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Tuberculous Meningitis: Diagnostic and Radiological Features, Pathogenesis and Biomarkers[*]

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ABSTRACT

Central nervous system tuberculosis is the most severe form of extrapulmonary tuberculosis disease. We aim to review the diagnostic and radiological features, pathogenesis, and biomarkers of tuberculous meningitis. We also aim to look at the latest development of research of the disease. The diagnosis of tuberculous (TB) meningitis is difficult because the disease presents with unspecific clinical features. However, the disease has excellent clinical response to antituberculous therapy. Good prognosis depends on prompt diagnosis with treatment and radiological findings are very important. There is an increase in the levels of serum and cerebrospinal fluid (CSF) TNF-in TB meningitis patients. IL-6 level is also increased in patients with tuberculoma and exudates. There is an increase in the levels of serum and CSF TNF-α and IFN-γ in TB meningitis patients. There is also a rise in the levels of IL-8, IFN-alpha, IFN-gamma, IL-10, CSF matrix metalloproteinases, CSF tissue inhibitors of matrix Metalloproteinases, VEGF level, caspase-1 and IL-1β. Signal-regulatory protein alpha is overexpressed at mRNA level. High dose intravenous rifampicin (800 mg daily) is associated with reduced mortality in patients with advanced disease.

Keywords: Tuberculous Meningitis; TB; Infection; Cerebrospinal Fluid

1. Introduction

Tuberculosis (TB) is a major health and clinical problem in the world [1-3]. There are eight million new cases annually [2]. The disease also results in three million deaths [2]. 15% of all tuberculous infections are extra-pulmonary [2]. Extra-pulmonary TB consists of TB lymphadenitis, genitourinary TB, central nervous system TB and others [2]. Central nervous system tuberculosis is the most severe form of extrapulmonary tuberculosis disease [1,4-6]. Central nervous system tuberculosis includes tuberculous meningitis (TBM) which occurs in 4% of all cases [2]. Extrapulmonary involvement can occur in isolation or along with a pulmonary TB in the patients with disseminated tuberculosis [1]. We aim to review the diagnostic features, pathogenesis, radiological features, biomarkers and treatment of tuberculous meningitis. The other objective is also to look at the latest progress of development of research of the disease.

2. Body

2.1. Diagnosis

The diagnosis of TB meningitis is difficult because TB meningitis presents with unspecific symptoms and signs [4,7]. Later in the disease, confusion, change in behavior, seizures and cranial nerve palsies can develop [4]. The difficult diagnosis of TB meningitis is also due to haematogenous spread of the tubercle bacillus [1]. Therefore, early diagnosis and treatment of the disease is very important as the disease can result in mortality [1,3,4,7,8]. However, the other factor that makes diagnosis difficult is the small number of bacilli in the CSF which reduce the sensitivity of conventional bacteriology [8]. In addition, the reason for early diagnosis is excellent clinical response to antituberculous drugs [1].

Diagnosis is based on the characteristic clinical features, radiological abnormalities, cerebrospinal fluid changes (acid-fast bacilli by direct staining of CSF or positive culture of acid-fast bacilli from CSF) [9] and the response (clinical and CSF) to anti-tuberculosis medications [1]. In addition to clinical features and radiological features, pathological features and biomarkers also help

with the diagnosis of TB meningitis.

2.2. Clinical Features

The clinical features are fever for more than seven days, headache, and neck stiffness [1,6,10-12]. The other common clinical features are vomiting, focal neurological deficits, vision loss, cranial nerve palsies and raised intracranial pressure [5,13]. In human immunodeficiency virus (HIV) infection, TB is often atypical in presentation, frequently causing extrapulmonary disease, and patients have a high incidence of TB meningitis [1,5].

Presence of recent exposure to tuberculosis and signs of active extrameningeal tuberculosis on clinical assessment is important [8]. Chest radiography reveals active TB, previous tuberculosis infection or military TB in 50% of patients with TB meningitis [8]. Mantoux test, which is skin testing with purified protein derivative of *M. tuberculosis* is of limited value in adults [8].

A diagnostic rule based on age (less than 36 years old), white blood cell count (less than 15,000), duration of illness (less than six days), cerebrospinal fluid white cell count (less than 750) and percentage of neutrophils in the CSF (less than 90%) had 86% sensitivity and 79% specificity [8]. There is a higher risk of TB meningitis with score of ≤4, and lower probability of TB meningitis when the score is more than four [8]. Basal meningeal enhancement, tuberculoma, or both, were 89% sensitive and 100% specific for the diagnosis of TB meningitis [8].

The diagnosis of TB meningitis is limited by the poor sensitivity of CSF microscopy. In addition, *Mycobacterium tuberculosis* (*M. tuberculosis*) culture takes a few months to come back [3]. A study demonstrated that acid-fast bacilli was seen in 58% of patients, and cultured from 71% of the patients [14].

M. tuberculosis nucleic acid amplification PCR can be used for rapid diagnosis of TB meningitis [1,3]. Real time PCR allows direct observation of amplicon reaction [3]. PCR tests are more sensitive and specific in detection of specific DNA sequences [1].

In a recent study, IS6110-PCR had the highest positivity rate (68%) in comparison to Ziehl-Neelsen microscopy (11%) and mycobacterial culture (36% - 44%) [3]. In 92% of patients with culture-positive, CSF IS6110-PCR was positive, whereas in culture-negative probable TB meningitis CSF TB IS6110-PCR was positive in 42% of patients [3]. For qRT-PCR (filtrate), the sensitivity is 87.6% and specificity is 92% [15]. In comparison, the sensitivity for IS6110-PCR (filtrate) is 85.2% and the specificity is 83.7% [15].

BACTEC MGIT 960 can be used as a rapid test for the diagnosis of TB meningitis [16]. The sensitivity of BACTEC MGIT 960 is 81.5% and specificity is 99.6% [16].

A recent study reported that the ELISA test for *Mycobacterium tuberculosis* anti-antigen A60 antibodies (IgM) is a rapid and sensitive tool for the rapid diagnosis of TBM [17]. This test can be used in addition to adenosine deaminase (ADA) determination [17]. The two tests are limited by poor specificities (80%) [17]. The sensitivity of anti-A60 IgM CSF antibody titres was 94% compared to 88% [17].

The cerebrospinal fluid (CSF) shows a high CSF white-cell count, which is predominantly lymphocytic, with a high protein and low glucose level (CSF plasma glucose is <50%) [8]. Total CSF white cell count can be normal in those with TB meningitis, especially in the people with depressed cell-mediated immunity, such as the elderly and HIV patients [8]. Low CSF white cell counts have been associated with worse outcome [8].

Neutrophils can be the predominant cells, especially early in the disease, and high proportions of neutrophils in the cell count have been associated with improved survival [8].

Multiple CSF sampling improves the sensitivity of Ziehl-Neelsen stain to more than 80% [18]. In addition, the chance of culturing *M. tuberculosis* from CSF depends on culture of a large volume (more than 5 mL) of CSF [14].

The severity of TB meningitis at presentation is divided into three stages according to the patient's Glasgow coma score and the presence/absence of focal neurological signs [8].

Movement disorders can present after basal ganglia stroke [8]. The most common movement disorder is tremor. The others are chorea, ballismus, and myoclonus [8].

2.3. Pathology

Pathologically from autopsies, there was a subcortical or meningeal focus ("Rich focus") from which bacteria had access to the subarachnoid space [17]. After the release of bacteria and granuloma into the subarachnoid space, a dense inflammatory exudate forms [17]. The inflammatory exudate that affects mostly the sylvian fissures, basal cisterns, brainstem, and cerebellum [8]. The gelatinous basal meningeal exudate is also found at the interpeduncular fossa involving the optic nerves, the internal carotid arteries and suprasellar region anteriorly [19,20].

The exudate extends and progresses along small proliferating blood vessels with the development of focal and diffuse ischemic and infarction of brain due to vasculitis [20]. Entrapment of large cerebral arteries, and vasculitis of large arteries, results in infarction [20]. Vasculitis typically affects middle cerebral artery [20, 21].

Hydrocephalus (occurring in 2/3 of TB meningitis patients) and tuberculoma are complications of TB meningitis [20]. The exudate envelops and surrounds the arteries and cranial nerves, resulting in blockage and obstruc-

tion of the flow of cerebrospinal fluid at the level of the tentorial opening, leading to hydrocephalus [8,19]. The exudate can also compress on the efferent cranial nerves [8]. Granulomas can coalesce to form tuberculomas [8].

TB meningitis can also be complicated by allergic tuberculous encephalopathy, which is perivascular demyelination on the basis of a hypersensitivity reaction to tuberculoprotein [20]. Tuberculous Encephalopathy is a rare complication, which is usually more common in younger people [22]. It is characterized by diffuse brain edema and demyelination, which usually is extensive [22]. Microscopically, there is microvascular necrosis with perivascular macrophage reaction, demyelination, focal glial nodules in the white matter and occasional haemorrhagic areas [22].

TB meningitis can also result in infiltrative, proliferative and necrotising vessel pathologies causing luminal thrombosis [21]. Vasospasm may mediate strokes early in the course of the disease and proliferative intimal disease cause stroke later on [21]. In addition, the prothrombotic condition in TB meningitis could contribute to stroke [23].

2.4. Radiological Features

Good prognosis depends on prompt diagnosis and treatment; therefore the importance of radiological findings is emphasized [2]. When a patient presents with a suspicion of TB meningitis, CT and MRI can be used to support the diagnosis and to look at the abnormalities of the brain and spine [2,8]. Early brain CT can help diagnose TB meningitis will provide important baseline information regarding surgical interventions for hydrocephalus [24].

MRI is also useful to monitor the development of complications of disease [2]. Brain MRI is better than CT in revealing brainstem and cerebellum pathology, tuberculomas, strokes, and the extent of inflammatory exudates [8]. Precontrast hyperdensity in the basal cisterns might be the most specific radiological sign of TM in children [8].

Stroke in tuberculous meningitis (TBM) occurs in 15% - 57% of patients especially in advanced stage and severe disease [25]. Magnetic resonance imaging (MRI) is more sensitive in detecting strokes in particular, acute stroke with diffusion weighted imaging (DWI) [25].

Bilaterally symmetrical strokes of the TB zone were common with TB meningitis (71%) but rare with noninflammatory ischemic stroke (IS) (5%) [23]. Most of the strokes in TBM are multiple, bilateral and located in the basal ganglia [25].

The locations of strokes were studied in 14 patients with TB meningitis and 173 patients with noninflammatory ischemic stroke (IS) in a study in Taiwan [23]. In patients with TBM, 75% of strokes were in the "TB zone" supplied by medial striate and thalamoperforating arteries;

as compared to only 11% occurred in the "IS zone" supplied by lateral striate, anterior choroidal and thalamogeniculate arteries [23]. In patients with IS, 29% of strokes occurred in the IS zone, 29% in the subcortical white matter, and 24% in the cerebral cortex [23]. Only 11% occurred in the TB zone [23].

MRI features of stroke due to TBM are divided into anterior (caudate, genu, anterior limb of internal capsule, anteromedial thalamus) and posterior (lentiform nuclei, posterior limb of internal capsule, posterolateral thalamus) [26]. Cortical strokes can occur rarely because of involvement of proximal portion of the middle, anterior and posterior cerebral arteries, in addition to the supraclinoid part of the internal carotid and basilar arteries [25].

Choroid plexus enhancement with ventricular enlargement on imaging is highly suggestive of TBM [24]. In TBM, MRI shows diffuse, thick, meningeal enhancement [24]. Contrast enhanced MRI is generally considered as the modality of choice [27]. 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%) [27]. A large lipid, lactate peak has been used to specifically identify tuberculomas by magnetic resonance spectroscopy [28].

In summary, the typical changes of TB meningitis are hydrocephalus, tuberculomas, basal cistern, sylvian fissure and gyral enhancement, with stroke at areas supplied by medial striate and thalamoperforating arteries [2,13].

2.5. Biochemical Markers

The release of *Mycobacterium tuberculosis* into the subarachnoid space results in a local T-lymphocyte-dependent response [8]. T-lymphocyte-dependent response is characterised macroscopically as caseating granulomatous inflammation [8].

In pulmonary tuberculosis, tumour necrosis factor (TNF) is believed to be important for granuloma formation [8]. TNF is also a main factor in host-mediated destruction of infected tissue [8]. Study of animal models of TB meningitis found that high CSF concentrations were associated with poorer outcome [8]. In a series of 16 patients with TB meningitis, TNF-α is found in 32% of patients [29]. Another case series reported that there was a tremendous increase in the levels of serum and CSF TNF-α in TB meningitis patients compared to 20 age and sex-matched controls [30].

Protein levels of interleukin-6 (IL-6) were increased in patients who had presence of tuberculoma and increasing exudates [29]. The cytokine levels however did not significantly correlate with stage of meningitis, clinical outcome and radiological imaging [29].

TB meningitis results in bacteria replication, which caused an increase in IL-8, interferon-alpha (IFN-alpha) and IFN-gamma [8]. The replication of the organism also

caused a rise in CSF white blood cells (neutrophils and lymphocytes) and IL-10 [8]. There is also an increase in the level of CSF matrix metalloproteinases and CSF tissue inhibitors of matrix Metalloproteinases [8]. This results in increased CSF lactate and CSF protein, with reduced CSF glucose and breakdown of blood brain barrier [8].

In addition, other cytokines, such as, IL-6, IL-10, and IL-1β are significantly higher in patients compared to controls, and the levels are reduced after three months of antituberculous therapy [29]. Levels of IL-6 are increased in patients with tuberculoma and worsening of exudates [29].

Serum and CSF IFN-γ levels are significantly associated with a marked rise in TB meningitis patients [30]. An increase in TNF-α and IFN-γ levels, especially in CSF, despite that these patients have multidrug therapy suggests the persistence of central nervous system inflammation [30]. The continuous release of cytokines despite these patients undergoing anti-tubercular therapy suggests that TBM severity may result mainly from the immune response rather than the organism itself [30].

Nitric oxide (NO) causes vascular and perivascular inflammatory central nervous system changes, which are possible aetiologies of tuberculous encephalopathy [20]. The nitric oxide (NO) levels of serum and CSF are higher significantly in TB meningitis patients [30]. There is no correlation between NO levels and severity of TB meningitis [30].

Neutrophils have a role in pathogenesis of TB meningitis [8]. The lymphocyte response, mainly the roles of different lymphocyte subsets are also important [8].

Signal-regulatory protein alpha (SIRPA) and protein disulfide isomerase family A, member 6 (PDIA6), is overexpressed at the mRNA level in TB meningitis [31]. The proteins, amphiphysin (AMPH) and neurofascin (NFASC) are overexpressed in TB meningitis [31]. Ferritin light chain [FTL] is downregulated in TB meningitis [31].

Infection with *Mycobacterium tuberculosis* results in activation of caspase-1 and IL-1β secretion [32]. Potassium efflux and the lysosomal proteases cathepsin B and cathepsin L are required for the Mycobacterium tuberculosis-induced caspase-1 activation and IL-1β production [32]. Tumour necrosis factor-α causes caspase-1 cleavage and IL-1β secretion [32]. In addition, there is also a rise of NLRP3 inflammasome (composed of NLRP3, ASC, and cysteine protease caspase-1) [32].

TB meningitis patients have higher serum vascular endothelial growth factor (VEGF) level [33]. Increase in VEGF level is associated with shorter duration of illness, MRI features of stroke, and paradoxical response [33].

In summary, biomarkers such as TNF-α, IL-6, IL-10, IFN-alpha and IFN-gamma aid with the diagnosis of TB meningitis.

2.6. Treatment and Management

Prompt diagnosis and early treatment are crucial [5]. Decision to start antituberculous treatment is often empirical [5]. WHO guidelines recommend a 6 months course of antituberculous treatment; however, other guidelines recommend a prolonged treatment extended to 9 or 12 months [5]. The recent British Infection Society guidelines indicate that treatment for TBM should comprise isoniazid, rifampicin, pyrazinamide and ethambutol for two months followed by isoniazid and rifampicin for at least 10 months [6]. Isoniazid is the most important of the first-line agents because of excellent CSF penetration and high bactericidal activity [34].

Streptomycin can be used instead of ethambutol as the fourth anti-TB agent but none of the drugs penetrates the CSF well in the absence of inflammation [34]. Other second-line therapy options includes ethionamide (bactericidal), cycloserine (bacteriostatic), para-aminosalicylic acid (bacteriostatic), aminoglycosides such amikacin (bactericidal), capreomycin (bacteriostatic), and thiacetazone (bacteriostatic) [34]. Ethionamide,is used in South Africa [35].

A recent study showed that a higher dose of rifampicin (600 mg, or 13 mg/kg) and standard-dose (400 mg daily) or high-dose moxifloxacin (800 mg daily) during the first two weeks is safe in patients with TB meningitis [36]. High dose intravenous rifampicin is associated with reduced mortality in TB meningitis patients with advanced disease [36].

The emergence of drug resistant tuberculosis poses a serious threat to the control of TB, and the development of drugs against the resistant strains is essential [1]. Resistance to antituberculous medications is associated with a high mortality [5].

Corticosteroids (dexamethasone) with antituberculous treatment reduce mortality and morbidity [1,5,6,23,37,38]. Adjunctive corticosteroid therapy more than two weeks improves survival, but treatment for more than 4 four weeks of use do not have effect on mortality [38]. Aspirin also reduces mortality [39]. Corticosteroids reduce the proportion of stroke after two months [11]. Corticosteroids result in decrease of hydrocephalus an stroke, therefore may affect clinical outcome [11]. Corticosteroids results in decrease of maturation of IL-1β through inhibition of mitochondrial reactive oxygen species generation [32]. Corticosteroids also reduce inflammasome activation [32].

Patients with hydrocephalus might require ventriculo-peritoneal shunting [5]. Bacillus Calmette-Guérin [BCG] vaccination protects to some degree against tuberculous meningitis in children [5].

2.7. Complications and Prognosis

The patients with TB meningitis with hydrocephalus will have worse prognosis and greater mortality [40]. The factors that are associated with hydrocephalus are stage three of disease, duration of illness (more than two months), and presence of neurological deficits such as, weakness with disability [40]. The presence of clinical features, such as, double vision, convulsions, visual blurring, papilloedema, and cranial nerve palsies are also positively associated with hydrocephalus [40]. CSF total cell count (more than 100/cu.mm), and CSF protein > 2.5 g/l are also associated with the presence of hydrocephalus [40]. Patients with TB meningitis with hydrocephalus requiring cerebrospinal diversion had a higher risk of significant short-term mortality [41].

Neuroimaging factors that are significantly associated with hydrocephalus are basal exudates, tuberculoma and strokes [40]. Multivariate analysis demonstrated that visual impairment, cranial nerve palsy and the presence of basal exudates as significant predictors of hydrocephalus [40]. Some patients with early TB meningitis can possibly have complete resolution of hydrocephalus [40].

The presence of stroke on admission, Glasgow coma scale ≤ 8 on admission, age of ≥30 years and presence of hydrocephalus with ventriculo-peritoneal shunt was significantly associated with mortality [41]. There was increased mortality according to British Medical Research Council grade with statistical significance [41]. TBM with hydrocephalus which needed cerebrospinal diversion had a higher risk of significant short-term mortality [41].

Poor conscious state was significantly associated with poor prognosis in TB meningitis patients [38,42]. Severity of disease at admission and delayed anti-tuberculous therapy was related to poor outlook for TB meningitis patients [38].

1/5 of the patients have complete neurological recovery in one year occur in 1/5, but only 50% of them are independent for activities of daily living [43]. As for the rest of the patients, they have neurological sequelae, such as, cognitive impairment, motor deficit, optic atrophy and other cranial nerve palsies [43]. Motor deficit on admission, such as hemiparesis, is the most important predictor of neurologic deficits in one year [42,43]. GCS score is a good predictor of cognitive and motor sequelae [39]. Sequelae are common in patients who have focal motor weakness, change of sensorium at admission and GCS level [43]. Cognitive impairment is significantly associated with exudates and tuberculomas [42]. Motor deficits are significantly correlated with strokes [42].

Positive TB culture and polymerase chain reaction of CSF are factors associated with poor prognosis [38].

Serial CT scan at three and six months is abnormal in most TB meningitis patients [42]. At six months, hydrocephalus, tuberculomas and exudates will disappear but changes of stroke remain the same [42].

A third of patients with TB meningitis may deteriorate within six weeks of initiation of treatment [42]. Worsening on treatment is related to motor weakness and GCS on admission [42]. Age less than one year old and presence of severe TB are risk factors for failure of antituberculous therapy [44].

3. Conclusions

The diagnosis of TB meningitis is difficult because of nonspecific presentation and clinical features. Good prognosis depends on prompt diagnosis (before further neurological deterioration) with treatment; therefore radiological findings are very important. A recent study has shown that high dose intravenous rifampicin (800 mg daily) is associated with reduced mortality in patients with advanced disease.

Analysis of biomarkers in TB meningitis is important. There is an increase in the levels of serum and CSF TNF-α and IFN-γ in TB meningitis patients. IL-6 level is also increased in patients with tuberculoma and exudates. There is also a rise in the levels of IL-8, IFN-alpha, IFN-gamma, IL-10, CSF matrix metalloproteinases, CSF tissue inhibitors of matrix Metalloproteinases, VEGF level, caspase-1 and IL-1β. Signal-regulatory protein alpha is overexpressed at mRNA level.

There is advancement of research for TB meningitis. The TB meningitis research is rapidly progressing. In future, we will be able to see the development with respect to treatment and management of disease. Through the knowledge of biomarkers, better and more advanced antituberculous therapy can be developed.

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