and blood cultures) (4 points)
    - PCR positive for M. tuberculosis from extraneural sources (4 points).
    - The maximum score from these criteria is 6 points.

Clinical entry criteria: Symptoms and signs of meningitis including one or more of the following: headache, irritability, vomiting, fever, neck stiff ness, convulsions, focal neurological deficits, altered consciousness or lethargy [38].

According to new consensus, TBM are classified as definite, probable and possible [38].

Definite tuberculous meningitis means the demonstration of the presence of M.tuberculosis in the CSF. The diagnosis of **probable TBM** requires a score of at least 12 points when imaging techniques are available or at least 10 points when radiological methods are not available, excluding alternative diagnoses.

The diagnosis of **possible TBM** requires a score of 6–11 points when imaging techniques are available or 6–9 points when they are not available, excluding alternative diagnoses.

The exclusion of differential diagnoses requires the performance of Gram stains, routine cultures, cryptococcal antigen, serology (e.g., Borrelia, syphilis) or histopathological examination of brain tissue/meninges (tumors and lymphoma).

7. Treatment of tuberculous meningitis

Various guidelines recommend an intensive first phase, with the use of four drugs: rifampicin, isoniazid, pyrazinamide (RHZ) + streptomycin (S) or ethambutol (E) or ethionamide [39–41]. There follows a continuation phase consisting in the administration of two drugs (RH), the total duration of treatment varying in different protocols between 9–12 months. For newly diagnosed TBM cases, intensive phase treatment will consist of 8 weeks of isoniazid, rifampicin, pyrazinamide and ethambutol. According to the recommendations of the Center for Disease Control and Prevention (CDC) and Infectious Diseases Society of America, the ideal duration of antituberculosis treatment should be between 9–12 months [39]. The British Infection Society recommends 12 months of treatment, and the WHO considers that 9–12 months of antituberculosis medication would be sufficient to reduce complications and sequelae [40, 41]. Clinical and biological monitoring should be performed at least once a month to observe any adverse reaction to the antituberculosis treatment. However, the optimal treatment of TBM has not yet been established in clinical trials. The same drug can have different pharmacokinetics in the blood and in the CSF.

7.1 Isoniazid

- Isoniazid is the first antituberculosis drug of choice among antituberculosis drugs, being bactericidal on growing bacteria and having good penetration into the CSF, where it achieves concentrations of 20% of the plasma titer.

- The dose is 5–10 mg/kg/day (maximum 300 mg) for adults and 15 mg/kg/day for newborns.

- Potential side effects are peripheral neuropathy due to pyridoxine deficiency, optic neuritis, hypersensitivity reactions manifested by skin rashes and fever.

- Isoniazid can also cause hepatoxicity, manifested by the increase of liver enzymes after 4–12 weeks of treatment and sclerotegumentary jaundice [42]. Antituberculosis treatment must be continued, combining hepatotrophic drugs, vitamins.

7.2 Rifampin

- It is bactericidal and it acts by inhibiting RNA polymerase.
- Penetrability in the CSF is lower than that of isoniazid and occurs slowly.
- The recommended dose 10–15 mg/kg/day (maximum 600 mg) and the duration of treatment minimum of 9 months.
- Potential side effects are hepatotoxicity, rash, flu-like syndrome and multiple drug interactions [42].

7.3 Pyrazinamide

- It is bactericidal in an acidic environment and easily penetrates the CSF.
- It is initially used as a third drug for 2–3 months
- The dose is 30–35 mg/kg/day (maximum 2 g)
- The main side effects are arthralgia, arthritis, hyperuricemia (gout).

7.4 Ethambutol

- Not recommended for children under 6 years of age.
- Dose 15–25 mg/kg (maximum 1 g) once a day.
- Side effects are optic neuritis and hypersensitivity reactions.

Due to the fact that the new generation of fluoroquinolones (FQs), e.g., levofloxacin, ofloxacin, and moxifloxacin, have potent activity against most strains of M. tuberculosis and have excellent CSF penetration and safety profiles, they could be used as part of therapy first line for TBM [43].

8. Pharmacokinetic activity and CSF penetration of anti-TB drugs

8.1 First-line drugs

- Rifampin bactericidal, 5–25%
- Isoniazid bactericidal, penetration into CSF 90–95%
- Pyrazinamide bactericidal, 95–100%
- Ethambutol bacteriostatic, 10–50%
- Streptomycin bacteriostatic, 20–25%

- Ciprofloxacin bactericidal, 15–35%
- Levofloxacin bactericidal, 60–80%
- Moxifloxacin bactericidal, 70–80%

8.2 2nd line drugs

- Ethionamide bactericidal 80–95%
- Bacteriostatic cycloserine 40–70%
- Amikacin bactericidal 10–25%
- Bactericidal streptomycin 10–20%
- Bacteriostatic capreomycin, penetration into CSF unknown
- Para-aminosalicylic acid bacteriostatic, unknown
- Bacteriostatic thioacetazone, unknown
- Linezolid bactericidal, 80–100%

8.3 New agents

- Bedaquiline (TMC207) bactericidal, unknown
- Delamanid (OPC-67683) bactericidal, unknown [39–45].

The treatment of tuberculous meningitis is a strictly supervised treatment (DOTS) for 12 months, intensive (2 months) + continuous phase (10 months). Why the treatment is so long, till routine DOTS regimen is 6 months? Because large doses are required to penetrate the blood–brain barrier and to prevent recidivism rates.

Children with TBM should be hospitalized, preferably for the first 2 months or until clinical stabilization. In intensive phase four drugs (RHZE/S) are recommended for 2 months and in continuation phase, isoniazid and rifampicin recommended for 10 months.

In recent years, resistance to antituberculosis drugs is increasing, and multidrug-resistant tuberculosis (MDR-TB) poses serious treatment problems. Clinical trials of examining the use of high-dose rifampicin and/or fluoroquinolones are likely to report in the near future [45].

HIV/AIDS infection significantly complicates the treatment of TBM by high prevalence of drug side effects, high risk of drug–drug interaction, reducing the absorption of antiviral drugs and risk of developing immune reconstitution syndrome (IRIS). In HIV seropositive patients, it is recommended to start the anti-tuberculosis treatment first and then, after 2–8 weeks, the antiviral one.

9. Adjuvant therapy with corticosteroids in TBM

Corticosteroids (dexamethasone, prednisone and methilprednisolon) are recommended for all children and adults with TB meningitis [46]. Patients with an average form of the disease will receive dexamethasone 0.3 mg/kg/day x 1 week, 0.2 mg/kg/day x 1 week after which oral treatment for 4 weeks. Patients with severe forms of TBM will receive for 4 weeks decreasing dexamethasone 0.4 mg/kg/day x 1 week, 0.3 mg/kg/day x 1 week, 0.2 mg/kg/day x 1 week, 0.1 mg/kg/day x 1 week, then oral treatment with the same preparation for another 4 weeks [47]. In HIV-positive patients, corticosteroid therapy is administered in the absence of life-threatening opportunistic infections. A study conducted in Vietnam in patients with TBM [46], randomized, double-blind, placebo-controlled trial (n=545), shows that dexamethasone is associated with a reduced risk of death or severe neurosequelae at 9 months, but does not prevent severe neurological disability [46]. It has been postulated that dexamethasone reduces the deleterious effects of the immune response and also reduces the incidence of hydrocephalus and brain infarction [32, 47].

10. Treatment of hydrocephalus in TBM

The most common classification system used in patients with TBM and hydrocephalus is Vellore grading system which was introduced for the first time in 1991 and later modified in 1998 [48, 49]. This system classifies TBM in four grades, grade I representing the patient with GCS 15 points, and grade IV representing the patient in a deep coma (**Table 1**).

There is no doubt that the treatment of TBM is represented by the prompt initiation of antituberculosis treatment (6). Regarding the treatment of hydrocephalus from TBM, we have two types of treatment: medical and surgical, the second being the most frequently used [7].

10.1 Medical treatment

Patients with communicating hydrocephalus are generally treated with medication. Studies have shown that the use of steroids reduces mortality in all patients with

Grading	Clinical characteristics
I	GCS 15 points Headache, vomiting, fever, neck stiffness without neurological deficit
II	GCS 15 points neurological deficit present
III	GCS 9–14 points neurological deficit may or not may be present
IV	GCS 3–8 points neurological deficit may or may not be present

GCS = Glasgow Coma Scale Score.

Table 1.
Modified Vellore grading for patients with tuberculosis meningitis and hydrocephalus [48, 49].

TBM; moreover, they reduce the incidence of neurological sequelae. Corticosteroid treatment reduces inflammation and vasogenic edema, improving the signs of intracranial hypertension [6, 46, 47]. Acetazolamides and diuretics can also be used, because they reduce CSF production and improve interstitial edema. In more severe cases, mannitol can be administered, especially to delay the surgical treatment of hydrocephalus [6].

10.2 Surgical treatment

The surgical treatment of hydrocephalus is reserved for patients who are refractory to drug treatment, or for patients in whom drug treatment no longer has any effect on hydrocephalus. The principle of surgical treatment of hydrocephalus is to divert the CSF flow. The main surgical options include bedside external ventricular shunt, ventriculoperitoneal shunt or endoscopic third ventriculostomy [7, 48].

A meta-analysis that included 19 studies and 1038 patients reported a good outcome in 58.3% of patients [49]. As expected, the best outcome was reported in patients with grade-I TBM, and the worst outcome was reported in patients with grade-IV TBM. Also, a frequently encountered complication is a malfunctioning shunt, which may require revision of the shunt [50]. The patients most exposed to this complication are those with very high CSF protein levels. Other complications included shunt displacement, shunt erosion or development of peritoneal cysts [51].

Endoscopic third ventriculostomy is an effective alternative method to ventriculoperitoneal shunt, this surgical method being particularly indicated in communicating hydrocephalus, such as Sylvius aqueduct stenosis occurred in TBM [51].

11. Evolution and complications

Among **short-term complications**, communicating hydrocephalus represents approximately 80% of cases of TBM, more common than non-communicative. Other frequent complications are paralysis of the cranial nerves (3,6, and 7). The VI nerve is the most frequently involved, its damage leading to relatively sudden ophthalmoplegia and diplopia. Blindness can occur due to compression of the optic nerve during the development of hydrocephalus, through optochiasmatic arachnoiditis or through optic nerve granuloma. The involvement of small and large vessels, with the development of vasculitis obliterans, can cause ischemic and hemorrhagic complications, which occur especially in the territory of the internal carotid artery, the middle cerebral artery and small perforating vessels. Ischemic vascular accidents occur in approximately 30% of TBM cases and can manifest in a variety of ways [52, 53].

Long-Term Complications are represented by cognitive disability, seizures, cerebrovascular accidents manifested by hemiparesis and aphasia, myelitis manifested by paraparesis and hydrocephalus complicated with increased intracranial pressure.

Affecting the hypothalamus in TBM can determine diabetes insipidus, obesity, adipose-genital syndrome, precocious puberty and delay in height growth [52].

The **sequelae** of TBM are represented by motor deficits, cognitive deficits, blindness, deafness, epilepsy, behavioral disorders, the decrease in school performance in children [52–54].

The appearance of hydrocephalus is clinically manifested by varying degrees of alteration of the state of consciousness in patients with tuberculous meningitis [5, 54]. Tuberculomas and brain abscesses can cause convulsions and motor deficits [54–56].

Hydrocephalus in infants with TBM can cause the following symptoms: vomiting, drowsiness, irritability, difficult feeding, convulsions, low muscle tone, "sunset" gaze, poor reactivity to external stimuli, lack of growth and development [49, 56].

The symptoms that make up the clinical picture of hydrocephalus in the case of a young child diagnosed with TBM are represented by headache, blurred vision or diplopia (double vision), increased cranial perimeter, drowsiness, loss of balance, poor coordination of movements, convulsions, decreased appetite and in certain situations, urinary incontinence (involuntary loss of urine) [49, 54, 56].

Behavioral and cognitive changes in children with hydrocephalus frequently include irritability, personality changes, delayed acquisition of age-specific skills (speech) or decreased school performance.

The treatment of hydrocephalus is etiological and involves performing a cerebral surgical intervention represented by

- Creation of a system of ventricular valves to ensure an optimal drainage of the cerebrospinal fluid, by diverting its circulation from the ventricles to the peritoneal level, with the help of flexible tubes equipped with valves;

- Endoscopic ventriculostomy of the third ventricle requires the creation of a continuity solution at the ventricular level to ensure a proper drainage of the cerebrospinal fluid [57, 58].

Drug treatment aims to reduce symptoms and involves the administration of diuretics and anticonvulsants to improve the patient's general condition. Medical therapy should be tried prior to any form of surgical intervention; manitol, furosemide, acetazolamide and dexamethasone should be used first. CSF pressure monitoring can be useful in cases where CSF (ventricular) drainage is considered in obstructive hydrocephalus, and the decision to perform the procedure must be based on the patient's level of consciousness and the degree of ventricular dilatation visualized on brain imaging (CT or MRI). If hydrocephalus is the cause of clinical deterioration, repeated lumbar punctures or external ventricular drainage has been recommended [49, 56, 57].

12. Prognosis of tuberculous meningitis

TBM prognosis depends on two factors: age of the patient and the stage of the disease at which the treatment began. Without treatment, the prognosis is fatal. In stage 1, a 100% cure rate is expected. Even with optimal therapy, mortality varies between 30–50%, and the incidence of neurological sequelae is 75–80%, especially in stage 3 [59]. In contrast, most patients diagnosed with stage 3 who survive have permanent disabilities: blindness, deafness, paraplegia, mental retardation and diabetes insipidus. Infants and young children have a poor prognosis compared to older children [60–62].

13. Conclusions

TBM is a severe form of extrapulmonary tuberculosis with a high mortality rate due to the delay in diagnosis and adequate treatment. In the absence of an early

diagnosis and treatment, tuberculous meningitis is characterized by high mortality (20–50%) and increased morbidity (20–30%). The diagnosis of TBM remains difficult as its presentation is non-specific and may mimic other causes of chronic meningoencephalitis. Cytological and biochemical analysis of the cerebrospinal fluid is the cornerstone for diagnosis, but there are often diagnostic difficulties in differentiating tuberculous meningitis from nontuberculous. Although the culture for mycobacteria from CSF remains the gold standard for the diagnosis of TBM, the diagnosis is often delayed due to the long time interval until cultures are obtained. Therefore, it is necessary to discover new rapid tests that optimize the diagnosis of TBM. The new molecular biology tests and those based on gamma interferon release have improved the prognosis through a faster diagnosis and promptly initiated anti-tuberculosis treatment. New studies on the pathogenesis of MTB would be necessary for a better understanding of the therapeutic mechanisms needed to improve the prognosis.

The optimal duration of antituberculosis treatment has not been established precisely, varying in different studies and recommendations. The discovery of new classes of drugs active on M.tuberculosis is imperative considering the growing number of patients diagnosed with multidrug-resistant TB (MDR-TB) or even extensively drug-resistant TB (XDR-TB). MTB in patients with HIV infection raises serious treatment problems due to drug interactions, the possibility of immune reconstruction syndrome and the more frequently unfavorable evolution, toward complications and death.

The role of corticosteroid treatment in MTB is controversial, the duration of treatment has not been clearly established, and their role in preventing complications and sequelae is not well defined.

More studies are needed to establish the role of surgical treatment, the optimal timing of surgery and the best method for the treatment of hydrocephalus.

Conflict of interest

The authors declare no conflict of interest.

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