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Tuberculous Meningitis

Pathoprofile

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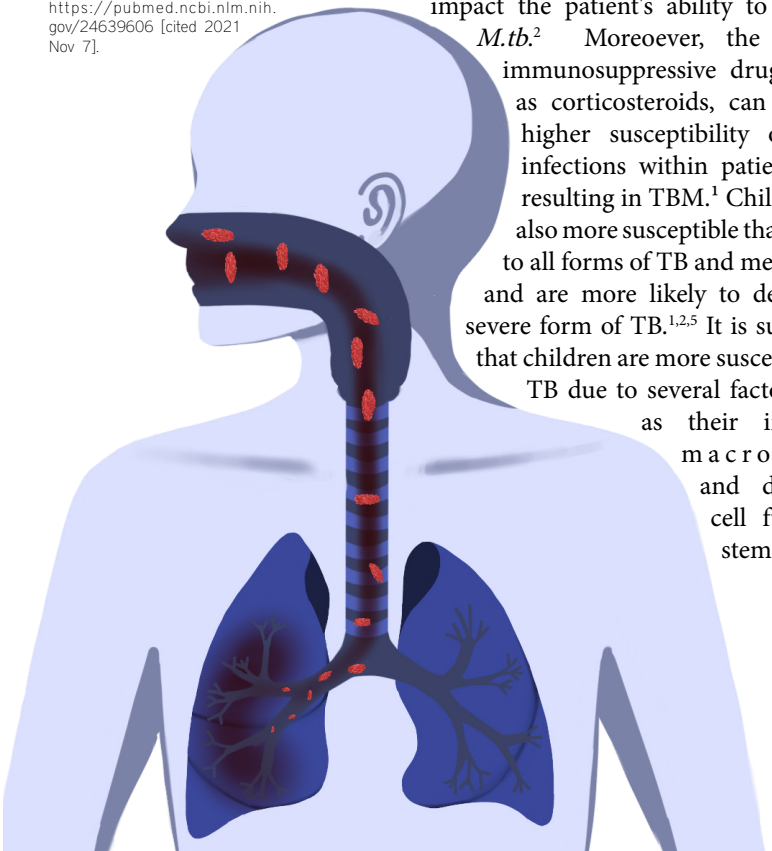
INTRODUCTION

With a death rate of 20-50%, tuberculous meningitis (TBM) is the most lethal form of one of the world's most devastating infectious diseases.[1-3] *Mycobacterium tuberculosis* (*M.tb*), the pathogen responsible for infiltrating cells, does so via parasitizing macrophages.[1] In TBM, *M.tb* travels from the lungs through the lymphatic system and infects the meninges of the central nervous system (CNS).[1,2] Through activation of the microglia, the predominantly affected cells in TBM, a pro-inflammatory response is initiated, beginning a cascade of pathological events that result in host damage and poor patient outcomes.[4]

RISK FACTORS

Infection with human immunodeficiency virus (HIV) is the most observed comorbidity for patients with TBM, with the severity of disease increasing if HIV is left untreated.[2] In fact, HIV positive patients are five times more likely to develop tuberculosis (TB) of the CNS and, overall, extrapulmonary-TB has become significantly more prevalent since the beginning of the HIV/autoimmune deficiency syndrome (AIDS) epidemic.[2] Additional predisposing conditions, including diabetes mellitus and silicosis, have also been observed to negatively impact the patient's ability to combat *M.tb*.[2] Moreoever, the use of immunosuppressive drugs, such as corticosteroids, can lead to higher susceptibility of *M.tb* infections within patient cells, resulting in TBM.[1] Children are also more susceptible than adults to all forms of TB and meningitis, and are more likely to develop a severe form of TB.[1,2,5] It is suspected that children are more susceptible to TB due to several factors such as their impaired macrophage and dendritic cell function, stemming from their lack of immunologic maturity.[11] Diagnosis in children is also more complex due to the lack of acid-fast bacillus in sputum, which is often observed in adult patients.[11] This causes additional concern as prompt treatment is necessary in effectively combating infection.[1,3,5]



DIAGNOSIS

TBM is a rare infectious disease that clinicians have trouble diagnosing due to its unfamiliar nature.[1] Magnetic resonance imaging (MRI) is typically the first diagnostic tool used for patients presenting with TBM symptoms, including hydrocephalus, infarction, and basal enhancement.[1,2] In brief, any abnormal shift or growth in the CNS is indicative of infection.[1,2] Unfortunately, imaging is not always accurate as symptoms may not present in early stages of infection. Furthermore, it is crucial that increased intracranial pressure is identified before conducting the next step in diagnosis, the lumbar puncture, in order to avoid causing herniation of the cerebellar tonsils.[1,2,6] There are several characteristics in the cerebrospinal fluid (CSF) that indicate the presence of *M.tb*, including low glucose, high protein, and high lymphocyte counts.[1] The determining factor, however, is the presence of acid-fast bacilli in the CSF, which confirms the diagnosis of TBM.[2] As aforementioned, TBM is the most lethal form of TB, with a mortality rate of 40% and 80% in patients presenting with symptoms 2 weeks and 4 weeks post-infection, respectively.[1,2,4] Consequently, current diagnostic techniques are imperfect as they lack the sensitivity required for early diagnosis, which is vital for improving chances of survival.[1,2,4]

MECHANISM
PART 1: HEMATOGENOUS SPREAD

Initial TB infection is contracted by the inhalation of airborne droplets of *M.tb*.[7] The bacteria crosses the lung epithelium and infects the alveolar macrophages, which secrete various antimicrobial peptides and cytokines.[5] The body's natural immune response can fester into active primary TB, allowing *M.tb* to invade and replicate within the lymphatic endothelial cells (LECs) of the regional lymph nodes.[4] Upon entry into LECs, macrophages phagocytose *M.tb* and carry it across the blood brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) of the CNS.[4] Exogenous *M.tb* are also able to

traverse the BBB and BCSFB by invading the cerebral vascular endothelial cells with the aid of various virulence factors.[4] Once *M.tb* reaches the meninges or brain parenchyma, limited local innate immunity promotes its replication.This leads to development of subpial or subependymal metastatic caseous lesions, called Rich Foci.[4,5] Rupturing of Rich Foci into the subarachnoid space infects the meninges and initiates the meningeal inflammatory response characteristic of TBM.[4,5]

PART 2: INFLAMMATORY RESPONSE

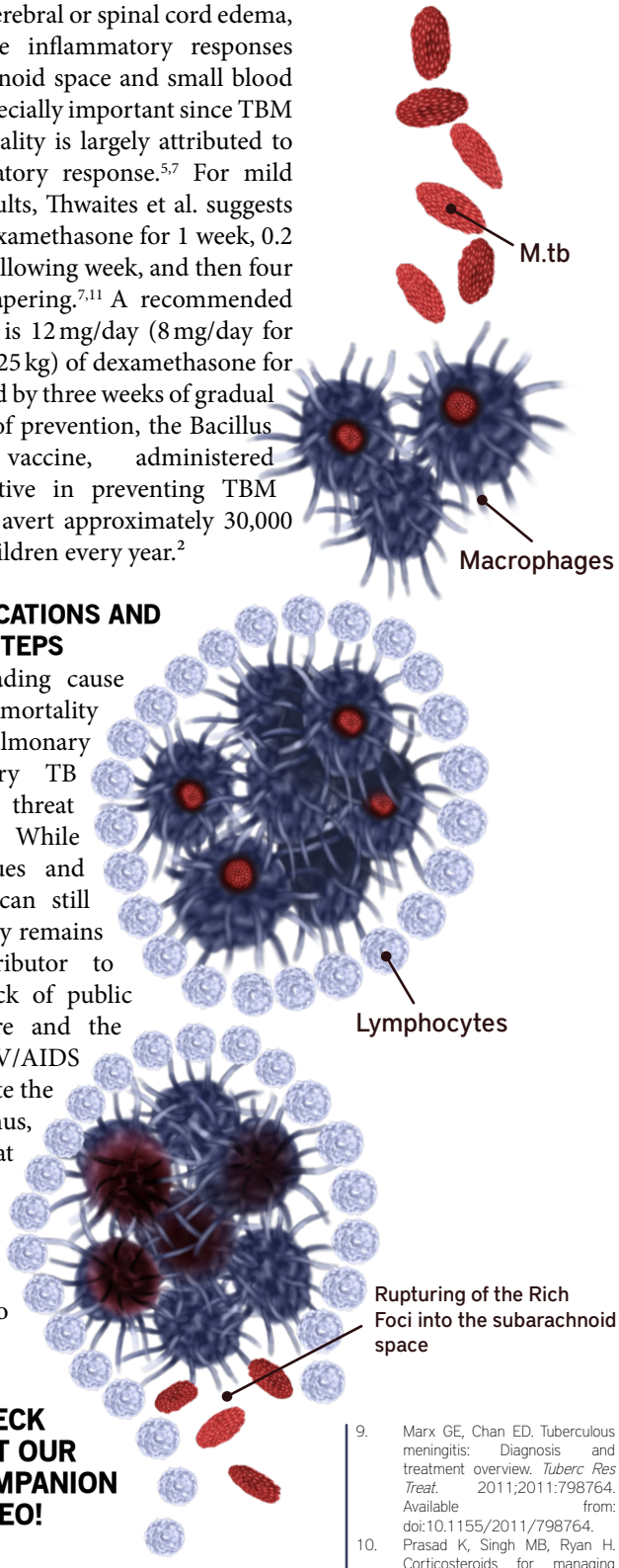
Microglia are the primary CNS cells infected by *M.tb*.[4] Upon activation, microglia secrete a multitude of proinflammatory cytokines, including TNF-α, IFN-γ, IL-6, IL-1, IL-1β, CCL2, CCL5, CXCL-10, IL-1α, and IL-12p40.[4,8] In particular, TNF-α plays a central role in the pathophysiology of TBM by inducing fever and releasing additional cytokines.[4] The permeability of the BBB is also disrupted by TNF-α, IL-6, and vascular endothelial growth factor, allowing for an additional influx of inflammatory mediators into the CNS.[4,6] The ultimate result is the formation of a thick and gelatinous inflammatory exudate in the basal cistern, subarachnoid space, and potentially, the spinal canal.[4,5] As a result, this exudate encases the major cerebral vessels, blocks CSF circulation, and compresses cranial nerves III, VI, and VII, rendering them dysfunctional.[4,5] Downstream complications of TBM include tissue damage, hydrocephalus, vasculitis, cranial nerve palsies, ischaemia, and death.[4,5,9]

TREATMENT

Following presentation of clinical symptoms, rapid treatment is vital to reduce poor patient outcomes.[7] Standard treatment of TBM includes two months of daily antimicrobial therapy, also known as RIPE therapy.[7] It consists of rifampin (RIF), isoniazid (INH), pyrazinamide, and either ethambutol or streptomycin, all of which are bactericidal and are capable of entering the CSF upon meningeal inflammation.[5,7] Daily treatment with INH and RIF is followed for an additional seven to ten months if *M.tb* is susceptible to these agents.[7] Adjunctive corticosteroid therapy is also recommended as it may help reduce brain tissue damage and cerebral or spinal cord edema, as well as mitigate inflammatory responses within the subarachnoid space and small blood vessels.[7,10] This is especially important since TBM morbidity and mortality is largely attributed to the host's inflammatory response.[5,7] For mild cases of TBM in adults, Thwaites et al. suggests 0.3 mg/kg/day of dexamethasone for 1 week, 0.2 mg/kg/day for the following week, and then four weeks of gradual tapering.[7,11] A recommended regime for children is 12 mg/day (8 mg/day for children weighing ≤25 kg) of dexamethasone for three weeks, followed by three weeks of gradual tapering.[7] In terms of prevention, the Bacillus Calmette-Guerin vaccine, administered neonatally, is effective in preventing TBM and is estimated to avert approximately 30,000 potential cases in children every year.[2]

GLOBAL IMPLICATIONS AND FUTURE STEPS

As the seventh leading cause of disability and mortality worldwide, both pulmonary and extrapulmonary TB pose a massive threat to global health.[5] While diagnostic techniques and treatment efficacy can still be improved, poverty remains the greatest contributor to TB.[5] The severe lack of public health infrastructure and the co-epidemic of HIV/AIDS continue to propagate the incidence of TB.[5] Thus, it is imperative that a holistic approach addressing these global disparities is considered for the foreseeable future to combat TBM cases.



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