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CLINICAL, LABORATORY, RADIOLOGICAL PROFILE OF TUBERCULOUS MENINGITIS AND PREDICTION OF PROGNOSTIC FACTORS IN SIX MONTHS OUTCOME

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ABSTRACT Only cases with typical symptoms and signs were included. Age group of less than 16 years was not included. Small sample size.

Objectives To study the clinical, laboratory & radiological features of tuberculous meningitis with special reference to the prognosis and outcome after 6 months follow up.

Methods The study was conducted including the patients admitted in Acute medical Care and medical wards at Osmania General Hospital, Hyderabad.

Results Majority of the patients are in the age group (16-35 yrs) 2nd, 3rd & 4th decades (30 out of 50) – 60%, 6 out of 50 are > 55 yrs age - 12%. No patient is below 16 years or above 65 yrs.

KEYWORDS : Laboratory, Radiological Profile of Tuberculosis Meningitis, Prognostic Factors.

INTRODUCTION

Tuberculosis has been a major cause of suffering and death since times immemorial. It is one of the oldest of human diseases. The word Tuberculosis is derived from the Latin word 'tubercula' meaning 'a small lump'. J.L. Schonlein is credited to have named the disease Tuberculosis[1].

Mycobacterium tuberculosis is the causative agent and it infects 1/3rd of the world's population. 90% of Tuberculosis cases are in the developing countries. About 3/4th of Tuberculosis cases are in economically productive age group. India bears about 1/3rd of the entire world's tuberculosis burden. The risk of developing tuberculosis among the individuals co-infected with HIV is 5-10% per year compared to lifetime risk of 5-10% for those without HIV.

The obstruction may be at the level of the interventricular foramina of Monroe, aqueduct of Sylvius or foramina of Luschka and Magendie. A subependymal tuberculoma projecting into the aqueduct acts as ball-valve causing hydrocephalus[2]

The dense basal exudates which surround large and small arteries including lenticulostriate artery cause vasculopathy leading to occlusion of vessels.

A fully formed tuberculoma has creamish white gritty caseating centre with crenated margins surrounded by firm to hard greyish rim (pseudocapsule) of granulomatous tissue and compressed gliotic brain matter.

Immunohistochemical methods may demonstrate tubercular antigen within the cytoplasm of giant cells and macrophages. The tuberculo protein or some of the antigenic components by complex immune reaction lead to the formation of the tuberculoma[3].

Spinal Meningitis is present along with cranial meningitis. Most cases are an extension of the tuberculous basal exudate downwards.

TB meningitis is based on neurological symptoms, signs and CSF findings. Supporting features include radiological evidence from CT or MRI such as basal exudates, hydrocephalus, infarcts, and tuberculomas[4].

INVESTIGATION

CSF ANALYSIS[5]

Typical CSF picture of TBM is a clear fluid under raised pressure with moderately raised cells and protein and low glucose levels.

In tuberculous meningitis the CSF protein is usually (100-500mg/dl), Glucose is less than 40mg (18-40mg/dl) half the level of simultaneous RBS. Cell count is raised (100-500/cu.mm) (varies from 20-1000/cu mm) with negative cytology for malignant cells.

MICROBIOLOGY

Demonstration of Acid fast bacilli (AFB) in the CSF by smear (Ziehl-Neelsen staining). CSF culture - Lowenstein-Jensen medium (4-8 wks). Yield can be increased by using liquid media such as Septi-chek AFB system and middle brook BACTEC radiometric system (7-10 days).

IMMUNOLOGICAL TESTS

Detection of mycobacterial antibodies. (against glycolipids, PPD, antigen-5 and lipoarabinomannan by ELISA, radioimmunoassay and immunoblot methods). Detection of mycobacterial antigens by ELISA, latex agglutination (antigen5, lipoarabinomannan (LAM), A60 antigen). Detection of immune complexes by ELISA.

INDIRECT TESTS MEASURING THE HOST RESPONSE

Estimation of Adenosine deaminase. It is produced by T- lymphocytes and is elevated in 60-100% of TBM patients. Bromide partition test - Measures the ratio of serum to CSF bromide ratio 24 hr after a loading dose. A ratio <1.6 is suggestive of TBM.

OTHER DIRECT TESTS

Estimation of CSF tuberculostearic acid by gas chromatography or mass spectroscopy. CSF 3,2-ketohexyl indoline estimation. Detection of mycobacterium tuberculosis DNA by PCR (Molecular method).

POLYMERASE CHAIN REACTION[6] (PCR)

A rapid diagnostic test. Invented in 1985 by Saiki. It involves amplification of a defined region of DNA from few starting copies. The first stage of applying PCR for diagnosis is to identify within the organism of interest a sequence of DNA within the genome unique to that organism. Some of the targets used in tuberculosis are IS6110 DNA sequence, 65kda gene, and MPB 64 gene. A negative PCR report cannot exclude the diagnosis. False negative PCR results may be due to extremely low bacterial counts, presence of inhibitory factors, small volume of CSF tested. Besides AFB smear examination PCR is the only technique which can confirm the diagnosis of tuberculosis on the same day.

AIMS AND OBJECTIVES

To study the clinical, laboratory & radiological features of tuberculous meningitis with special reference to the prognosis and outcome after 6 months follow up.

MATERIAL & METHODS

The study was conducted including the patients admitted in Acute medical Care and medical wards at Osmania General Hospital. Sample size - 50 cases, Follow Up for 6 months.

INCLUSION CRITERIA: Patients presenting with fever, headache for 2 weeks (or) more and neck stiffness at admission and supportive evidence from CSF. Age more than 15 yrs upto 65 yrs. Both sexes

EXCLUSION CRITERIA: Age less than or equal to 15 yrs and more than 65 yrs, Acute onset of symptoms. Patients who could not attend for follow up.

Investigations

All the patients were subjected to investigations including complete blood picture ESR, Random Blood sugar, Blood Urea, Serum Creatinine, Serum Electrolytes.

- Liver function tests, Chest X ray and Mantoux test, Lumbar puncture is done under aseptic precautions, (Guarded LP done in the patients with papilloedema).
- Cerebro spinal fluid examination done regarding gross appearance elevated pressure, cobweb formation, the level of protein, globulin, sugar, chloride, adenosine de aminase (ADA) levels, Cell count, cytology for malignant cells. Microscopy, India Ink. preparation, AFB smear (Ziehl – Neelsen Staining).
- Bacterial & fungal culture, LJ (Lowenstein–Jensens) medium culture, and polymerase chain reaction for TB (IS6110) were done in all the samples. Those with CSF findings suggestive of alternative diagnosis were excluded from follow up (5 out of 55 cases).
- All the patients were subjected to neuroimaging (CT brain).

The presence of hydrocephalus, tuberculoma, infarctions and exudates were recorded.

OBSERVATIONS & RESULTS

Age wise distribution

Age Group (in yrs)	Male	Female	Total
16 – 25	6	9	15
26 – 35	9	6	15
36 – 45	5	3	8
46 – 55	5	1	6
56 – 65	5	1	6
Total	**30**	**20**	**50**

Majority of the patients are in the age group (16-35 yrs) 2nd, 3rd & 4th decades (30 out of 50) – 60%, 6 out of 50 are > 55 yrs age - 12%. No patient is below 16 years or above 65 yrs.

Clinical stage of Meningitis

Stage	Male	Female	Total
Stage – I	6	6	12 (24%)
Stage – II	8	5	13 (26%)
Stage – III	16	9	25 (50%)

12 patients – 24% 6 males, 6 females are in stage I meningitis, (Conscious oriented, no focal deficit, no cranial nerve palsy). 13 patients - 26% 8 males and 5 females are stage II (consciousness is disturbed but not comatose focal neurological signs (or) cranial nerve palsies may be present). 25 patients (50%) 16 males, 9 females are in stage III. (Deeply comatose with decerebrate or decorticate posturing , irregular pulse and respiration).

Cerebro spinal fluid analysis

CSF	Range	Mean
Protein (mg/dL)	60 – 800	150
Sugar (mg/dL)	15 – 45	27
Chloride (meq/L)	90 -120	105
A.D.A. (U/L)	6 – 36	11
Cell count (per cu.mm)	60 – 360	102

Mean CSF protein is 150 mg/dL (60 – 800), Mean CSF sugar is 27 mg / dL, Mean CSF chloride is 105 meq/L (90-120), Mean CSF ADA (Adenosine deaminase) is 11 units / L, Mean cell count is 102 / cu mm. (60 – 360).

Laboratory profile

Test	Positive	Negative
CSF AFB (Smear)	1 (2%)	49 (98%)
CSF culture (LJ Medium)	3 (6%)	47 (94%)
CSF PCR - TB	24 (48%)	26 (52%)
HIV I & II	10 (20%)	40 (80%)
Absolute CD4 < 200	5	-
Absolute CD4 > 200	5	-
Mantoux test	26 (52%)	24 (48%)

Microbiological investigations depict

- CSF smear positivity - 2%, Culture positive – 6%, Polymerase chain reaction – TB is positive in 48% of the cases, 20% of the patients are HIV positive (one half of them have CD4 count below 200), Mantoux test is positive in 52% of cases.

Neuro Imaging (CT brain)

Imaging finding	Number	Percentage (%)
Hydrocephalus	28	56
Basal meningeal enhancement	20	40
Infarct	13	26
Tuberculoma	4	8

Hydrocephalus is the most common finding seen in 56% of cases (All are of communicating variety), Basal meningeal enhancement is seen in 40% of cases. Infarct seen in 26%, Tuberculomas seen in 8%, All are supratentorial in location.

Hydrocephalus on Neuroimaging Vs Mortality & outcome

Hydrocephalus	Total	Mortality	Outcome good	Outcome poor
Present	28	10 (35.71%)	9 (32.14%)	19 (67.86%)
Absent	22	3 (13.64%)	14 (63.64%)	8 (36.36%)

Out of 50 patients CT brain evidence of Hydrocephalus is found in 28 patients, In those patients with Hydrocephalus mortality is 35.71%, good outcome is 32.14%, poor outcome is 67.86%. In those without hydrocephalus, mortality is 13.64%, good outcome is 63.64%, poor outcome is 36.36%. Presence of hydrocephalus is associated with poor long term outcome.

DISCUSSION

Tuberculosis is becoming an increasingly troublesome public health problem mostly because of incomplete therapy of existing cases and because of increase in immunodeficiency states from various causes. Tuberculous meningitis is the commonest form of Neurotuberculosis. It is a serious neurological illness with significant mortality and morbidity. In addition neurological complications such as cerebral infarcts and hydrocephalus are common and worsen the long term prognosis.

In this study 50 patients were studied for their clinical presentation laboratory profile and neuroimaging features and were followed up for 6 months and prognosis and outcome were evaluated.

Focal neurological deficit was seen in 20% of the patients which ranged from mild weakness of one limb to severe quadriplegia. Encephalopathy, vasculitis resulting in infarction, granuloma formation and arachnoiditis in isolation or in combination can result in focal weakness.

Cranial nerve palsies were seen in 14 out of the 50 patients, most common cranial nerve involved being abducent (6th) nerve[7]. Facial nerve palsy was seen in 5 patients. Two patients presented with multiple cranial nerve palsies.

The clinical presentation of patients in this study was almost similar to that in the study of 232 cases of TBM done by ***Thomas MD, Chopra JN, Walia BNS et al.*** **PGIMER Chandigarh.**

Cerebro spinal fluid analysis depicted the mean protein value of 150 mg/dl (60-800), sugar 27 mg/dl (15-45), chloride 105meq/l(90-120),cell count 102/mm^3 (60-300) and ADA 11U/L(6-36). These findings were consistent with previous studies.[8]

Neuroimaging depicted hydrocephalus in 56% of cases and was the most common abnormality seen, infarcts were seen in 26% and tuberculoma in 8% of cases (***CT-study: TB meningitis; Bhargava[3] et al,*** had shown the similar findings).

Out of the total 50 patients 13 expired, 11 out of them during hospital stay and 2 during 6 months follow-up period. Mortality was included in poor outcome group (Barthel Index less than 12)[9].

Hydrocephalus was seen in 56 % patients on Neuro imaging and was the most common abnormality. In those patients with hydrocephalus 67.86% had poor outcome compared to 36.36% in those without hydrocephalus[10].

LIMITATIONS

Small sample size, only cases with typical symptoms and signs were included. Age group of less than 16 years was not included.

CONCLUSIONS

1. In Tuberculous meningitis duration of illness 3 weeks or more at diagnosis, stage-III meningitis, GCS score less than 9 at admission, presence of focal deficit, and hydrocephalus on neuroimaging are the predictors of poor outcome.
2. Patients can be categorized into high risk and low risk groups depending on the presence or absence of poor prognostic factors.
3. The prognosis and outcome in HIV-Reactive patients is worse only in those with absolute CD4 count less than 200.
4. Early diagnosis and prompt initiation of treatment reduces the mortality and morbidity.

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