TUBERCULOUS MENINGITIS

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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 Hayat Abad 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. Group1: 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.

Key words: Tuberculous meningitis, diagnosis, PCR

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[1].

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[2]. Tuberculosis is the seventh most important cause of global premature mortality and disability[3].

Tuberculous meningitis is an important serious extrapulmonary complication of TB, related with high mortality and morbidity in developing countries[4] and have recently shown resurgence in developed ones[5].

Presentation of TBM is often nonspecific, early recognition of this potentially treatable disease remains a challenge to clinicians[6]. 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[7].

Confirming the clinical suspicion of TBM has always been problematic. Acid-fast bacilli staining of CSF has a very low sensitivity[8]. Although conventional bacterial culture is the gold standard for diagnosis, the inherent

time limitation of the culture-based test, limits its value[9,10]. The culture of M. tuberculosis from CSF takes 4–6 weeks and leads to a delay in diagnosis[11,12]. Analysis of CSF using antibody detection is suggestive but not diagnostic of TBM[13].

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[14]. 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[15].

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.

Group1. 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.

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 having direct evidence of TBM in CNS in form of positive CSF smear for AFB and remaining 17 (85%) patients to Group 2 with indirect evidence in form of typical CSF findings of TBM or x-ray chest or CT brain findings or positive montoux test or history of TB contact or evidence of tuberculosis elsewhere in the body.

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

Table-I. Clinical features of TBM patients

Symptoms	No. of patients	%age
Fever	20	100%
Headache	20	100%
Productive Cough	08	40%
Weight loss	07	35%
TB contact	07	35%

Table-II. Neurological signs of TBM patients

Signs	No. of patients	%age
Nuchal rigidity	18	90%
Cranial nerve palsies	05	25%
Hemi Paresis	02	10%
Impairment of consciousness	07	35%

Table-III. X-ray chest findings of TBM patients

X-ray chest findings	No. of patients	%age
Pulmonary cavity	02	10%
Miliary shadow	02	10%
Pleural effusion	01	5%
Apical fibrosis	01	5%
Hilar lymphadenopathy	01	5%
Normal x-ray chest	13	65%

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

Table-IV. CT brain findings of TBM patients

CT brain findings	No. of patients	%age
Meningeal enhancement	06	30%
Hydrocephalus	03	15%
Meningeal enhancement plus hydrocephalus	11	55%
Cerebral infarct	03	15%

Table-V. CSF results

	CSF PCR result	
	Positive CSF PCR	Negative CSF PCR
Group 1	3 (100%)	-
Group 2	12 (64%)	5 (36%)

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 lymphohematogenious system to the brain and meninges. Tuberculosis bacillii are then discharge from these foci directly in to subarachenoid space to cause meningitis[16].

Tuberculous meningitis affects young patient[17] in our study Median age was 35 years as observed by Christensen et al[18].

Tuberculous meningitis presents in its early course with an indolent phase with the symptoms are fever, vomiting, lethargy, headache and seizures[20]. Fever and headache were the predominant symptoms in our study present in all patients as evident in other studies by Etlik et al[19] and Kalita et al[21] while Malik et al[17] 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[19] reported it in all patients. Weight loss

was seen in 35% patients in our study while Kalita et al[21] and Malik et al[17] observed it in 80% and 56% respectively. Tuberculous contact was revealed in 35% patients in our study matching 23% in local study by Malik et al[17] while it was reported 13% by Etlik et al[19] in study performed at Turky where TB is less prevalent.

The neurological signs of TBM are nuchal rigidity, cranial nerves deficit and hemiparesis[22]. Neck stiffness was elicited in 90% patients in our study matching the findings in local study by Malik et al[17]. Cranial nerve palsies were examined in 25% while it was 13% by Etlik et al[19] and 50% by Malik et al[17]. Hemiplegia was present in 10% patient in our study while 33% and 23% in other studies by Kalita et al[21] and Malik et al[17]. Impairment of consciousness was detected in 35% patient matching the findings by Kalita et al[21] and Etlik et al[19].

X-ray was normal in 65% patients while in local study by Malik et al[17] it was normal in 54% cases. CT brain showed meningeal enhancement in 30% and hydrocephalus in 15% matching figures from a study by Etlik et al[19]. Combined hydrocephalus and meningeal enhancement was present in 55% matching local study by Malik et al[17].

Tuberculous meningitis is the most severe form of TB, causing death or disability in more than half of Those affected, despite antituberculous chemotherapy[23]. Prompt diagnosis is crucial as delayed treatment is known to be associated with poor outcome[24]. The clinical features of TBM mimic those of other chronic meningoencephalitides, Causing considerable diagnostic difficulty[25]. The prompt and accurate diagnosis of TBM is a daunting challenge[26]. Definitive diagnosis requires detection of Tubercle bacilli in CSF. Smear microscopy is inexpensive and rapid but insensitive while culture techniques are unacceptably slow and insensitive. Polymerase chain reaction has emerged as potentially important tool for rapidly diagnosing TBM[27].

In our study CSF PCR was 100% positive in group 1 (definitive group) compare to 90% by S. Haldar[28] While it was 64% in group 2 (possible group) compare to 76%,66% and 78% by J.S. Micheal et al[7], Bonington et al,[29] Honore Bouakline et al[30].

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.

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Patriotism is the virtue of the vicious.

Oscar Wilde