

## ORIGINAL ARTICLE

## TUBERCULOUS MENINGITIS: PREDISPOSING FACTORS IN ADULTS ADMITTED IN TERTIARY CARE HOSPITALS OF CENTRAL PUNJAB

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**Background:** Tuberculous Meningitis (TBM) is an infection that is caused by dissemination of *Mycobacterium tuberculosis* to the Central Nervous System. In patients suffering with chronic diseases such as type 2 diabetes mellitus (T2DM) and hepatitis C viral infection (HCV), immune resistance to the organism is low, hence, rapid dissemination of the bacterium is facilitated. The objective of this study was to observe the predisposing factors of TBM in a group of adults admitted to tertiary care hospitals. **Method:** Case records of 50 patients diagnosed with TBM admitted in various hospitals of Central Punjab, were examined during Sep 2015 to Aug 2016. Demographic characteristics including age, sex, socioeconomic status, history of pulmonary tuberculosis and presence of other chronic diseases like T2DM and HCV was noted. **Results:** The mean age of patients was  $43 \pm 18.72$ ; 60% were males and 40% females. Of the chronic diseases, most (22%) had T2DM. Although total number of females was less, 73% had diabetes mellitus. Of the other risk factors 20% had history of smoking and 18% had history of previous exposure to mycobacterium tuberculosis. **Conclusion:** T2DM is a predisposing risk factor for developing active tuberculosis alongside other chronic diseases like HCV. Screening of the high risk groups is recommended.

**Keywords:** Diabetes mellitus, Meningitis, Tuberculosis, T2DM,

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## INTRODUCTION

Tuberculous meningitis (TBM), an infection of the Central Nervous System (CNS), is a serious life threatening condition accounting for about 5–10% of all tuberculosis cases in the world.<sup>1</sup> Organs such as CNS are affected when the bacteria reach there from the initial site of infection. TBM is the 5<sup>th</sup> commonest cause of extra-pulmonary tuberculosis (EPTB).<sup>2</sup>

According to WHO Report 2009, Pakistan ranks 5<sup>th</sup> among 22 high burden countries of TB in the world. It accounts for 61% of the tuberculosis (TB) burden in the WHO Eastern Mediterranean region. Little literature is available regarding the incidence and prevalence of TBM in Pakistan although it is quite often diagnosed in the tertiary care hospitals.<sup>3</sup> It has been seen that patients with type 2 diabetes mellitus (T2DM), due to their susceptibility to infections, are at three times the risk of developing active TB.<sup>4</sup>

There are considerable gaps in knowledge regarding pathophysiology and immunology and treatment approach in the co-infection of the above disease states.<sup>5</sup> Moreover the predisposing, protective and host factors for CNS TB are little understood. The objective of this study was to observe the impact of risk factors such as T2DM, HCV and smoking in a group of patients with TBM.

## SUBJECTS AND METHODS

Our study retrospectively reviewed the case records of 50 hospitalised patients who were diagnosed with TBM. Clinical data of these patients, with age range 15–78

years, was identified in a span of one year; from Sep 2015 to Aug 2016. Data was collected from Mayo Hospital, General Hospital, and Sir Ganga Ram Hospital, Lahore, Nishtar Hospital Multan, and Allied Hospital, Faisalabad.

Permission to see the patients' case records was sought from the authorities. The demographic characteristics observed included age, sex, socioeconomic status, smoking and history of drug abuse. History of past illness included that of pulmonary or extra-pulmonary TB, HIV, HCV and T2DM. It was difficult to ascertain the duration of these illnesses or whether T2DM was controlled or not, as most patients were illiterate, belonging to low socioeconomic strata. Patients with heart disease, renal or other endocrine disturbances were not included in the study.

The case records of the patients who were diagnosed on the basis of history and clinical examination correlating with cerebrospinal fluid (CSF) abnormalities were examined. The results were tabulated as frequency and percentage.

## RESULTS

Most of the patients had had an insidious onset of fever and headache for the past 10 days or more. The classical sign of meningeal irritation was found in only three fourths of the patients. Less than half the patients had an altered mental state. CSF abnormalities included high protein, lymphocytic predominance and a low sugar. Positive CSF culture for *Mycobacterium tuberculosis* was found in only 22 patients; the most common neuro-

radiological finding being meningeal enhancement and tuberculomas.

The mean age of male patients was  $40.13 \pm 16$  and that of females was  $48 \pm 20.77$  years. Eleven patients had history of smoking either cigarettes or 'hukka' out of which 9 were males and 2 females. There was no relationship between smoking in TBM patients with T2DM, indicating that smoking is an independent risk factor for developing EPTB. All 5 drug addicts (taking either/and heroin, hashish, alcohol) were males. Nine patients, 6 males and 3 females, had history of having had pulmonary TB during in the past five to seven years. Neither did any of the patients have history of HIV infection, nor were they tested for it. Five patients

had HCV infection when tested for it and one female patient tested positive for hepatitis B viral infection as well.

Among the 50 TBM patients, eleven (3 males and 8 females) were diagnosed as having T2DM. The mean age of male patients was  $44 \pm 6.55$  while that of female patients was  $60.75 \pm 18.68$ . Two diabetic patients, one male and one female, both incidentally 45 years of age, had past history of pulmonary TB too.

Forty (80%) patients were in lower-middle socioeconomic class and 10 (20%) were in lower socioeconomic class according to Kuppuswamy's socioeconomic scale<sup>6</sup>. (Table-1).

**Table-1: Demographic characteristics and risk factors in tuberculous meningitis patients [n (%)]**

Parameters	Male	Female	Total
Gender	30 (60%)	20 (40%)	50
Age (Years)	$40.13 \pm 16.76$	$48.44 \pm 20.77$	$43 \pm 18.72$
History of Smoking	8 (16%)	2 (4%)	10 (20%)
Past History of pulmonary tuberculosis	6 (12%)	3 (6%)	9 (18%)
Diabetes Mellitus Type II (T2DM)	3 (6%)	8 (16%)	11 (22%)
Hepatitis C Viral Infection (HCV)	1 (2%)	4 (8%)	5 (10%)
Drug History	5 (10%)		5 (10%)

## DISCUSSION

*Mycobacterium tuberculosis*, an aerobic bacterium, can persist in host tissues for years without replication but resumes growth when host immunity wanes. Pulmonary TB is the most common presentation of *Mycobacterium tuberculosis* from where dissemination can occur into other organs and cause EPTB.<sup>7</sup> TBM is the most lethal form of EPTB, responsible not only for severe disability in most survivors, but also, with a mortality rate averaging 33%, despite treatment.<sup>8</sup>

T2DM is an increasingly recognised co-morbidity that can trigger reactivation of TB, accelerate the disease and complicate its treatment.<sup>9</sup> It has been shown to increase the risk of incident TB by three-fold.<sup>10</sup> It is well understood that both innate and adaptive immune responses are necessary to prevent TB infection to become an active disease. T2DM may impair multiple aspects of the coordinated response.

In the present study the highest incidence (22%) of a co-infection that could predispose the patient to TBM was found to be T2DM. Our study is in accordance with the previous work<sup>11-13</sup>. In our study there was also co-existence of advanced age and female gender in diabetics with TBM which is in accordance with Yaser et al<sup>12</sup>.

People with T2DM are more susceptible to infections and suffer from relatively severe form of illness due to their immunocompromised states.<sup>10</sup> It has been found that DM/TB patients have significantly reduced concentration of interferon gamma, interleukin 2, total helper T-cell population; especially the helper subclass and impaired alveolar macrophage activation

due to glycation of binding sites as compared to non-diabetic patients.<sup>5</sup>

Even though TB is much strongly associated with other immune deficiency states such as HIV, as the load of diabetic patients is much greater, it makes T2DM a more significant risk factor for TB at the population level.<sup>13</sup> As the global prevalence of DM increases, especially in low-to-middle-income countries, there will be a greater incidence of the co-morbidities of these two diseases.<sup>14</sup>

Twenty percent of our TBM patients had history of active smoking for at least past five to ten years. Tobacco smoke increases the risk of *Mycobacterium tuberculosis* infection by many ways: immune suppression of pulmonary lymphocytes, defective muco-ciliary clearance and reduction of killer T-cells.<sup>15</sup> It has been seen that both active and passive smoking increases the risk of latent TB infection and of pulmonary and EPTB. Extra-pulmonary involvement can occur with or without pulmonary infection sites.<sup>7</sup>

Ten percent of TBM patients had HCV infection. Several studies have reported increased incidence of viral hepatitis infection in TB patients. Also, that chronic HBC and HCV prevalence in TB patients were 9 and 5 times greater.<sup>16</sup> HCV infection may increase the risk of active TB because the virus binds to and inhibits tumour necrosis factor alpha receptor; the former being an important cytokine for TB control.<sup>17</sup>

Ten percent patients had history of drug and alcohol abuse. With multiple exposures, a study concluded, that tobacco use, alcohol and T2DM were

significant individual risk factors associated with triple the risk of TB.<sup>18</sup>

Priority should be placed on early detection of these diseases. Hence screening of high risk groups (other than HIV) namely diabetics, smokers and other immunocompromised states like Hepatitis B and C infection within the population is necessitated.<sup>19</sup>

South Asia is called the diabetes capital and the TB capital of the world. The global burden of T2DM is expected to double by year 2030 with 80% of adult cases occurring in low and middle income countries.<sup>20</sup> Convergence of these two epidemics, i.e., TB and diabetes is most likely to occur in places where least amount of health care resources are available.

## CONCLUSION

T2DM is indeed a risk factor for developing active tuberculosis in this case, TBM. There is a preponderance of advanced age and female gender in the above two co-morbidities. Other risk factors such as smoking, HCV and drug abuse in the low and middle income strata should also be considered.

## RECOMMENDATION

Scarce data exist on the relationship between T2DM and EPTB. Regional research is required to ascertain how TBM risk varies with the type, duration and control of T2DM so that a thorough understanding of the relationship could be extrapolated to a clear public health message.

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