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REVIEW ARTICLE

Tuberculous meningitis in Asia

Lin Zhang *BS*, Guodong Feng *PhD MD*, Gang Zhao *PhD MD*

Deparment of Neurology, Xijing Hospital, Fourth Military Medical University, Xi'an, China.

Abstract

Tuberculous meningitis is an important global medical problem which gives rise to high morbidity and mortality. It is the most severe form of extrapulmonary *Mycobacterium tuberculosis*. Comprehensive prevention effort, prompt diagnosis and rational treatment are all keys to improving treatment outcomes; yet many unsolved problems remain. On the other hand, the new problems, such as HIV co-infection and drug-resistance are posing important challenges. This review outlines the epidemiology, pathogenesis, diagnosis, management and prognosis of tuberculous meningitis. We mainly focus on research carried out in the recent decades, giving special attention to the work done among the Asian populations.

INTRODUCTION

Tuberculous meningitis (TBM) is a common and the most severe form of extrapulmonary tuberculosis (TB) whose mortality and morbidity is close to half of the patients affected.[1] TB has been a challenge worldwide for many years. Although the spread of TB is already partially controlled sometime in the past history, the incidence of severe and drug resistant TB has been shown to increase in the last 20 years, partly due to the population mobility, the spread of HIV infection, and the wide use of immuno-suppressive agents, resulting also in the increase in the number of TBM patients. Children and adults co-infected with HIV are particularly vulnerable to TBM.[2-4] Since the clinical manifestations of TB infection are non-specific, and diagnostic methods are insensitive, these often result in the delay of diagnosis, affecting the outcome of treatment and prognosis. Consequently for TBM, we still encounter many challenges.[2] In this paper, we mainly focus on the burden of TBM among Asians, to draw attention to researchers and physicians practicing in the region.

EPIDEMIOLOGY

According to estimate by the WHO, there have been approximately 8.8 million new TB cases every year until 2010, of which 1.45 million died. Of these, India, China, Indonesia, Nigeria and South Africa have the most number of cases[5], among which the first three countries belong to Asia.[6] Especially in the developing countries with poor resources, the morbidity is high, due to poor sanitary conditions, delayed diagnosis, non-optimal treatment, and inadequate immunization by BCG. In comparison to other regions, the number of HIV-negative TBM cases remains the majority in Asia.

There are six main lineages of *Mycobacterium tuberculosis* which has a clonal genetic population structure that is restricted in their geographic distribution.[7,8] In terms of Asia strains, four lineages dominated. They are Indo-Oceanic lineage, East Asian lineage, East African-Indian lineage, Euro-American lineage. Sebastien *et al.* found that the first and second lineages are found mainly in the East and Southeast Asia, the first and third lineages in the Indian subcontinent, and the second and fourth lineages are seen mainly in Central Asia.[9]

CLINICAL PROFILE

It is acknowledged that the key factor to effective treatment and improved outcome is early diagnosis.[6] However, the early clinical manifestations of TBM are often non-specific. Malaise, anorexia, fatigue, myalgia, and headache are the most common nonspecific symptoms. In most TBM patients, there is a history of symptoms of being unwell of over two weeks prior to the development of meningeal irritation. Patients can also present with symptoms of less than a week.[5] Adult patients often present with the classic meningitis symptoms of fever, headache, stiff

Address correspondence to: Dr. Gang Zhao, Department of Neurology, Xijing Hospital, Forth Military Medical University.No.15 Changle-Xi Road, Xi'an, Shaanxi province, China. Email: zhaogang@fmmu.edu.cn

neck, with focal neurological deficits, behavioral changes and change in consciousness. On the other hand, children often present with fever, stiff neck, seizures, vomiting, alteration in sensorium and cranial nerve palsies. Headache occurs less often and sometimes absent.[5,10] Optic nerve abnormality is also a common abnormality.[10]

HIV-infected patients are more likely to have extrameningeal involvement with abnormal clinical findings outside the central nervous system (CNS).[11]

PATHOGENESIS

In the early course of *M. tuberculosis* infection, bacteremia is a critical step for the extra-pulmonary dissemination and essential for the development of meningitis.[12] Investigators have demonstrated that the TBM was triggered when an earlier bacteremia phase resulted in formation of the tuberculous granulomas (or Rich foci), which released the bacteria into the subarachnoid space.[13] To date, this pathological process is well accepted as the key process in the development of TBM.

A number of investigations have focused the gene, *Rv0931c* (also called *pknD*) which encodes a serine/threonine protein kinase. This kinase is thought to play an essential role in brain endothelial invasion in association with TBM.[14-17] There is another mycobacterial gene, *plcD*, whose polymorphisms has been found to be associated with extrapulmonary tuberculosis.[18] However, there are still many uncertainties in this, while the pathogenesis mechanism continues to unravel.

PATHOGEN GENETIC

The whole genome of *Mycobacterium tuberculosis (Mtb)* has been sequenced.[19] A considerable amount of research has been performed concerning the various TB strains during the last decade. There is growing evidence that the genetic diversity of *Mtb* may contribute to the variance in virulence, dissemination, immuneregulation, as well as clinical manifestations and outcome.[20] For example, Beijing and Indo-Oceanic strains were more likely to cause disseminated tuberculosis than those from the Euro-American lineage in Vietnam.[21] Furthermore, Euro-American lineage strains were less likely to cause TBM than strains from the Indo-Oceanic or Beijing lineage.[7]

The Beijing genotype has in particular been more extensively investigated recently. It is distributed widely in Asia. It is associated with a number of characteristics. The Beijing genotype shows significant association with HIV status, and drug resistance.[22-25] The Beijing lineage of *Mtb* has been shown to be of increasingly virulence, which is associated with many outbreaks[26], and extra-pulmonary TB.[27] This genotype is thought to be less sensitive to BCG vaccination.[28-30] It is also associated with a shorter duration of symptoms, and lower numbers of CSF leukocytes. This in turn suggests an influence on disease progression and intracerebral inflammatory response, which in turn will affect the mortality rate and clinical outcome.[20]

These characteristics have been partly attributed to the capability of Beijing strains to produce a kind of phenolic glycolipid that weak the host's innate immune response, and thus the ability to control the infection.[31] However, the specific mechanism involved is still unsolved.

DIAGNOSIS

Early diagnosis and treatment are keys to better outcome in TBM. Although there is a proposed scoring system to facilitate early diagnosis, till to date, there are no widely accepted guidelines to diagnosis of TBM.[1,32]

Microbiological

The gold standard for diagnosis of TBM is the detection of acid fast bacilli (AFB) in the CSF samples, either by Ziehl–Neelsen (ZN) smear microscopy or *Mtb* isolated by culture. But the sensitivity of the two techniques is still at 10-20% and 8.6% –55% respectively. Furthermore, culture result of *Mtb* takes time. To depend on the result to commence therapy will result in treatment delayed.[33-35] To overcome this, increasing the sample volume (minimum 6 ml) and duration of slide examination could increase the sensitivity of smear microscopy up to 60%.[36] Filtration of CSF is another simple method to improve mycobacterial isolation.[37] Fluorescent microscopy using specified fluorochrome dye has improved the sensitivity of smear microscopy by approximately 10% and reduce the examination time.[38] Cheaper light-emitting diode fluorescent microscopes have further improved this technique.[39] Investigators from China have developed a modified Ziehl-Neelsen stain, by pretreatment with Triton X-100, which can clearly identify *Mtb* within the immune cells and significantly improved detection of extracellular *Mtb* from a very small amount (0.5ml) of CSF samples.[40] Another approach proposed is to combine this modified Ziehl-Neelsen stain and white cell ESAT-6 immunocytochemical staining

of CSF, which has been found to improve the sensitivity to 90.0%.[41] All these can potentially improve the early diagnosis of tuberculosis, and may also provide new insights into the pathogenesis and immunological characteristics of tuberculosis.

Nucleic acid amplification techniques (NAATs)

During the past decade, technological revolutions have been seen in the development of nucleic acid amplification techniques (NAATs). The advent of Xpert MTB/RIF technology has had a significant impact on the MTB diagnosis which shows both high sensitivity (27-86%) and specificity (99-100%) in CSF culture, in addition to screening rifampin-resistant strains.[33,42,43] Besides, studies have showed Xpert MTB/RIF assay to be potentially a good rule-in test for the diagnosis of TBM in HIV-infected populations.[44] Although the results are truly impressive, the value of diagnosis in CSF still needs to be confirmed. Although this kind of method is easy to operate, there are challenges for adopting this technology in source-limited regions.[35]

Another latecomer NAATs used for TB diagnosis is the loop-mediated isothermal amplification (LAMP), which is simple, rapid and cost-effective because it do not need special equipment and skilled technologists.[45,46] One study evaluating the use of LAMP on CSF for TBM diagnosis has demonstrated a high sensitivity88% and specificity 90%.[33,47,48] Overall these technologies are still being investigated, in terms of further refinement of techniques as well as applications.

Interferon-gamma release assays

Interferon-gamma (IFN-γ) plays a major role in the immune response to MTB, thus the measurement of interferon-gamma release in response to stimulation with specific MTB antigens, has been used to diagnose TB infection.[35] The sensitivity and specificity of this method on CSF specimens is estimated to be 89-100% and 50-82% respectively.[33] This testing assay may be combined with other rapid testing kits to enhance its clinical usefulness.

Microscopic observation drug susceptibility assay (MODS)

MODS is a newly emerging inexpensive and simple technique that can identify drug-resistant *Mtb* through drug susceptibility testing (DST) in liquid culture. In TBM patients, MODS on CSF specimens, with sensitivity of 65% and specificity of 98-100%, using a mean CSF volume 4.6 ml, promises several advantages. There is significantly short detection time of median 6 days.[33] The method is also simple to operate, and of low costs.[49-51]

Biomarkers

Biomarkers have also been used to screen for diagnosis of TB[52], among the methods used are MTB-specific antigen and antibody, with sensitivity of 84-94%, and specificity of 92-99%.[33] Lipoarabinomannan (LAM) is a MTB cell wall lipopolysaccharide antigen, which has been proposed to be used for TBM diagnosis in immune suppressed HIV-infected patients, and have been shown to have a sensitivity of 64% and specificity of 69%.[33,53] There are other biomarkers candidates being investigated.[54]

Imaging

Computed tomography and magnetic resonance imaging are commonly used in the evaluation of TBM. It can help to identify the complications and assessing responses to treatment. Studies have shown that the most common imaging features of TBM are hydrocephalus, tuberculoma and meningeal enhancement.[35] Brain CT, particularly with contrast enhancement, can also reveal basal meningeal enhancement, infarcts, hydrocephalus, and tuberculomas.[55] MRI is superior to CT at early diagnosis since it can define the neuroradiological features of TBM better, especially when they involve the brainstem.[2,35] MRI showing optochiasmatic arachnoiditis and hydrocephalus have been shown to be significant predictors of cranial neuropathy, which are associated with poor outcome.[56]

MANAGEMENT

As for treatment, WHO and UK Guidelines have recommended the use of rifampicin, isoniazid, pyrazinamide and streptomycin (or ethambutol) for 2-3 months in the intensive phase, followed by at least 6-month treatment with rifampicin and isoniazid[32](WHO).

The penetration capacity of blood-brain barrier is the first concern when choosing the anti-tuberculous drugs. According to the investigation, isoniazid and pyrazinamide penetrate more easily.[57,58] Rifampicin penetrates the CSF less

efficient, but the high mortality owning to rifampicin resistant TBM has confirmed its key role in the treatment of CNS disease.[59] It is been demonstrated that increasing the dose of rifampicin (13 mg/kg) may lead to higher sterilize activity in the brain and in turn result in a higher survival rate.[60,61] Ethambutol and streptomycin's penetration of blood-brain barrier is poor and have severe side effects. Thus, patients taking these two medications should be under close monitoring, with use of alternative drugs when indicated.

Fluoroquinolones is an outstanding option for the treatment of TBM especially for multidrug resistant cases. Previous research has found levofloxacin to have excellent CSF penetration as compared to gatifloxacin and ciprofloxacin.[62]

Adjunctive corticosteroids have been advised to be used in TBM.[32] This is because of corticosteroids' effect on the inflammatory response of patients which could directly associated with morbidity and mortality.[63] There have been a series of recent studies indicating that the use of dexamethasone should be tailored to individuals according to the polymorphism of LTA4H gene.[64,65] Further studies should thus be carried out among different populations including among Asians with larger sample sizes to investigate these.

Drug-resistance TBM

Drug resistance may be a greater challenge in TBM than in other forms of TB. There are no uniform recommendations how to manage MDR-TBM. The treatment should be tailored to drug susceptibility test and CSF penetration. A study based on 489 Chinese TBM patients suggested that resistant to fluoroquinlones strains are few (2/25, 8.0%).[67]

PROGNOSIS

The outcome of TBM is poor and undoubtedly lead to high morbidity and mortality which we have mentioned before. Overall, approximately 26% of the patients has good outcome, 16% had moderate disability, 7% were severely disabled and the mortality is 51%.[66] The major prognostic factors influencing survival and disability include the delay in treatment, TBM severity grade upon admission, the occurrence of stroke, seizures, hyponatremia, hydrocephalus, cranial nerve involvement, CSF cell count and lactate level, HIV co-infection and multidrug resistance.[35] Hydrocephalus is more common in children than adults, and patients with communicating hydrocephalus should be treated by ventriculo-peritoneal shunting.[67]

CONCLUSIONS

This review summarizes the recent investigation of TBM, and suggests some future directions of research for TBM. The emphasis is on studies performed in the Asia populations. Although a lot of efforts have been placed on improving the diagnosis and care of TBM particularly in the developing countries, much more things need to be done. There are three particular issues on TBM in Asia, besides India and China, a number of other developing countries in Asia are also seriously affected by TB. However, because of smaller population, there is inadequate attention given to these countries. Secondly, the most common strain in Asia is Beijing type which is the most virulent, and the most difficult to treat. There also an urgent need for further research to clarify the pathogenesis process, optimal diagnostic strategies as well as the uniform guidelines on treatment. There should also be strengthening of the international cooperation to synergize the resources and enhance the TBM research.

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