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Clinical And Laboratory Profile of Tuberculous Meningitis In Patients

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Abstract
Background: *Tuberculous meningitis kills or disables more than half of those affected. The diagnosis of TBM is difficult. Delay in diagnosis and treatment are regarded as the major contributing factors in the high mortality reported.* ***Methods:*** *Total 50 cases of meningitis aged 18 years above were included in the study out of which 40 cases were proved to be TBM, and were studied in detail about clinical and laboratory profile.* ***Results:*** *Patients ranged from 18-70 years. Peak incidence was in age group 20-30 years (40%). Majority of patients had fever, headache, vomiting, altered sensorium and neck stiffness. 17.5% patients were comatose. Cranial nerve palsy was present in 40% cases, 6th nerve being the commonest. Motor deficit like hemiparesis/ plagia (10%), quadriplegia (2.5%) was present in 12.5% cases.* ***Conclusion:*** *TBM continue to be a serious illness mostly affecting the young adults. CSFanalysis continues to be a key in establishing the diagnosis. One should not wait for the microbiological proof to start the therapy. Early diagnosis and treatment can make complete recovery even in comatose patients.*

Keywords: *Tuberculous Meningitis, Cerebrospinal fluid, Adenosine deaminase.*

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I. Introduction

The total number of tuberculosis (TB) cases in the world is increasing. It is estimated that most of these new cases will be in South East Asia fuelled by rapid spread of HIV. The physician need to be aware of these changes, as less common form of tuberculosis such as TBM (Tuberculous Meningitis) will be encountered more often[1]. Before HIV the most important determinant for the development of tuberculosis was age. In population with a high prevalence, CNS tuberculosis differ from pulmonary and other extra pulmonary tuberculosis in that, the peak age is from 0 to 4 years. In population with lower prevalence most cases are in adults. Risk factors include alcoholism, diabetes mellitus, malignancy and recent corticosteroid use but co-infection with HIV now dwarf all these. The main reason for the spread of tuberculosis is poverty, with resulting homelessness, malnutrition and break down of public health infrastructure[1]. Involvement of CNS by tuberculosis is the most hazardous type of systemic tuberculosis because of its high mortality rate and possible serious neurological complications and sequelae. CNS tuberculosis occurs in 2.5% of all patients with TB and in 10% those with AIDS – related TB[2]. Delay in the diagnosis and treatment are regarded as major contributing factor in the high mortality reported. The diagnosis of TBM relies on isolation of mycobacterium TB from the CSF. Unfortunately culture is too slow and insensitive to aid clinicaldecision making. Direct ZN staining of the CSF for acid fast bacilli remains the cornerstones of rapid diagnosis but this technique lacks sensitivity. Newer diagnostic techniques, such as those use PCR have not been assessed completely and are notpossible in most settings in the developing countries where most cases of TBM are seen. Consequently the decision to treat patient for TBM is frequently empirical, irrespective ofthe diagnostic facilities available to clinicians. Until new, affordable, sensitive and specific diagnostic assays becomes available, clinician must depends on the discriminative clinical and laboratory features of the disease for successful diagnosis and treatment.

Objectives

To study the role of CSF adenosine deaminase activity in tuberculous meningitis. To study the neurological complications at presentation of tuberculous meningitis.

II. Review of Literature

Tuberculosis has been known since the pre-historic era. Tuberculous lesions have been discovered in the bones of the Neolithic man (Kirly, 1962). Hippocrates named this conditions as 'Phthiasis' (to dry up). In

1839 Johan Schonlein named the disease Tuberculosis. The word is derived from the Latin word 'Tuberculoma' which means 'small lump'.The existence of meninges is known since very long time and has been mentionedin the Edwin Smith papers 3 (3000 BC). Galen discovered duramater. Arachnoid mater was not clearly defined until 17th century by Blasius (1666). Pia mater was discovered by Aristotle and Gala. CSF (cerebrospinal fluid) was discovered by Domenico Lentango in 1774 and Carning was first to puncture the subarachonid space in living person. Robert Koch discovered the acid fast bacilli on 24th March 1882. The termmeningitis was first time used by Herpin in 1803. Robert Whytt (1768) for the first time gave classical description of tuberculous meningitis in his celebrated work "Observation on the dropsy in Brain" Papavoin described in 1830 the anatomical nature of tuberculous meningitis and called it as "Arachnoiditis Tuberculosa". Gren PH coined the term tuberculous meningitis in 1836. In 1933 Rich and McCordick demonstrated that TBM is due to subarachnoid spillage of caseous material with bacilli from subpial focus of brain[4]. Henrich Quineke in 1891 devised plain needle for lumber puncture thus greatly facilitating the study of CSF for diagnostic purposes. Leithein isolated tubercle bacilli from the CSF. Masterzed (1912) reported chemical composition of CSF in meningitis. Home's described the clinical symptoms in adult. Inflammation of the subarachnoid space activates the protective reflexes and results in nuchal rigidity, hyperextension of neck and spine, and the traditional signs of meningeal irritation. Reflex painful spasm of hamstring muscles from stretching of inflamed sciatic nerve is noted on passive extension of knee when the hip is flexed. It was first described by Valdmer (Valdmer Kernig(1884), this sign goes with his name Kernig's Sign. Brudzinski in 1909 described neck sign consisting of passive flexon of neck resulting in flexon of knee and hips. The Brudzinski's sign is more sensitive if neck flexon is attempted with patient in a sitting position with legs extended parallel to the floor. In the original paper he also describedleg sign. 1n 1921 Calmette & Guerin declared that BCG vaccine is safe. In 1944 Waksmann reported the isolation of streptomycin. This was followed by the use of PASin 1944 and INH in 1951. Ethambutol was produced in 1962. Rifampacin in 1966, and pyrazinamide in 1975. India is classified along the subsaharian countries to be among those with a high burden of disease. The average prevalence of all forms of tuberculosis in India is estimated to be 5.05 per 1000; prevalence of smear positive cases 2.27 per thousand; and average annual incidence of smear positive cases at 84 per 1,00,000 annually[9].The true incidence of neurotuberculosis is not known. It is estimated that 5 to10% of all patient of TB have central nervous system involvement[10]. Tuberculous meningitis, the most dangerous forms of extra pulmonary TB occurs in 7 to 12% of TB patients in developing countries. Delay in diagnosis and institution of proper treatment is directly related to poor outcome and sequelae which may be seen in 20-25% of cases[11]. Tuberculous meningitis is 3 times more common in children than adults[12]. This condition is commonly characterized by diffuse brain damage due to oedema in the absence of overt infarction, tuberculoma or severe hydrocephalus. Less frequently perivascular myelin loss and rarely a picture identical to that of haemorrhagic leuco encephalopathy is seen, Since neuro tuberculosis is usually a sequelae to occult or obvious pulmonary infection, the results of studies from pulmonary tuberculosis have been extrapolated to CNS tuberculosis, the main contending factor being CSF penetrance. Poor CSF penetrance of most drugs makes it necessary to continue the treatment for longer periods than that requires in pulmonary tuberculosis. HIV infected persons are at markedly increased risk for progressive primary or reactivation of latent tuberculosis and for second episodes of tuberculosis from exogenous reinfection. Peripheral blood lymphocytes from HIV infected patients with tuberculosis produce less interferon- as compared with lymphocytes from HIV-negative patients with tuberculosis on exposure to mycobacterium tuberculosis. These findings suggest that the reduced T1 response in HIV-infected patients contributes to their susceptibility to tuberculosis. The treatment protocol for mycobacterium tuberculosis related meningitis does not vary for seropositive patients though chances of adverse reactions and drug resistance are higher. There are no definite guidelines for MAI complex related meningitis but drugsused include azithromycin, clarithromycin with ethambutol or clofazimine. Steroids are not found to significantly alter the outcome in seropositive patients with tuberculous meningitis.

III. Material And Methods

The study was conducted in Darbhanga medical college and Hospital, Laheriasarai Darbhanga, Bihar. Study duration of two years. Fifty patients aged 18 years and above presenting with signs and symptoms of meningitis, were selected for the study. Out of 50 cases selected, 40 were tuberculous meningitis and 10 were pyogenic meningitis. A meticulous history was taken from all the cases, followed by a thorough physical examination. A search for extra meningeal tuberculous foci were carried out in each case. Later various laboratory tests were performed. Observations were made on the modes of presentation and a criteria was applied for diagnosis in the individual patients. Criteria for diagnosis was not stringent in allcases and in some patients was based mostly on clinical suspicion and history of tuberculosis in the past or evidence of co-existing tuberculosis. Cases presented like meningitis clinically initially, but later on correlation and confirmation with respective investigations proved to be cases of cerebrovascular accidents, viral encephalitis, cerebral malaria were excluded from the study. Patients HIV status was determined and those found to be

positive were also excluded from the study. Out of 50 meningitis cases, 10 cases were pyogenic meningitis. Diagnosis was done by gram staining, culture & sensitivity, increase in protein level, decrease sugarlevel and increase cells with a neutrophilic predominance. Treatment was initiated with appropriate antibiotics and all cases responded well with the therapy and were separated from the study. Collect specimen prior to use of antimicrobial agent. Wherever possible, indicate clearly that patient is on antitubercular drugs.CSF**:** Collect as much as possible in a syringe, clean skin with alcohol before aspirationspecimen. ADA is reported to be stable in serum for 3 days at 2-8C and in biological fluids for 2 days at 2-8C, as after this, ammonia may be released in the samples even without any microbial contamination.

IV. Results

Sex Wise Distribution of Cases

Sex	No. of Cases	Percentage
Male	21	52.5
Female	19	47.5
Total	40	100

Out of fifty meningitis patients 40 were found to have tuberculous meningitis and were included in the study. It has been observed that 21 were male (52.5%) and 19 were female (47.5%).

Age Wise Distribution of Cases

Age in years	Male		Female		Total	
	No.	Percent	No.	Percent	No.	Percent
18-20	7	33.33	4	21.05	11	27.5
21-30	7	33.33	9	47.36	16	40
31-40	1	4.76	2	10.53	3	7.5
41-50	2	9.52	1	5.26	3	7.5
51-60	3	14.29	--	--	3	7.5
61-70	1	4.76	3	15.79	4	10
Total	21	100	19	100	40	100

Patients aged 18 and above were included in the study, youngest patient being 18 years and the oldest patients was of 70 years. The majority of patients were in the second to third decade. There were 16 patients in this age group (40%).

History of Past or Evidence of Coexisting Tuberculosis

Category	Past Tuberculosis		Coexisting Tuberculosis	
	No.	Percent	No.	Percent
Pulmonary	3	7.5	6	15
Extrapulmonary	--	--	--	--

Past history of TB were present in 3 cases. Coexisting TB, in the form of miliary TB in 3 cases, tuberculous pleural effusion in remaining 3 cases.Out of 3 cases of miliary TB, one patient was having co-existing left sided hydropneumothorax. Out of 40 cases, who were treated as TBM 30 cases improved completely withoutany sequelae during the hospital stay. Of these 30 patients, 25 came for follow up and observed that, no late sequelae or drug toxicity developed. 5 cases lost from the follow up study. 2 cases improved but had neurological sequelae in the form of optic atrophy in onecase and hemiparesis in the other one. These deficits were found to be persistent during follow up also. Three cases has not improved (excluding mortality) with the therapy, even thoughtherapy was initiated immediately. All these three cases had multiple focal deficit at the time of presentation in the form of quadriparesis in one case, hemiparesis in 2nd one, and hemiplegia in third one, with associated cranial nerve involvement. Out of 3, two cases presented in stage III of the disease, one in stage II. History of pulmonary tuberculosis was present in one patient and was on irregular treatment. There were 5 death out of which 4 were male and one was female. In two cases, duration of illness was one month and in the other three it was 20 days. Oldest patient was of 60 years and youngest one of 18 years. Four cases presented in stage III of thedisease, and remaining one in stage II of the disease. The patient who was in stage II of the disease had evidence of co-existing < ilitaryKoch's lesions. 2 cases had focal deficit, first one in the form of hemiparesis with facial palsy, other one with lateral rectus palsy. Out of five, two cases had seizure at the time of presentation and during hospital stay. History of altered sensorium was present in all cases.

V. Discussion

50 patients of adults with signs and symptoms of meningitis were studied out of which 40 cases diagnosed to be tuberculous meningitis and were studied in detail regarding the clinical and laboratory profile. Symptoms and signs, The peak incidence in the present study was found in the young adults in the age group of 21 to 30 years (40%) followed by 27.5% cases in the age group of 18-20 years.It is similar to Virmani et al., who observed 35.5% in their study. According to the present study there is a male (52.5%) predominance over the females (47.5%), earlier studies done by S. Hosoglu et al., noted a male to female ratio of 1.53. Duration of illness was 15-30 days in majority of cases (45%) followed by a duration of 2 weeks which was consistent with earlier studies by Grigis et al. Fever and headache was the predominant symptoms in the present study which was present in all cases. Hosoglu et al., observed 91.1% incidence of fever and 96% incidence of headache in their study. Altered sensorium was present in 72.5% of cases on presentation, but seizure was present only in 7.5% of cases. This was also similar to studies by Hosoglu et al. History of tuberculosis or evidence of TB in the form of miliary koch's or pleural effusion was present in 15% of cases. Where in Ahuja et al., study it was 10%. In present study neck rigidity was present in 95% of cases and Kernig's sign in 50% of cases, but could not demonstrate Brudzinski's sign in any cases. Khatua et al.,in their studies noticed neck rigidity in 54% cases, Kernig's sign in 40% cases, but no cases had Brudzinski sign. But Thwaites[3] et al., noticed neck rigidity in 91% of cases. Papilloedema was present in 22.5% of cases, optic atrophy in (2.5%) but none of the cases revealed choroid tubercles on fundoscopy. Girgis et al had a 7% cases with papilloedema, 4% cases with optic atrophy in their study. Cranial nerve palsies were present in 40% of the cases, 6^{th} nerve being the most common nerve involved. (17.5%), followed by 7^{th} nerve and 3^{rd} nerve. Girgis et al. hadnoticed cranial nerve palsies in 50% of cases, 6^{th} nerve being the most common followed by 3^{rd} and 7the nerves. CSF cells were moderately increased in all the cases, with a ranges from 18-600 cells. Girgis et al. noticed a range of cells from 30-900 cells/mm^3. Minimum cells noticed in the present study was 18, and maximum being 600. All had >60% lymphocytes. CSF ADA activities known to be raised in TBM and there use has been suggested to help differentiate tuberculous meningitis from other form of meningitis. There has been no agreement about the cut off value of CSF ADA activity. It may differ from one human race to other. One of the objective of present study was to study the role of CSF ADA, for the immediate diagnosis of tuberculous meningitis. An attempt was also made, to find difference of CSF ADA activity in pyogenic meningitis and TBM and to findsome correlation between CSF ADA and other CSF parameters. At cut of value 10, the sensitivity, specificity and positive predictive value of CSFADA in TBM were 75%, 90% and 96.77% respectively. Kim KI et al, in their studies found that, the mean value of CSF ADA in TBM (15.5 4.6) was significantly higher than other meningitis. The sensitivity of diagnosing TBM in their study was 80% and a specificity of 98% respectively. Rajendra Prasad et al, in their studies found that, mean ADA level in TBM was 6.43 1.93 U/L, where as in pyogenic meningitis and in aseptic meningitis it was 1.89 0.91 and 0.90 + 0.45 U/L repectively. Satya Vate Rane et a[11], in their studies in children, found a mean ADA of 18.22 in TBM , 7.98 U/L in pyogenic meningitis, 6.28 U/L in partially treated meningitis and 3.43in aseptic meningitis. At cut off value of 10, sensitivity of ADA was 66.6% and specificity was 90%. They also found a positive correlation between CSF ADA and protein, but not with CSF pleocytosis. Out of 40 cases 8 cases (including mortality) did not respond to therapy even though therapy was started immediately. The reason for detoriation or death in these cases, may most probably due to late stage of disease itself. Earlier studies noticed 30- 50% of mortality at stage III presentation and due to late presentation to hospital. The possibility of multi drug resistant tuberculosis could not be excluded. A least possibility of alternate diagnosis due to decreased efficacy of CSF analysis by present criteria also need to be considered as none of the cases were smear positive. The study had few limitations also. Stringent diagnostic criteria could not be formulated or implemented because of various reasons like affluence of the patient and availability of facilities. Investigations like CSF culture for AFB could not done as this facility was not available in our hospital. CT scan could not be done in all cases because of affordability. Few cases were missed from the follow up group, hence the long term sequelae could not be evaluated in all cases.

VI. Conclusion

Tuberculosis remains a global problem and a public health issue of considerable magnitude. While the commonest form of the disease is pulmonary infection, one of the most dangerous forms is that effecting CNS. Tuberculous meningitis is by far the commonest form of neurotuberculosis.TBM has been a major problem and cause of death in developing countries. Mycobacterium TB is responsible for most cases. In western countries, the incidence of TBM has fallen in parallel with tuberculosis as a whole, but the incidence has remained more or less same in developing countries. Recently there has been an increase in the incidence of tuberculosis and its complications like TBM due to HIV infection.

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