‘A STUDY ON CEREBROSPINAL FLUID ADENOSINE DEAMINASE LEVELS AS A MARKER OF CENTRAL NERVOUS SYSTEM TUBERCULOSIS’

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M.D. (GENERAL MEDICINE) BRANCH - I

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CERTIFICATE

This is to certify that this dissertation entitled '**A STUDY ON CEREBROSPINALFLUID ADENOSINE DEAMINASE LEVELS AS A MARKER OF CENTRAL NERVOUS SYSTEM TUBERCULOSIS**' submitted by Dr. T.BALAMURUGAN to The Tamil Nadu Dr. MGR Medical University is in partial fulfillment of the requirement of the award of M.D. DEGREE (GENERAL MEDICINE) (BRANCH-I) and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I solemnly declare that the dissertation entitled '**A STUDY ON CEREBROSPINALFLUID ADENOSINE DEAMINASE LEVELS AS A MARKER OF CENTRAL NERVOUS SYSTEM TUBERCULOSIS**' was done by me at Government Stanley Medical College Hospital and Tambaram Hospital during 2009-2011 under the guidance and supervision of PROF. and HOD Dr.S. MAGESHKUMAR M.D. The dissertation is submitted to the Tamil Nadu Dr.MGR Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE (BRANCH –I) in General Medicine

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LIST of ABBREVIATIONS

CNS-Central nervous system

ADA-Adenosine deaminase

TB-Tubercle bacilli

MTB-Mycobacterium tuberculosis

ZN staining –Ziehl - Neelsen staining

PTB- Pulmonary tuberculosis

RNTCP- Revised national tuberculosis control programme

TBM- Tuberculous meningitis

FND- Focal neurological deficit

CT scan- Computed tomography scan

MRI-Magnetic resonance imaging

TST-Tuberculin Skin Test

CSF- Cerebro Spinal Fluid

MGIT-Mycobacterium Growth Indicator Tube

ELISA-Enzyme Linked Immuno Sorbent Assay

DNA-Deoxyribo Nucleic Acid
IGRA-Interferon Gamma Release Assays

BCG-Bacillus Calmette Guerin

ATT-Anti tuberculous therapy

BBB-Blood brain barrier

MDR-TB-Multi drug resistant tuberculosis

TNF-alpha-Tumour necrosis factor alpha

HIV-Human immuno deficiency virus

IRIS-Immune reconstitution inflammatory syndrome

LP-Lumbar punture

ESR-Erythrocyte sedimentation rate

Mx-Mantoux

AFB-Acid fast bacilli

SIADH-Syndrome Of Inappropriate ADH Secretion

FLAIR –Fluid Attenuated Inversion Recovery Sequence

CMV-cytomegalovirus

BPT-bromide partition test

PPD-purified protein derivative

ESAT-6-early secreted antigenic target

CFP-10-culture filtrate protein

RD-1-region of difference-1

QTF-G-quanti feron-TB Gold

CNS-TB- central nervous system tuberculosis

INH,H-isoniazid

R-rifampicin

Z-pyrazinamide

S-streptomycin

E-ethambutol

CONTENTS

INTRODUCTION

Tuberculosis is one of the oldest human diseases. Tuberculosis affects almost all organs of the human body. Tuberculosis affection of the central nervous system is seen in 1 % of all cases of tuberculosis. It's a major extra-pulmonary manifestation of Tuberculosis.Central nervous Tuberculosis{CNS-TB} is a devastating disease. It may lead to unacceptable increase in mortality and morbidity. Tuberculous meningitis is commonly seen especially in developing countries . The key to cure the disease is early diagnosis and initiation of treatment. The definitive diagnosis requires the demonstration of acid fast bacilli via a smear or culture. The diagnostic yield of this test is low. And hence the exact diagnosis of Central nervous system tuberculosis still remains a formidable challenge.

A number of indirect methods have been used to diagnose Central nervous system tuberculosis . The Cerebro spinal fluid{CSF} analysis for concentration of protein and sugar and Cerebro spinal fluid cell count have been important in the diagnosis of Tuberculous meningitis. However there is a need of other markers for the diagnosis of Tuberculous meningitis in

equivocal cases. One such marker that is widely used is Cerebro spinal fluid- Adenosine deaminase level. Cerebro spinal fluid – Adenosine deaminase activity has been used for the diagnosis of Tuberculous meningitis in many studies. However there is no unanimously accepted cut-off value to rule out tuberculosis affection of the central nervous system.

This study was undertaken to evaluate the role of adenosine deaminase in the diagnosis of tuberculous meningitis and to find out an appropriate cut-off value to achieve acceptable sensitivity and specificity levels

OBJECTIVES

The study was conducted with the objective of

(i) Evaluating the efficacy of CSF adenosine deaminase activity in diagnosing tuberculous meningitis

(ii) to find out a appropriate cut-off value for CSF ADA level for the diagnosis of tuberculous meningitis.

REVIEW OF LITERATURE

HISTORY

Tuberculosis is one of the oldest human diseases. Hippocrates (460-373BC) called the disease pthisis, a Greek word which meant to consume, to spit and to waste away[1]. There has been references in the Vedas and it was called RAJAYAKSHMA. On 24th March, 1882, Robert Koch discovered the bacilli causing TB. This day (March 24) is being observed worldwide as TB day[2].

INTRODUCTION

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis{MTB}. This disease mainly spreads by droplet infection. Whenever a sputum positive patient coughs or sneezes, he throws millions of bacilli in to the surrounding air. When a healthy person inhales these bacilli, he gets TB infection. But in most conditions the development of TB in healthy individual is kept in a check by the immune system. When the immunity is deranged, the person develops the disease. TB affects all the organs except hair and nail. One sputum positive patient can infect 10-15 persons in one year and remain infectious for 2-3 years if left untreated.

TB is called “CAPTAIN OF THE MEN OF DEATH”. TB is the leading killer disease among the infectious diseases. Among women, compared to the maternity related deaths, TB ranks higher[3].

In India, per day 40,000 people are infected with TB bacilli and relatively 5000 people develop the disease. One death every one and a half minute is being reported due to tuberculosis[4].

Microbiological aspects of MTB

Mycobacteria are gram-positive rods. They measure 1 to 4 mm long and 0.3 to 0.6 mm in diameter; they are seen as clear rod-shaped zones in Gram’s stain.[5] The high content of lipids in the cell wall of all MTB bacilli make them acid-fast. This is in the outer layer of the cell wall (glycolipids and esters of fatty acids). One of the water-soluble glycolipids is known as ‘cord factor’. This has been related to the virulence of MTB. Mycolic acid though is specific for MTB, it is positive in many other organisms like Nocardia , Rhodococci , Cornyebacteria , Microsporidium , Cryptosporidium and few others[6]. Pathogenic MTB is fastidious with regards to culture conditions. The various methods of demonstrating MTB are:

- Ziehl-Neelsen staining
- Modified ZN staining
- Auramine- Rhodamine staining[7]

NEUROLOGICAL TUBERCULOSIS

INTRODUCTION

Neurological tuberculosis comprises five to ten percent[43] of the cases of extra-pulmonary TB. With the emergence of TB as an increasingly common secondary infection in patients with HIV infection and AIDS there, is a resurgence of neurological TB cases.[6] Even after the invent of modern day antituberculosis treatment, neurological TB continues to have a high morbidity and mortality rate.

CLASSIFICATION OF NEUROLOGICAL TUBERCULOSIS:

- Tuberculous meningitis
- Tuberculous arachnoiditis (TB radiculomyelitis)
    - Basal
    - Opticochiasmatic
    - Spinal

- Tuberculoma
    - Intracranial
    - Spinal
- Tuberculosis abscess

TUBERCULOUS MENINGITIS

Tuberculous meningitis, the commonest form of neurological TB, accounting for about 70 to 80 percent of the neurological cases in developing countries, is a major health problem faced by the developing countries. Inspite of its common occurrence, extensive research and wide spread awareness, there is often a delay in the diagnosis and institution of specific therapy for TBM.

EPIDEMIOLOGY:[56]

It is estimated that there are 3.3 million prevalent case of all forms of TB disease (smear positive Pulmonary tuberculosis, smear negative PTB and Extra-Pulmonary TB). The no. of TB suspects is gradually increasing over the last 10 years in INDIA. In India according to the 2010 data there was an incidence of 1.98 million (168/lakh/year) cases of tuberculosis (in all forms) and the prevalence was 2.18 million (185/lakh/year) . The

proportion of HIV positive patients in the Tuberculosis group was found to be 6.7%

However , this data refers to the tuberculosis in all forms for which Revised national tuberculosis control programme{RNTCP} was started. The data on extra-pulmonary TB is very minimal and there is hardly any data regarding the country wide incidence and prevalence of CNS tuberculosis.

PATHOGENESIS[8,13,15,16]

Many of the symptoms, signs, and sequelae of tuberculous meningitis (TBM) are the result of an immunologically directed inflammatory reaction to the infection. TBM develops in 2 steps. Mycobacterium tuberculosis bacilli enter the host by droplet inhalation, the initial point of infection being the alveolar macrophages. Localized infection escalates within the lungs, with dissemination to the regional lymph nodes to produce the primary complex. During this stage, a short but significant bacteremia is present that can seed tubercle bacilli to other organs.

In persons who develop TBM, bacilli seed to the meninges or brain parenchyma, resulting in the formation of small subpial or subependymal foci of metastatic caseous lesions. These are termed Rich foci, after the original pathologic studies of Rich and McCordick. Tuberculous pneumonia develops with heavier and more prolonged tuberculous bacteremia. Dissemination to the central nervous system (CNS) is more likely, particularly if miliary tuberculosis (TB) develops.

The second step in the development of TBM is an increase in size of a Rich focus until it ruptures into the subarachnoid space. The location of the expanding tubercle (ie, Rich focus)[10,11] determines the type of CNS involvement. Tubercles rupturing into the subarachnoid space cause meningitis. Those deeper in the brain or spinal cord parenchyma cause tuberculomas or abscesses. While an abscess or hematoma can rupture into the ventricle, a Rich focus does not.

A thick gelatinous exudate infiltrates the cortical or meningeal blood vessels, producing inflammation, obstruction, or infarction. Basal meningitis accounts for the frequent dysfunction of cranial nerves (CNs) III, V,VI, and VII, eventually leading to obstructive hydrocephalus from

obstruction of basilar cisterns. Subsequent neurological pathology is produced by 3 general processes: adhesion formation, obliterative vasculitis, and encephalitis or myelitis.

PATHOLOGY OF TBM[13,14,15,16]

The pathology of TBM comprises of 1)inflammatory meningeal exudates, 2)ependymitis 3)vasculitis, 4)disturbance of cerebrospinal fluid circulation and absorption.

- Meningitis
    - Inflammatory leptomeningeal exudates
    - Caseous necrosis
    - Proliferative opticochiasmatic arachnoiditis
- Vasculitis
    - Arteritis /
    - Phlebitis
- Ependymitis and choroid plexitis
    - Cortical
    - Subependymal
    - Vasculitis and infarction
- Hydrocephalus
    - Communicating
    - Obstructive

CLINICAL FEATURES

Prodromal phase is non specific and usually lasts for 2-3 weeks. This phase includes apathy, anorexia, vague ill-health, irritability and behavioural changes. As a part of prodrome headache, vomiting and fever may occur and heralds the onset of meningitis. Focal neurological deficits and features of raised intracranial tension may precede the signs of meningeal irritation. Focal and generalized convulsions are more common in children and elderly persons. Cranial nerve palsies can occur. Sixth nerve involvement being the most common[13,14,15,16,55].Exudates around the optic chiasma is the central feature of the pathology. Complete or partial loss of vision is the major complication of the disease.

In untreated cases, adhesions in the basal brain progress and result in extensive cranial nerve palsies. Internal carotid occlusion and stroke, pupillary abnormalities, increasing hydrocephalus with tentorial herniation, pyramidal signs and progressive deterioration in the conscious state occur. In the terminal stage of illness, patient becomes comatose and result in decerebrate or decorticate posturing. Without treatment, death usually occurs in 5-8 weeks.

According to the severity of the illness, patient with TBM can be categorized into four clinical stages

STAGE	DESCRIPTION[10,42]
1	Conscious and rational, with or without neck stiffness, but no focal neurological signs or signs of hydrocephalus
2	Conscious but confused or has focal signs, such as cranial nerve palsies or hemiparesis
3	Comatose or delirious with or without dense neurological deficit
4	Deeply comatose with decerebrate or decorticate posturing

The prognosis of TBM is determined by the clinical stage at the time of initiation of treatment.

TUBERCULOMA[17,18,19,20,21]

Tuberculoma is a mass of granulation tissue made up of a conglomeration of microscopic small tubercles. It is due to hypersensitivity reaction to tubercular proteins in the susceptible individuals. The size of cerebral tuberculomas is highly variable. In most cases the diameter range from a few mm to 4 cm. Intracranial

tuberculomas in patients under the age of 20 years are usually infratentorial but supratentorial lesions predominate in adults.[16,19] Solitary tuberculomas are more frequent than multiple lesions.

DIAGNOSIS

Diagnosis of TBM is based on history neurological symptoms, signs and CSF findings. Supportive features include radiological evidence from CT and MRI such as basal exudates, hydrocephalus, infarct, tuberculomas and gyral enhancement.

DIFFERENTIAL DIAGNOSIS FOR TBM

- Partially treated bacterial meningitis
- Cryptococcal meningitis
- Viral meningo encephalitis
- Carcinomatous meningitis
- Neurosarcoidosis
- Parameningeal infection
- Neurosyphilis

INVESTIGATIONS

- Chest X ray – reveals findings consistent with pulmonary TB in 30-50 percent of adults.
- Neuro imaging – CT/MRI[22-26]
    - May reveal thickening and enhancement of basal meninges, hydrocephalus, infarction, periventricular edema and mass lesions due to associated tuberculoma or TB abscess.
    - Common site of exudate are basal cisterna ambiens, suprasellar cistern and sylvian fissures
    - Hydrocephalus is the single most abnormality reported in more than 50 percent of the cases
    - Vasculitis and thrombosis associated with TB are seen on CT as multiple areas of hypodensity secondary to ischemic lesions.
    - Gadolinium enhanced MRI is superior to CT in detection of basal meningeal enhancement and small tuberculomas.

- Tuberculin Skin Test{TST}
    - TST with purified protein derivative has been reported to be positive in 40-65 percent of cases. But this test lacks specificity.

CSF FLUID STUDY :[27]

CSF analysis forms a very important part in the diagnosis of TBM.

CSF physical examination:

The opening pressure of CSF may be high in some cases of TBM. The CSF can be clear , turbid or in some cases hemorrhagic. If allowed to stand a pellicle or cobweb may form indicating the presence of fibrinogen.

CSF glucose:

The CSF glucose level is abnormal in majority of cases, being less than 40 percent of the corresponding blood glucose level. Median glucose levels are reported to be between 18-45 mg/dl

CSF protein:

Protein content is 100-800 mg/dl. In the presence of co-existing spinal meningitis and spinal block, the values can exceed 1000 mg/dl.

CSF cell count and cytology:

In TBM, leukocyte count ranges between 100-500 cells/µlitre but rarely can exceed 1000 cells/µlitre. Predominantly lymphocytes are increased but in acute stage neutrophils dominate the picture

CSF for ZN staining :

The detection rate of MTB in CSF by ZN staining ranges from 12.5 – 69 %. The yield may marginally increase with auramine staining . The centrifuged CSF sample (30 min) and thick smear examination from the precipitate may enhance the detection rate of MTB. If there is a high index of suspicion, repeated samples should be sent for staining.

CSF culture:

The positivity of culture of CSF for MTB is 25-70% of cases using LJ media. However in many Indian reports, the yield has been poor up to 19%. The yield can be increased by using liquid culture media such as septi-check AFB system and MGIT media. This may raise the sensitivity up to 80 percent of the cases. Culture remains the gold standard for diagnosis. The isolation rate of Mycobacterial tuberculosis is higher from cisternal and ventricular CSF than a lumbar puncture sample.

CSF ADA:

It is elevated in CSF in 60 –100 % patients with TBM.

CSF inferferon – □:

It can be used to diagnose latent TB infection and the sensitivity may reach up to 80%.

CULTURE METHODS:[28-32]

It detects fewer bacilli. It is a definitive diagnosis. It helps to distinguish between Mycobacterial tuberculosis{MTB} and other mycobacterial organisms(atypical mycobacteria) . growth of MTB is extremely slow. The generation time is 18-24 hours. It requires special media and this adds to the cost of diagnosis and treatment. Culture can detect as few as 10-100 bacilli /ml of sputum.

Culture characters:

Growth of MTB appears in 2 weeks but may be delayed up to 6 – 8 weeks. Optimal temperature required is 37 degrees.

IMAGE ATLAS:

Figure 1: Growth of MTB on the LJ media. MTB grows as discrete dry wrinkled and irregular cream – buff coloured colonies.

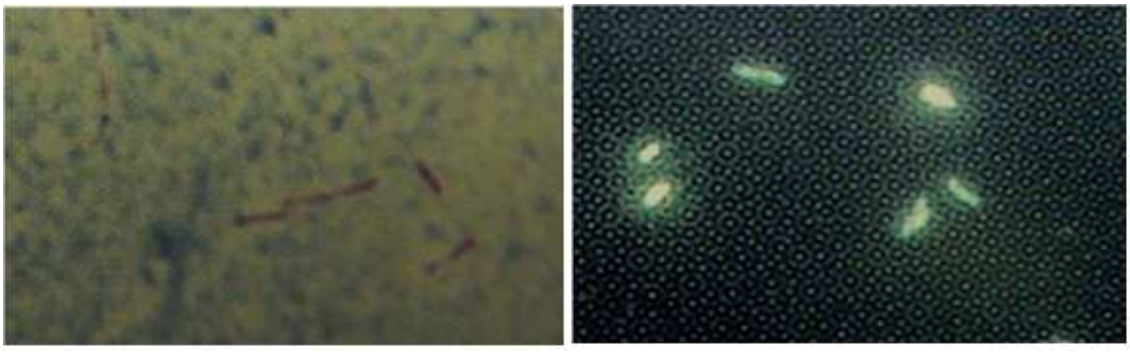


Figure 2: The image on the left is the demonstration of AFB (MTB) using the ZN staining method and the image on the right is the demonstration on MTB using the Auramine – Rhodamine flouroscent staining method.

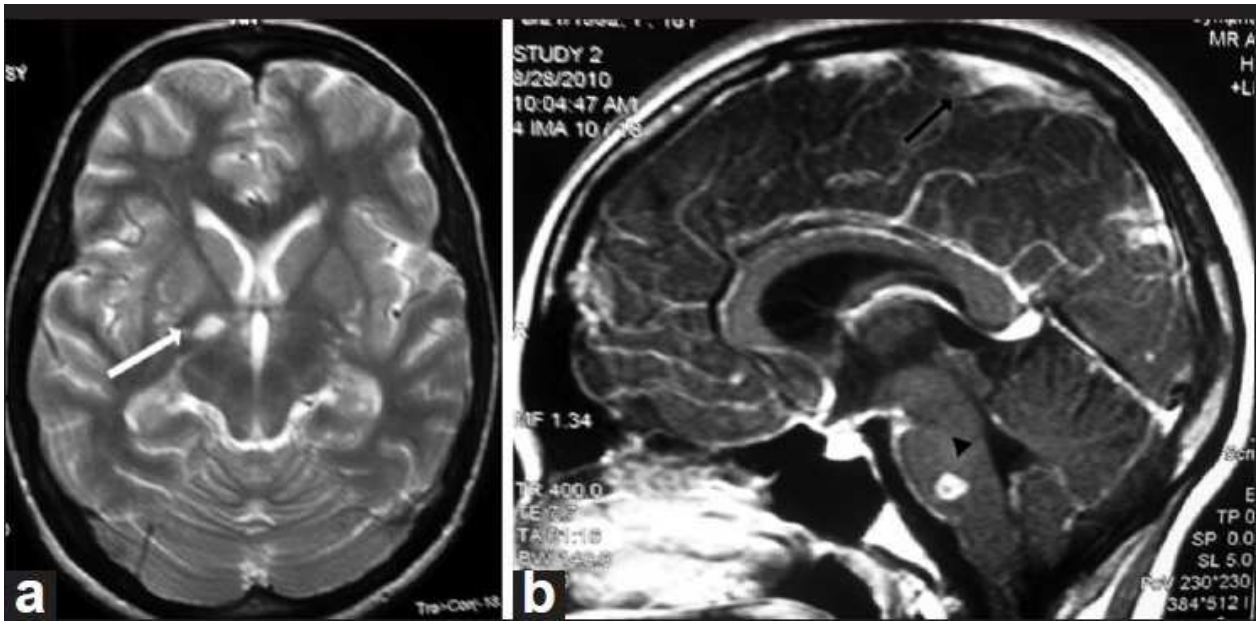


Figure 3: MRI Image of a patient with TBM. Figure on the left is a T2 sequence showing a right thalamic infarct (white arrow). Figure on the right is a post Gandolinium contrast T2 FLAIR sequence showing meningeal enhancement in the parietal , occipital lobe surfaces (black arrow) and a tuberculoma (seen a ring lesion)in the pontine region (black arrowhead) .This image demonstrates the multiple findings seen in TBM.

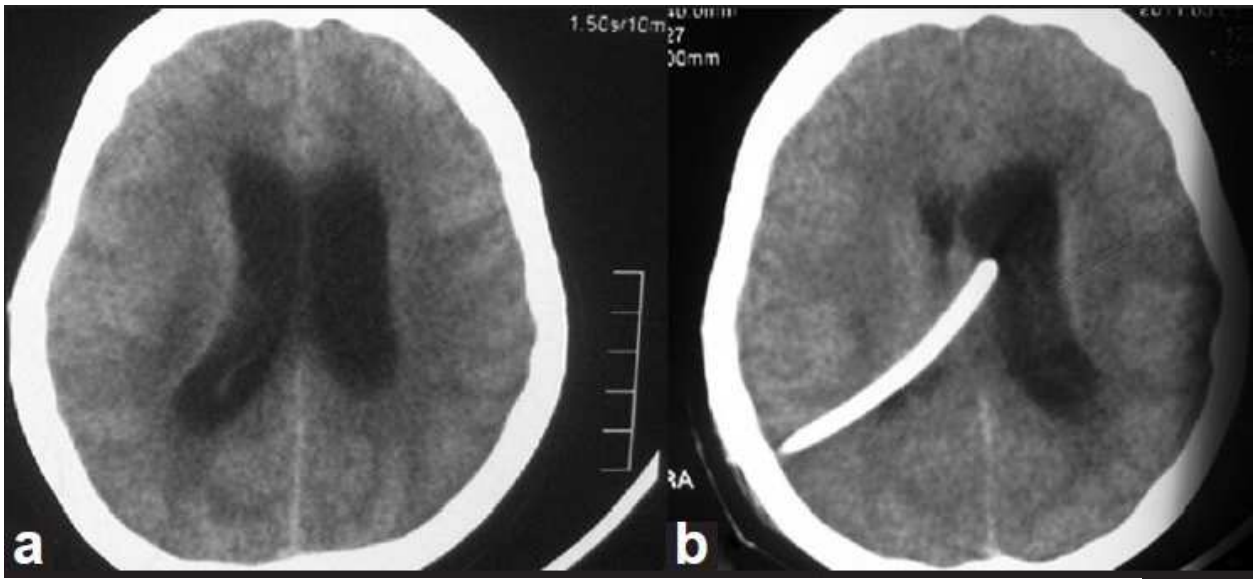


Figure 4: Neuro imaging in TBM. The image on the left shows the presence of dilated ventricles and cerebral oedema suggestive of hydrocephaleus and the image on the right shows the neuro-surgical intervention needed to relieve the hydrocephalus (Ventriculo – peritoneal shunting).

Culture Media :

They can be divided into solid and liquid media.

Solid Media: It is useful for isolation of organisms, antigen preparation and chemical tests. Common examples are:

Lowenstein Jensen Media (most common){contains Glycerol,egg,Asparagine,indicator Malachite green,certain mineral acids} , Loffler's serum slope , Pawlowsky's medium (potato medium), Tarshis medium (Blood medium).

Liquid Media : They are more useful for sensitivity testing. Common Examples are: Dubois media, Middlebrook's medium, Sula's and Sauton's Media.

Colony Characteristics:

On solid media, MTB gives rise to discrete dry wrinkled and irregular colonies. Creamy white to begin with and then later become buff colour. In liquid media MTB grows as a wrinkled pedicle. A diffuse growth can be obtained by adding a wetting agent. Eg Tween 80. Serpentine cords

are generally formed by virulent strains while avirulent strains grow in a disperse fashion.

Incubation is done at 37degrees and cultures are examined initially after 3-4 weeks. This is done to rule out the growth of rapidly growing atypical mycobacteria and fungi. A negative growth is said only after 8 weeks of incubation.

Rapid Culture methods:

In case of extra pulmonary specimen the time taken may be even longer. A technique for automated detection of bacterial metabolism is available. This measures radioactive carbon dioxide. This is generated from decarboxylation of carbon 14 labelled substrates. This principle is used in BACTEC culture methods. When the BACTEC 12B vial is inoculated with the specimen, the MTB in the specimen starts to grow using the palmitic acid (radio C-14 labelled substance) and release radioactive CO2. The BACTEC instrument then measures quantitatively the radioactivity in terms of numbers on a scale ranging from 0 -999. This is designated as the growth index. The daily increase in the growth index is directly proportional to the rate and amount of growth in the medium. When an

inhibitory agent is introduced in the medium then metabolism gets inhibited. This is indicated by reduction in the growth index.

Septi Check Acid Fast Bacilli Method is also a novel biphasic culture approach is available for the growth of MTB.

Rapid liquid MTB culture methods

This is also known as MGIT(MTB Growth Indicator Tube). This culture is done using manual or automated systems. The tubes contain enriched Middlebrook's 7H9 broth and oxygen sensitive fluroscent sensor. This is embedded in the silicon layer at the bottom of the tube. An actively growing MTB consumes the dissolved oxygen and the sensor blooms and this indicates MTB growth. This can be observed with a 365nm UV lamp.

MTB phage based Detection test:

Phage based tests require limited culture facilities and promise rapid results. Results can be obtained in about 2 days.

IMMUNODIAGNOSIS:

Antibody Detection Tests:[33]

The A60 antigen is the most extensively used antigen for both pulmonary and extra pulmonary TB in both adults and children. Ig G and IgM have been evaluated. The sensitivity is 30 – 100 %.

Antigen detection tests:

- Lipoarabinomannan urine test

Nucleic Acid Amplification Tests:

- Nucleic acid probes:

This detects small amount of MTB with no cross hybridization with non mycobacterial respiratory pathogens. It has a sensitivity equivalent to smear examination by ZN staining.

Polymerase Chain Reaction[35,36]:

This is a very sensitive as well as specific method. A protocol for the detection of insertion element (IS6110) was described. It has a positive result in 60 % of MTB effusions. While a PCR for conserved region was positive in 20% of such patients. However, reports also say that when different specimens from the same patient were analysed intermittently positive results were obtained.

Initially generations of PCR technique were able to detect as low as 10 bacilli in the specimen. Recent modifications have enabled the DNA extracted from a fraction of a bacilli to be found after suitable amplification. DNA ligase functions to link two stands of DNA together to continue a double strand segment. The seal can reliably take place only if the ends are complementary and there has to be exact match. In Ligase chain reaction the fragmented primers are 4 in number and are added in excess. Results are available in 3 days as compared to culture . It has been said the power of PCR is so high that its most important drawback is detection of a smallest amount of contaminated DNA of MTB and subsequently resulting in misdiagnosis.

Genotype Assay:[34]

Two genotype assay are currently available , the first assay is for the diagnosis of MTB and the second is for the detection of MTB – drug resistance (Rifampicin and Isoniazid).

Polymerase chain reaction sequencing:

Most protocols include the use of repeat insertion sequence IS6110 as a target for amplification. This sequence is specific for MTB. This sequence is present in multiple copies in the genome of MTB.

Identification of MTB by High Performance Liquid Chromatography:

This rapid method is developed by the CDC (centre for Disease Control, Atlanta) for the analysis of species specific MTB mycolic acids present in the cell wall of MTB bacilli.

ADENOSINE DEAMINASE:[57-85]

The conversion of adenosine to inosine is catalysed by the enzyme ADA. It is a T-lymphocyte enzyme. The plasma activity of ADA is rich in cellular immunity stimulated diseases. The proliferation and differentiation of lymphocytes, mainly T-lymphocytes are being influenced by ADA. ADA is released by the stimulation of live intracellular microorganisms. This is why, ADA is considered as cell mediated immunity marker, in particular for the activation of the T lymphocytes.

Among the several isoforms of ADA, the most significant ones are ADA1 andADA2.

ADA1 has got equal affinity for both adenosine and 2'-deoxyadenosine, where as ADA2 has got more affinity for adenosine.

2'-deoxyadenosine/ADA1 activity ratio=0.75

2'-deoxyadenosine/ADA2 activity ratio=0.25

ADA1 is present in all cells whereas ADA2 is present only in monocytes and macrophages.

False Positive ADA levels are seen in :

- Neuro-brucellosis
- Lymphoma
- Few patients with Cryptococcal Meningitis
- AIDS

INTERFERON – □

INTERFERON-GAMMA RELEASE ASSAYS:{IGRA}

It is used to diagnose latent tuberculous bacterial infection. Interferon gamma is a cytokine, and a classic marker of Th-1type cellular immune response. It detects only some components of the cellular immune response . for eg. IGRAs detect only one cytokine (interferon-□). Several factors including host, microbial exposure and disease can impact the result

of this test. Early versions of IGRAs used PPD as the stimulating antigen. But newer versions use antigens that are more specific to mycobacterium tuberculosis than PPD. These antigens include early secreted antigenic target 6 (ESAT6), culture filtrate protein 10 (CFP10). These are encoded by genes located with in the region of difference 1 (RD1) segment of the MTB genome. They are more specific than PPD. This is due to non sharing property of it with any of the BCG vaccine strains or certain species of non tuberculous mycobacteria like mycobacterium avium.

COMMERCIALLY AVAILABLE IGRAs:[37-41]

- QuantiFERON-TB Gold{QTF-G}
- T-SPOT.TB test

The estimated sensitivity in patients with active TB is 75-95%. The estimated specificity in healthy individuals with no known TB disease or exposure is 90-100%. Using this test, results can be obtained in 1-2 days.

LIMITATIONS OF IGRA:

- High material cost
- Requires well infrastructure laboratory
- Requires highly trained personnel.

COMPLICATIONS OF TUBERCULOSIS MENINGITIS:

- Raised intracranial pressure, cerebral edema, stupor
- Basal meningitis with cranial nerve palsies
- Focal neurological deficits
- Hydrocephalus
- Tuberculoma
- Tuberculous abscess
- Opticochiasmatic pachymeningitis resulting in visual loss
- Tuberculosis arteritis and stroke
- Endocrine disturbances
- Hypothalamic disorder leading to loss of control of blood pressure and body temperature
- Diabetes insipidus
- SIADH
- Internuclear ophthalmoplegia
- Hemichorea
- Spinal block
- Spinal arachnoiditis

TREATMENT:[47,48]

Confirmation that a particular case is TBM seldom happens in each case scenario even after the employment of sensitive tests like culture , BACTEC ,PCR and ADA levels. This is especially a common scenario in developing countries like India. Sheller et al concluded that the most important principle in the successful management of CNS TB is the prompt

start of ATT on the basis of clinical suspicion even before the culture reports are awaited.

Before starting the ATT it is of utmost importance to stage the disease and then decide on the treatment plan. The entire treatment of TBM can be divided into the following parts :

- Role and duration of ATT
- Role of steroids
- Surgical management

ATT: (RNTCP guidelines):

ATT under RNTCP for CNS tuberculosis is considered under a special category which includes Spinal TB as well. Patient should be referred to a tertiary care centre for evaluation as early as possible as the disease is fatal if left untreated. The total duration of treatment is 8 – 9 months. The continuation phase should be given for 6 – 7 months . Steroids should be given initially and then gradually reduced over a period of 6 – 8 weeks.

Patient should be started on the following drugs:

- Isoniazid (10-15 mg/kg) 600 mg /d thrice weekly
- Rifampicin (10 mg/kg) 450 mg /d (if > 60 kg then 600 mg/d) thrice weekly
- Pyrazinamide (30-35 mg/kg) 1500 mg/d thrice weekly
- Streptomycin (15 mg/kg) 0.75 gm i.m.(if > 50 years then 0.5 gm) thrice weekly

In patients with TBM on category I{CAT-I} treatment the four drugs used in the intensive phase should be HRZS instead of HRZE. The continuation phase consists of HR regimen.

This recommended ATT protocol has been an extrapolation of the RNTCP guidelines for the management of pulmonary TB. This is because of the lack of randomized control trials to establish an optimal treatment course for CNS tuberculosis. There is an obvious difficulty in conducting such trials. This is due to the rarity of the disease , difficulty in confirming the diagnosis and a high mortality rate in advanced cases. Among the ATT drugs, it is found that both isoniazid and pyrazinamide pass very easily through the Blood brain barrier{BBB][49,50] and isoniazid remains the backbone of TBM treatment. Rifampin and ethambutol have comparatively

significantly less CNS BBB penetration . Yet they still play a significant role in the treatment of CNS tuberculosis.

The emergence of Multi drug resistant tuberculosis{ MDR – TB}[51] has worsened the confusion on optimal treatment time to identification of the resistant bacilli is often prolonged and hence the time for appropriate ATT is often delayed by up to 2-3 months.It has been reported that the delay may even lead to the disease to progress to an advanced stage before the start of optimal ATT. There is no grading system that could predict MDR – TB. The MDR TB mortality is high and part of it can be definitely be attributed to the lack of adequate ATT when the disease was first identified.

MDR TB should be considered if

- there is a positive history of prior Anti tuberculous therapy.
- contact with a patient with MDR tuberculosis
- poor clinical response to first-line TB therapy within 2 weeks despite a firm diagnosis and an adequate adherence to treatment.

Much like the standard ATT , there is lack of Randomised control trail for MDR TBM . Hence this adds to the further controversy on what should be

considered as a optimal ATT in MDR TB patients. The presence of inflamed meninges help the CNS penetration of second-line agents such as aminoglycosides, Fluoroquinolones, even though are able to penetrate the CNS, have been shown to have lower CSF levels than in the serum. Cycloserine and ethionamide are other second-line agents that have good CNS penetration. They form a strong basis of ATT for MDR TB. Though INH resistance is common in resistant TBM it has been proven to be effective and hence is included in the TBM treatment regimen. DOTS PLUS [Cat-IV] Regimen is used to treat MDRTB patients under RNTCP programme.

ROLE OF STEROID THERAPY :

Since early 1950 , the role of steroid in treatment of TBM has been contemplated and till date it continues to be a controversial issue. The rationale behind the use of steroids is [44,45,46] :

- reduction in the deleterious aspects of the immune response from the inflammatory mediators(proinflammatory cytokines and chemokines like TNF-α, IL-6, IL-1β, CCL2, CCL5, and CXCL10) to the MTB in the CNS

- ability to prevent the development of communicating hydrocephalus
- prevention of vasculitis and related infarction
- lowers CSF protein and globulin levels
- achieves higher glucose levels sooner suggesting inhibition of bacterial growth and its metabolism.
- Possible role in immune modification that influence the response of microglial cells

Controversies in the use of steroid in CNS TB management:

- steroids do not affect intracranial pressure
- steroids do not reduce the extent of infarction
- do not reduce the basal lepto - meningeal enhancement
- may not reduce the formation of tuberculoma

Thwaites[45,46,55] et al did a large placebo-controlled trial using dexamethasone as an adjunct to ATT for TBM in a population in Vietnam. They conclude a significant reduction in mortality in adults. Subgroup analyses revealed that the mortality benefit of steroids happened to all severity types of TBM and its complications. However this benefit was not

significant in patients who are coinfected with HIV. This study was a landmark trial and did resolve some of the controversies in the favour of use of steroids as an adjunct to ATT in the treatment of TBM.

Centers for Disease Control(CDC), and American Thoracic Society(ATS) hence in their guidelines endorse the use of steroids in TBM treatment. Recommended dosing regimen is dexamethasone , to be initially started at a dose of 8 mg/day for pediatric patients weighing less than 25 kg and 12 mg/day for pediatric population children weighing above 25 kg. A dose of 12 mg / day was advised for the adult patients of TBM. This should be continued for for 3 weeks and then dose reduction should begin gradually during the next 3 weeks. The recommended oral steroid regimen for the treatment of TBM is predisolone 0.75 – 1 mg/kg/day in adults and 0.25 – 1 mg/kg/day in children.

POSSIBLE INDICATIONS FOR CORTICO STEROIDS IN TUBERCULOUS MENINGITIS:

- Clinical
    - Clinical stages 2 and above
    - Evidence of raised intracranial pressure

- Focal neurological deficits suggesting arteritis

- Radiological
  - Cerebral or perilesional edema
  - Hydrocephalus
  - Infarcts
  - Opticochiasmatic pachymeningitis

ROLE OF SURGERY [54]:

The role of surgery in the management of TBM is revolves around the dealing of serious complications like hydrocephalus, reduction of the mass effect of developing tuberculomas and drainage of MTB brain abscesses. The development of hydrocephalus is thought to be due to

- basal meningitis that blocks the exit of CSF from its absorption in the arachnoid villi
- possible destruction of the arachnoid villi.

Hydrocephalus can be managed by serial lumbar punctures and surgically by external ventricular drainage, or ventriculoperitoneal shunting procedures. Communicating hydrocephalus usually requires surgical drainage but there is a definite role for the use of steroids and diuretics

while non-communicating hydrocephalus needs surgical drainage in almost all cases. There is a controversy in the timing of surgery especially in the pediatric age group given a success rate of about 40 % and a complication rate of 30 %. The outcome of patients co-infected with HIV is poorer as compared to non HIV infected patients with hydrocephalus. Recent advances include the role of neuro-endoscopy in relieving hydrocephalus which may reduce the dependence on shunt procedures.

The use of ATT and steroids had almost reduced the need of surgery for tuberculomas and it is now reserved for only those cases with tendency to cause a mass effect. MTB brain abscess requires drainage, either an aspiration via a burr hole fractional drainage, or repeated aspiration through a stereotactic approach or in some cases total excision of the abscess.

PROGNOSIS:

Clinical symptoms may improve quite slowly. Transient worsening may happen despite appropriate ATT. New tuberculomas may develop. Such developments do not require the change in the treatment strategy in almost all cases. The possible exception could be the need to prolong the use of steroids which may mitigate the complications developing.

The mortality rate of treated TBM ranges from 20 to 50% . A large case series from Egypt about 1430 TBM patients. They found a mortality rate was 57%. A major prognostic marker for mortality is the stage of disease at which the ATT was started. It ranged from 18% for stage 1 to up to 70 % for stage 3 disease.

Other prognostic markers of poor prognosis are :

- the duration of symptoms (4 weeks symptomatology period had a 40 % mortality)
- use of steroid
- children with an advanced stage are having a poor prognosis than adults.
- presence of any vasculitic infarct
- HIV coinfection
- isoniazid and rifampin resistance
- high CSF lactate
- CSF leucopenia
- low CSF glucose

A study done by Mishra et al[53]. concluded that features such as presenting high intracranial pressure, cytokines in the CSF, streptomycin

resistance and MTB have been shown not to be significant predictor of a poor outcome.

SEQUELAE OF TUBERCULOUS MENINGITIS :

Among the survivors of TBM, some form of neurological impairment afflicts approximately 20 to 30%. They include :

- Psychological or psychiatric disturbances
- Visual defects
- Focal neurological deficit
- Endocrine disturbances
- Seizures
- Intracranial calcifications
- Hearing defects(often drug induced)

TUBERCULOUS MENINGITIS AND HIV INFECTION[52]

HIV infection is now considered as the single most important risk factor for the activation of latent tuberculosis. And it has become almost routine to look out for HIV – TB co infection in patients diagnosed as HIV infected or Tuberculosis first.

HIV infection increases the prevalence of neurological tuberculosis also as it increases the prevalence of pulmonary TB. The profound immuno compromised state in HIV infection is probably responsible for the

significant change in the clinical presentation, radiologic manifestation and histopathology of the affected organs.

In the case of neurological tuberculosis there is more cognitive deficit if the patient is HIV co-infected. The Neuro-radiological imaging in such patients shows a lesser incidence of meningeal enhancement and communicating hydrocephalus. There is remarkable less amount of gramulamatous exudates in the basal cistern regions. However periventricular white matter infarcts are more common. Tuberculoma like lesion seen in HIV patients usually turn out to be cerebral toxoplasmosis. There is co-existence of multiple infection affecting the CNS in HIV infection.

There is a controversy if the HIV infection predisposes to the higher rate of treatment failure and resistant bacilli incidence. Controversy also exists on the management of HIV – TB coinfection . This is due to reduced adherence to polypharmacy, prolonged treatment duration, overlapping side-effects, and the development of IRIS.

LUMBAR PUCTURE:

A commonly done bedside procedure to collect cerebrospinal fluid (CSF). It is a useful diagnostic tool in diagnosis of central nervous system infective and inflammatory diseases. A therapeutic lumbar puncture can be done to relieve increased intracranial pressure and for administration of anaesthesia and intrathecal chemotherapy.

INDICATIONS:

1. Central nervous system infections: meningitis, encephalitis, myelitis
2. Inflammatory diseases: multiple sclerosis, Guillian barre syndrome
3. Carcinomatous meningitis
4. Subarachnoid hemorrhage
5. Spinal and epidural anaesthesia
6. Intrathecal chemotherapy

CONTRAINDICATIONS:

1. Cardiorespiratory compromise
2. Cerebral herniation
3. Bleeding diathesis
4. Local sepsis
5. Previous lumbar surgery

PROCEDURE:

The lumbar puncture technique and the risks involved should be explained to the patient and an informed consent should be obtained. A fundoscopic examination should be done prior to the procedure. Computed tomography of the brain should be done if needed.

The patient should be in a lateral decubitis in a fetal position with full flexion of neck and full flexion of knees upto chest. This posture widens the gap between the spinous processes. Another alternative position would be to have the patient sitting in a stool with head and shoulders bent forward. The needle should be inserted in the midline at the level of a line joining the superior aspects of the two iliac crests in the space between L3/L4 or L4/L5 vertebrae. Palpate the bony landmarks.

Mark the site of insertion. Paint the area with topical disinfectant in concentric circles. A local anaesthetic is injected subcutaneously. Insert the spinal needle at the marked site with the stylet in place at the superior border of inferior spinous process directed towards the umbilicus.

The spinal needle will pass through the following layers: skin and subcutaneous tissue, supraspinous ligament, interspinous ligament,

ligamentum flavum, posterior epidural space, dura into the subarachnoid space and in between the nerve roots of cauda equina. When the ligamentum flavum is reached a popping sensation is obtained. Insert the needle in 2mm increments and withdraw the stylet to look for CSF. If there is no flow, withdraw the needle upto the subcutaneous plane and redirect the needle. If there is poor flow, rotate the needle by 90 degrees and check for CSF. If there is traumatic bleeding, the initial CSF is blood stained but with collection of additional fluid the blood tinge clears. The smallest volume of fluid required should be collected, usually around 10 ml. Replace the stylet and withdraw the needle. Dispose it in appropriate containers. The patient should be monitored for any complications for atleast 24 hours.

COMPLICATIONS:

1. Cerebral herniation
2. Pain- local or referred
3. Bleeding
4. Infection
5. Subarachnoid epidermal cyst
6. CSF leakage

METHODOLOGY:

Source of Data:

A total of 55 patients attending the department of Internal Medicine of Government Stanley Medical College, Chennai and Government Hospital of Thoracic Medicine, Tambaram under Government Stanley Hospital on in-patient basis were included in this study.

Duration of Study :

6 months[April 2011 to September 2011]

Inclusion criteria:

Patients with features of subacute / chronic Central nervous system infection

Exclusion criteria:

1. Paediatric population.
2. Proven non-mycobacterial meningitis
3. Proven carcinomatus meningitis

Methodology:

All patients with features of sub acute/ chronic meningitis and with clinical features suggestive of Central nervous system infection were admitted in the internal medicine department wards. After getting an informed consent from the patients, they were included in this study.

The following data were noted:

1. Age, sex

2. Clinical features – fever duration , cough duration , weight loss, seizure, headache, neck pains, neck stiffness, vomiting , limb weakness and other features suggestive of focal neurological deficit.

3. Previous history of tuberculosis, contact with tuberculosis,

4. Co morbid illness: HIV and Diabetes mellitus

5. Personal Habits : smoking , alcoholism

Then the patient was clinically examined and the following data was collected.

The following investigations were done:

1. Complete Haemogram
2. ESR
3. Mantoux test

4. Chest X ray PA view
5. Sputum Analysis (AFB staining)
6. HIV ELISA test
7. In some cases , according to the affordibiltiy of the patient, neuro-imaging was done. These included CT scan (plain or with contrast)of the Brain and MRI imaging (with or without contrast)of the Brain.
8. A CSF analysis was planned.

In all our patients included in this study , a written informed consent was taken and then according to the above mentioned standard method with aseptic precautions , a lumbar puncture was done. About 10 ml of CSF was collected (including 5 ml for LJ media culture inoculation)

The following things were analysed in the collected CSF samples:

1. CSF sugar , protein
2. CSF cytology and cell count
3. CSF Gram's staining
4. CSF AFB staining
5. CSF culture in Aerobic and Anerobic Media

6. CSF culture in LJ media
7. CSF ADA levels

The CSF - ADA level was calculated by using the Colorimetric method.

The 5 ml CSF sample collected in a sterile test-tube was sent in a cold box immediately to TAMBHARAM SANATORIUM for culture using the Lowenstien-Jensen medium. The inoculated culture media was followed at 4 weeks and 8 weeks intervals. If there is no growth even after 8 weeks, the culture was considered to be negative. Treatment with ATT and steroids was primarily started on the basis of high CSF protein levels ,low CSF glucose levels and characteristic neuroradiological imaging (if present). In all patients before starting ATT counseling about the treatment , its duration and side-effects was given. A basal liver function test was done. Then patients were started on ATT under national RNTCP programme(tab. Isoniazid 600mg/d ; tab.Rifampicin 450-600 mg/d ; tab Pyrazinamide 1500 mg/d ; tab Ethambutol 1200 mg/d anf Inj. Streptomycin 0.75 gm/i.m/d given on 3 days every week) during the hospital in - patient stay they were started treatment with inj. dexamethasone 8 mg tds i.v. for 1 week , followed by 8 mg iv bd for 1 week followed by 8 mg i.v. od for 1

week and later it was converted to oral prednisolone 1mg/kg/day od for 2 weeks and then tapered to 0.5 mg /kg/day for the next 3 weeks. Repeat LFT was taken at the end of 2 weeks of ATT to ensure no hepatotoxicity. Patients who showed symptomatic improvement at the end of 15 days and continued to be asymptomatic on the follow up of 2 months were considered to be showing a good response to ATT.

The following present in X-Ray Chest PA view were considered to be marker of TB infection :

- Cavity (thin walled , thick walled) B/L extensive parenchymal infiltration , miliary shadows)

The following features if present in MRI imaging were considered to be a marker of CNS TB infection:

- Basal meningeal exudates , hydrocephalus and Tuberculomas

The patients were divided into two groups:

1. TBM group (based on positive C/S reports , typical neuro-radiological imaging features or a good response to given ATT)
2. Non TBM group (based on positive gram's staining , positive India Ink staining , absence of typical neuro-radiological findings , poor response to the ATT)

The efficacy of CSF- ADA level in the diagnosis of tuberculosis and in differentiating from non tuberculous causes of meningitis was evaluated. The data collected was submitted for statistical analysis. The significance was calculated using the Chi-square test and independent variable T test.

RESULTS:

Age Distribution :

Table-1 : Age distribution of the entire study population

Age Group (Yrs)	No of Patients	Percentage	No of Patients in TBM group	Percentage in TBM group
< 20 Yrs	4	7.30	4	7.30
21 – 30	13	23.60	11	25.60
31 – 40	22	40.00	19	44.20
41 – 50	12	21.80	8	18.60
51 – 60	4	7.30	1	2.30
Total	55	100	43	100
Mean ± Sd	35.18 ± 9.97		33.37 ± 9.13	

In both the groups the age group (31-40) had maximum no. of patients.

Gender Disribution :

Table-2 :Gender Distribution

Sex	No.	Percentage	No(TBM group)	Percentage
Male	31	56.40	23	53.50
Female	24	43.60	20	46.50
Total	55	100	43	100

According to this table there is a higher prevalence of TBM in male individuals.

FEVER DURATION: (TBM group)

Table-4: Fever duration (in days)

Sex	Mean	Sd	Min	Max	t-value	P-value
Mean	19.26	3.66	13	30	1.67	0.102
Female	21.30	4.33				
Total	20.21	4.07				

According to this table, in our study the average duration of fever was about 20 days in the TBM group. And there was no statistical difference in the duration of fever according to sex.

SYMPTOM ANALYSIS(TBM group):

Table 5 : symptoms in the TBM group

Variable	Male(N=23)		Female(N=20)		Total(N=43)	
	No.	%				
LOW	17	39.53	17	39.53	34	79.06
Head ache	23	53.48	19	44.18	42	97.67
Neck Pain	6	13.95	7	16.27	13	30.23
Vomiting	16	37.20	10	23.25	26	60.46
Meningeal Signs	12	27.90	8	18.60	20	46.51
FND	4	9.30	6	13.95	10	23.25
Seizures	5	11.62	8	18.60	13	30.23
Positive TB Contact	4	9.30	7	16.27	42	25.58
Positive Chest X-Ray	11	25.58	9	20.93	13	46.51
Montoux	11	25.85	7	16.27	18	41.86
HIV Co-infection	5	11.62	1	2.32	6	13.95

According to this table, Loss of weight was complained by about 79% patients while headache , neck pain and vomiting was complained by 98% , 30 % and 60 % respectively. 14% patients had HIV – TB coinfection. Chest radiography showed positive findings in 47%. 30 % had

seizures and 23% had a focal neurological Deficit. Meningeal signs were present in 47%.

Table 5: CSF ANALYSIS

CSF ANALYSIS	Male	Male (%)	Female	Female(%)	total	Total %
Clear	13	56.50	10	50.00	23	53.50
Turbid	10	43.50	10	50.00	20	46.50
COBWEB	3	-	0	-	3	6.97
Grams	0	0	0	0	0	0
Positive growth of MTB in LJ media.	16	37.20	13	30.23	29	67.44
	Male mean	Female Mean	Total Mean	Min	Max	t-value
Sugar	35.57±5.47	31.70±3.90	33.77	24	46	2.63
Protein	59.61±7.96	57.35±4.65	58.56	46	86	1.11
Lymphocytes in CSF	10.60±3.83	10.55±4.16	10.60			0.084
ADA	15.66±3.61	15.03±3.24	15.36	7.40	23.40	0.600

According to this table, the CSF in the TBM group was more often clear (54%) than turbid (46%). Cobweb formation was seen in only 3 patients (7%). There was a positive MTB growth in LJ media in only up to 67% of patients. The biochemical parameters of the CSF in the TBM group were Sugar -33 mg % , Protein 60mg % with a lymphocyte predominant CSF cytology and a mean lymphocyte count of 11 cells/mm. The mean ADA level was 15.66 ± 3.61 for males, 15.03 ± 3.24 for females.

Table-8: Haemogram parameters in the TBM group

	Male	Female	Total	Min	Max	t-value	P-value
Hb	13.34±1.39	11.06±1.14	12.28±1.71	10	15	5.83	0.000
TC	6102.17±1220.2	6612.50±1385.6	6339.53±1309.5	4400	9800	1.28	0.206
P	39.48±4.51	39.25±4.59	39.37 ±4.49	29	50	0.16	0.870
L	57.52±3.86	56.90±3.63	57.23±3.72	50	64	0.54	0.591
M	1.70±1.40	2.00±1.38	1.84 ± 1.38	0	4	0.51	0.478
ESR	43.83±8..51	39.20±4.46	41.67 ± 1.38	33	64	2.18	0.035

According to this table, the mean TC was 6340 and a mean DC was (P-39 , L-57, M-2). Mean ESR was 39.2 mm /hr.

ADA and its Cut – off value for TBM

Table: ADA at different cut-off values:

ADA cut – off	Sensitivity %	Specificity %	PPV %	NPV %	P value
10.5	90.7	50	86.67	60	0.0042
11	90.7	50	86.67	60	0.0042
12	90.7	83.33	95.12	71.43	0.0001
12.5	86.05	83.33	94.87	62.50	0.0001
13	79.07	83.33	94.44	52.63	0.0001
13.5	72.09	83.33	93.94	45.45	0.0008
14	65.12	91.67	96.55	42.31	0.0007
14.5	60.47	100	100	41.38	0.0001

According to this table , as the CSF ADA activity level increases there is an increase in the specificity. The sensitivity drops if a higher cut-off is chosen. If a cut-off of 14.5 IU/L is chosen the specificity and positive predictive value reaches 100% but the sensitivity falls to 60%. A Cut-off of 12 IU/L gives a sensitivity , specificity , positive predicitive value and a negative predictive value of 90.7, 83.33 , 95.12 and 71.43 respectively.

The causes of Non TBM group

Table: Non TBM group

Possible Etiology	Number (percentage)	Tests used to confirm and other remarkable findings.
Bacterial Meningitis other than MTB	6 (50%)	Gram's Stain. Strep pneumonia was isolated in 4 of the samples.
Cryptococcal Meningitis	2 (16.67%)	Confirmed with India Ink Staining , both cases were HIV positive.
Carcinomatous meningitis	2 (16.67%)	1 case had Gastric Adenocarcinoma 1 case had a CML based bone marrow aspiration study
Unknown	2 (16.67%)	

According to this table the most common etiology in the Non TBM group was bacterial meningitis which was probably partially treated(50%). There were 2 patients with cryptococcal meningitis and carcinomatous meningitis each (16.67 % each). There were 2 patients where we were unable to fix a final diagnosis with the available set of facitlites.

Table :Comparison between the Groups

	HIV Positive patients	Non TBM group	TBM group
No. of patients (%)	9 (16.36%)	12	43
Age (mean)in years	42.11	41.67	33.37
Sex ratio (M : F)	5:3	2:1	1.15 : 1
Mean Fever duration(days)	19.77	20.33	20.21
LOW/ LOA (%)	66.67	16.67	79.06
Headache(%)	100	100	97.67
Neck pains(%)	44	66.67	30.23
Vomiting(%)	56	83.33	60.47
Meningeal Signs(%)	66	75	46.51
FND(%)	22	25	23.25
Cough with expectoration(%)	56 %	25 % (average duration of cough 19 days)	39.53% (average duration of cough 18.11 days)
Seizures(%)	44	25	30.23
HIV infection(%)	---	3 of 12 (25 %)	6 out of 43 (13%)

	HIV Positive	Non TBM group	TBM group
TB contact(%)	11	None	25.58
Sputum AFB(%)	0	None	
X- chest Lesion of TB(%)	11	8	46
Response to ATT(%)	67	None	100
Mean Hb (gm %)	13.35	12.7	12.28
Mean Total Count (P , L , M)	6637 (47.22, 49.22, 2.11)	8505 (53.91,41.66,1.75)	6339 (39.37, 57.23,1.84)
ESR mean	43.22 mm /hr	42.33	41.67
Positive Montoux test (%)	11	None	41.86
CSF (clear : turbid)	5:4	3:9	23:20
CSF sugar	33.55	31.58	33.77
CSF protein	59.55	64.08	58.56
CSF Lymphocytes	11.33	8.16	10.60
Mean CSF ADA levels	13.36 (TBM group and HIV positive – 15.4 ; non TBM group and HIV positive -9.16)	9.56	23.40
Positive Culture for TBM in LJ media	(4 out of 5) 66.67 % in HIV and TBM group	Nil	67.44 %

According to this table the non TBM group patients had a mean age around 42 years with a male preponderance. All had headache as their presenting complaint , 17 % complained of weight loss. 25% patients had either seizure or focal neurological deficit or were having a HIV positive status.

	Culture Positive TBM	Proven Non TBM	Total
CSF ADA > 12	27	2	29
CSF ADA < 12	2	8	10
	29	10	39

According to this table , the yield of CSF for MTB in patients with TBM and HIV co-infection is the same as the patients with Non HIV positive – TBM. The calculated sensitivity,specificity,positive predictive valve and negative predictive valve for this table at ADA >12iu/l is 93.1%,80%,93.1%,80% respectively.

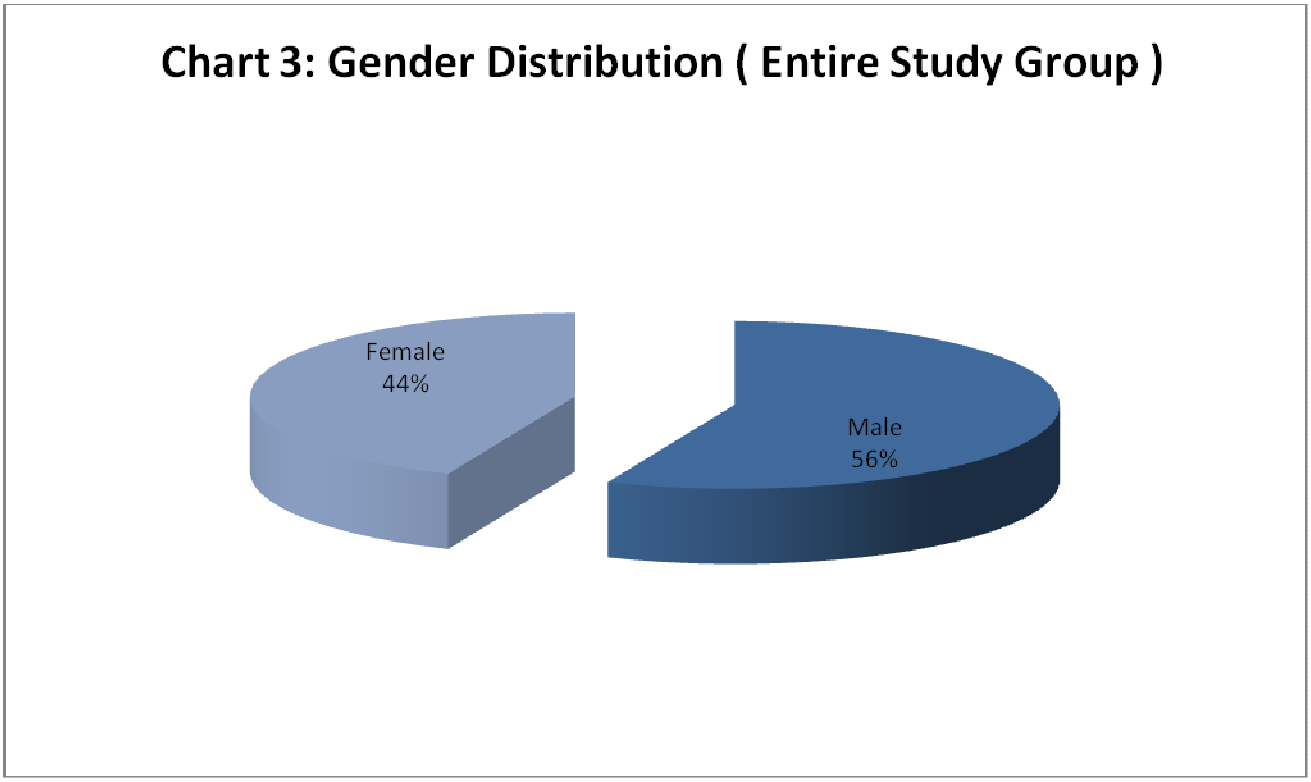


Chart 3: Gender Distribution (Entire Study Group)
Female
44%
Male
56%

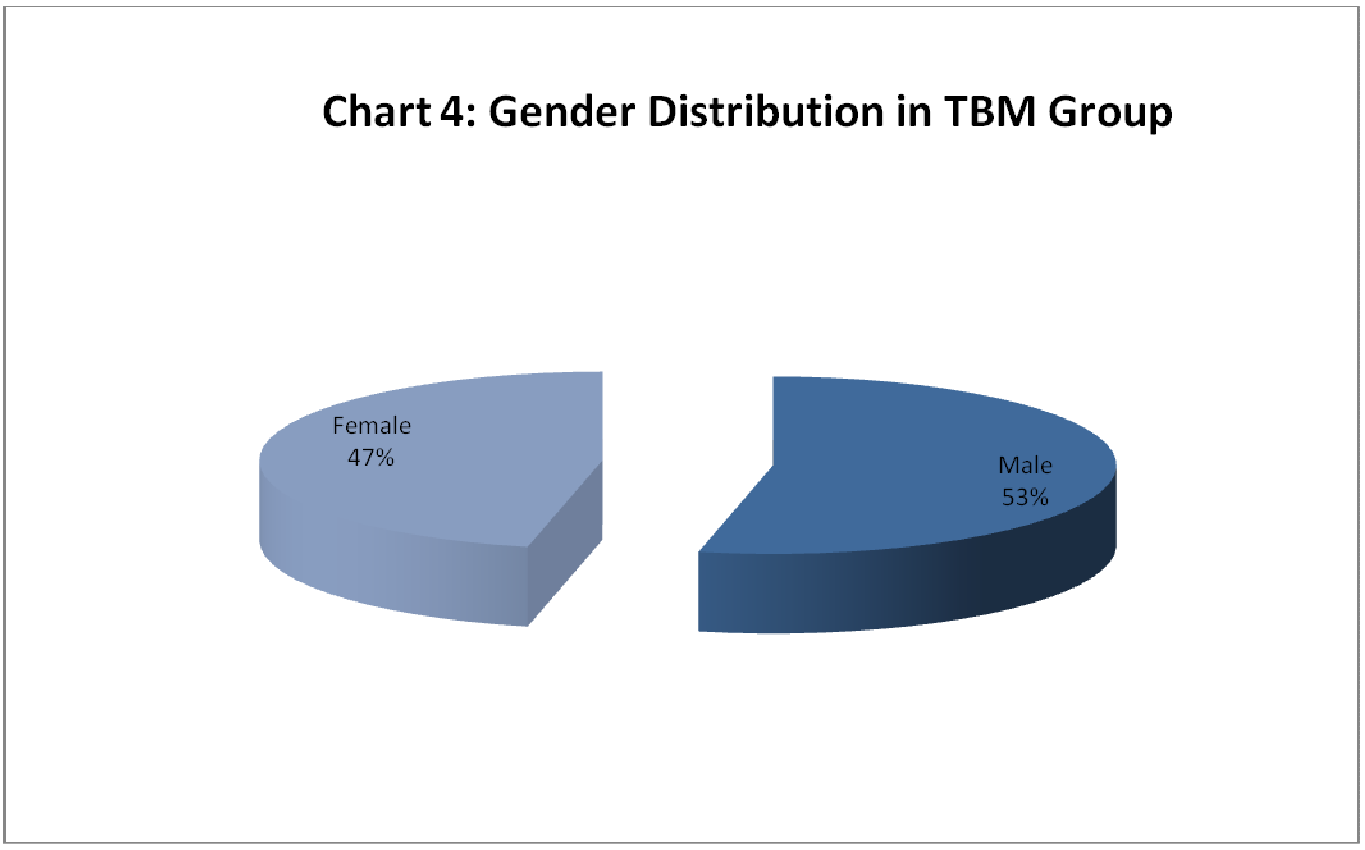


Chart 4: Gender Distribution in TBM Group
Female
47%
Male
53%

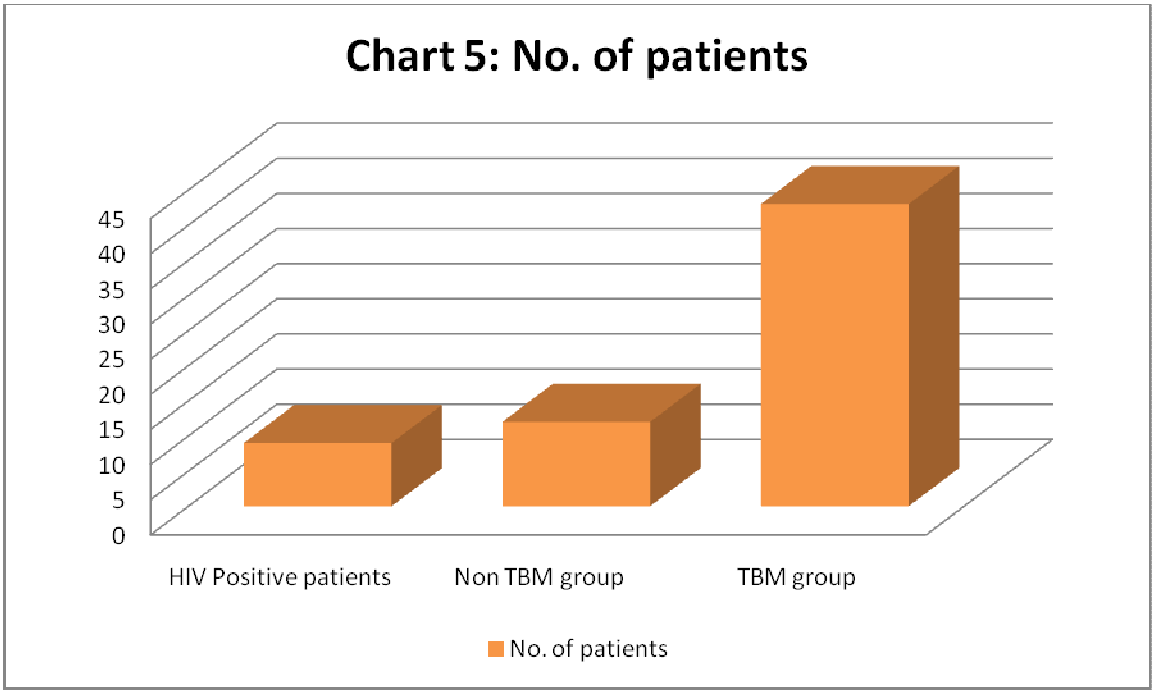


Chart 5: No. of patients
45
40
35
30
25
20
15
10
5
0
HIV Positive patients
Non TBM group
TBM group
No. of patients

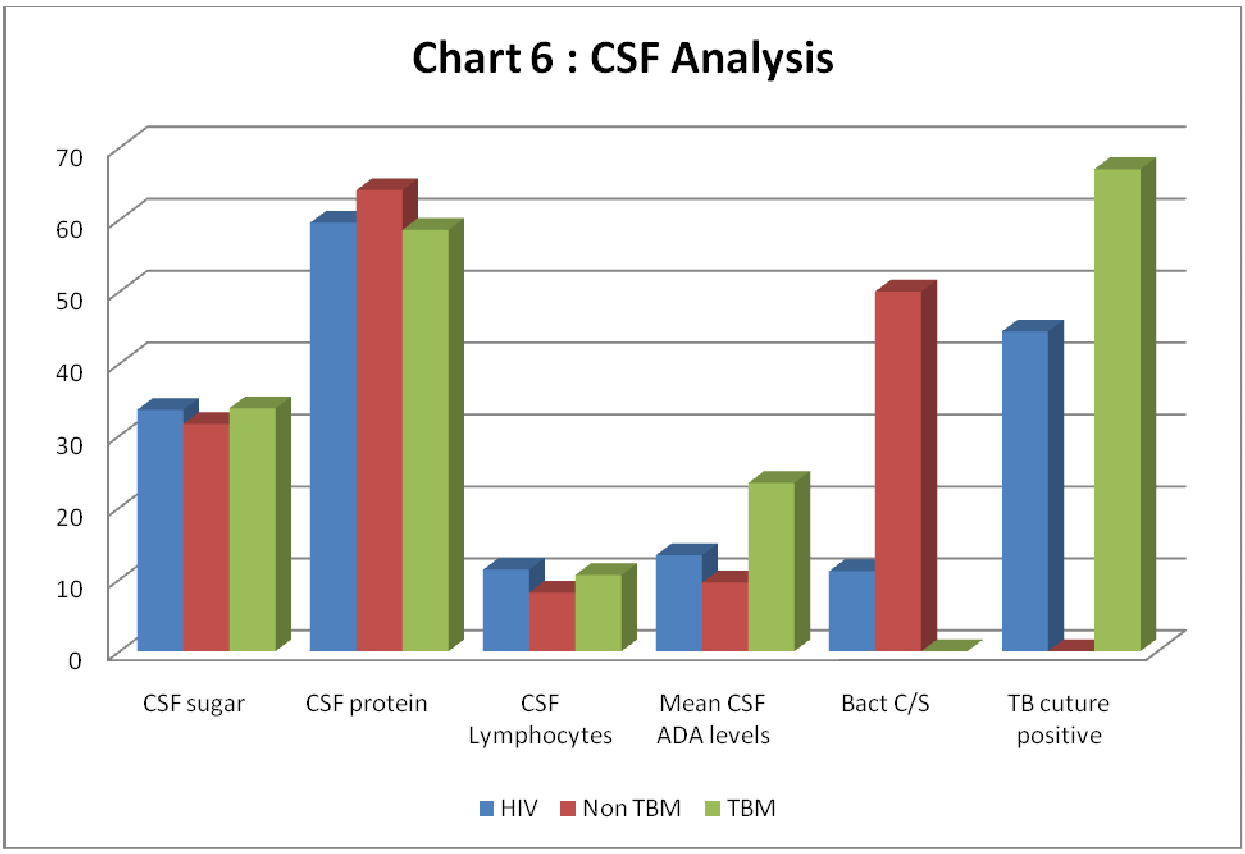


Chart 6 : CSF Analysis
70
60
50
40
30
20
10
0
CSF sugar
CSF protein
CSF Lymphocytes
Mean CSF ADA levels
Bact C/S
TB cuture positive
HIV
Non TBM
TBM

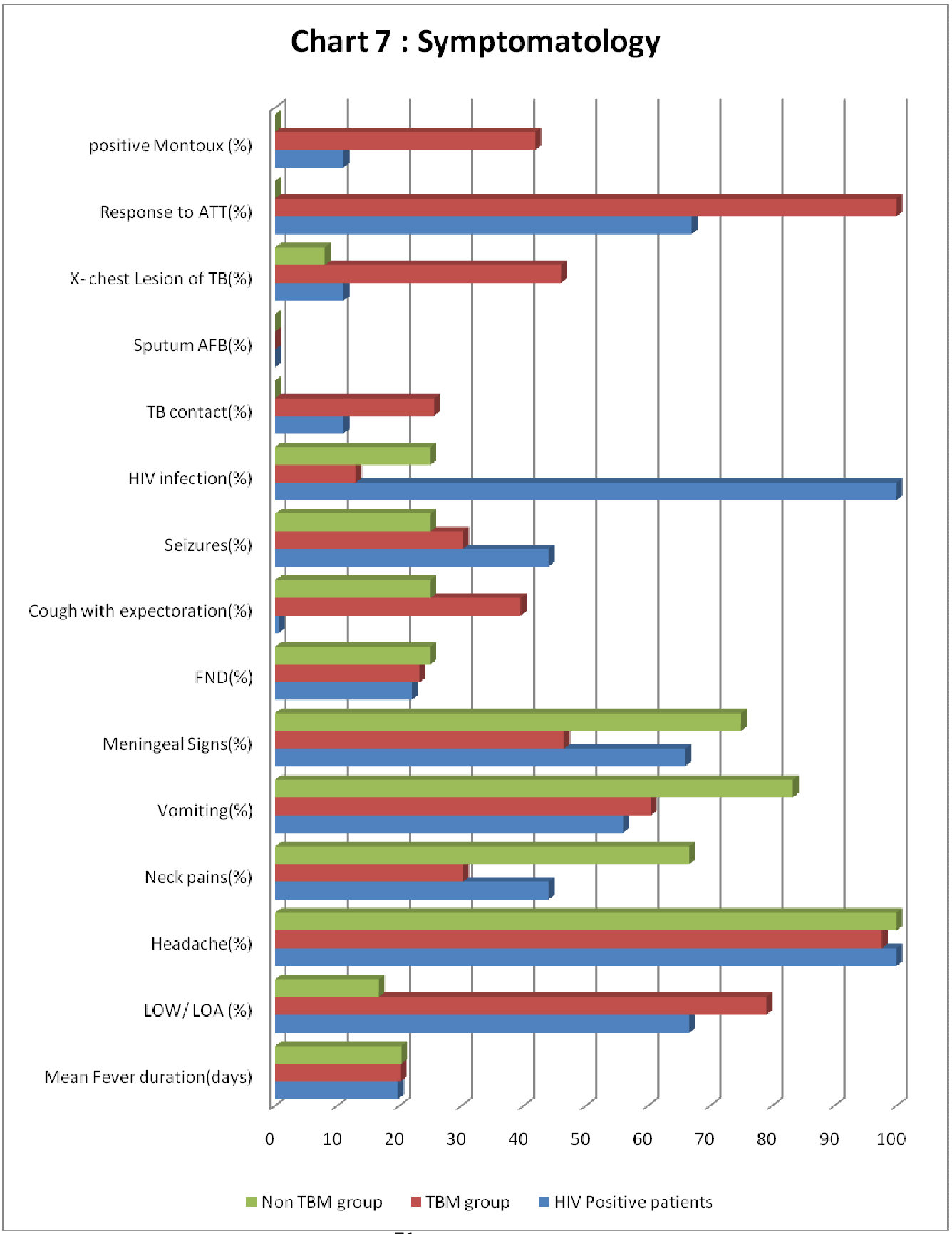
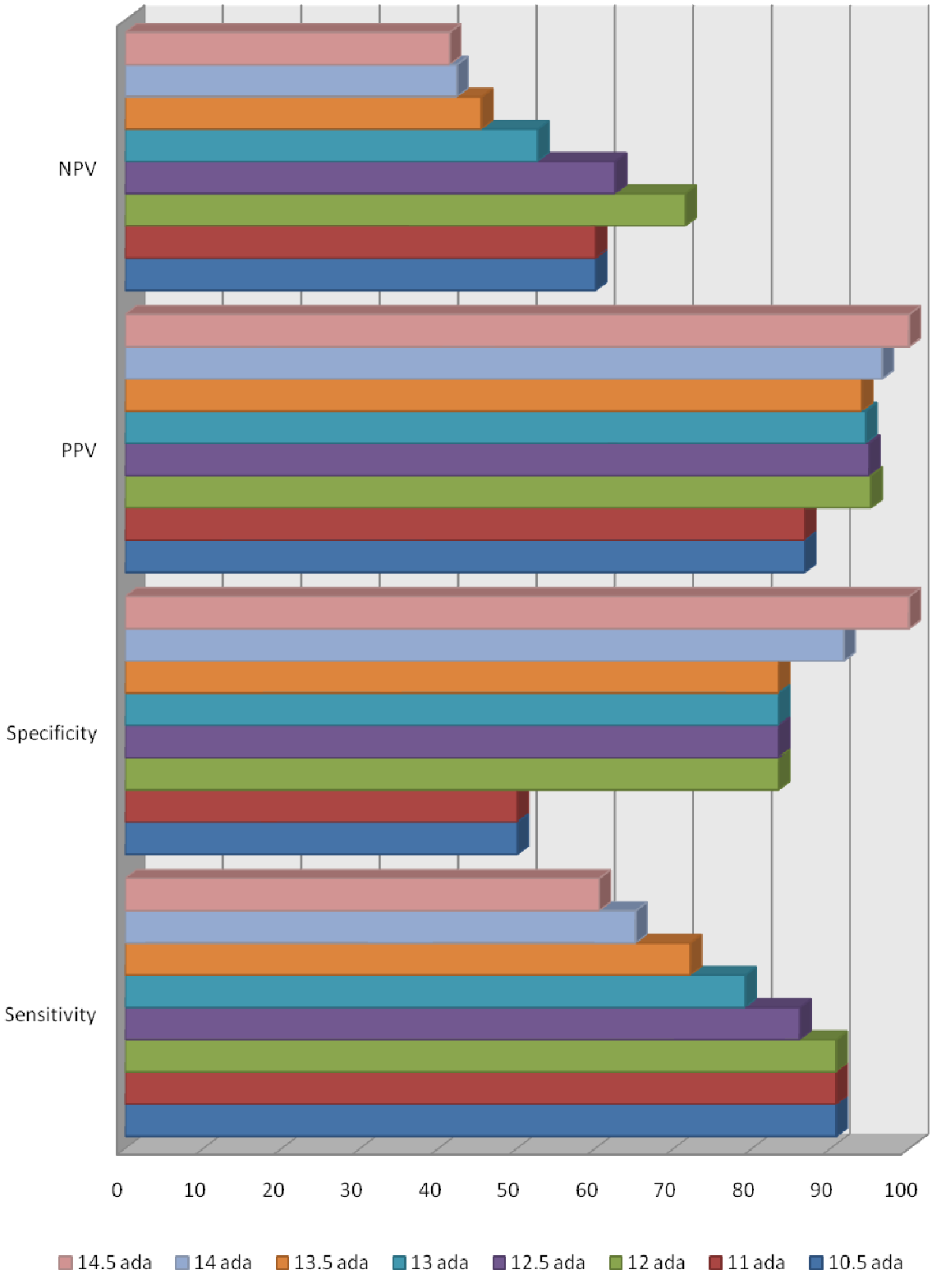


Chart 7 : Symptomatology
positive Montoux (%)
Response to ATT(%)
X- chest Lesion of TB(%)
Sputum AFB(%)
TB contact(%)
HIV infection(%)
Seizures(%)
Cough with expectoration(%)
FND(%)
Meningeal Signs(%)
Vomiting(%)
Neck pains(%)
Headache(%)
LOW/ LOA (%)
Mean Fever duration(days)
0
10
20
30
40
50
60
70
80
90
100
Non TBM group
TBM group
HIV Positive patients

Chart 8: Comparison at different ADA cut - off levels



DISCUSSION

In our study , from a total of 55 patients ,we included a total of 43 patients in TBM group and 12 patients in the non TBM group. The yield of CSF culture in LJ media is low and considering only culture positive patients in the TBM group would include significant no. of true negatives into the non TBM group. This may lead to a large defect in the interpretation of results. Hence patients were considered to be suffering from TBM based on the results of CSF culture for MTB and positive neuro-radiological imaging findings and a good response to ATT. This is also supported by the following studies where there was a division among patients as TBM and non TBM based on findings other than positive culture alone.

There has always been a controversy on the cut-off value of ADA in the CSF to consider it to be positive and suggestive. The following has been the analysis of similar studies in the past.

According to Gupta[57] BK et. Al, when a study on 19 tubercular patients, 18 had CSF ADA above the cutoff value. Among 21 patients with non-TB patients, 2 had ADA levels above the cutoff value They concluded that ADA level estimation in CSF with 10 U/L as a cutoff value had 94.73% sensitivity ,90.47% specificity, 90.00% positive predictive value. They suggest ADA should be given a place in routine evaluation of chronic meningitis

According to Karsen et al[58]. a cut-off value of 12.5 IU/L had a sensitivity of 92% and specificity of 98% in differentiating TBM from non –TBM cases.They also found that if a cut-off of 6.45 IU/L is used then the sensitivity becomes 100% but specificity remains 92%. They suggested to use cut-off of 11 IU/L (sensitivity 92% and specificity 90%) and concluded in favour of cost-effectiveness of use of ADA.

According to Xu et al[59] , a study of 10 patients when undertaken. Sensitivity – 79% , specificity 91%, positive likelihood ratio 6.85 , negative likelihood ratio 0.29 and diagnostic odds ratio 26.93, was obtained with a cut-off of 12 IU/L.

According to Moghtaderi A et al[60]., when a study on 42 patients was done the TBM had an median ADA of 22 and in the non-TBM group it was 8.0. They suggested the cut-off value of 10.5IU/L and achieved a sensitivity and specificity of 81% and 86% respectively.

Pinheiro FV, et al[61] did a study to investigate CSF- ADA as additional marker of HIV infection in 26 patients with HIV. ADA activity correlated well with a sensitivity of 50% and specificity of 82.76%.

According to Rana SV et al[62]., a study when done to compare ADA activity TB-PCR in CSF as a marker of TBM on 54 patients with suspected TBM found that a cut off of 10U/L, gave a sensitivity of 92.5% and specificity of 97% . They also suggested that ADA is a more sensitive indicator of TBM than TB-PCR in CSF.

Feres MC et al[63]., compared the pleural fluid and CSF ADA activity in suspected TB patients. 94 pleural fluid and 40 CSF samples were studied.0.96 and 0.95 were the correlation coefficients for Pleural fluid and CSF samples. They suggested a cut-off of 9 IU/L and also validate the automated method for ADA estimation in samples.

According to Gautam N[64] and others, CSF- ADA in TBM was calculated in 20 (TBM) and 25 (non – TBM) patients. The sensitivity was 85% and specificity was 88.0% at cut-off value of 6.97 IU/L. They conclude that ADA activity should be considered as a better and reliable approach especially in developing countries.

According to Kashyap RS et al[65]., studied CSF - ADA activity in 153 patients; 27 TBM patients, 39 clinically suspected TBM and 87 non-TBM patients. They concluded that ADA has a sensitivity of 83% and specificity of 86%. They also suggested that performing ADA (by any method) is useful in low income countries.

Chotmongkol V et al[66],studied CSF – ADA in 16 cases of TBM, 53 cases on non – TBM and 108 controls. They found that the mean in TBM group was 39.44 which was significantly higher than both the other groups. They suggested a cut-off of 15.5 U/I . This gave them sensitivity - 75% and specificity - 93%. They also supported the use of CSF ADA activity as a useful tool in the rapid diagnosis of TBM.

Kainthla RP et al[67]., also found a significantly higher CSF – ADA activity in TBM than in non TBM patients. The mean was 14.31 in TBM

group, 9.25 in non-TBM group and 2.71 in control population. According to them a 11.39 IU/L can be taken as cut-off value. This gave sensitivity of 82% and specificity of 83%. They validated its use in countries with less sophisticated facilities.

Jakka S et [a68l] tried to evaluate the role of ADA in predicting the adverse outcome in TBM. After eliminating confounding factors like age, gender, CSF parameters, including cell count, lymphocyte and glucose, protein, and LDH levels between the two groups of patients. Patients with adverse outcome had CSF-ADA level 17.1IU/l which was significantly higher than patients with no adverse outcome (11.3 IU/L). They concluded that higher ADA activity may be associated with adverse neurological outcome in patients with TBM.

Corral I et al[69]., ADA activity was studied in 417 CSF samples of HIV positive patients with neurological symptoms. They found that ADA levels were not significantly elevated in HIV-associated neurological disorder and progressive multifocal leukoencephalopathy. They suggested a cut-off of 8.5 IU/l for the diagnosis of TBM and this had 57% sensitivity and 87% specificity. But they also noted that false-positive results could be

obtained from CMV, candidial , cryptococcal, lymphomatous meningitis. Hence they conclude that the TBM diagnostic utility of ADA is limited in HIV positive patients.

Correa MF[70] studied ADA activity in Spanish population. They suggested a cut-off of 8.0 U/L. This gave a sensitivity of 81% and specificity of 91%. The TB - PCR sensitivity was 80 % and specificity of 97 %. They too validate use of CSF- ADA activity for TBM diagnosis.

Choi SH et al[71]., studied CSF – ADA in 182 patients with meningitis. This study included 36 patients with TBM ,130 cases of aseptic meningitis,9 cases of bacterial meningitis and 7 cases of fungal meningitis. The mean ADA in the TBM group was 12.76. This was significantly higher than that in the rest of the groups. The sensitivity of 83% and specificity of 95% was calculated using a cut-off value of 7 U/l was used. Values >15 U/l were not seen in any of the non-TBM patients. Hence they conclude that ADA activity >15 U/l can be used as a strong indicator TBM. They conclude that CSF ADA activity can be used to diagnose TBM early from other causes of chronic CNS infection with good reliability.

Schutte CM et al[72]. analysed the role of ADA isoenzymes with an intention to note the ratio of ADA-2 : total ADA in TBM (15 patients) and non-TBM group(11 patients). The ratio of ADA-2 : Total ADA > 0.8 in almost all patientsTBM.This ratio was significantly different in the non-TBM group and hence this reflected the monocyte-macrophage origin of the ADA-2.

Gambhir IS et al[73]. studied 60 by dividing them into TBM and non TBM group of 24 and 36 patients respectively. Non-TBM group included pyogenic meningitis ,viral encephalitis, aseptic meningitis, cerebral malaria and enteric encephalopathy.CSF- ADA activity was 9.61 and was significantly elevated as compared to non-TBM group. They suggested use of 8 IU/L as cut off value for diagnosis of TBM .They gave a sensitivity of 44% and specificity of 75% at this level.

According to Mishra OP et al[74]. who studied 27 pateints with TBM ,29 non TBM patients and 10 control subjects. CSF ADA activity level was significantly high ($p < 0.001$) in TBM patients. They suggested a cut –off of 5 IU/L It had a sensitivity and specificity of 89 and 92 %. They also concluded that the levels did not differ significantly with different stages of

TBM. They also found that there is significant correlation between CSF – ADA and CSF lymphocyte count, protein concentration and lymphocyte : neutrophil ratio.

Rohani MY et al[75]. also studied the value of CSF – ADA in Malaysian population. They suggest a cut of 9 IU/L after studying 14 patients with TBM. They gave a specificity of 87.6% at this level. They suggested that CSF-ADA level should be interpreted as a rapid marker for tuberculosis along with clinical correlation.

Machado LD et al[76]. studied CSF - ADA activity in 263 patients with AIDS. They found that an elevated CSF - ADA activity can be present in CSF with toxoplasmosis, neuro-syphilis, neuro - CMV , cryptococcal meningitis and lymphomatous meningitis. Hence they concluded that the utility of CSF –ADA activity is limited in HIV positive patients with neurological manifestations as compared to patients who are not infected by HIV.

According to Mishra OP et al[77]. CSF-ADA activity measurement and levels of C-reactive protein when done in 27 patients with TBM and 8 patients with non-TBM showed significant alterations. A cut-off ADA

level of 5 IU/L and CRP positivity was suggested to be used as a tool to differentiate TBM from non TBM patients. Their study had a 75 % and 100 % sensitivity and specificity. Since both the tests are simple and generate rapid results, they stress the importance of this test to differentiate TBM from non-TBM causes of meningitis.

López-Cortés LF[78] ,Egido JA[79] ,Abduljabbar MS[80] pointed out that CSF – ADA may give false positive results with neuro brucellosis and that the efficacy of CSF –ADA is reduced in HIV positive individuals.

Yu SZ et al[81], Baki A et al[82] , Coovadia YM et al[83] assert the use of CSF – ADA in TBM diagnosis in their studies.

Donald PR et al[84] studied 27 TBM patients, 40 with aseptic meningitis, 31 with bacterial meningitis. Both the CSF: serum ADA ratio and the absolute CSF ADA levels were higher in TBM . They conclude that both values can distinguish TBM from non TBM but they suggest correlation with the other CSF markers of TBM like Glucose , protein and lymphocyte count.

Blake J et al[85]. conclude that TB effusion have higher ADA activity than the non TB causes of effusion .They obtained these results from a study of 359 patients with TB effusion and TBM . They conclude that cut-off levels 30 IU/L in effusions and 6 IU/L in the CSF indicate the probable diagnosis of tuberculosis.

In our study we conclude that a cut-off of 12 IU/L gives optimal sensitivity with high specificity and positive predictive values. (90.7 ,83.33 and 95.12 respectively). A comparison was done only in the culture positive TBM patients with the patients with known non –TBM group at a cut – off level of 12 IU/L. in this the sensitivity

Drawback of this study :

The good response to ATT in some of our culture negative patients in the TBM group could partially be attributed to the presence of steroids in the treatment regimen. The CSF was inoculated in the LJ media and the sensitivity of culture could have been increased with the used of liquid media (Eg: BACTEC or MGIT). Only one CSF sample was used for inoculation.

CONCLUSION

1. Tuberculosis of the central nervous system is the most common cause of chronic meningitis.
2. Increased ADA activity in the CSF is a reliable indicator of TBM.
3. A Cut-off of 12 IU/L gives a sensitivity , specificity , positive predicitive value and a negative predictive value of 90.7 ,83.33 , 95.12 and 71.43 respectively

ABSTRACT:

Background: Tuberculosis affection of the central nervous system is seen in 1 % all cases of tuberculosis. It's a major extra-pulmonary manifestation of Tuberculosis.CNS TB is a devastating disease and the yield of AFB staining , CSF culture for MTB is low. The CSF – ADA levels have been found to be a good indirect evidence to the presence of TBM.

Methods: A total of 55 patients suffering from clinical features suggestive of sub-acute / chronic meningitis were included in this study and they were divided into TBM (43 patients) and non TBM group (12 patients) based on their CSF analysis , neuro – radiological imaging and response to treatment. The CSF – ADA level activity in both the groups was analysed.

Results: A Cut-off of 12 IU/L gives a sensitivity , specificity , positive predicitive value and a negative predictive value of 90.7 ,83.33 , 95.12 and 71.43 respectively.

Conclusion: ADA at a cut-off of 12 IU/L can be a reliable and rapid indirect indicator of TBM.

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PROFORMA

A Study on CSF Adenosine Deaminase levels as a marker of CNS Tuberculosis in 50 patients

Serial.no:

Name: Age;
sex:

Height: weight:
BMI

Occupation: socio economic status:

Presenting complaints:

H***/o presenting complaints:***

Past history:

Tuberculosis:

Bronchial Asthma:

Diabetes Mellitus:

Hypertension:

Cancers;

Ischemic Heart Disease:

Liver Disorders;

Renal Disorders:

Transfusions:

HIV

personal history:

Smoking:

No. Of Packs/Day Duration:

Any Other Tobacco Use:

Alcoholism:

Any Other Substance Abuse:

Family history:

EXAMINATION:

General examination:

Pallor:

Icterus:

Cyanosis:

Clubbing:

Pedal Edema:

Lymph Node Enlargement;

Pupil

External marker of TB

CNS:

Higher functions

Cranial Nerves

Motor

Sensory

Cerebellar

Neck stiffness

Spine , skull

RESPIRATORY SYSTEM:

CARDIOVASCULAR SYSTEM:

ABDOMEN

INVESTIGATIONS:

Complete Hemogram:

Haemoglobin:

Total Count:

Differential Count:

Hematocrit;

MCV; MCHC: MCH

Reticulocyte Count:

Platelet Count;

CSF ANALYSIS

Appearance

Colour

Protein

Pressure

Sugar

Cells

Cytology

Grams stain

AFB stain

Culture (bacterial)

Culture (L-J medium for TB)

ADA levels

CHEST XRAY

ECG

CT BRAIN

MRI BRAIN

Sl. No.	Hb	TC	P	L	M	ESR	Mx	CSF	C-web	Sgr	Prtn	L-csf	Grams'	ADA	ATT Rx	C/S (Bact)	C/S AFB	St	Imaging	HIV
1	11	4900	40	52	4	46	-	clear	-	32	86	17	-	13.6	+	-	+	1		-
2	13	5400	41	54	3	36	-	clear	-	29	80	18	-	14.2	-	-	neg	0	Cncr	-
3	11	4600	36	60	3	39	+	turbid	-	42	72	10	-	17.4	+	-	neg	1	M	-
4	12.4	4900	41	56	2	34	+	clear	-	37	58	7	-	14.7	+	-	+	1		+
5	13.6	5200	40	60	0	44	-	turbid	-	36	57	6	-	18.1	+	-	+	2	M	-
6	10.6	7700	40	53	3	51	-	clear	-	33	61	6	-	15.3	+	-	+	1		-
7	13.3	6600	36	61	2	49	-	clear	-	40	59	6	-	16.3	+	-	+	1	M	-
8	14.2	4560	39	58	3	46	+	turbid	+	40	56	12	-	16.1	+	-	neg	1	M	-
9	9.8	4400	29	62	4	46	-	clear	-	37	59	6	-	12.6	+	-	+	1		-
10	11.2	6100	33	60	3	39	-	clear	-	46	53	5	-	13.4	+	-	+	1		-
11	13.6	5900	33	61	3	61	-	clear	-	43	51	8	-	12.6	+	-	neg	1	T	-
12	12.9	9600	44	50	3	53	-	clear	-	50	59	2	+	3.5	-	+	neg	0		-
13	12.6	6100	40	60	0	64	+	turbid	-	40	69	14	-	23.4	+		+	1		-
14	13.4	5300	41	59	0	39	-	clear	-	35	60	10	-	16.4	+	-	neg	1	H,VP,M	+
15	12.9	5900	40	56	2	44	-	clear	-	36	59	8	-	7.4	+	-	+	1		-
16	13.9	5800	33	64	3	46	+	turbid	+	39	66	8	-	16.4	+	-	neg	2	M,I	-
17	11	5600	40	60	0	44	-	turbid	-	39	47	6	-	14.1	+	-	+	1	M	-
18	14.6	5900	41	59	0	44	+	clear	-	39	46	8	-	7.9	+	-	+	1		-
19	15.4	6100	50	50	0	64	-	clear	-	40	60	11	-	18.1	+	-	neg	2	M	+
20	14.4	11900	55	45	0	49	-	turbid	-	40	56	3	-	7.5	-	+	neg	0	M	-
21	14.9	5700	45	55	0	29	-	clear	-	39	71	8	-	11.9	-	-	neg	0		-
22	11.6	5600	36	61	2	41	-	turbid	-	36	55	7	-	13.1	+	-	neg	1	M,T	-
23	10.2	6100	31	60	4	37	-	turbid	-	34	56	5	-	13.7	+	-	neg	2		-
24	11.8	9400	60	36	1	44	-	turbid	-	30	64	2	+	5.9	-	+	neg	0		-
25	9.8	7300	50	50	0	35	-	turbid	+	24	59	13	-	16.4	+	-	+	1	M,T	-
26	10.6	6300	44	53	2	41	+	turbid	-	26	54	15	-	17.4	+	-	+	1		-

27	10.4	6700	43	53	2	35	-	turbid	-	28	56	17	-	8.1	+	-	neg	1	T	-
28	10.2	5700	44	53	2	36	+	clear	-	28	54	9	-	20.4	+	-	+	1	M	-
29	13.1	7600	40	56	1	38	+	clear	-	30	60	7	-	21.6	+	-	+	2		-
30	10.8	8600	41	54	3	36	+	clear	-	30	55	9	-	12.4	+	-	neg	2	T	-
31	9.6	5400	40	54	1	33	-	clear	-	30	55	14	-	12.4	+	-	+	1	M	-
32	14.1	8600	39	56	3	42	-	turbid	-	28	54	7	-	13.9	+	-	+	1		+
33	10.8	6100	40	56	3	40	+	turbid	-	30	60	18	-	17.2	+	-	+	2		-
34	11.4	8300	41	54	2	36	+	clear	-	33	64	7	-	10.1	+	-	neg	1	H,VP,M	-
35	13.9	6300	36	60	3	35	-	clear	-	30	60	9	-	14.3	+	-	+	1		-
36	10.4	5900	36	60	3	37	-	turbid	-	32	59	16	-	16.2	+	-	+	1		-
37	10.6	6800	39	60	0	44	+	clear	-	33	66	8	-	17.3	+	-	neg	2	M	-
38	13.8	4700	36	60	2	40	-	clear	-	30	54	14	-	14.9	+	-	+	2		-
39	14.9	5800	39	56	3	41	-	clear	-	33	60	17	-	16.3	+	-	+	1		+
40	12.4	8650	36	60	3	37	-	turbid	-	30	66	14	-	17.4	+	-	neg	1		-
41	10.6	9400	54	40	3	46	-	turbid	-	20	66	11	-	11.8	-	-	neg	0	Cncr	-
42	13.8	8250	46	50	2	39	+	turbid	-	24	60	14	-	12.8	+	-	+	2	M,T	-
43	13.6	10460	56	41	2	42	-	turbid	-	20	76	3	+	6.4	-	+	neg	0		+
44	12.8	10700	56	40	1	40	-	turbid	-	22	59	2	+	9.1	-	+	neg	0		-
45	12.8	5200	56	36	2	40	-	turbid	-	29	70	12	-	11.9	-	-	neg	0	M	-
46	10.8	10300	60	34	0	42	-	turbid	-	24	56	2	+	11.5	-	+	neg	0		-
47	12.4	5600	60	34	3	43	-	turbid	-	36	56	17	INDIA INK +	7.5	-	-	neg	0	M	+
48	11.6	4900	39	56	3	40	-	clear	-	33	56	12	-	13.4	+	-	+	2	M,I	+
49	14.8	6640	40	60	0	38	-	turbid	-	36	56	16	-	17.4	+	-	+	1		-
50	13.4	6100	39	59	0	34	-	clear	-	30	60	11	-	18.9	++	-	++	1		-
51	13	5900	40	60	0	38	-	turbid	-	30	56	11	-	21.2	++	-	++	1		-
52	10.4	6100	36	59	3	41	-	clear	-	38	52	8	-	16.4	+	-	+	1		-
53	12.4	8400	60	35	3	44	-	turbid	-	40	56	18	INDIA INK	13.6	-	-	neg	0	M	+

													+							
54	15.4	8900	50	50	0	40	-	Turbid	-	30	56	13	-	16.4	+	-	neg	1		-
55	12.4	9800	40	60	0	38	-	Turbid	-	32	56	17	-	17.4	+	-	+	1		-

S.No.	Name	Age	Sex	Fever	LOW/LOA	Headache	Neck pain	Vomiting	Mngl Sgn	FND	COUGH	Sizre	TB Cntct	Spt AFB	CXR	HIV
1	Rajini	29	m	22	+	+	-	-	+	-	14	-	-	-	+	-
2	Krishnan	41	m	18	-	+	-	+	-	-	-	-	-	-	-	-
3	Kosman	52	m	26	+	+	-	-	+	-	-	-	-	-	+	-
4	Jaffer	46	m	13	+	+	-	+	+	-	16	-	-	-	-	+
5	Ajith	17	m	22	+	+	+	+	+	+	12	+	-	-	+	-
6	Rajeswari	19	f	28	+	+	-	-	-	-	20	-	+	-	+	-
7	Ramesh	32	m	17	+	+	-	-	-	-	-	-	-	-	-	-
8	Jaya kumar	31	m	18	-	+	-	+	+	-	10	-	+	-	-	-
9	Sindhya	21	f	26	+	+	+	+	+	-	17	+	-	-	+	-
10	Murugesh	17	m	20	-	+	-	+	+	-	-	-	+	-	+	-
11	Ragaiah	46	m	23	+	+	-	-	-	-	-	-	-	-	-	-
12	Duraisamy	39	m	24	-	+	-	-	-	-	-	-	-	-	-	-
13	Venkatachalam	36	m	13	+	+	+	+	+	-	-	-	-	-	+	-
14	Penicillaiah	50	m	18	+	+	-	-	-	-	18	-	-	-	+	+
15	Senthil Kumar	33	m	19	-	+	-	+	-	-	-	-	-	-	-	-
16	Kannan	32	m	18	-	+	-	+	-	+	-	+	-	-	+	-
17	Poongodhai	27	f	16	-	+	-	-	-	-	-	-	-	-	-	-
18	Anand	23	m	18	-	+	-	+	-	-	21	-	+	-	+	-
19	Balaji	34	m	24	+	+	-	+	+	-	-	+	-	-	-	+
20	Sakthivel	41	m	19	+	+	-	+	+	-	19	-	-	-	+	-

21	Raj mohan	39	m	34	+	+	+	+	+	-	-	-	-	-	-	-
22	Kavitha	33	f	30	+	+	+	+	-	-	14	-	-	-	+	-
23	Chandra	27	f	17	-	+	-	+	+	-	13	+	+	-	+	-
24	Senthil Kumar	24	m	13	-	+	+	+	+	-	-	-	-	-	-	-
25	Kushboo	23	f	18	+	+	-	+	-	+	22	-	-	-	+	-
26	Hasinabee	41	f	24	+	+	-	-	-	-	-	-	+	-	-	-
27	Jaya	30	f	20	-	+	-	+	+	-	-	-	-	-	-	-
28	Muniyammal	33	f	26	+	+	+	+	+	+	15	-	-	-	+	-
29	Raja	34	m	20	+	+	-	+	-	+	22	+	-	-	+	-
30	Raziya	38	f	18	+	+	-	+	-	-	-	-	+	-	-	-
31	Panjali	36	f	24	+	+	-	+	-	+	-	-	-	-	-	-
32	Pandi	32	m	20	+	+	-	+	-	-	-	-	-	-	-	+
33	Swathi	19	f	20	+	+	-	-	-	+	19	+	+	-	+	-
34	Sivasankari	30	f	20	+	-	-	-	-	-	-	-	-	-	-	-
35	Vimala	33	f	22	+	+	-	-	-	-	26	-	+	-	+	-
36	Rajesh	30	m	14	+	+	-	+	-	-	-	-	-	-	-	-
37	Anna neena	36	f	22	+	+	-	-	-	+	-	+	-	-	-	-
38	Kumar	33	m	20	+	+	-	-	-	-	-	+	+	-	-	-
39	Mahendran	49	m	23	+	+	-	-	-	-	-	-	-	-	-	+
40	Amala	24	f	20	+	+	-	-	-	-	-	+	-	-	-	-
41	Palayi	44	f	20	-	-	+	+	+	+	-	-	-	-	-	-
42	Joseph	39	m	21	-	+	+	+	+	+	23	-	-	-	+	-
43	Velkumar	41	m	20	-	+	+	-	+	-	-	+	-	-	-	+
44	Mathiyas	56	m	20	-	+	+	+	+	+	-	-	-	-	-	-
45	Anbu	27	f	18	-	+	-	+	-	-	-	+	-	-	-	-
46	Mariyappan	60	m	24	-	+	+	+	+	-	-	-	-	-	-	-
47	Jamuna	36	f	20	-	+	+	+	+	-	18	+	-	-	-	+

48	Asha	39	f	26	+	+	+	-	+	+	26	+	+	-	-	+
49	Rajesh	33	m	14	+	+	+	+	+	-	-	-	-	-	-	-
50	Kamarullah	46	m	24	+	+	+	+	+	-	-	-	-	-	+	-
51	Lakshmi	27	f	16	+	+	+	+	+	-	-	-	-	-	-	-
52	Kanchana	44	f	15	+	+	+	-	+	-	-	+	-	-	+	-
53	Grebha	52	f	14	-	+	+	+	+	+	20	-	-	-	-	+
54	Mani	31	m	16	+	+	+	+	+	-	-	-	-	-	-	-
55	Rukmani	50	f	18	+	+	+	+	+	-	-	+	-	-	-	-

Hb – hemoglobin , TC – Total Count , P – polymorph , L- lymphocyte ,M- Monocyte , Mx – Montoux test , C web – Cob web formation , Sgr – CSF sugar concentration , Prtn – CSF protein Concentration , l_csf – lymphocytes / high power field in the CSF , Gram's – result of Gram's Staining , ADA – Adenosine Deaminase levels in the CSF , ATT Rx – response to anti Tubercular treatment , c/s Bact – result of culture in bacterial media , c/s afb – result of the inoculation in LJ media , Mnngl sgn – denotes the presence of meningeal signs , Sizre – Seizures , FND – Focal neurological deficit , TB Cntct – Presence of TB contact , Spt AFB – result of Sputum for presence of Acid fast Bacilli , CXR – Chest X ray findings , M – menigeal Enhancement , H – Hydrocephalus , VP – ventriculo peritoneal shunting procedure , T - Tuberculoma