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Tuberculous Meningitis

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1. Introduction

Tuberculosis (TB) was initially described during the fifth century B.C. by Hippocrates who reported patients with “consumption” (the Greek term is *phthisis*), a term used to describe wasting associated with chest pain, coughing and blood in the sputum. Since then it remains a devastating disease with more than 9 million new cases and over 1 million related deaths among human immunodeficiency syndrome (HIV) negative populations every year (Smith, 2003; Yasar et al., 2011). *Mycobacterium tuberculosis* complex, the causative agent of human TB is the most common pathogen of both pulmonary and non pulmonary tuberculosis cases, nevertheless as a result of their association with HIV infections nontuberculous *Mycobacteria* (NTM) species are encountered with increasing frequency. While pulmonary disease is the most common manifestation of TB, the involvement of the central nervous system (CNS) and associated tuberculous meningitis (TBM) represents its most severe form (Christensen et al., 2011; Puccioni-Sohler & Brandão, 2007; Venkataswamy et al., 2007). The case fatality rate of untreated TBM is almost 100% and a delay in treatment may lead to permanent neurological damage, therefore prompt diagnosis is needed for the timely initiation of antituberculous therapy in order to prevent secondary complications (Chandramuki et al., 2002). TBM may also involve children with the peak incidence during the first 4 years of life (van Well et al., 2009; Haldar et al., 2009).

2. Causative agents of tuberculous meningitis

Mycobacteria are aerobic, nonmotile, gram-positive rods ranging in appearance from spherical to short filaments, which may be branched. Their cell wall contains lipids, peptidoglycans, and arabinomannans. One distinct characteristic is their ability to retain dyes that are usually removed from other microorganisms by alcohols and dilute solutions of strong mineral acids such as hydrochloric acid. This ability is attributed to a waxlike layer composed of mycolic acids in their cell wall. As a result, they are termed acid-fast bacilli (AFB) after Ziehl-Neelsen (ZN) staining (Panicker et al., 2010; Rajni et al., 2011). The causative agents of TBM are mainly the members of *M. tuberculosis* complex and less commonly NTM. The incidence of CNS infection due to the latter has increased substantially since the onset of the HIV epidemic (Lai et al., 2008; Puccioni-Sohler &

Brandão, 2007). According to literature, although the NTM species involved in the aetiology of meningitis include all four groups of the Runyon classification, those more commonly encountered are the *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, *M. bovis*, *M. abscessus*, *M. fortuitum* and *Mycobacterium nonchromogenicum*, the latter being a nonpigmented, slow growing organism which belongs to Runyon group III and a part of the *Mycobacterium terrae* complex. It is reported that *M. avium* complex remains the most common organism causing systemic opportunistic bacterial infections in patients with HIV infection, carrying a higher mortality rate despite appropriate treatment, while *M. kansasii* meningitis is similar to *M. tuberculosis* meningitis. Therefore, when NTM are isolated in culture of cerebrospinal fluid (CSF), they should not routinely be dismissed as contaminants but considered a significant finding (Cegielski & Wallace, 1997; Flor et al., 1996; Jacob et al., 1993; Koirala, 2001; Lai et al., 2008; Maniu et al., 2001; Mayo et al., 1998; Puccioni-Sohler & Brandão, 2007; Wu et al., 2000).

3. Epidemiology

Tuberculosis of the central nervous system is the most severe manifestation of extrapulmonary TB and constitutes approximately 1% of all new cases annually, with TBM being the commonest form of the disease (Christensen et al., 2011). Several studies have attempted to assess its epidemiology with variable conclusions as the disease's incidence and mortality rates differ from country to country according to their individual socioeconomic and public health statuses. Mortality rates for instance have been described to range from 7 - 40% in developed countries, while the percentages from TB endemic countries as well as countries with high HIV prevalence have been found to be significantly higher, reaching a 69% in South Africa (Karstaedt et al., 1998; Kent et al., 1993). The key point in understanding the epidemiological pattern of the disease is the fact that TBM and tuberculosis infection are closely related in this aspect, so that it is generally accepted that occurrence of the former in a community is correlated with incidence of the latter and vice versa (Chakraborty, 2000). It is therefore considered safe to assume that at a global level these two entities share a common trend. According to the latest available data, in 2009 the global incidence of TB was 9.4 million cases which is equivalent to 137 cases per 100 000 population with most of them occurring in Asia and Africa and a smaller proportion occurring in Europe and the Region of the Americas. Developing countries in particular account for more than 80% of the active cases in the world. The global incidence rate after an initial fall during the 20th century rose due to the HIV epidemic with a peak in 2004 and a subsequent slow but steady decline that also involves the absolute number of TB related deaths. This impact of HIV on TB has accordingly influenced the pattern of TBM's incidence rates (Dye et al., 2009; Varaine et al., 2010; World Health Organization [WHO], 2010). In fact, HIV infection constitutes the most important determinant for the development of TBM followed by age. As far as the latter is concerned it is in turn determined by the socioeconomic status of a certain population. Therefore in populations with a low TB prevalence adults seem to be more affected than children. This is reversed in populations with a higher TB prevalence. Concerning childhood disease, TBM appears to affect mainly children under the age of 5 years with the mean age ranging from 23 to 49 months and according to literature close contact with a confirmed case of pulmonary tuberculosis is usually the culprit (van Well et al., 2009).

4. Pathophysiology

Since the first description of the disease in 1936 there has been undisputable progress in the understanding of the pathogenesis of TBM, with further ongoing research in the field. Nevertheless, the exact mechanism of establishment of this uncommon yet devastating manifestation of tuberculosis has not been fully elucidated. The disease develops as a result of a new infection or of reactivation of a latent one, but in both cases it constitutes a disseminated form of a primary extrameningeal focus rather than a primary localization of the tuberculous infection. According to recent evidence certain strains seem to be more capable of dissemination and might be more predominant in the development of CNS disease with the exact mechanisms of neurovirulence being uncertain (Arvanitakis et al., 1998; Nicolic, 1996). In this direction, studies have demonstrated the possible influence of the *M. tuberculosis* genotype in association with the host's genetic polymorphisms on the disease phenotype as different mycobacterial genotypes seem to induce separate patterns of host immune response (Dormans et al., 2004; Manca et al., 2004; Reed et al., 2004). For instance, there is evidence that some strains of *M. tuberculosis* commonly found in Europe and America are less likely to cause tuberculous meningitis in Vietnamese adults than strains predominantly found in Asia (Caws et al., 2008). The pathogenesis of TBM at a cellular level is incompletely understood. According to modern concepts the triad of macrophages, T helper lymphocytes and the host plays a central role and through interactions of its components the produced γ -interferon, interleukin 1- β and tumour necrosis factor promote granuloma formation in a manner similar to pulmonary disease. On a macroscopic level it is evident that the development of TBM is a two-step process, the onset of which is the entrance of the bacilli into the host with subsequent lung invasion and regional lymph node dissemination leading to the primary complex formation. In case of central nervous system involvement the characteristic lesions known as Rich's foci, first described in the early 1930s, which represent tuberculous subpial or subependymal foci about 1 mm in diameter, are formed through spread of the bacilli to the meninges or brain parenchyma (Be et al., 2009; Drevets et al., 2004). Although it is unclear whether *M. tuberculosis* crosses the blood brain barrier as an extra-cellular organism or via infected phagocytes (Chackerian et al., 2002), the spread takes place haematogenously. This transport occurs either during the short stage of bacteremia that accompanies the primary complex formation or as a result of a more prolonged bacteremia in those cases in which the primary complex fails to heal and which account for the 10% of all cases. If miliary TB develops, dissemination to the CNS is more probable and seems to be particularly involved in the pathogenesis of TBM in childhood (Donald et al., 2005). The infrequent possibility of direct spread from a site of tuberculous otitis or calvarial osteitis also exists. When mycobacteria are deposited in large numbers as part of primary tuberculosis in infants or young children, they form the characteristic lesions and cause TBM usually within six months of primary infection (Garg, 1999; Prince, 2002). However, in adults and older children deposited mycobacteria may not elicit any immune response and may cause latent disease until immune recognition or reactivation causes formation of the CNS lesions. The second step of the process involves the rupture of a Rich's focus and the release of bacilli into the subarachnoid space giving rise to a T cell dependent granulomatous inflammatory response resulting in the development of tuberculous meningitis (Burns, 1997). This inflammatory reaction can lead to adhesion formation due to the cell and fibrin rich basal meningeal exudates, to obliterative vasculitis mainly affecting the internal carotid artery, proximal

middle cerebral artery and perforating vessels of the basal ganglia, or may even extend into the parenchyma leading to encephalitis. If the adhesions compromise the interpedicular fossa, cranial nerves (mainly II, IV and VI) are affected while in case of obstruction of the basal cisterns, the outflow of the fourth ventricle or the cerebral aqueduct, hydrocephalus develops, the presence of which has been associated with poor prognosis and therapeutic failure (Lu et al., 2001). Vasculitis and parenchymal involvement lead to infarctions (most often involving the distribution of the middle cerebral artery and striate arteries) and encephalitis respectively, which account for the majority of the neurological deficits of the disease. Another entity of tuberculous meningitis is that affecting the spinal cord. Spinal meningitis can either develop due to direct extension from the vertebrae, secondary to downward extension of intracranial TBM or less commonly as a primary tuberculous lesion. In the first case, tuberculous involvement of vertebral bodies known as Pott's disease is established through either haematogenous spread of the bacillus or less frequently through spread from involved contiguous para-aortic lymph nodes. In case of extension of intracranial disease, the most usual mechanism is the rupture of a Rich's focus into the spinal arachnoid space instead of the basal meninges (Dass et al., 2002; Garg, 1999; Harsha et al., 2006).

5. Clinical features

Tuberculosis of the central nervous system may take several forms, which cannot be easily classified (Table 1). Besides inflammation of the meninges, which is the most common form (Blaivas et al., 2005), it also includes space-occupying lesions in the brain parenchyma as well as focal disease of the spinal cord and its osseous structures.

Intracranial central nervous system tuberculosis	Tuberculous meningitis Tuberculous meningitis with miliary tuberculosis Tuberculous encephalopathy Tuberculous vasculopathy Central nervous system tuberculoma Tuberculous brain abscess
Spinal central nervous system tuberculosis	Pott's spine and paraplegia Tuberculous arachnoiditis Non osseous spinal tuberculoma Spinal meningitis

Table 1. Classification of central nervous system tuberculosis

Each of these variable entities may represent a distinct subset of the central nervous system tuberculous infection or severe sequelae of TBM. Due to the significant overlap that exists between the clinical features of TBM and those of its complications, in this section besides TBM we will also emphasize on those manifestations that are part of its continuum, without differentiating them from the disease's spectrum.

5.1 Intracranial tuberculous meningitis

TBM is characterized by a broad spectrum of manifestations, posing a diagnostic challenge and requiring a high index of clinical suspicion (Table 2). TBM tends to present subacutely,

over a period of variable duration that ranges in literature from weeks to months (Christensen et al., 2011; Komolafe et al., 2008; Newton, 1994) but in the majority of patients there is a history of vague non specific symptoms of a duration of two to eight weeks prior to meningeal irritation. These prodromal symptoms are constitutional and include malaise, fatigue, anorexia, fever and headache. According to studies, 75% of individuals have a tuberculous infection at least twelve months before admission for meningitis and radiological evidence of active pulmonary tuberculosis is present at a 30-50% of the cases upon admission (Cherian & Thomas, 2011; D'Souza et al., 2002). At the time of examination adults usually present with altered mental status ranging from lethargy to coma, meningeal symptoms and focal neurological signs but studies have demonstrated that meningeal stiffness may be absent in as many as three quarters and headache and fever in as many as 25% of the patients (Christensen et al., 2011). In infants prodromal symptoms include irritability, drowsiness, poor feeding, and abdominal pain often associated with neck retraction and bulging fontanelles. As far as the elderly are concerned, headache and mental status changes are more common, on the other hand fever is frequently absent (Berger, 1995). Atypical presentations include a rapid progression mimicking pyogenic meningitis, dementia, and a predominant syndrome of encephalitis with frequent convulsions occurring at any stage (Christie et al, 2008; Golden & Vikram, 2005). Cranial nerve palsies occur in 20-30% of patients due to adhesions and may be the presenting manifestation of the disease or complicate its course. They most commonly involve cranial nerves II, III, IV, VI and VII, with VI being the one most commonly affected. Focal neurological deficits may also include hemiplegia, monoplegia and aphasia. Visual manifestations include visual impairment and ophthalmoplegia and are attributed to optochiasmatic arachnoiditis, compression of optic chiasm in the setting of hydrocephalus, or optic nerve granulomas (Malik et al., 2002; Sinha et al., 2010). In case of tuberculomas or tuberculous brain abscess complicating meningitis the clinical features vary in accordance to their location. Tuberculous arachnoiditis is a rare complication of intracranial TBM, as a result of downward extension of the latter, that can lead to severe peripheral neurological deficit (Poon et al., 2003) often after an initial response to antituberculosis treatment, while syndrome of inappropriate antidiuretic hormone (SIADH) secretion is not an uncommon complication and is linked to a poor prognosis. As the inflammatory process progresses it might result in foci of encephalitis properly described as a diffuse meningoencephalitis with symptoms of cerebral disorder predominating and evolving from increasing lethargy to terminal illness coma (Drevets et al., 2004)

5.2 Spinal tuberculous meningitis

The clinical picture of spinal tuberculous meningitis is variable, depending on the stage of the disease and the mechanism involved in its pathogenesis. When secondary to a Rich's focus rupture, it may present acutely with fever, headache, radiating root pain and myelopathy, or progress gradually with symptoms of spinal cord compression dominating the picture which may lead to misdiagnosis of an intradural tumor. The clinical spectrum may also include paradoxical reaction after initiating antituberculous therapy, spinal arachnoiditis, and simultaneous or preceding manifestations of TBM. If Pott's disease is in the background, chronic manifestations of variable intensity reflecting the progressive destruction of the involved disc space and vertebral elements precede the meningeal

involvement and should guide the diagnosis. In such cases spinal meningitis is associated with focal tenderness over the spinous processes, focal kyphosis and cord compression phenomena, depending on the level of the spine that is affected (Garg, 1999; Harsha et al., 2006; McLain & Isada, 2004).

Symptoms	Signs
Headache Vomiting Low grade fever Lassitude Depression Confusion Behavioural changes	Meningism Oculomotor palsies Papilloedema Depressed level of consciousness Focal hemisphere signs

Table 2. Most common clinical features of tuberculous meningitis (adapted from Allen & Lueck, 2002)

6. Staging

TBM tends to be classified according to its severity at presentation in an attempt to assess prognosis. The Medical Research Council staging system has been applied since 1948 to patients with TBM and uses three stages of increasing severity. Stage I refers to alert patients without focal neurological signs, stage II to non comatose patients with altered consciousness and focal neurological deficits and stage III to comatose patients and those with multiple cranial nerve palsies and hemiplegia or/and paraplegia (Prasad & Singh, 2008). Modifications of the above mentioned staging system have been adopted in recent literature (Heemskerk et al., 2011). The Acute Physiology and Chronic Health Evaluation II as well as the Glasgow Coma Scale have also been proposed for predicting the outcome of patients with TBM and are considered superior to the Medical Research Council scoring system by certain authors (Chou et al., 2010). Nevertheless, it is uniformly accepted that the stage of TBM at the onset of treatment seems to be the most crucial determinant of outcome, with mortality being highest if treatment started at Medical Research Council stage III.

7. Differential diagnosis

The diagnosis of TBM is challenging as it may mimic a wide range of medical conditions. It is generally based on clinical grounds and cerebrospinal fluid (CSF) examination (Table 3). The differential diagnosis of the disease is particularly wide and at a clinical basis includes:

1. Infections: bacterial (partially treated bacterial meningitis, brain abscess, listeriosis, *Neisseria* species infection, tularemia, brucellosis), spirochetal, viral (herpes, mumps, retrovirus, enterovirus), fungal (cryptococcal, histoplasmosis, actinomycetic, nocardiasis, candidiasis, coccidiosis) and parasitic (cysticercosis, acanthamoebiasis, strongyloidiasis, toxoplasmosis)
2. Non infective conditions: vasculitis, systemic lupus erythematosus, neoplastic, chemical meningitis, cardiovascular, Behçet disease, acute hemorrhagic leukoencephalopathy etc.

CONDITION	WHITE BLOOD CELLS	PROTEIN	GLUCOSE
TBM	Elevated, L > PMN	Increased	Decreased
Cryptococcal meningitis	Elevated, L > PMN	Increased	Decreased
Partially treated bacterial meningitis	Elevated	Increased	Decreased
Viral meningitis	Elevated, L > PMN	Increased	Normal or decreased
Acute syphilis	Elevated, L > PMN	Increased	Normal
Late stage trypanosomiasis	Elevated, L > PMN	Increased	Decreased
Malignancy	Elevated, L > PMN	Increased	Decreased
Leptospirosis	Elevated, L > PMN	Increased	Decreased
Amoebic	Elevated, L > PMN	Increased	Decreased

PMN: polymorphonuclear leucocytes, L: lymphocytes

Table 3. Differential diagnosis of TBM based on CSF findings (adapted from Harries et al., 2004)

From a radiological point of view, taking into consideration the fact that bacterial meningitis, therefore TBM as well, is not an imaging diagnosis, such investigations are carried out in order to exclude the presence of other conditions mimicking meningitis and to detect possible contraindications for lumbar puncture such as increased intracranial pressure. Based on radiological findings the differential diagnosis of TBM also includes other infectious agents as well as non-infectious inflammatory diseases affecting the leptomeninges and neoplastic meningeal involvement (meningiomas, neoplastic meningitis from a peripheral tumor source etc.) (Junewick, 2010).

8. Laboratory diagnosis

Taking into consideration the fact that the high mortality rate associated with TB meningitis is related to its late diagnosis as well as the difficulties not only in obtaining a precise history but also in collecting an adequate volume of CSF for laboratory investigation, lumbar puncture and the examination of CSF are key points in its diagnosis.

8.1 CSF parameters

Examination of CSF in TBM usually reveals an increase in pressure with the fluid's appearance ranging from clear to slightly turbid with, occasionally, a delicate web-like clot formation, due to the high protein level that is typical to the disease and a pleocytosis of 10-1000 leucocytes/ mm³ with a lymphocytic predominance. The cell count rarely exceeds these values, on the contrary it is less than 500/ mm³ in the majority of cases. CSF biochemistry reveals reduced glucose levels, increased lactate levels, while protein levels are increased, especially in cases in which there is a CSF flow obstruction and which are associated with a worse prognosis. Early in the course of the disease a polymorphonuclear reaction as well as normal biochemical parameters might be found complicating the differential diagnosis,

particularly from bacterial meningitis. This polymorphonuclear predominance has been associated with a higher culture positivity and may even have a prognostic value, especially in HIV positive patients. In fact these patients occasionally exhibit a persistent polymorphonuclear predominance, which has been associated to higher survival rates, as it seems to have a protective role against *M. tuberculosis* (Hooker et al., 2003; Puccioni-Sohler & Brandão, 2007). For the performance of a total cell count of the CSF a fresh sample is loaded into an improved Neubauer chamber. A proportion of the fluid is centrifuged at 3000 g for 15 min and from the sediment obtained, a Giemsa stained smear must be examined for the differential cell count (Christensen et al., 2011; Hooker et al., 2003; Kashyap et al., 2010; Puccioni-Sohler & Brandão, 2007; Ramachandran, 2011; Thwaites et al., 2004).

8.2 Microscopy

As far as the direct microscopy of a Ziehl-Neelsen stained smear is concerned, it should be conducted in all cases despite the low sensitivity of the examination attributed to the paucibacillary nature of the CSF. Each slide must be examined under the oil immersion lens for about 30 min, with care being taken to view at least 300–500 high power fields. It is proposed for each slide to be re-examined by an independent examiner to ensure accuracy. The sensitivity of the method ranges from 10–87% depending on the volume and the number of the samples and might drop to 2% after 5–15 days following the onset of treatment (Puccioni-Sohler & Brandão, 2007; Thwaites et al., 2004). The Ziehl-Neelsen stain remains an important diagnostic tool in tuberculosis since its first introduction in 1882 by Robert Koch as it identifies the most infectious cases, it is rapid, inexpensive, technically simple, and specific for AFB. However, it is unable to discriminate between *M. tuberculosis* and other mycobacteria, lacks sensitivity, and cannot be applied in the monitoring of treatment, as it does not discriminate between viable and non-viable bacilli. Its sensitivity appears to be lower in non-respiratory specimens due to the lower bacterial load as well as for some NTM species due to poorer staining of their cell wall (Mamoucha et al., 2010).

8.3 Solid and liquid culture media

Mycobacterial culture is the microbiological Gold Standard method for the confirmation of TBM as the isolation of *M. tuberculosis* from CSF makes a definite diagnosis of the disease, although in the setting of a strong clinical suspicion the isolation of the agent from other specimens such as gastric aspirate, bronchial aspirate, sputum or lymph node also guides the diagnosis (Kashyap et al., 2010; van Well et al., 2009). There is a variety of culture media used for this purpose. These include egg-based (Löwenstein-Jensen-LJ, Petragani, 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. In order to shorten the time of detection, Centers for Disease Control and Prevention (CDC) have recommended the use of liquid media for primary culture. Liquid culture medium has been designed to significantly reduce incubation time to 12–15 days and has been reported in various studies. Liquid TB culture media and Middlebrook 7H10 agar-based media, have been shown to increase the yield of TB particularly from body fluids but the highest recovery rate has been obtained using a combination of both (Fadzilah et al., 2009; Kashyap et al., 2010; Khosravi et al., 2009; Mamoucha et al., 2010; Panicker et al., 2010).

Piersimoni & Scarparo, 2008; Sorlozano et al., 2009). This may be attributed to the fact that in liquid cultures a mix of growth supplements (OADC- Oleic acid, Albumin, Dextrose, Catalase) and antibiotics (PANTA- Polymyxin B, Amphotericin B, Nalidixic acid, Trimethoprim, Azlocillin) are used, which collectively prevent the growth of environmental bacteria. According to literature, the isolation rate on MGIT 960 has been found 7.4% (Tortoli et al., 1999), 18.36% (Rishi et al., 2007) or 11.6% (Selvakumar et al., 1996), while using LJ medium the isolation rate has been found 4.3-6.5% (Rishi et al., 2007; Venkataswamy et al., 2007). Growth on the surface of the LJ slope is indicated by the production of raised, dry, cream coloured colonies while on Kirchner media by the formation of a surface pellicle, which should then be subjected to ZN stain and subcultured onto LJ slopes for confirmation and further identification (Hooker et al., 2003; Panicker et al., 2010). A positive result must be confirmed by performing a ZN smear of the colonies, with AFB being demonstrated. Furthermore, owing to the paucibacillary nature of cerebrospinal fluid, some authors propose filtration of the sample and inoculation of the residue on the culture media in order to increase the sensitivity of the method (Kumar et al., 2008).

8.4 Adenosine deaminase levels and TBM

Adenosine deaminase (ADA) is an enzyme involved in the purine catabolism by catalyzing the deamination of adenosine to inosine and of deoxyadenosine to deoxyinosine and is found in all tissues, particularly those of the lymphoid system. High ADA levels in tuberculosis are related to the activated T lymphocytes and macrophages in response to the tuberculous antigens (Blake & Berman, 1982) and in our laboratory their determination in pleural fluid has been routinely used as an aid in the establishment of tuberculous or nontuberculous aetiology of pleural effusion in variable clinical settings. As far as its role in the diagnostic approach of TBM is concerned, although still controversial, it is considered to be an inexpensive, simple and rapid method that could be used routinely following a lumbar puncture. On this basis certain methods have been developed for the determination of ADA activity with the Giusti-Galanti one being the most commonly used (Laniado-Laborin, 2005; Oosthuizen et al., 1993). Moreover several studies have been conducted indicating that the ADA levels in CSF are higher in TBM than in nontuberculous meningitis. Depending on each study's selected cutoff values the sensitivity and specificity for ADA have exhibited slight heterogeneity. In fact, CFS ADA cutoff value of 6.5 IU/L showed a sensitivity of 95.83% and a specificity of 92.85% (Baheti et al., 2001), while cutoff of 10 IU/L has been associated with a sensitivity and a specificity of 94.73% and 90.47% respectively (Gupta et al., 2010). However a meta-analysis study that was conducted recently in order to evaluate its diagnostic use concluded that ADA, irrespectively of the cutoff levels adopted, cannot distinguish between TBM and nontuberculous meningitis, but suggested that the use of ranges of its CFS values could have a role in improving TBM diagnosis, especially after bacterial meningitis has been excluded (Tuon et al., 2010). Thus the role of ADA activity determination in the diagnosis of TBM is still questionable by many scientists, with emphasis on the need of standardization of the methodology applied as well as of its cutoff values. Nevertheless, the enzyme's levels are still considered as an additional diagnostic tool.

8.5 Molecular diagnosis

The need of a rapid diagnosis in the case of TBM has made the use of molecular techniques essential. Although the majority of commercial tests are licensed for nonrespiratory

specimens only, many of them have been in use along with in-house techniques and will be mentioned here, keeping in mind the fact that the data concerning their diagnostic value are based at large on the experience from studies emphasizing on respiratory samples. Even in such specimens, due to the need for further standardization between the different protocols and for implementation of solid guidelines concerning the evaluation of their results - attributed to the methods' innate disadvantages of practical nature as well as to the paucity of clinical data - their exact role remains controversial (Dora et al., 2008; Soini & Musser, 2001). Nucleic acid-based amplification (NAA) tests allow the direct detection of mycobacterial DNA or RNA and they include both in-house and commercial tests with the latter being more standardized and therefore more reliable. Post-amplification analysis includes electrophoresis, hybridization, restriction or sequencing of the products with hybridization being the most commonly used one. The Amplified *Mycobacterium tuberculosis* Direct Test (AMTD2, Gen-Probe, bioMerieux, Marcy, L'Etoile, France) which is based on the amplification of a *Mycobacterium tuberculosis* specific region of 16S rRNA using a reverse transcriptase was the first one to be approved by the Food and Drug Administration (FDA) in 1995, with its recommendations also including extrapulmonary samples, followed by the Amplicor *M. tuberculosis* test (Roche Diagnostic System Inc., Basel Switzerland) in 1996, which targets a segment of the same gene with the use of standard polymerase chain reaction (PCR). Other methods described include the BD ProbeTec ET Direct TB System (DTB, Becton Dickinson) which is a strand displacement amplification method targeting the IS6110 and 16S genes, the GenoType Mycobacteria Direct (Hain LifeScience, Nahren, Germany) and the INNO-LiPA Rif. TB kit (Innogenetics, Gent, Belgium), both using nucleic acid sequenced based amplification (NASBA) and offering the advantage of detecting not only members of the *M. tuberculosis* complex but certain common NTM as well. Newer techniques based on real-time PCR amplify simultaneously different DNA targets followed by fluorimetric detection and are considered promising. Among them the GeneXpertMTB/RIF (Cepheid, Sunnyvale, CA, USA and FIND Diagnostics, Geneva, Switzerland), which also offers the possibility for detection of RIF resistance, has recently been approved by the WHO (Alcaide & Coll, 2011; Dora et al., 2008; Soini & Musser, 2001). On the other hand, the in-house techniques use the PCR in order to amplify specific regions of *Mycobacterium tuberculosis* genome varying from one institution to another, with the IS6110 (Insertion sequence 6110) element and devR element (Haldar et al., 2009; Michael et al., 2002) being the ones most commonly used. Reported results of the molecular tests in CSF specimens vary in different studies with reported sensitivity and specificity ranging from 50%-87.6% and 92%-98.6% respectively (Dora et al., 2008; Haldar et al., 2009; Pai et al., 2003). This low sensitivity could be attributed to the volume of the sample, given the lower number of bacteria usually found in the CSF compared to other compartments, therefore the minimum suggested volume of the fluid is 2ml (Michael et al., 2002). In conclusion both commercial and in-house molecular techniques might have a role in confirming TBM, although their low sensitivity doesn't seem to allow them to exclude it with certainty.

9. Treatment of TBM

The most important determinant of TBM's prognosis is the stage of the disease at the time of initiation of appropriate treatment with evidence indicating that timely onset during the early phase of infection can significantly improve the outcome. Therefore, any patient suspected of having TBM based on the clinical symptoms and - when present - signs of

increased intracranial pressure as well as CSF findings compatible with the disease should be started on anti-tuberculous chemotherapy without awaiting for the CSF laboratory results. The recommended first line treatment agents for all forms of CNS tuberculosis administered daily either individually or in a combination form are isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), streptomycin (SM), and ethambutol. Second-line therapy includes ethionamide, cycloserine, para-aminosalicylic acid (PAS), aminoglycosides, capreomycin, thiacetazone, while potential new agents include oxazolidinone, isepamicin and a new rifamycin called rifapentine. Fluoroquinolones that have a role in the treatment of TBM include ciprofloxacin, ofloxacin, and levofloxacin. Finally, because of the intensity of the inflammatory and fibrotic reactions at the meningeal site, adjunctive corticosteroids, in addition to standard antituberculous therapy, are recommended (Girgis et al., 1998; Ramachandran, 2011). Taking into consideration the fact that the same regimens are recommended for the treatment of pulmonary and extrapulmonary disease, isoniazid, rifampicin and pyrazinamide are considered mandatory at the beginning of TBM treatment and some centers use all three for the whole duration of therapy. There are no data from controlled trials to guide the choice of the fourth drug. Most authorities recommend either streptomycin or ethambutol, although neither penetrates the CSF in a satisfactory degree in the absence of inflammation, and both can produce significant adverse reactions. According to the guidelines recommended by the World Health Organisation (WHO) however, ethambutol should be replaced by streptomycin (Thwaites et al., 2009; WHO, 2010). The duration of therapy in tuberculous meningitis is controversial with considerable variation in recommendations by different expert groups on this issue (Prasad & Sahu, 2010). Some experts recommend 9-12 months of treatment for TB meningitis given the serious risk of disability and mortality (WHO, 2010). The Indian Academy of Paediatrics (Indian Academy of Paediatrics [IAP], 2011) recommends that the continuation phase of treatment in TB meningitis should last for 6-7 months, extending the total duration of treatment to 8-9 months. The recommended by the British Infection Society (Thwaites et al., 2009) first line treatment regimen for all forms of CNS tuberculosis is given in Table 4.

Drug	Daily dose		Route	Duration
	Children	Adults		
Isoniazid	10-20mg/kg (max 500mg)	300mg	oral	12 months
Rifampicin	10-20mg/kg (max 600mg)	450mg (<50 mg) 600mg (≥50 mg)	oral	12 months
Pyrazinamide	30-35mg/kg (max 2g)	1.5g (<50 mg) 2.0g (≥50 mg)	oral	2 months
Ethambutol	15-20mg/kg (max 1g)	15 mg/kg	oral	2 months

Table 4. Recommended treatment regimen for CNS tuberculosis caused by fully susceptible *M. tuberculosis* (adapted from Thwaites et al., 2009)

Among the bactericidal agents INH, RIF, and PZA, isoniazid has the best CSF pharmacokinetics with concentrations (C_{max}), being only slightly less than in blood (Donald, 2010). It penetrates the CSF freely, has potent early bactericidal activity and at standard dosages it achieves CSF levels of 10-15 times the minimum inhibitory

concentration of *M. tuberculosis*. Its main disadvantage is that resistance develops quite quickly when used as a monotherapy though this does not seem to happen when it is used for chemoprophylaxis (Cherian & Thomas, 2011). PZA also exhibits a good CSF penetration and in children receiving appropriate dosages the achieved C_{max} exceeds the proposed minimal inhibitory concentration of 20 µg/ml. In this patient group rifampicin is more successful in reaching CSF concentrations above its minimum inhibitory concentration than in adult adjusted dosages but it can achieve optimal levels only when the meninges are inflamed. Streptomycin, other aminoglycosides and ethambutol have a poor CSF penetration and cannot be administered as first line agents (Ramachandran, 2011). Among the second line agents ethionamide, fluoroquinolones, with the exception of ciprofloxacin, and cycloserine display a relatively good CSF penetration and can be administered in TBM (Donald, 2010).

9.1 Use of steroids in TBM

The British Infection Society recommends that all patients with TBM should receive adjunctive corticosteroids regardless of disease severity at presentation. The value of adjuvant corticosteroids lies in reducing the harmful effects of inflammation while antibiotics kill the organisms and studies have demonstrated significant decrease in mortality and morbidity of patients receiving dexamethasone compared with those not receiving it (Girgis et al., 1998; Ramachandran, 2011; Thwaites et al., 2009).

9.2 Treatment of TBM and HIV infection

Determination of HIV status is mandatory in all patients with suspected CNS TB not only because TB may be the first indication of an underlying HIV infection and because of the increased frequency of extrapulmonary involvement in persons with immunosuppression, but also due to the impact that TB might have on the antiretroviral (ART) treatment decisions. In case of a positive HIV status the choice and duration of anti-TB therapy remains unaltered and patients should receive the drug regimen that is recommended for HIV negative individuals with rifampicin being administered when possible, taking into consideration the fact that this agent induces the metabolism of the protease inhibitors, delavirdine and nevirapine reducing their levels (Thwaites et al., 2009). According to WHO the recommended first line ART regimens for TB patients are those that contain efavirenz (EFV) since its interactions with anti-TB drugs are minimal. In individuals who require an ART regimen containing a boosted protease inhibitor (PI), it is recommended to give a rifabutin based TB treatment. If rifabutin is not available, the use of rifampicin and a boosted antiretroviral regimen containing lopinavir or saquinavir with additional ritonavir dosing is recommended but this regimen should be closely monitored. Adjunctive corticosteroids are also recommended (Cherian & Thomas, 2011; WHO, 2010).

9.3 Treatment of multi-drug resistant TBM

Despite the fact that multi-drug resistant (MDR) tuberculous meningitis is at present a worldwide reality, in contrast to MDR pulmonary TB, it has not been well described, with the exception of limited reports (Byrd & Davis, 2007; Daicos et al., 2003; Schutte, 2001). The low sensitivity of CSF smears and culture as well as the prolonged time required for

culturing and susceptibility testing, which underestimate its true incidence, have contributed to this. The emergence of multi-drug resistant TB meningitis complicates the management of the disease, because the first line anti-TB regimen is inadequate. Second line agents with the exception of ethionamide, cross the blood-brain barrier poorly, resulting in suboptimal concentrations in CSF and since there are not enough pharmacokinetic data for drugs such as cycloserine and thiacetazone, the management of CNS disease caused by bacilli resistant to both INH and RIF is challenging (Daicos et al., 2003; Patel et al., 2004). Suspected isoniazid resistant disease, without rifampicin resistance, should be treated initially with conventional 4-drug first line therapy. If a low level resistance is proven or the cultures are uninformative, the British Infection Society recommends 12 months of treatment including rifampicin, isoniazid, and pyrazinamide and ethambutol, the latter being discontinued after 2 months. If a high level isoniazid resistance is proven, exchanging the agent for levofloxacin or moxifloxacin for at least 12 months in combination with rifampicin and pyrazinamide is recommended. For patients with suspected or proven MDR CNS tuberculosis the British Infection Society recommends initial therapy with at least a fluoroquinolone, pyrazinamide, ethionamide or prothionamide, and amikacin or capreomycin, unless there is resistance to any of these agents (Thwaites et al., 2009). The standard treatment regimens, which are designed according to the general principles of the therapeutic approach to MDR TB, should be changed to individualized ones once the results on drug susceptibility concerning other agents besides INH and PZA are available (WHO, 2010). As far as paediatric groups are concerned, further studies of the sensitivity patterns are required in order to standardise and optimise the second line treatment protocols (Padayatchi et al., 2006).

9.4 Neurosurgery

Besides its diagnostic value and although it is used in the management of the late complications of the disease, neurosurgery plays a minor role in the treatment of TBM. Hydrocephalus, tuberculous brain abscess (TBA), and vertebral tuberculosis with cord compression, may be indications for urgent neurosurgical intervention, even though early hydrocephalus and tuberculous brain abscess can be successfully treated by drugs alone. So early recognition and timely treatment is critical in avoiding the surgery. The aim of surgical management of TBA is to reduce the size of the space-occupying lesion and subsequently diminish intracranial pressure. Anti-TB therapy prior to the surgery is considered mandatory and appears to reduce the risk of postoperative meningitis. Urgent surgical decompression should also be considered in all the cases with extradural lesions causing paraparesis (Cherian & Thomas, 2011).

10. Conclusion

Tuberculosis is a serious public health issue with tuberculous meningitis being the most severe extrapulmonary form as well as the most common manifestation of central nervous system disease. The causative agents are members of *M. tuberculosis* complex and NTM, which should be strongly considered as important CNS pathogens in patients with HIV infection. The three most commonly used laboratory methods of TBM diagnostics are smear microscopy, culture and molecular techniques but as the stage of the disease at the time of treatment onset is the most important determinant of prognosis, anti-TB therapy should be

initiated even before their completion. Nevertheless, the disease's wide clinical spectrum combined with the significant overlap between its syndromes pose a diagnostic challenge, underlining the importance of a high index of clinical suspicion. We should keep in mind that rapid diagnosis of TBM besides its impact in the disease's outcome is also central to controlling primary tuberculosis, especially in the wake of the emergence of multi-drug resistant TB and its severe implications particularly for HIV infected patients.

11. References

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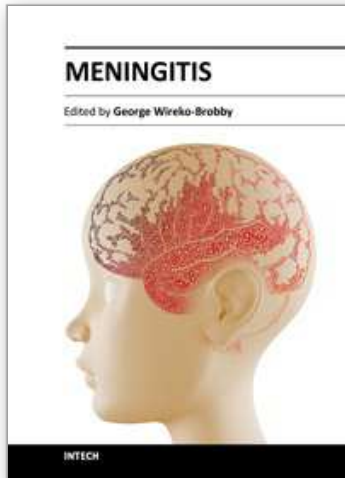
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Meningitis

Edited by Prof. George Wireko-Brobby

ISBN 978-953-51-0383-7

Hard cover, 232 pages

Publisher InTech

Published online 30, March, 2012

Published in print edition March, 2012

Meningitis is a medical emergency requiring a rapid diagnosis and an immediate transfer to an institution supplied with appropriate antibiotic and supportive measures. This book aims to provide general practitioners, paediatricians, and specialist physicians with an essential text written in an accessible language, and also to highlight the differences in pathogenesis and causative agents of meningitis in the developed and the developing world.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Maria Kechagia, Stavroula Mamoucha, Dimitra Adamou, George Kanterakis, Aikaterini Velentza, Nicoletta Skarmoutsou, Konstantinos Stamoulos and Eleni-Maria Fakiri (2012). Tuberculous Meningitis, Meningitis, Prof. George Wireko-Brobby (Ed.), ISBN: 978-953-51-0383-7, InTech, Available from:
<http://www.intechopen.com/books/meningitis/tuberculous-meningitis>

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