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Should we Think beyond Dexamethasone in Tuberculous Meningitis (TBM): A Focus on Immunopathogenesis and Adjunctive Treatment?

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Abstract

Tuberculous Meningitis (TBM) is the most serious form of tuberculosis both in children and adults. Even after early detection and treatment late complications like optic atrophy, hydrocephalus, epilepsy and focal neurological deficits is common. Mortality in TBM is very high especially if it is associated with HIV infection. In year 2004 role of dexamethasone was explored in TBM as adjuvant therapy with antitubercular drugs. Since then it is routine practice and guidance to use steroids in TBM for 6-8 weeks of initial treatment. Mortality is undoubtedly reduced after use of steroids in TBM but its role in reducing morbidity is still unclear. Immunopathogenesis of TBM showed major role of Interferon gamma and Tumor Necrosis Factor alpha (IFN/TNF) for causing various secondary complications. But steroids had little impact on IFN/TNF pathogenesis so how they work in TBM is still in doubt. Later on adjuvant treatment with aspirin and thalidomide was also explored in TBM. Our review is presented to highlight all these aspects in last 2 decades and future prospects for better outcome in TBM patients.

Keywords: Tumor necrosis factor; Tuberculous Meningitis (TBM); Immunopathogenesis; Tumor Necrosis Factor (TNF); Aspirin

Introduction

According to one estimate from World Health Organization (WHO) in year 2019, 10.4 million people become ill with tuberculosis each year and about 1% suffered from Tuberculous Meningitis (TBM) [1]. TBM is the most serious extra-pulmonary complication of tuberculosis. According to clinical and investigation findings three TBM can have three levels of diagnostic confirmations; definitive, probable and possible. Definite TBM was defined as clinical meningitis (nuchal rigidity and abnormal cerebrospinal fluid parameters) and acid-fast bacilli seen, or *M. tuberculosis* cultured, from the cerebrospinal fluid. Probable TBM was defined as clinical meningitis and one or more of the following: Suspected active pulmonary tuberculosis on chest radiography; acid-fast bacilli found in any other specimen; clinical evidence of other extrapulmonary tuberculosis. Possible TBM was defined as clinical meningitis and at least four of the following: History of previous tuberculosis; predominance of lymphocytes in the cerebrospinal fluid; illness duration 5 days; cerebrospinal fluid-blood glucose 0.5; altered consciousness; yellow cerebrospinal fluid; and focal neurological signs [2]. According to severity of signs and symptoms patients of TBM can be graded into three stages from 1 to 3. According to modified British Medical Research Council (BMRC) criteria, stages of TBM are as follows; stage I disease patients had a score on the Glasgow coma scale of 15 (possible range, 3 to 15, with higher scores indicating better status) with no focal neurologic signs; patients with stage II had a score of either 11 to 14, or of 15 with focal neurologic signs; and patients with stage III had a score of 10 or less with focal neurological signs [3]. Prognosis of TBM depends on stage of disease, bacterial virulence, and drug responsiveness. TBM is associated with high death rate and reported data suggest 25% mortality in HIV negative TBM while 65% mortality in HIV positive cases. About 50% of TBM survivors are left with permanent neurological deficit even after full and adequate treatment [4]. Up to 57% patients of TBM who undergo MRI testing and 22%-56% on autopsy study showed cerebral infarction as complication but it is much higher in children and reaches up to 80% [5]. The most important acute complications of TBM include raised intracranial pressure (including hydrocephalus), seizures, and cerebral infarctions.

Literature Review

Various adjuvant treatments are recommended for reduction or prevention of TBM related death and complications [6]. In last two decades main stay of adjuvant treatment along with adequate antitubercular regimen is steroids supplementation for initial phage of treatment. But the adjuvant steroids treatment had not shown consistent benefits in reducing TBM related complications especially cerebral infarction. The current knowledge of immunopathogenesis in TBM cases and alteration of immune cascade by steroids is still not clear and under exploration. The purpose of this review is to find out current status of immunopathogenesis of TBM and role and mechanism of corticosteroids with or without other adjuvant therapy like aspirin and thalidomide.

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Immunopathogenesis of TBM

Entry and initial containment of tubercular bacteria: As first step the infectious droplets of TB Bacilli reaches to macrophages and dendritic cells of lung alveoli. Under the influence of IL-12 and chemokines CCL 19/21 these infected cells migrate to local draining lymph nodes [7]. T helper cells–1 in lymph nodes release Interferon (IFN) gamma and Tumor Necrosis Factor (TNF) alpha which helps for the development of containment zones of TB bacteria in form of granuloma and results into latent infection. In future, development of any immunocompromized state will leads to reactivation of this latent infection. Pathogenesis of tuberculosis is the product of the interaction between bacterial virulence and host immunity. About one third of world population is exposed to infection and only 5% of exposed persons really develop disease that eventually results in 8 million new cases per year [8]. Tuberculosis is an index disease of HIV infected individual and develops when CD4 number are still much higher than those with other opportunistic infections. The acquired cellular response, as represented largely by CD4 T cells that provides protective immunity and the rapidity of cellular response in important factor to prevent bacterial entry and routing to containment zone. Therefore, if burden or bacterial load at the time of exposure is too high then cellular response can't prevent them to make a permanent latent focus in body. Studies later confirmed that both CD4 T cells response and cytokines mediated macrophages activation were the primary mediators for anti-tuberculous immunity. After low dose Mycobacterium exposure, first cellular response can only be appreciated at about 9th day of exposure and then activation of cellular response is seen in form of CD4 and CD8 cells proliferation, followed by development of T effectors cell at around third week of exposure for complete control over invading organism [9].

Dissemination to blood stream: Mycobacteria which are able to survive, can replicate in macrophages and lymphatic endothelium surrounding the granuloma in lymph nodes. Mycobacterial genetic locus that is termed as "Region of Difference 1" (RD1) helps the bacteria to escape them from phagosomes of cytosol. Various other mechanisms are also responsible for the dissemination of TB bacilli into blood stream from bacterial containment zone. These mechanisms are based on either increase cell lysis or transfer of bacteria without cell lysis. Bacterial proteins like Early Secretary Antigen 6 kDa (ESAT 6) and Culture Filtrate Protein 10 (CFP 10) are involved in cell lysis while Heparin Binding Hemagglutinin (HBHA) helps the mycobacterium for the translocation across the epithelium without lysis.

Dissemination to brain: Brain is protected from invasion of bacteria by two barriers known as blood brain barrier and blood CSF barrier. *Mycobacterium* gene *Rv0931c* is identified as potential virulence factor responsible for CNS invasion of mycobacteria. Another potential rout of entry is through "Trojan Horse" where it is trafficked in infected macrophages and neurtrophils across BBB [10]. After TB bacilli enter to brain limited local innate immunity allow their survival and replication in local tissue and it helps in development of silent tubercular lesions in brain. TBM results from rupture of one of these lesions known as "Rich Focus" located under cortical pia or adjacent to meninges or ventricles, which release mycobacterium in subarachnoid space causing granulomatous inflammation of meninges.

Host immune response to tuberculosis in brain: Microglia is the principal CNS cells in brain which get first encounter with tubercular bacilli although astrocytes and neuronal cells can also be directly infected by TB bacteria. TB bacilli are recognized by Microglial cell with the help of innate immunity and neuro-specific receptors including Pattern Recognizing Receptors (PRR). Toll Like Receptors (TLR), a family of ten pattern recognition molecule plays a crucial role in innate immunity. Internalization of TB bacteria by microglia cells is dependent of CD14, a monocyte differentiation antigen, which bind to lypopolysaccharide with TLR–4. Activation of microglia leads to cytokines release plays a crucial role in host defense to mycobacterial infection but can also induce inflammatory response leading to secondary injury. Tumor Necrosis Factor (TNF) alpha is central factor for the pathogenesis of CNS tuberculosis. It plays important protective role with intense immunological response and mobilization of other cytokines to local area [11]. TNF alpha is responsible for febrile response by activation of hypothalamic adrenal axis by triggering release of other cytokines. Direct correlation is being demonstrated with levels of TNF alpha and extent of cerebral pathology as measured by CSF leukocytosis, protein accumulation, meningeal inflammation, persistence of bacillary load and clinical deterioration. Concentration of CSF IL-6 is also independently associated with disease severity in TBM patients. Thus if we have targeted molecules to control TNF alpha and IL-6 related cascade then we can limit the TBM related complications to some extent.

Recent focus has turned to the pathogenic role of inflammatory mediators such as DAMPs (Damage Associated Molecular Patterns) and PAMPs (Pathogen Associated Molecular Patterns) in secondary CNS injury after TBM. PARP 1 (Poly ADP Ribose Polymerase 1) is essential for initiating various reactions required for DNA repair in damaged tissues by mobilizing DAMPs, which includes HMGB1 (High Mobility Group Box 1) and S100 B. PAMPs which have been correlated with severity of disease are IL-17 and S100A8/9 levels.

Now we can understand that TBM is associated with multiple neurological complications due to the intense inflammatory response rather than primary disease. Thus along with antitubercular treatment we also need agents which helps in prevention of these complications due to intense inflammation [12]. Currently, steroids are the mainstay of adjunctive treatment in TBM for control complications. Most common and recommended form of steroid in TBM is dexamethasone.

Role of steroids in TBM

Steroids are being used in cases of various complications of pulmonary and extrapulmonary complications since 1950 but the change in clinical practice was after a large Randomized

Controlled Trial (RCT) published in year 2004, which first time systemically evaluated the effect of dexamethasone in TBM and found better survival with steroid. In year 2016, Cochrane review done on the basis of 9 more studies on steroids in TBM in which 6 studies used dexamethasone, 2 studies used prednisolone and one compared dexamethasone with methylprednisolone [13]. Finally the latest is one systematic review and meta-analysis published in year 2022 found 230 eligible articles among 1645 and finally analyzed 11 articles according their inclusion criteria. Our final conclusions on response of corticosteroids in TBM are based on these above mentioned articles.

Dexamethasone in HIV negative TBM: Dexamethasone therapy is currently recommended by all guidelines in HIV negative TBM as adjunctive treatment for 6-8 weeks depending on stage of disease for better survival. Dexamethasone helps in reduction in vascular permeability, cerebral edema, intracranial pressure, improvement in cerebral blood flow and promote brain metabolism. According to recent meta-analysis there are convincing evidence for effectiveness of corticosteroids in TBM as in this systematic review author found that conventional antituberculosis drugs combined with dexamethasone therapy can improve cerebrospinal fluid cell count, protein content, glucose, and chloride levels in patients with TBM. Although in Cochrane review it was found that dexamethasone does not alter the morbidity of TBM but meta-analysis in 2022 showed that steroidal treatment can reduce the incidence of adverse reactions it provide strong evidence in favor of dexamethasone in TBM. Other than dexamethasone two other forms of steroids were also tried in TBM that were intravenous methylprednisolone and oral prednisolone. One study from Jharkhand, India in year 2021 showed that intravenous Methyle Prednisolone (MPS) pulse therapy in TBM is associated with significant improvement in clinical, laboratory and radiological outcome as compared to dexamethasone. However, study by J Kalita, et al. had shown no improvement in clinical and electrophysiological parameters in MPS group after 3 months of treatment [14]. One study done by Shah, et al., in which author had compared high dose versus low dose oral prednisolone in children with TBM. Author had enrolled 63 children with TBM and divided in three groups according to doses of prednisolone given. Group 1 (prednisolone 2 mg/kg/day for 4 weeks), group 2 (prednisolone 4 mg/kg/day for one 1 weeks and 2 mg/kg/day for the next 3 weeks) and group 3 (prednisolone 4 mg/kg/day for 4 weeks) were compared for optic atrophy, tuberculoma, hydrocephalus, mental retardation, vasculitis and mortality in TBM when used with standard antitubercular regimen. Optic atrophy, infarcts, hydrocephalus and mental retardation was higher in group 3, tuberculoma more in group 1 and hearing loss was higher in group 2. There was no difference in mortality among different groups. Author concluded that group 2 was associated with fewer tuberculoma and infarcts but higher incidences of hearing loss. A prolonged period of steroids increases the risk of optic atrophy and hydrocephalus.

To summarize there is difference in opinion regarding reducing morbidity by corticosteroids in TBM patients both adults and pediatric age groups and higher doses or methylprednisolone is not seems to be beneficial. Overall best results seems to be there with dexamethasone therefore most of the guidelines specifically recommends for this molecule [15]. We will now specifically look for effect of steroids on cerebral infarction in TBM patients which results from immune mediated vasculitis and should have better results with immune modulation.

TBM related cerebral vasculitis is one of the most devastating complications and leads to long term disability in about 50% of patients. Even proven role of corticosteroids in reducing TBM related mortality, its role in prevention of cerebral infarction was not convincing and initial RCT in NEJM and Cochrane review specifically mentioned that there is no effects of dexamethasone on cerebral infarction. A subgroup analysis in year 2007, done by the same author who did RCT in year 2004, with serial MRI scan on 43 patients of TBM up to 60 days and showed about significant (50%) reduction in cerebral infarction load after steroids in TBM without significant impact on morbidity. In view of controversial role of corticosteroids in prevention of cerebral infarction with TBM, combination of aspirin to steroids was tested whether it can improve outcome with reduction in infarction load. After few small scale studies shown an improvement in outcome of TBM patients and reduction in cerebral infarction with aspirin in TBM patients, one systematic review (year 2019) included 4 RTC and showed that aspirin did not significantly reduce the mortality but significantly reduces the risk of cerebral infarction. Author had speculated that disability should also be less when aspirin is given with dexamethasone in TBM patients. Overall current observations suggested that aspirin with corticosteroids can be beneficial in reducing cerebral infarctions and possibly morbidity also in TBM patients.

Steroids in HIV positive TBM: In HIV positive cases no clear recommendation but available small number cases also suggest better survival with 6-8 weeks dexamethasone therapy. The number of HIV positive people included in the Cochrane review was small, so authors were not sure about the benefits in terms of reduced mortality are preserved in HIV positive TBM patients. One large study ACT HIV is under process and results of this study can answer this question.

Mechanism of action of dexamethasone in TBM: How does dexamethasone helps in reducing death and TBM related complication is still under evaluation. The mechanism by which dexamethasone reduces the death rate and infarction in TBM is still not well understood on the basis of immune alteration. Other than alteration in primary immune response in TBM dexamethasone can show betterment due to reduction in brain edema. Brain edema in TBM can be due to all three mechanism (vasogenic, cytotoxic and interstitial) and dexamethasone is the most effective way to treat vasogenic and to some extant cytotoxic cerebral edema. No significant change in status of hydrocephalus found in TBM patients with or without dexamethasone therapy in serial MRI study [16]. The hypothesis that survival benefit of dexamethasone in TBM should be related to its ability to alter local immune response in brain was not found to be associated with measurable attenuation of peripheral or local immune response in CSF analysis.

In one study by Simmons et al, dexamethasone group had marginally non-significant difference of CSF–IFN gamma levels

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after 1st week therapy with steroids as compared to placebo. No alteration was noted in rest of the cytokines (IL-6, IL-8 and IL-10) in CSF after one week dexamethasone therapy. Dexamethasone also did not able to alter the kinetics of any of the CSF cytokines or chemokines over the 2 months of steroid therapy. Concentration of IFN-gamma, IL-6, IL-8, and IL-10 fell slowly with all other cytokines over the duration of 2 months but all remained detectable even at the end of 2 months. TNF levels were found high in more than 70% of pretreatment CSF samples and levels fell rapidly with treatment without detectable influence of dexamethasone. Dexamethasone significantly modulated acute cerebrospinal fluid protein concentrations but marginally reduced IFN-gamma concentrations; other immunological and routine biochemical indices of inflammation were unaffected. It seems that improved survival TBM with adjuvant dexamethasone therapy cannot be explained by attenuating immunological mediators of inflammation in the subarachnoid space or by suppressing peripheral T cell responses to mycobacterium antigens. These findings challenge previously held theories of corticosteroid action in this disease about effects on inflammatory cytokines.

Variable response to dexamethasone therapy in TBM patients was not fully explained by immune mechanism till now. It is quite possible that few patients with TBM are more susceptible for dexamethasone response while others are refractory to steroids. One experimental study on genetic polymorphism has shown that few patients with TBM are more susceptible for dexamethasone.

Discussion

Role of genetic polymorphism for personalized use of dexamethasone therapy: A focus of recent research is the identification of genetic polymorphisms in immune response genes, in particular a single polymorphism in the Leukotriene A4 Hydrolase (LTA4H) promotor which plays a role in the balance of pro-inflammatory and anti-inflammatory eicosanoids, thereby influencing expression of TNF alpha. Studies in zebrafish and subsequently in humans have shown that expression of LTA4H can determine the drug susceptibility to disease as well as response to corticosteroids [17]. In a retrospective analysis of patients enrolled to a trial of adjunctive dexamethasone in TBM, survival benefit was restricted to homozygotes with a TT genotype of the LTA4H (hyper-inflammatory) in contrast to CC (hypo-inflammatory) genotypes where dexamethasone was associated with harm. More recently in an analysis of patients enrolled to a study of intensified anti-tuberculous regimens and adjunctive dexamethasone, LTA4H genotype predicted survival in HIV-1 uninfected patients with the TT genotype patients significantly more likely to survive than those with the CC genotype. In this study, patients with the LT14H TT genotype had high pro-inflammatory cytokine concentrations (IL-1B, IL-1 and IL-6). However, those with CT and CC genotypes had intermediate or lower concentrations respectively. This may suggest that the suppression of inflammation by dexamethasone leads to survival benefit in patients with the TT genotype however may be non-beneficial or even harmful in those with CT or CC genotypes [18]. This highlights the potential role for individualized immunotherapy where adjunctive corticosteroids are given on the basis of pre-treatment genotyping. Further work to explore this hypothesis in randomized controlled trials is required.

Thalidomide as an adjunctive treatment with dexamethasone in TBM: Other than steroids and aspirin there is one more agent used as adjuvant treatment in TBM cases for reduction of long term complications and that is thalidomide an INF-gamma/TNF-alpha inhibitor. As we know most of neurological sequels of TBM are largely driven by abnormal high levels of INF-gamma/TNF-alpha and corticosteroid is not very effective against these cytokines [19]. This prompted for a better and more targeted molecule which can modulate the INF/TNF levels and alter the complications related to this inflammatory cytokines. Thalidomide is one of such molecule which has better ability to alter the INF/TNF as compared to corticosteroids. Thalidomide is shown to be highly effective in the treatment of patients with chronic or recurrent Erythema Nodosum Leprosum (ENL) and it acts by inhibition of selective gene expression of TNF-alpha. In year 2000, thalidomide was found effective in reduction of TNF alpha in TBM patients with HIV and also shown improvement in HIV related muscle wasting. However, a subsequent double blind trial of high dose (24 mg/kg) thalidomide therapy in children with TBM was discontinued early due to high rates of adverse reactions. However, in a subgroup analysis more rapid resolution of basal meningeal enhancement and tuberculoma was observed with thalidomide, therefore a low dose (<5 mg/kg) regimen of thalidomide was tried in TBM patients. This low dose regimen found to be safe and effective in treatment of tubercular abscess and suprasellar inflammation and resulted in reversal of blindness due to optochiasmatic arachnoiditis in TBM [20]. Future studies and large controlled trial would be able to find out the reliable answer for use of thalidomide in TBM.

Conclusion

To conclude, we still lacking the definitive evidences for mechanisms by which dexamethasone is helping for morbidity reduction in TBM patients. Current knowledge of clinical, radiological and immunological response of dexamethasone in TBM patients is based on large controlled trial done in year 2004 with subgroup analysis later on by same group. We definitely required more longitudinal follow-up studies to look for the role of steroids and other adjuvant therapies in TBM especially in view of current knowledge of immunopathogenesis related with TNF-Alpha. Since now placebo controlled trial with dexamethasone in TBM is not possible due to ethical reasons. Future RCT on TBM patients can be done by comparing dexamethasone with or without low dose thalidomide with looking at impact on clinical, radiological and immunological findings in follow-up.

References

1. Malhotra HS, Garg RK, Singh MK, Agarwal A, Verma R (2009) Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. Ann

Trop Med Parasitol 103:625-634

2. Feng B, Fei X, Sun Y, Zhang X, Shang D, et al. (2021) Prognostic factors of adult tuberculous meningitis in intensive care unit: Asingle-center retrospective study in East China. BMC Neurol 21:2-11
3. Wang W, Gao J, Liu J, Qi J, Zhang Q (2022) Clinical efficacy of dexamethasone in the treatment of patients with tuberculous meningitis: A meta-analysis. Contrast Media Mol Imaging 2022:2180374
4. Murthy JMK (2019) Tuberculous meningitis-adjunctive therapy: Corticosteroids, aspirin, or both. Neurol India 67:1003-1005
5. Cooper AM (2019) Cell-mediated immune responses in tuberculosis. Annu Rev Immunol 27:393-422
6. Kalita J, Misra UK (2001). Effect of methyl prednisolone on sensory motor functions in tuberculous meningitis. Neurol India 49:267
7. Dye C, Scheele S, Dolin P, Pathania V, Raviglione M (1999) Global Burden of Tuberculosis. Estimated Incidence, Prevalence, and Mortality by Country. JAMA 282:677–686
8. Havlir D, Barnes P (1999) Tuberculosis patients with human immunodeficiency virus infection. N Eng J Med 340:367–373
9. Mogues T, Goodrich ME, Ryan L, LaCourse R, North RJ (2001) The relative importance of T cell subsets in immunity and immunopathology of airborne *Mycobacterium tuberculosis* infection in mice. J Exp Med 193:271–280
10. Reiley W, Calayag M, Wittmer S, Huntington J, Pearl J, et al. (2008) ESAT-6-specific CD4 T cell responses to aerosol *Mycobacterium tuberculosis* infection are initiated in mediastinal lymph nodes. Proc National Acad Sci USA 105:10961-10966
11. Lerner TR, de Souza Carvalho-Wodarz C, Reonik U, Russell MR, Borel S, et al. (2016) Lymphatic endothelial cells are a replicative niche for Mycobacterium tuberculosis. J Clin Invest 126: 1093–108
12. Krishnan N, Robertson BD, Thwaites G (2010) The mechanisms and consequences of the extra-pulmonary dissemination of *Mycobacterium tuberculosis*. Tuberculosis 90:361–366
13. Be NA, Kim S, Bishai WR, Jain SK (2009) Pathogenesis of central nervous system tuberculosis. Curr Mol Med 9:94-99
14. Nguyen L, Pieters J (2005) The Trojan horse: survival tactics of pathogenic mycobacteria in macrophages. Trends Cell Biol 15:269–276
15. Donald PR, Schaaf HS, Schoeman JF (2005) Tuberculous meningitis and miliary tuberculosis: The rich focus revisited. J Infect 50:193-195
16. Rock RB, Hu S, Gekker G, Sheng WS, May B, et al. (2005) *Mycobacterium tuberculosis*–induced cytokine and chemokine expression by human microglia and astrocytes: Effects of dexamethasone. J Infect Dis 192:2054-2058
17. Wright SD, Ramos RA, Tobias PS, Ulevitch RJ, Mathison JC (1990) CD14, a receptor for complexes of Lypopolysaccharide (LPS) and LPS binding protein. Science 249:1431–1433
18. Tsenova L, Bergtold A, Freedman VH, Young RA, Kaplan G (1999) Tumor necrosis factor alpha is a determinant of pathogenesis and disease progression in mycobacterial infection in the central nervous system. Proc Natl AcadSci USA 96:5657–5662
19. Ramilo O, Saez-Llorens X, Mertsola J, Jafari H, Olsen KD, et al. (1990) Tumor necrosis factor alpha/cachectin and interleukin 1 beta initiate meningeal inflammation. J Exp Med 172:497–507
20. Chen Y, Zhang J, Wang X, Wu Y, Zhu L, et al. (2016) HMGB1 level in cerebrospinal fluid as a complimentary biomarker for the diagnosis of tuberculous meningitis. Springerplus 5:1775

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