

Study of ADA Levels in Cerebrospinal Fluid In Relation To Stages of Tuberculous Meningitis And Prognostic Significance of Staging in Tuberculous Meningitis.

Dr. Chandra Bhushan Sharma¹, Dr. Shiny Kumari Khess², Dr. Rishi Tuhin Guria³

¹Department Of Medicine/Associate Professor/R.I.M.S/Ranchi University/India

²Department Of Medicine/Junior Resident/R.I.M.S/Ranchi University/India

³ Department Of Medicine/Assistant Professor/R.I.M.S/Ranchi University/India

Abstract

Introduction: Tuberculous meningitis is a chronic meningeal infection by *Mycobacterium tuberculosis* characterized by fever, headache, nausea, vomiting, various levels of consciousness, seizures and raised intra cranial pressure.

Materials and methods: The present study "study of ADA levels in cerebrospinal fluid in relation to stages of tuberculous meningitis and prognostic significance of staging in the patients" was carried out in the Department of Medicine, Rajendra Institute of Medical Sciences, Ranchi.

• Study Design:- Prospective observational study

• Sample Size:- 118

• Study Period:- Sept. 15 to Aug. 16

Results: Increased levels of CSF ADA was found in all cases of tuberculous meningitis (>6mg/dl). Mean level of CSF ADA was higher in MRC stage III (14.97±1.45) than in stage I (9.22±1.45). Mortality was also higher in stage III (20.6%).

Conclusion: CSF ADA levels correlate with stage of disease at time of presentation as well as outcome and can be used as a prognostic indicator. Late stage of presentation along with raised CSF ADA levels have bad prognosis and poor chances of survival.

Keywords: Tuberculous meningitis, CSF ADA, MRC stages

I. Introduction

Tuberculosis remains a major public health problem all over the globe. Currently more than 2 billion people are infected with tuberculosis. The World Health Organization (WHO) data suggest that the number of death due to tuberculosis and incidence of tuberculosis continue to fall globally since 2006. Despite this achievement, TB continues to be one of the top ten causes of death worldwide. 1.4 million deaths and more than 10 million new cases of tuberculosis were reported in 2015. Tuberculosis involves almost every organ of the body. Involvement of the central nervous system (CNS) is the most dreadful type of systemic tuberculosis. CNS tuberculosis, particularly tuberculous meningitis (TBM) remains a serious clinical problem. Delayed diagnosis and treatment result in significant rise in morbidity, mortality and disease sequelae. *M. tuberculosis* and *M. bovis* are the common species affecting humans. Other atypical mycobacteriae like *M. phlei*, *M. smegmatis*, *M. kansasii*, *M. microti* etc seldom cause any serious infections in humans, but they can be frequently isolated from human body. *M. avium intracellulare* can cause serious infections in HIV patients. It may also cause serious forms of neuro tuberculosis as well (Jacobs, 1993)⁵.

Pathogenesis

The development of TBM is a two step process²¹; *M. tuberculosis* bacilli enter the host by droplet inhalation, the initial point of infection being the alveolar macrophage. Escalating localised infection within the lung with dissemination to the regional lymph nodes produces the primary complex. During this stage there is a short but significant bacteraemia that can seed tubercle bacilli to other organs in the body. In those who develop TBM, bacilli seed to the meninges or brain parenchyma, forming small subpial or subependymal foci. These are called Rich foci, after the original pathological studies of Rich and McCordick

The second step in the development of TBM is rupture of a Rich focus into the subarachnoid space. This heralds the onset of meningitis, which if left untreated, will result in severe and irreversible neurological pathology. In 75% of children the onset of TBM is less than 12 months after the primary infection²². Three general processes produce the subsequent neurological pathology: adhesion formation, an obliterative

vasculitis, and an encephalitis or myelitis⁷. Adhesions result from a dense basal meningeal exudate that develops after inoculation of bacilli into the subarachnoid space. The exudate contains lymphocytes, plasma cells, and macrophages, with increasing quantities of fibrin. Blockage, through adhesion formation, of the basal subarachnoid cisterns can result in obstruction of the CSF and hydrocephalus. Adhesions around the interpedicular fossa and related structures can compromise cranial nerves, particularly II, IV, and VI, and the internal carotid artery. An obliterative vasculitis of both large and small vessels develops that can result in infarction and stroke syndromes. These commonly occur in the territories of the internal carotid, proximal middle cerebral, and the perforating vessels to the basal ganglia⁶. Infarction through vasculitis is the mechanism by which many of the diverse clinical neurological abnormalities in TBM occur, and accounts for an appreciable part of the irreversible neurological sequelae. The intensity of the basal inflammatory process extends into the parenchyma resulting in encephalitis. Oedema occurring as a consequence can be marked throughout both hemispheres. This will contribute to rising intracranial pressure and the global clinical neurological deficit.

In the majority of cases tuberculous meningitis has a definite clinical pattern. In adults there is a history of vague ill health lasting for 2 or more weeks. Intermittent low grade fever is present. This is followed by headache, vomiting and giddiness which become prominent later when signs of neurological irritation appear. If the illness is not recognized and treated at this stage, complications and sequelae are likely to occur. Acute onset of illness can occur in 50% of children, but in only 14% of adults¹². Signs of meningeal irritation include neck rigidity, Kernig's sign and Brudzinski's sign. Cranial nerve palsies occur in 20-30% of cases and may be the presenting feature. 6th cranial nerve is most commonly involved followed by 3rd, 4th, 7th, 8th, 10th, 9th, 11th and 12th nerves. Raise intracranial tension is a common and serious complication of tuberculous meningitis. It causes increasing headache, vomiting and altered sensorium. Hydrocephalus often accompanies increased intracranial tension. Fundus shows papilledema and choroidal tubercles in 10% of cases. As disease progresses convulsions appear (generalized or focal). Vasculitis leads to focal neurological deficits like monoplegia, hemiplegia.

In later stages patient becomes comatose and stuporose. There may be signs of brainstem damage like decerebrate rigidity, irregular breathing (Cheyne Stokes/Bitots). The untreated cases usually die within a week or so. Even with aggressive treatment total recovery is seldom possible and sequelae are likely.

Hypothalamic symptoms have been recorded at various stages of illness. These include disturbances of sleep rhythm, hypertension, glycosuria, diabetes insipidus, hyperpyrexia, delirium tremens, Korsakoff's syndrome.

Staging

In 1948, the british medical research council (MRC) developed a method for staging the severity of the disease^{12,13}, as follows:

stage I : describes the early nonspecific symptoms and signs including apathy, irritability, headache, malaise, fever, anorexia, nausea, and vomiting, without any alteration in the level of consciousness

stage II : describes altered consciousness without coma or delirium but with minor focal neurological signs; symptoms and signs of meningism and meningitis are present, in addition to focal neurological deficits, isolated CN palsies, and abnormal involuntary movements

stage III : describes an advanced state with stupor or coma, dense neurological deficits, seizures, posturing, and/or abnormal movements.

II. Materials And Methods

The present study was carried out in the Department of Medicine, Rajendra Institute of Medical Sciences, Ranchi.

Inclusion criteria:

- 1) Primary pool- patients hospitalized with complain of fever, headache, nausea, vomiting and clinical diagnosis of meningitis.
- 2) Secondary pool- the cases from primary pool with highly probable and probable cases of tuberculous meningitis.

Exclusion criteria:

Diagnosed cases of subarachnoid hemorrhage, cerebral malaria, bacterial, fungal or viral meningitis.

118 cases of different age above 14 years of age and sex with highly probable and probable cases of tuberculous meningitis were selected.

The following investigations have been done in cases under study:

1. Total count, differential count of WBC, total RBC count, Hb%, Erythrocyte sedimentation rate
2. Peripheral smear for malarial parasite
3. Blood urea, serum creatinine

4. Random blood sugar
5. Montoux test
6. Sputum for AFB
7. Fundus examination
8. HIV
9. Chest X-ray PA view and CT scan of brain
10. CSF examination for physical appearance such as colour and presence of cobweb; level of protein, sugar; total and differential count of WBC; CSF ADA level.

III. Statistical Analysis

ANOVA was used to find the significance of mean values of CSF ADA levels among different stages of the disease and mortality among them.

IV. Result

The total no of cases studied (n=118). 70 (59.3%) were male while 48 (40.7 %) were female. The age of cases varied from 14 years to 58 years of age. The maximum incidence of the disease was observed in 31 – 40 years of age group (39.8%). The disease was less common after 50 years . Maximum number of cases were from the labourer group (49 cases ie 41.5%). Number of cases from rural areas were 79 (66.9%) and those from urban areas were 39 (33.1%). History of fever and headache were present in 100% of the cases. Vomiting was present in 57.6%. Convulsions occurred in 19.1%. 11% of the cases had squint or diplopia. 16.9% of the patients developed hemiparesis and 73.6% had impaired level of consciousness. Signs of meningeal irritation were present in 94.% of the cases. upon fundoscopy papilloedema was present in 11.9%. Past history of tuberculosis was present in 19.5%. Evidence of extraneural tuberculosis were present only in 16.1% of the cases. Hydrocephalus was present in 26.3% cases on CT scan of the brain. Cerebral infarcts were present in 17.8%. Tuberculomas were found in 6.8%. Acute renal failure was present in 21.2% of the patients. 7.6% of the patients developed ARDS, among whom mortality was 77.8% (p<0.05).

According to MRC staging 22.9% patients were in stage I, 48.3% patients in stage II and 28.8% patients in stage III of the disease. Mean cerebrospinal fluid ADA level was 9.22mg/dl in stage I of the disease, 13.66mg/dl in stage II. In stage III of the disease it was 14.79mg/dl with a standard deviation of 1.45(p<0.05). Mortality was 3.7% in stage I, 8.8% in stage II and 20.6% in stage III respectively. ANOVA was applied and p value was found significant ie <0.05.

Table 1-Age distribution of cases under study

Age	Male		Female		Total	
	No.	Percent	No.	Percent	No.	Percent
14-20	16	22.9	14	29.2	30	25.4
21-30	29	41.4	18	37.5	47	39.8
31-40	14	20.0	9	18.8	23	19.5
41-50	6	8.6	4	8.3	10	8.5
>50	5	7.1	3	6.2	8	6.8
	70	59.3	48	40.7	118	100

Table 2-showing mean CSF ADA level in each stage of the disease

	No. of cases	Mean ADA	SD
Stage I	27	9.22	1.45
Stage II	57	13.66	1.35
Stage III	34	14.79	1.45

Annova f value=2.91, p value=0.031

Table 3-showing relationship between stage of disease and mortality

Stage	Death	Discharge	Total	Percentage of death	Percentage of survival
I	1	26	27	3.7	96.3
II	5	52	57	8.8	91.2
III	7	27	34	20.6	79.2

t=4.564, df=3, p=0.017

Figure 1 - Showing Age & Sex Distribution Of Patients

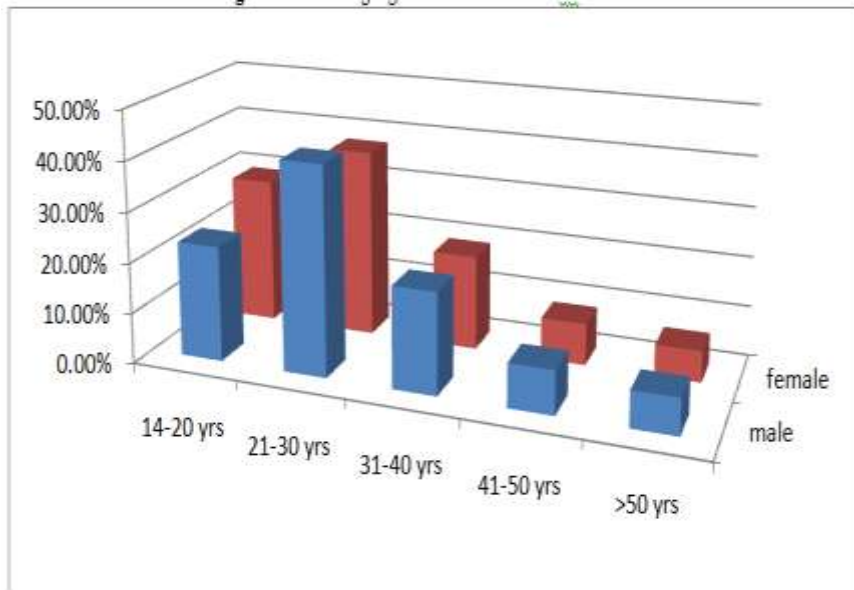


Figure 2 - showing mean CSF ADA level in each stage of the disease

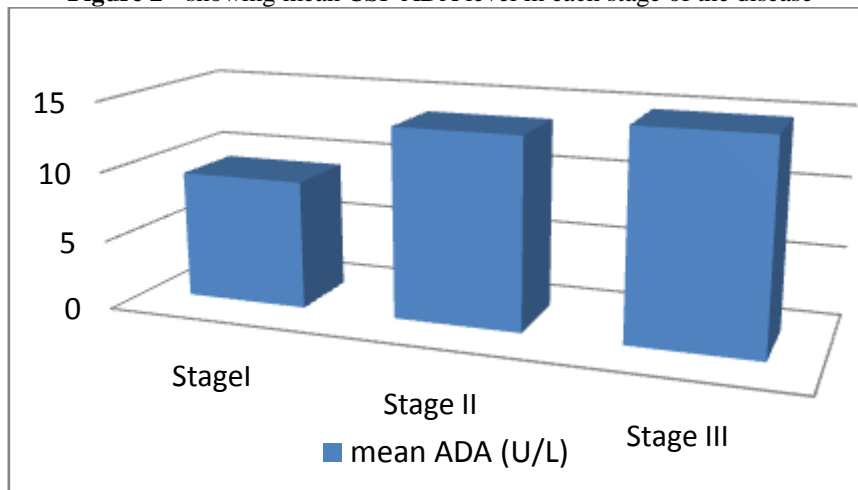
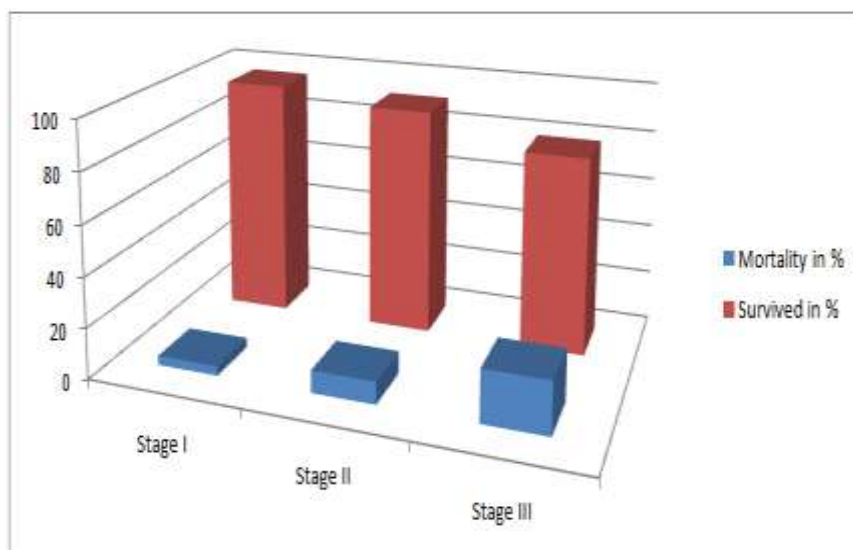


Figure 3 - showing relationship between stage of disease and mortality



V. Discussion

In the present study peak incidence was found in young adults in the age group of 21-30years (39.8%) which was similar to study carried out by Virmani et al¹⁹ in 1980 who observed 35.5% incidence in this age group. The disease affected mostly the males. Out of 118 patients under study 59.3% were male and 40.7% were female. Affected population mostly belonged to rural areas and labourer class. History of fever and headache were the most common presenting complaints found to be present in 100% of the patients. Convulsions were present in 19.1% and focal neurological deficits were found in 47.3% of the patients.

According to MRC staging 22.9% patients were in stage I, 48.3% in stage II, and 28.8% in stage III. At the time of admission mean CSF ADA level was found to be highest in MRC Stage III 14.79 ± 1.45 , 13.66 ± 1.35 in stage II and 9.22 ± 1.45 in stage III which was close to 16.63 ± 8.24 in stage III, 15.89 ± 10.92 in stage II and 10.3 ± 11.29 in stage III as observed by Mathur et al¹⁷ in 2016. In the present study mortality was 20.6% in MRC stage III, 8.8% in stage II and 3.7% in stage I respectively, as compared to a study by Bang et al¹⁶ in 2016, in which mortality was 33.3% in stage III, 9.1% in stage II and 6.3% in stage I of the MRC staging.

VI. Conclusion

CSF ADA level has significant value in diagnosing TBM. CSF ADA levels correlate with stage of disease at time of presentation as well as outcome and can be used as a prognostic indicator. Late stage of presentation along with raised CSF ADA levels have bad prognosis and poor chances of survival, unless energetic and efficient management is done to save the patient.

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