ABSTRACT... Objective: To evaluate the role of cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for Mycobacterium Tuberculosis in rapid diagnosis of tuberculous meningitis (TBM). Study Design: Prospective observational study. Place and Duration of Study: Medical A unit Hayatabad Medical complex Peshawar from 1st September 2010 to 30th August 2011. Methodology: A total of 20 Patients having fever, constitutional symptoms (malaise, vague ill health, headache, vomiting), nuchal rigidity with altered mental and behavior changes were suspected as TBM and hence included in the study. Patients were divided into two groups based on direct and indirect evidence of tuberculosis in central nervous system (CNS) of patients. Group 1: Patients having direct evidence of mycobacterial infection in CNS as Acid Fast Bacilli smear positive in CSF. Group 2: Patients with indirect evidence of TB in CNS in form of typical CSF findings of TBM, positive sputum smear for Acid fast bacilli (AFB) or computed tomographic (CT) Scan brain findings suggestive of TBM or evidence of TB in x-ray chest or family History of tuberculosis and/or history of contact with TB patients or positive Mantoux Test or evidence of TB elsewhere in the body. Results: Out of total 20 patients, 3 (15%) belonged to Group 1 having direct evidence of TBM the remaining 17 (85%) patients belonged to Group 2. Female patients were 60% while 40% patients were male. Mean age was 35.8 years. All patients had fever and headache. Productive cough was present in 40% patients. Thirty five percent had lost weight. Contact with TB patients was revealed in 35% patients. Signs of meningeal irritation were elicited in 90% patients. Cranial nerve palsies were seen in 25% patients, 10% had hemiparesis while 35% had impairment of consciousness. X-ray chest was normal in 65%.Computed tomographic scan was showing meningeal enhancement in 30% patients, hydrocephalus in 15% patients, meningeal enhancement plus hydrocephalus in 55% patients and infarct in 15% patients. Three patients were enrolled in group 1 and all had PCR positive for mycobacterium tuberculosis. Of 17 patient in group 2, 64% patients had positive CSF PCR. Conclusions: Tuberculous meningitis is an important serious extrapulmonary complication of TB, related with high mortality and morbidity. The prompt and accurate diagnosis of TBM is a daunting challenge. CSF PCR for Mycobacterium tuberculosis is an excellent test for rapid diagnosis of TBM.

INTRODUCTION
Robert Koch’s discovery of the Tubercle bacillus in 1882 was a major event in the history of medicine, a turning point in our understanding and conquest of tuberculosis (T.B.), Deadly disease which had plagued mankind for millenia.

Globally, roughly two billion people are infected by Mycobacterium Tuberculosis and roughly 2 to 3 million people die from active TB each year despite the fact that it is curable. Tuberculosis is the seventh most important cause of global premature mortality and disability.

Tuberculous meningitis is an important serious extrapulmonary complication of TB, related with high mortality and morbidity in developing countries and have recently shown resurgence in developed ones.

Presentation of TBM is often nonspecific, early recognition of this potentially treatable disease remains a challenge to clinicians. It occurs in 7 to 12% of tuberculous patients and has high fatality despite availability of effective chemotherapy and delay in diagnosis is directly related to neurological sequelae in 20% of patients who do not receive early treatment.

Confirming the clinical suspicion of TBM has always been problematic. Acid-fast bacilli staining of CSF has a very low sensitivity. Although conventional bacterial culture is the gold standard for diagnosis, the inherent
time limitation of the culture-based test, limits its value. The culture of M. tuberculosis from CSF takes 4–6 weeks and leads to a delay in diagnosis. Analysis of CSF using antibody detection is suggestive but not diagnostic of TBM.

Tuberculous meningitis is a potentially curable infectious disease of the CNS, and thus there is a need to design an alternative rapid diagnostic method to the conventional microbiological method for the early laboratory diagnosis of TBM so that an effective therapeutic modality can be instituted quickly in patients with TBM. Hence, rapid detection of M. tuberculosis is of vital importance for the proper diagnosis and management of tuberculous meningitis. Polymerase chain reaction is considered to be one of the most specific diagnostic methods among the many rapid methods studied. Polymerase chain reaction is the method of choice for the diagnosis of tuberculosis in cases where the suspicion is high.

EXCLUSION CRITERIA
Patients with CSF positive for Gram staining of other organisms; CSF typical of pyogenic meningitis; response to antimicrobial therapy, past history of stroke, epilepsy, cranial nerve palsies; patients having other sources of infections e.g., pneumonia, malaria and enteric fever, were excluded from the study.

After detailed history and examination and investigations review, lumbar puncture was performed on each pt according to standard procedure guidelines. CSF PCR for mycobacterium tuberculosis was sent in special cabinet to private laboratory with CSF PCR facility.

Patients were managed along the standard guidelines. Demographic characteristics were recorded. Data was entered in objectively structured proforma. SPSS 14 version was used for statistical analysis.

RESULTS
A total of 20 patients with suspected TBM admitted in Medical A Ward Hayat Abad Medical Complex Peshawar fulfilling the inclusion criteria from 1st September 2010 to 30th August 2011.

Out of total 20 patients 3 (15%) belonged to Group 1 as TBM and hence included in the study. Patients were divided into two groups based on direct and indirect evidence of tuberculosis in CNS.

Group 1. Patients having direct evidence of mycobacterial infection in CNS as Acid Fast Bacilli smear positive in CSF.

Group 2. Patients with indirect evidence of TBM in CNS in form of typical CSF findings of Tuberculous Meningitis i.e., predominantly lymphocytic pleocytosis, low sugar and high protein concentration or positive sputum smear for AFB or CT scan brain findings suggestive of TBM or evidence of tuberculosis in x-ray chest or family history of tuberculosis and/or history of contact with tuberculous patients or positive Mantoux Test of more than 10 mm or evidence of tuberculosis elsewhere in the body.

MATERIAL AND METHOD
We conducted this cross sectional study in Medical “A” unit Hayat Abad Medical complex Peshawar from 1st September 2010 to 30th August 2011. All consenting patients were assessed according to inclusion criteria mentioned below.

INCLUSION CRITERIA
Patients having fever, constitutional symptoms (malaise, vague ill health, headache, vomiting), nuchal rigidity with altered mental and behaviour changes were suspected as TBM and hence included in the study. Patients were divided into two groups based on direct and indirect evidence of tuberculosis in CNS.

Group 1. Patients having direct evidence of mycobacterial infection in CNS as Acid Fast Bacilli smear positive in CSF.

Group 2. Patients with indirect evidence of TBM in CNS in form of typical CSF findings of Tuberculous Meningitis i.e., predominantly lymphocytic pleocytosis, low sugar and high protein concentration or positive sputum smear for AFB or CT scan brain findings suggestive of TBM.

Female patients were 12 (60%) while 8 (40%) patients were male. Age of patients ranged from 16 to 63 years with mean age 35.8 years.

All patients had fever and headache. Productive cough was present in 8(40%) patients. Seven patients (35%) had lost weight. Contact with TB patients was revealed in
from 19mg/dl to 51mg/dl. Three patients were enrolled in group 1 and all had PCR positive for mycobacterium tuberculosis. Of 17 patient in group 2, 12 (64%) patients had positive CSF PCR for mycobacterium while 5(36%) had negative CSF PCR for Mycobacterium tuberculosis.

**DISCUSSION**

Infection with mycobacterium tuberculosis begins with inhalation of mycobacterium tuberculosis bacilli, which then spreads through lymphohematogenous system to the brain and meninges. Tuberculosis bacillii are then discharge from these foci directly in to subarachenoid space to cause meningitis.

Tuberculous meningitis affects young patient in our 7(35%) patients. Signs of meningeal irritation were elicited in 18(90%) patients. Cranial nerve palsies were seen in 5(25%) patients, two (10%) had hemiparesis while 7(35%) had impairment of consciousness. X-ray chest was normal in 13(65%). Two(10%) patients had pulmonary cavity and military mottling each. apical fibrosis, pleural effusion and hilar lymphadenopathy was seen in 1(5%) each. Computed tomographic scan was showing meningeal enhancement in 6(30%) patients, hydrocephalus in 3(15%) patients, meningeal enhancement plus hydrocephalus in 11(55%) patients and infarct in 3(15%) patients. Elevated CSF Protein ranged from 57mg/dl to 630mg/dl and low glucose varied from 19mg/dl to 51mg/dl. Three patients were enrolled in group 1 and all had PCR positive for mycobacterium tuberculosis. Of 17 patient in group 2, 12 (64%) patients had positive CSF PCR for mycobacterium while 5(36%) had negative CSF PCR for Mycobacterium tuberculosis.

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Tuberculous meningitis affects young patient in our study Median age was 35 years as observed by Christensen et al. Cranial nerve palsies were seen in 5(25%) patients, two (10%) had hemiparesis while 7(35%) had impairment of consciousness. X-ray chest was normal in 13(65%). Two(10%) patients had pulmonary cavity and military mottling each. apical fibrosis, pleural effusion and hilar lymphadenopathy was seen in 1(5%) each. Computed tomographic scan was showing meningeal enhancement in 6(30%) patients, hydrocephalus in 3(15%) patients, meningeal enhancement plus hydrocephalus in 11(55%) patients and infarct in 3(15%) patients. Elevated CSF Protein ranged from 57mg/dl to 630mg/dl and low glucose varied from 19mg/dl to 51mg/dl. Three patients were enrolled in group 1 and all had PCR positive for mycobacterium tuberculosis. Of 17 patient in group 2, 12 (64%) patients had positive CSF PCR for mycobacterium while 5(36%) had negative CSF PCR for Mycobacterium tuberculosis.

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Tuberculous meningitis presents in its early course with an indolent phase with the symptoms are fever, vomiting, lethargy, headache and seizures. Fever and headache were the predominant symptoms in our study present in all patients as evident in other studies by Etlik et al and Kalita et al while Malik et al found it in 80% the reason being inclusion of paediatric population in that study. Productive cough was present in 40% patient in our study while Etlik et al reported it in all patients. Weight loss
CONCLUSIONS

Tuberculous meningitis is an important serious extrapulmonary complication of tuberculosis, related with high mortality and morbidity. The prompt and accurate diagnosis of TBM is a daunting challenge. CSF PCR for mycobacterium tuberculosis is an excellent test for rapid diagnosis of TBM.

REFERENCES


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PREVIOUS RELATED STUDIES


- Hina Ayesha, Farhan Javed. TUBERCULOUS MENINGITIS (TBM) AN EXPERIENCE OF 100 PAEDIATRIC PATIENTS (Original) Prof Med Jour 9(1) 65-70 Jan, Feb, Mar 2002

Patriotism is the virtue of the vicious.

Oscar Wilde