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Tuberculosis Affecting the Nervous System: Can we Trace the Source of Infection?

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TUBERCULOSIS AFFECTING THE NERVOUS SYSTEM: CAN WE TRACE THE SOURCE OF INFECTION?

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ABSTRACT

Objective: To trace the source of tuberculous infection of patients with CNS tuberculosis. **Material and methods:** We analyzed clinical records of 100 patients with tuberculosis affecting the central nervous system, who presented to Department of Neurology Civil Hospital Karachi,between Jan 2007 To June 2010. All patients with confirmed diagnosis of CNS tuberculosis, supported by clinical, laboratory, and radiological evidence were included. Case histories were analyzed and notes were made in each case of past history of tuberculosis, history of affected family members at that time and in past, and presence or absence of concurrent extra-neural tuberculosis. All patients with disseminated tuberculosis were investigated for immunocompromised states like HIV. Patients with positive contact history were divided into those with tuberculosis affected person within their household, those with their first degree relatives with history of tuberculosis, and those with workmates or other regular contacts with tuberculosis. Contacts of all these patients were also investigated to find out the new cases amongst them according to the WHO guidelines. Results were analyzed on SPSS 17.**Results:** Among the total of 100 patients, male to female ratio was 1:3 with ages ranging from 8 to 82 years. Mean age was 34. Fifty six people had tuberculosis affecting brain and 44 had spinal involvement. Thirty five patients had tuberculous meningitis, 13 had tuberculous meningitis with tuberculomas, and 8 had tuberculomas only. Major complications of tuberculous meningitis, like stroke(60%), hydrocephalus(40%) and optic neuropathy(1.5%) were seen in 20 patients. One patient had sagittal sinus thrombosis in addition to tuberculous meningitis. 44 patients had spinal cord involvement, they presents with compressive myelopathy, (tuberculous abscess &/or prolapsed vertebrae) and/or myelitis. Twelve patients showed involvement of cervical spine, 16 dorsal spine and 15 had lumbar spine involvement. One patient had disease of dorsolumbar spine. Neurosurgical procedures were required in those who developed hydrocephalous and epidural spinal cord abcesses. At the time of presentation, 20 patients had tuberculous infection in extra-neural tissues /organs as well. Four patients had abdominal tuberculosis, 6 had disseminated tuberculosis, and 10 had pulmonary tuberculosis. Baseline chest xray was abnormal in 20% of patients (10% with active concurrent pulmonary tuberculosis while other 10% were asymptomatic. Fourteen patients had history of tuberculosis in past. Six had pulmonary tuberculosis in past but x-ray evidence of tuberculosis was available in other two, 2 were diagnosed with abdominal tuberculosis, 3 had tuberculous lymph adenitis, and one patient was diagnosed as tuberculous meningitis. Twenty six percent of patients could trace the source of infection among their relatives, while majority (74%) did not give history of any affected family member, relative or contact, at that time or in past. Fourteen percent had an affected household (parent, sibling), and 12% gave history of an affected first degree relative. **Conclusion:** Tracing the source of infection with clinical methods alone was not very much beneficial. We need advance strategies to supplement our clinical methods to find out the source of transmission of this illness and to eradicate and manage effectively the spread of infection in our community.

INTRODUCTION

Tuberculosis remains a worldwide burden, with a large majority of new active tuberculosis cases occurring in underdeveloped and developing countries[1].The annual number of new cases of TB has continued to grow all over the world reaching 9.4 million in 2009[2].Demographic factors such as poverty, crowding, malnutrition and a compromised immune system play a major role in emergence of 80% of new tuberculosis cases worldwide[3]. Pakistan ranks 8th amongst the high burden TB countries in the world and harbor 63% of tuberculosis burden in the Eastern Mediterranean Region of WHO4. Every year 420,000 new Tuberculosis cases emerge and 69,000 people die from Tuberculosis in Pakistan[4].According to the WHO the incidence and

prevalence of TB in Pakistan is 230 per 100,000and 310 per 100,000 respectively[5].

CNS tuberculosis represents one of the most severe forms of extra pulmonary tuberculosis. 6.3% of extra pulmonary cases (1.3% of total tuberculosis cases) involve the CNS.6Diagnosis of CNS Tuberculosis requires a high index of suspicion, thorough contact tracing, and appropriate investigations with early treatment to reduce morbidity and mortality.Despite treatment, mortality and long-term disability remain high. Although a lot of local and international research has been done regarding different aspects of CNS tuberculosis, fundamental questions regarding the source of the infection of the index case remain unanswered. Source tracing is the key ofbetter managementand eradication of every communicable disease. In our study we try to find out clinically the cause of this devastating illness through contact tracing.

MATERIALS AND METHOD

We analyzed completed records of 100 consecutive patients with tuberculosis affecting the central nervous system, who presented to Department of Neurology Civil Hospital Karachi, to trace the source of infection in each patient. These included patients with tuberculous meningitis (TBM), tuberculomas of brain and spinal cord, Pott's disease with compressive myelopathy and tuberculous myelitis.

These patients presented to our department between Jan 2007 To June 2010. We did not include records of those patients which were incomplete, or those patients who left against medical advice before completion of investigations.

All patients with confirmed diagnosis of tuberculosis, supported by clinical, laboratory, and radiological evidence were included. Case histories were analyzed and notes were made in each case of past history of tuberculosis, history of affected family members at that time and in past, and presence or absence of concurrent extra-neural tuberculosis. All patients with disseminated tuberculosis were investigated for immunocompromised states like HIV. Contacts of all these index patients were also investigated to find out the new cases amongst them according to the WHO guidelines.

Patients with positive contact history were divided into those with tuberculosis affected person within their household (parents, sibs, husband, wife or children), those with their first degree relatives with history of tuberculosis (uncles, aunt, grandparents), and those with workmates or other regular contacts with tuberculosis. Results were analyzed on SPSS 17.

RESULTS

Among the total of 100 patients, 24 were males and 76 were females (male to female ratio 1:3) with ages ranging from 8 to 82 years with a mean age of 34 years. Maximum number of patients belonged to age group 21-40 years which had 48 patients. Age group ≤ 20 years had 35 patients (out of these 25 were vaccinated with BCG while 10 were not vaccinated); 11 patients were in age group 41-60 years and 6 patients wereover 60 years of age.

Fifty six people had tuberculosis affecting brain and 44 had spinal involvement.

Thirty five patients had tuberculous meningitis, 13 had tuberculous meningitis with tuberculomas, and 8 had tuberculomas only. Mycobacterium tuberculosis was cultured in 18 % whileidentified by PCR in cerebrospinal fluid of other 20% patients.Major complications of tuberculous meningitis, like stroke (12), hydrocephalus (8) and optic neuropathy (3) were seen in 20 (57% of brain infection)patients. Two patients had both stroke and hydrocephalus and one patient had simultaneous optic neuropathy and hydrocephalus. One patient had sagittal sinus thrombosis in addition to tuberculous meningitis. Stroke, due to both small and middle vessel vasculitis, was seen in 12 patients with meningitis and 7 patients had meningitis, tuberculomas and stroke. 44 patients had spinal involvement withcompressive myelopathy, (tuberculous abscess &/or prolapsed vertebrae) and/or myelitis. Twelve patients showed involvement of cervical spine, 16 dorsal spine and 15 had lumbar spine involvement. One patient had disease of dorsolumbar spine.

Chest x-ray was abnormal in 20 patients. Ten of them had concurrent active pulmonary tuberculosis, while remaining 10 were asymptomatic.

Only 14 patients had history of tuberculosis in past. Six had pulmonary tuberculosis in past but x-ray evidence of tuberculosis was available in other two, 2 were diagnosed with abdominal tuberculosis, 3 had tuberculous lymph adenitis, and one patient was diagnosed as tuberculous meningitis. Thepatient, who was diagnosed with tuberculous meningitis 7 years back, took treatment for 6 months only (while our current practice is to treat patients with tuberculous nervous system disease for duration of 18 to 24 months). All other patient reportedly continued treatment and completed therapy for prescribed duration. However,

Only 26 patients could trace the source of infection among their contacts, while majority (74) did not give history of any affected family member, relative or regular contact, at that time or in past. 14 patients had contact with their house holds (6 had an affected parent, 8 had affected sibling),12 gave history of an affected first degree relative, while none gave the history of affected workmate or other regular contacts. None of these contacts had active tuberculosis at that time. Except for the two all these contacts were treated and not currentlytaking anti-tuberculous therapy. All ofthem were alsocompliant withthe treatment.

At the time of presentation, 20 patients were found to be harboring tuberculous infection in extra-neural tissues /organs as well during investigations for tuberculosis of the nervous system. Four patients had abdominal tuberculosis, [6] had disseminated tuberculosis, and 10 had pulmonary tuberculosis.

Anti-tuberculous therapy was given according to the standard 18 to 24 months; concurrent steroids were given to all patients with tuberculous meningitis with or without tuberculomas, tuberculomas alone and myelitis. Neurosurgical procedures were required in those who developed hydrocephalous and epidural spinal cord abcesses, these were 23 patients. Follow up imaging done during treatment where clinically indicated and at the end of therapy.

DISCUSSION

This is a prospective case series of 100 patients with central nervous system tuberculosis presented at tertiary care hospital during the period of Jan 2007 - June 2010.Mean age of presentation wasthe same as compare to otherlocaldata.[7] In our study male to female ratio was 1:3(24 were males and 76 were females). This gender distribution was different as compare to the recently published local data[7] while similar to other studies.[8] Almost all of our patients belonged to the low socioeconomic group. Majority of women had poor nutritional status (guided by the body mass index calculated at the time of initiation of therapy). Begum et al studied the reasons of female disease preponderance and find out that women havepoorer nutritional status than their male counterparts and socialstigma associated with TB discourages women fromseeking early medical care.[9]

Patients with neurotuberculosis may have chest radiographic evidence of pulmonary TB even in the absence of pulmonary signs and symptoms at presentation. There is a strong association of clinical grade II and grade III with positive chest radiographic findings.[10] In our study we found chest x-ray abnormalities in 20% of patients. 10 of them had active pulmonary tuberculosis while remaining 10 were asymptomatic. Another study suggests that the presence of active pulmonary tuberculosis on chest X ray may rangesfrom 30 to 50%[11].

According to the WHO in 2011 there were 270394 no of notified tuberculosis and 344 no ofnotified MDR TB cases in Pakistan.[12]In view of the MDR tuberculosis, it is essential to isolate M. tuberculosis and determine its sensitivity at the outset. In our study routine CSF culture was positive in only 18% of patients while PCR identified the Mycobacterial DNA in 20%others. As we were unable to isolate the bacteria in all patients we were not able to document the trend of drug resistant in our patients. In such cases we followed clinical and radiological response to the standard treatment, and added second line therapy if no response was seen after 6-8 weeks.

International literature showed that approximately 10% of patients with CNS tuberculosis gave the history of tuberculosis in past[11]. In our study only 14% of patients gave the past history of tuberculosis and 26% patients could trace the contact with tuberculosis patients in the past. These observations were exactly similar to the recently published local data.[7]This shows that on the basis of clinical history alone we were unable to trace the source of infection of this illness. To evaluate the various transmission routes of tuberculosis,National Tuberculosis Control Program should develop an effective method for contacts' investigations.

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history of any affected family member, relative or regular contact, at that time or in past. 14 patients had contact with their house holds (6 had an affected parent, 8 had affected sibling),12 gave history of an affected first degree relative, while none gave the history of affected workmate or other regular contacts. None of these contacts had active tuberculosis at that time. Except for the two all these contacts were treated and not currentlytaking anti-tuberculous therapy. All ofthem were alsocompliant withthe treatment.

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Modern DNA analysis proved to be a very effective tool to better target and evaluate TB control interventions in developed countries.It providesinsights into the process of tuberculosis transmission, which may otherwise go unrecognized by conventional contact investigations. Additionally, it plays an important role in identifying places of tuberculosis outbreaks. A Japanese study reviewed the records of 21 tuberculosis patients involved in an outbreak of tuberculosis; the records were collected by conventional epidemiological studies. Mycobacterium tuberculosis isolates were genotyped using IS6110-based restriction fragment length polymorphism (RFLP).They conclude that RFLP surveillance forms the bridge between conventional contact investigation and targeted active case finding.[13]Another large-scale tuberculosis investigation was conducted in Harlingen in 1993 when a 2.5 year old patient with tuberculous meningitis was reported. Source tracing and contact tracing was extended from Harlingen to the west of the Netherlands and even abroad. Modern DNA analysis (RFLP) was used to map the tuberculosis transmission. A total of 6519 persons

were screened and 276 infected people were identified, of whom 49 were suffering from active tuberculosis. RFLP analysis showed in 27 of them a 'Harlingen' type Mycobacterium tuberculosis DNA pattern identical to that of the index patient. The source patient was finally traced in England[14].

Although wegave shortcourse of steroidsto all patients with tuberculous meningitis, tuberculomas, and myelitis, still 20% developed complications like hydrocephalous (40%), stroke (60%) and optic neuritis (1.5%).As we did not randomized the patients in two groups (steroid treatment vs placebo), we were unable to postulate the effects of steroids in improving disability or survival. Looking at the impact of dexamethasone on hydrocephalus and infarction, Schoeman et al. reported that steroids did not appear to affect intracranial pressure or the extent of infarction in children despite having a positive influence on survival.[15]Thwaites et al. used serial MRI to assess the effect of dexamethasone on hydrocephalus, basal meningeal enhancement, the presence of tuberculoma, and infarction, and they were unable to demonstrate that dexamethasone influenced any of these parameters as well,[16]while some other studies have shown that corticosteroids improved both survival rate and neurological outcome in patients with tuberculous meningitis.[17]

In our study 44% of patients had spinal tuberculosis. Patients presents with compressive mylopathy (tuberculous abscess &/or prolapsed vertebrae) and/or myelitis. 12% showed involvement of cervical spine, 16% dorsal spine and 15% had lumbar spine involvement. One patient had disease of dorsolumbar spine. Literature also revealed that dorsal spine is the mostly affected spinal region.[18]

There is no consensus on the length of treatment of CNS tuberculosis. We rationally used to treat for 18 to 24 months and followed the therapeutic response both clinically and radiologically. According to the British infectious society guidelines patients should be treated for a minimum of 10 months. Therapy should be extended to at least 12 months in those who fail to respond, or if treatment interruptions have occurred for any reason19.According to the National TB Manual, chemotherapy should be given for 12 months for tuberculous meningitis.[17] Treatment duration of tuberculomas depends on CT resolution and must sometimes last as long as 24 months [20]. Treatment of spinal TB - consist of induction phase for 2 months with prolongation of the continuation phase to next 7 months[21].

In our study 35 patients belonged to the age ≤ 20 years (out of these 25 were vaccinated with BCG while 10 were not vaccinated). We found difference in terms of severity of clinical presentation between vaccinated and unvaccinated group (vaccinated grade I and II vs. nonvaccinated grade II and III). This observation was contradictory to previously published local data[21].

CONCLUSION

CNS tuberculosis is a devastating illness.Clinical methods alone are not helpful to trace the source of infection and to find out the active cases amongst contacts. For finding out the potential sources of infection and thus better eradication of disease we need to supplement our clinical methods with modern DNA analysis techniques. Mass screening programs for the screening of cured and contacts of under treatment index cases should be launched.

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Among smokers 11/37, five (45% among smokers) had raised homocysteine more than 15 umol/lit showing that not all smokers have raised Homocysteine above critical levels. On the other hand five of nineteen patients with raised Homocysteine were smokers which come out to be 26.3%. In comparison, among nineteen patients with raised Homocysteine fourteen 78.94% were either nonsmokers or had quit smoking more than five years back.

It is evident from our study that raised Homocysteine levels are commonly found in patients of ischemic stroke and every other patient is having raised level which is more frequent than published in international studies. This finding is also independent of smoking status and gender of the patients. Either this finding can be generalized for population at large, needs further community based study. We recommend regular investigation in all patients of ischemic stroke and Folic acid and Vit. B 12 should be given as a routine in ischemic stroke patient considering high prevalence of raised Homocysteine as giving B12, Folic acid and Pyridoxine has shown reduction in stroke incidence in international literature [25]. Bushnell CD and colleagues reported in their study a threshold of 14.5 umol/Lit of Homocysteine to treat the patient [26].

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