Tuberculosis Meningitis

Subjects: Others

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Worldwide, Tuberculosis (TB) remains the most important infectious disease in causing morbidity and death. About one-third of the population worldwide has currently contracted TB infection through Mycobacterium tuberculosis. The human host serves as the natural reservoir for M tuberculosis. The underlying mechanisms responsible for successful dissemination of M tuberculosis to the meninges to cause TB meningitis remains poorly understood. Given the magnitude of the health problem and the emergence of drug-resistant strains of the organism, a better understanding of the protective immunity and pathogenesis of TB meningitis, development of reliable rapid laboratory diagnosis, therapeutics and effective vaccine are highly desirable.

Keywords: Tuberculosis ; TBM ; Immunosuppression ; Mycobacterium Tuberculosis ; Meningitis ; Adjunctive Therapy ; Infection ; Glutathione ; GSH

1. Introduction

Worldwide, Tuberculosis (TB) remains the most important infectious disease in causing morbidity and death [1]. About one-third of the population worldwide has currently contracted TB infection through Mycobacterium tuberculosis [1]. Recently, the WHO reported that there are about eight million new TB cases yearly. In addition, the incident of TB is expected to increase [1]. Notably, patients who suffer from immunosuppression are much more likely to contract extra-pulmonary tuberculosis [2][3][4], and of the extra pulmonary variants of TB, TBM shows the highest mortality rate [5][6][7][8].

TBM is characterized as a severe manifestation of TB and usually requires emergent intervention, due to the quick hematogenous dissemination of the tuberculosis bacillus. This dissemination is quickly advanced and seen clinically with focal neurological defects, altered mental status, cerebral infarcts, prolonged fever, and highly likelihood of stroke. The presence of stroke is a general indicator of basal ganglia damage and a poor prognosis at three months [3][4][5][6][7][8]. Unfortunately, TBM is difficult to diagnose due to its clinical similarity with other neurological disease manifestations. It has been concluded in several research articles that a better prognosis is expected through early treatment and diagnosis. Failure to do so is highly associated with death or severe neurological impairment [3][4][5][6][7][8].

2. Pathogenesis, Clinical Presentation of TBM and Adjunctive Therapy

2.1. Pathogenesis of TBM

Extrapulmonary TB begins when the bacteria disseminate from the lungs to the lymph nodes, and during this time, there is bacteremia which seed M. tuberculosis to other organs in the body for TB, specifically the meninges and the brain parenchyma [9][10]. During hematogenous dissemination, mycobacteria may be deposited adjacent to the ventricles or subarachnoid space, leading to granuloma formation at those sites of deposition [11][12]. M. tuberculosis can breach the blood brain barrier (BBB) extracellularly or intracellularly via dendritic cells or macrophages [9][13].

TBM occurs when subependymal or subpial tubercles, also known as “rich foci” seed during bacillemia of primary infection or disseminated disease [9][10][14][15]. This rupture of the granuloma into the subarachnoid space leads to an intense inflammatory response, which eventually causes meningitis [10][11][13][15]. The tissue damage seen in the brain is due to a host inflammatory response rather than over-replication in the CSF [13][15].

The inflammatory response is due to rupture which includes a collection of a tuberculous, thick gelatinous exudate (erythrocytes, mononuclear cells, neutrophils, and bacilli) at the basal brain and vasculitis within the cerebral arterial system, including branches of the middle cerebral artery, the vertebrobasilar system, and the vessels of the Circle of Willis [10][11][16]. All of this can lead to long-term neurological defects from either infarction or compression by the exudate, which can encase cranial nerves and cause nerve palsies, entrapment of blood vessels, and blocking of CSF flow in the cerebral aqueduct to cause hydrocephalus. These processes produce adhesions, obliterative vasculitis (internal carotid, middle cerebral arteries), and encephalitis [10][11][15].

On average, TBM occurs 6 to 12 months after the primary infection, and patients show a prolonged inflammatory response [16]. The risk factors for TBM include malignancy, malnutrition, alcoholism, HIV, the use of immunosuppressive agents, and cortisol deficiency [9][17].

TBM can eventually lead to intracranial tuberculomas in an immunocompromised patient [9][18]. Focal neurological signs result from formation of tuberculomas and abscess after infection, with basal ganglia the most common site of infarction [18].

Although the role of TNF--α is crucial for the formation of granuloma and enhanced killing of infected cells in the lungs during the primary infection, concentrations of TNF-α in CSF correlate with clinical correlation of TBM [19][10]. Intervention with thalidomide, an anti-TNF agent, resulted in an improvement in survival and neurological outcome due to TBM [10].

One study showed that there was also significant elevation of cathelicidin LL-37, interleukin (IL)-13 and vascular endothelial growth factor (VEGF) and reduction of IL-17 in the CSF of children with TBM, compared to children with viral and bacterial meningitis [20]. This biomarker pattern suggests a host immune response which is disease-specific and may be of diagnostic and therapeutic importance [16].

2.2. Clinical Presentation of TB Meningitis

The clinical presentations of TBM have many similar features to those of generalized bacterial meningitis, which include, but are not limited to, headache, fever, stiff neck, nausea, and vomiting. However, according to data obtained from many clinical trials, there are clinical features that are present more commonly in TBM than in generalized bacterial meningitis and may have values in distinguishing TBM in clinical practice. The presence of neurologic signs and symptoms are frequently observed. In a study involving 160 patients, the frequency of altered mental status, change in personality, and coma were noted in 59, 28, and 21 percent of patients, respectively [21]. Cranial nerve palsy is also common and most frequently involve cranial nerve II, which affects vision, and cranial nerve VI, which affects lateral movement of the eyeball. The frequency of cranial nerve palsy was observed in 33 percent of patients in a studying involving 158 patients [22].

TBM has three clinically distinct phases, which are the prodromal phase, the meningitic phase, and the paralytic phase. In the prodromal phase, which lasts from one to three weeks, patients experience nonspecific signs and symptoms, which include, but are not limited to, malaise, headache, low-grade fever, and change in personality. In the meningitic phase, patients experience more prominent neurologic signs, which include nausea, vomiting, headache, lethargy, confusion, and cranial nerve palsies. Finally, in the paralytic phase, the illness progresses quickly, and patients can deteriorate into coma, seizure, and possibly paralysis. For patients in this stage, death follows quickly if they are not treated [23][24][25][26].

Aside from the typical presentations above, TBM can also present atypically in some patients, potentially mimicking other neurologic conditions, complicating the diagnosis and treatment. Instead of an acute condition, it can present as a slowly progressing dementia over a period of years, potentially mimicking Alzheimer, and characterized by personality change, social withdrawal, memory deficits, and impaired executive functions. Alternatively, patients can present with signs of encephalitis instead of meningitis. Signs and symptoms of encephalitis include coma and convulsions [27].

TBM can appear in patients who have no previous history of signs and symptoms from M. tuberculosis infection. In one paper studying 61 patients with TBM, only 6 patients reported that they were aware of previous M. tuberculosis infection [28].

2.3. Adjunctive Therapy

Immuno-adjunctive therapy appears to be promising in improving the outcome of clinical control of refractory mycobacterial infections. Dr. Venketaraman’s research group has reported that individuals with active pulmonary TB exhibit a marked deficiency in glutathione (GSH), the principal non-protein thiol responsible for cellular homeostasis and maintenance of the intracellular redox balance. GSH levels are significantly compromised in peripheral blood mononuclear cells (PBMCs) and red blood cells (RBCs) isolated from individuals with active pulmonary TB and this decrease correlated with increased production of pro-inflammatory cytokines and enhanced growth of M. tuberculosis [29]. GSH possesses a direct antimycobacterial activity in vitro and at physiological concentrations (5 mM) [20][30]. In combination with cytokines such as IL-2 and IL-12, GSH enhances the functional activity of natural killer (NK) cells to inhibit the growth of M. tuberculosis inside human monocytes [31][32]. Similarly, GSH activates the functions of T lymphocytes to control M. tuberculosis infection inside human monocytes [33]. GSH levels have also been shown to be compromised in HIV positive subjects and in individuals with uncontrolled type 2 diabetes (T2DM) who have increased

risks for susceptibility to both pulmonary and extrapulmonary TB [31][33][34][35][36][37][38][39]. Importantly, Dr. Venketaraman's research also demonstrated in the autopsied human brain tissues that the levels of total and reduced forms of GSH were significantly compromised in HIV-1 infected individuals who have increased risks for susceptibility to TBM [40].

Put together, these findings (1) unfold a novel and potentially important innate defense mechanism adopted by human macrophages to control M. tuberculosis infection [20][29][30][31][33][34][35][37][38][41] and (2) indicate that GSH controls M. tuberculosis infection by functioning as an antimycobacterial agent as well as by enhancing the effector functions of immune cells [20][29][30][31][32][33][34][35][36][37][38][41]. However, the underlying mechanisms by which GSH-deficiency alters the immune responses leading to increased susceptibility to TBM remains unknown, and the potential use of GSH as a possible anti-TB therapeutic agent remains untapped.

3. Conclusions

The human host serves as the natural reservoir for M tuberculosis. The ability of the organism to efficiently establish latent infection has enabled it to spread to nearly one-third of the world's population. The underlying mechanisms responsible for successful dissemination of M tuberculosis to the meninges to cause TB meningitis remains poorly understood. Given the magnitude of the health problem and the emergence of drug-resistant strains of the organism, a better understanding of the protective immunity and pathogenesis of TB meningitis, development of reliable rapid laboratory diagnosis, therapeutics and effective vaccine are highly desirable.

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